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FIELD OF VISION

Primary colon resection or Hartmann's procedure in malignant left-sided large bowel obstruction? The use of stents as a bridge to surgery

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Abstract

There is still significant debate regarding the best surgical treatment for malignant left-sided large bowel obstruction. Primary resection and anastomosis offers the advantages of a definite procedure without need for further surgery. Its main disadvantages are related to the increased technical challenge and to the potential higher risk of anastomotic leakage that occurs in the emergency setting. Primary resection with end colostomy (Hartmann's procedure) is considered the safer option. Tan *et al* compared in a systematic review and meta-analysis the use of self-expanding metallic stents (SEMS) as a bridge to surgery *vs* emergency surgery in the management of acute malignant left-sided large bowel obstruction. The authors concluded that the technical and clinical success rates for stenting were lower than expected. SEMS was associated with a high incidence of clinical and silent perforation. Stenting instead of loop colostomy can be recommended only if the appropriate expertise is available in the hospital. The goal of stenting, a decrease of the stoma rate, may be advocated only if the complication rates of stenting are lower than those of stoma creation in the emergency situation. Until now, this was not demonstrated in a prospective randomized trial.

COMMENTARY ON HOT TOPICS

There is still significant debate regarding the best surgical treatment for malignant left-sided large bowel obstruction. In a multicenter German observation study, out of 15 911 patients with cancer of the left colon a total of 743 patients (4.7%) underwent emergency surgery, performed as a radical resection. In 57.9% (n = 430) a one-stage operation, in 11.7% (n = 87) a primary anastomosis with protective stoma, and in 30.4% (n = 226) Hartmann's procedure (HP) were performed[1]. The morbidity and hospital mortality rates (overall hospital mortality, 7.7%, n = 57) did not differ significantly between the groups. With comparable mortality, HP was recommended for high risk patients in the emergency situation. On the basis of a literature search, Trompetas[2] came to a similar conclusion: primary resection with end colostomy (HP) is considered the safest option in malignant left-sided colonic obstruction. The main advantages are that there is no risk of anastomotic dehiscence and the operation can be performed by less experienced and non-specialist surgeons. The main disadvantages of HP are the need for a second major operation to reverse the colostomy, and the fact that 40%-60% of patients do

not have their colostomy reversed, thereby significantly affecting their quality of life (QOL)[2]. The decision whether a one-stage procedure (resection and anastomosis) should be chosen or not, therefore mainly depends on the clinical assessment of the patient's condition. This is also demonstrated by a survey among members of the Society for Surgery of the Alimentary Tract, performed in the year 2001. With left-sided colonic emergencies in "high-risk" patients, most surgeons opted for a HP (88%) or a diverting colostomy (7%), but in "good-risk" patients 53% of the responders would have selected a one-stage procedure[3]. A Consensus Conference of the World Society of Emergency Surgery (WSES) and Peritoneum and Surgery (PnS) Society held in 2010, gave the following recommendations on management of obstructive left colon carcinoma: (1) HP should be preferred to loop colostomy (C) or loop ileostomy and subsequent resection (2 or 3 staged procedure), since C appears to be associated with longer overall hospital stay and need for multiple operations but not with a reduction in perioperative morbidity (Grade of recommendation 2B); and (2) HP offers no overall survival benefit compared to segmental colonic resection with primary anastomosis in obstructive left colon carcinoma (Grade of recommendation 2C+); HP should be considered in patients with high surgical risk (Grade of recommendation 2C)[4].

The choice of surgery also depends on the specialization of the surgeon. In a series of 336 emergency colorectal procedures performed in the United Kingdom for cancer and diverticular disease, a primary anastomosis was performed in 142 (64.3%) patients by colorectal surgeons and in 42 (36.5%) by non-colorectal surgeons. The overall morbidity and mortality rates were lower for colon and rectal surgeons (14.5% *vs* 24.3% and 10.4% *vs* 17.4%, respectively)[5].

Undisputed are the disadvantages of HP. Vermeulen *et al*[6] assessed the long-term QOL after emergency surgery for perforated diverticulitis in a cohort of 76 patients with HP and 53 patients with primary anastomosis. After 71 mo follow-up, 30 HP patients (39%) still had an end colostomy, but only two patients with primary anastomosis still had a loop ileostomy (4%). Survivors from acute perforated diverticulitis reported worse QOL compared to the Dutch population. QOL in patients who had undergone HP was lower compared to patients who underwent primary anastomosis, both from the patient's and a social perspective. After reversal of HP, this difference disappeared, but HP reversal was performed in only 61% of the patients. QOL in patients after perforated diverticulitis was mainly influenced by the presence of a stoma postoperatively.

The restoration of bowel continuity usually should take place 3 mo after HP. In practice, however, the patients have to live longer with the stoma. van de Wall *et al*[7] provided a systematic overview of 35 studies on HP reversal in 6249 patients. Diverticular disease in 67% and colorectal malignancies in 17% were the main indications for HP. The mean reversal rate after HP was 44%, and the mean time interval between HP and reversal was 7.5 mo.

Even though HP was preferred so far in high-risk patients, the results, nevertheless, are not convincing. Rather than to query in an acute situation whether a single-stage procedure is still acceptable or whether better HP should be carried out for malignant left-sided bowel obstruction, it should be tried to avoid the emergency surgery (including the stoma) in order to attain a risk reduction for the patient[8]. Stoma complications after emergency surgery are underestimated. In a prospective audit of the United Kingdom, a total of 3970 stomas were recorded, of which 1329 (34%) were identified as problematic within 3 wk of surgery[9]. Patients undergoing an emergency procedure were more likely to have a problematic stoma. Another audit, too, revealed emergency surgery as a significant risk factor for stoma complications after colorectal cancer surgery[10].

An at least theoretical approach to circumvent the emergency operation and its complications is the bridging of the obstruction with a stent. It allows after decompression of the left colon and mechanical bowel preparation scheduled surgery of the patient with a high rate of primary anastomoses[11-13].

In this context, I read the recent systematic review and meta-analysis published by Tan *et al*[14] with great interest and I strongly recommend it to readers.

It was the aim of this article to compare the use of self-expanding metallic stents (SEMS) as a bridge to surgery *vs* emergency surgery in the management of acute malignant left-sided large bowel obstruction. Four randomized clinical trials with 234 patients were identified. In terms of efficacy of SEMS placement, the technical and clinical success rates were 70.7 % and 69 % respectively. SEMS intervention resulted in significantly higher successful primary anastomosis [risk ratio (RR), 1.58] and lower overall stoma (RR, 0.71) rates. The clinical perforation rate was 6.9 (8 of 116) and the silent perforation rate 14% (11 of 77). There was no significant difference in anastomotic leak, 30-d reoperation, in-hospital mortality and surgical-site infections rates between stenting and emergency surgery. The authors concluded that the technical and clinical success rates for stenting were lower than expected. SEMS was associated with a high incidence of clinical and silent perforation. However, as a bridge to surgery, SEMS had higher successful primary anastomosis and lower overall stoma rates, with no significant difference in complications or mortality.

A Cochrane review published a few months earlier was more cautious with the recommendation of SEMS[15]. According to this evaluation the use of colonic stent in malignant colorectal obstruction seems to have no advantage over emergency surgery. The clinical success rate was statistically higher in emergency surgery group. The advantages of colorectal stent included shorter hospital stay and procedure time and less blood loss. However, due to the variability in the sample size and trial designs in the included studies, further randomised trials with bigger

sample size and well defined trial design are needed to achieve the robust evidence[15].

In the meantime a further small randomised trial has been published which cannot change this conclusion[16]. In this study 20 patients were randomized to stenting as a bridge to elective surgery and 19 patients to emergency surgery for left-sided malignant colonic obstruction. Technical stent failure occurred in five patients (25%). Two of 20 patients in the stenting group required defunctioning stomas compared to 6 of 19 in emergency surgery group. There was a trend towards lower morbidity and mortality in the stenting group, but the differences were not statistically significant.

The results of the Dutch Stent-in study illustrate the difficulties in interpreting the available data[17]. In this multicentre randomised trial 98 patients with acute left-sided malignant colonic obstruction were assigned to receive colonic stenting (n = 47) as a bridge to elective surgery or emergency surgery (n = 51). No difference was recorded between treatment groups in 30-d mortality, overall mortality, morbidity, and stoma rates during a 6-mo follow-up, and mean global health status did not differ between both interventions. However, the emergency surgery group had an increased stoma rate directly after initial intervention. These authors concluded that colonic stenting has no decisive clinical advantages to emergency surgery. It could be used as an alternative treatment in as yet undefined subsets of patients, although with caution because of concerns about tumour spread caused by perforations[17].

Finally, a meta-analysis should be mentioned which compared the outcomes of stent use as a bridge to surgery and emergency surgery in the management of obstructive colorectal cancer in 8 studies and included also the Chinese Biomedical Literature Database[18]. About 232 patients (38.6%) underwent stent insertion and 369 (61.4%) underwent emergency surgery. The primary anastomosis rate in the stent group was higher (RR, 1.62), and overall complications (RR, 0.42), including anastomotic leakage (RR, 0.31) were reduced by stent insertion. Nevertheless, also in this study, stent insertion before subsequent surgery had no effect on perioperative mortality and long-term survival.

Some authors[19] guessed that SEMS intervention in patients with acute colonic obstruction should be cost-effective since it allows single-stage surgery, a shorter stay in the intensive care unit, and shorter hospitalization in comparison to emergency surgery. A Canadian study based on a decision analytical model even suggested that the use of colonic stenting for patients with acute malignant colonic obstruction is less expensive than emergency resective surgery[20]. Whether this is so, in fact, cannot be confirmed and should be prospectively proven by true comparative studies.

Critically, it should be noted that in the few trials and small case series reported so far the patient should be transferred by means of stenting from an emergency situation to elective surgery. For this purpose, a loop colostomy is a simple alternative which can be performed in any hospital and by non-specialized surgeons. This procedure avoids the hazards that arise when inexperienced apply a SEMS. Stenting instead of loop colostomy can be recommended only if the appropriate expertise is available in the hospital. The Consensus Conference of the WSES and PnS Society, gave the recommendation that HP should be preferred to loop colostomy[4]. But in fact the basis of this recommendation is weak. So far, the sole randomized trial which compared emergency colostomy with acute resection could not demonstrate major disadvantages with colostomy, besides a longer hospital stay[21]. A Cochrane review which was worked out to answer the same question (primary or staged resection for obstruction from primary left colorectal carcinoma?) found that the limited number of identified trials together with their methodological weaknesses did not allow a reliable assessment of the role of either therapeutic strategy in the treatment of patients with bowel obstruction from colorectal carcinoma[22]. Therefore, the second goal of stenting, a decrease of the stoma rate, may be advocated only if the complication rates of stenting are lower than those of stoma creation in the emergency situation. Until now, this was not demonstrated in a prospective randomized trial.

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Primary liver transplantation *vs* liver resection followed by transplantation for transplantable hepatocellular carcinoma: Liver functional quality and tumor characteristics matter

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Abstract

Liver resection (LR) and primary liver transplantation (LT) are two potentially curative treatment modalities for patients with hepatocellular carcinoma (HCC). If an underlying chronic liver disease exists, however, making a decision on which method should be selected is difficult. If a patient has no chronic liver disease, LR may be the preferable option with salvage transplantation (ST) in mind in case of recurrence. Presence of a moderate-to-severe liver failure accompanying HCC usually warrants primary LT. The treatment of patients with HCC and early-stage chronic liver disease remains controversial. The advantages of "LR-followed-by-ST-if-needed" strategy include less complicated index operation, no need for immunosuppression, use of donor livers for other patients in today's organ shortage setting and comparable survival rates. However, primary LT has its own advantages as it also treats underlying chronic liver disease with carcinogenic potential, removes undetected tumor nodules and potentially eliminates need for a ST. An article recently published by Fuks *et al* in *Hepatology* offers an approach by which selecting between LR-followed-by-ST and immediate LT might be easier. Here we discuss the results of the aforementioned report in the light of currently available knowledge.

Key words: Hepatocellular carcinoma; Chronic liver disease; Liver transplantation; Liver resection; Salvage transplantation; Survival

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COMMENTARY ON HOT TOPICS

Liver transplantation (LT) remains the most effective treatment modality for patients with hepatocellular carcinoma (HCC) and underlying chronic liver disease provided that the procedure can be justified by a potentially curable tumor stage. In today's Model for End-Stage Liver Disease (MELD) based practice, Milan Criteria (MC) (one lesion < 5 cm or up to three lesions each < 3 cm with the disease confined to the liver) constitute the main parameter by which to predict patients who would benefit most from LT[1]. While the incidence of HCC is believed to have an increasing trend likely parallel to the increasing number of patients who have had a long lasting course of viral hepatitis infection[2], global donor organ shortage continues to be the most important issue for patients on wait lists as well as for health care providers in the field. This has led the surgery community to look at liver resec-

tion (LR) as a comparable alternative treatment. Patients could be treated by LR followed by the so-called "salvage transplantation" (ST) in cases of tumor recurrence or hepatic decompensation. This would also help the community and other transplant candidates to gain maximum possible benefit from organs of deceased donors. Indeed, thousands of patients have undergone LR as a result of the adoption of this policy over the last decade, and many of them survived subsequent LT. However, this strategy must be carefully evaluated, as there is no guarantee that every patient with HCC undergoing an initial LR with ST in mind will have recurrent disease within the indications of LT. ST may not be an option if: (1) the recurrence is beyond MC; or (2) the patient has developed contraindications to LT, such as advanced age or medical comorbidities. In addition to these factors, the technical challenges of LT will likely be increased in a patient having undergone previous hepatic resection due to scarring and vascularized adhesions.

Bridge therapy, defined as LR followed by a planned LT, regardless of whether the disease recurs, is another strategy to treat HCC. This approach significantly reduces the chance of progression while awaiting an appropriate organ; the strategy is considered to have become successful if a donor liver is offered by the organ allocation system before the patient drops off of the list due to non-transplantable disease recurrence. However, it has been reported that this approach may be associated with greater technical difficulty during transplantation[3,4], particularly if the hepatic hilum and the peri-caval area were dissected extensively during the preceding LR. One other downside to use of LR as bridge therapy is that, in the United States for example, resection of HCC removes the opportunity to use that tumor to gain extra MELD points as a "MELD exception".

For the aforementioned reasons, management of patients with chronic liver disease accompanied by transplantable HCC is an ongoing controversy, leading researchers to seek reliable measures by which to discriminate patients who would benefit from its initial LR from those patients for whom LT should be the first-line treatment.

HOT TOPIC ARTICLE

Fuks *et al*[5] recent study published in *Hepatology* in January 2012 may have the potential to provide a new insight into the issue. Looking to clarify this controversy, the authors compared the outcomes of patients (n = 138) who underwent LR for transplantable HCC within MC, considering ST in case of recurrence, with those of patients who were primarily listed to undergo LT (n = 191). They performed an intent-to-treat based analysis to reveal independent predictors of failure to receive timely ST after initial LT. Out of 138 patients who were supposed to undergo ST in case of recurrence, 26 were excluded because they either underwent LT before recurrence or were diagnosed with a different disease based on final histology. Thus, only 112 patients were planned for ST. Of these, 90 had recurrent disease, of which 30 (33%) did not receive ST because of a recurrence outside the MC. Of remaining 60 patients with recurrence within MC, 21 were not eligible to undergo a major transplant surgery, leaving only 39/90 patients (44%) successfully receiving ST. In the primary LT group, 163 patients underwent LT. After excluding early postoperative deaths and histological diagnoses other than HCC based on explant pathology, this group finally had 146 patients who received a successful LT for HCC. What we can conclude from the results are: (1) One fifth of patients in the initial LR group survived recurrence free. None of those patients required LT for any reason during follow-up; (2) While the median follow-up of whole study population was about 5 years, recurrences (if any) occurred usually much earlier. The median time to recurrence was around 16 mo and was similar in patients regardless of whether they had a recurrent disease within MC or outside MC; (3) The overall 1, 3 and 5-year survival in patients undergoing ST was 94%, 81% and 71%, respectively. The two most frequent reasons for not receiving a ST in within MC group were patient refusal (n = 10) and advanced age (n = 9); (4) In the group beyond MC, tumor > 5 cm, number of lesions > 3 and major vascular involvement were the most frequent contraindications for a ST, occurring in 8 patients each; (5) Multivariate analysis revealed five factors independently associated with recurrence beyond MC: microscopic vascular invasion, presence of satellite nodules, tumor size > 3 cm, poor tumoral differentiation, and existence of cirrhosis. The authors suggested that presence of $\geqslant$ 3 poor prognostic factors should warrant LT before recurrence; (6) ST strategy seemed to save 26 grafts which would otherwise have been used unnecessarily; and (7) However, as a result of this strategy, only 28% of patients included in intention-to-treat analysis and only 39% of patients with recurrence could receive ST, suggesting that primary LT rather than "LR followed by ST if needed" strategy should be the treatment of choice in most of patients with HCC and underlying chronic liver disease.

DISCUSSION

We believe that some important points should be taken into consideration when evaluating the results of this study. As the authors stated in part, a selection bias could not completely be eliminated in this study. All patients in the LR followed by ST group had quite good liver function as determined by having Child-Pugh class A disease and significantly lower mean MELD score (6.5 *vs* 19.8) compared to those in primary LT group. In addition, none of the patients in the earlier group had portal hypertension or reduced thrombocyte count. Moreover, the proportion of patients with Metavir score of F3 in that group was lower than that in the primary LT group. This data suggests that the severity of underlying liver disease was the main parameter to decide the surgical approach selected to manage patients. This kind of study design may be considered inevitable, however, for comparison

of LT with subsequent ST *vs* LT, as implemented by Facciuto *at al*[6] in their retrospective study. Similarly, the average Child-Pugh score and MELD score were lower in the primary LR subsequent ST group than in the primary LT group, though they did not include Child-Pugh class C patients in their analysis. Of 51 patients with HCC undergoing LR as initial treatment, 32 developed recurrence. However, 21 (66%) of those were not eligible to receive ST. Tumor size > 3 cm and high MELD score were shown to be independent risk factors indicating poor survival. There was no difference between the groups in 1- and 4-year overall survival. In a study by Shah *et al*[7], patients with Child-Pugh class A and B disease and HCC within MC were treated by either initial LR (n = 121) or listed for primary LT (n = 140). The drop-out rate in the primary LT group was 21.4% (30 patients). There was no information reporting the number of patients who could undergo ST due to recurrence in the LR group. The authors concluded that primary LT yields better overall survival compared to LR if waiting time from listing for LT was < 4 mo. Of note, histological examination of explants in the primary LT group revealed that 46% of patients actually had a disease outside MC. Margarit *et al*[8] reported that only 6 out of 18 patients with recurrence after LR were able to undergo ST during a 50-mo median follow-up.

Fuks *et al*[5] included only patients within MC. Despite adoption of these criteria by the United Network for Organ Sharing as well as by the majority of centers outside the United States as an integral part of liver allocation systems, some authors have reported that University of California San Francisco (UCSF) criteria (one tumor < 6.5 cm, maximum of 3 tumors with none > 4.5 cm, and cumulative tumor size < 8 cm) can also be used reliably and could yield a long-term outcome comparable to MC[9,10]. However, expanding the inclusion criteria beyond the UCSF model resulted in worse survival compared to meeting UCSF criteria[10,11]. It has to be highlighted that a tumor is likely to result in a drop-out from waiting lists as a waiting list death if it has aggressive histological and genetic features. Perhaps favorable outcomes yielded in patient groups within UCSF criteria result from a relatively good nature of histology despite the tumor size exceeding MC. We don't know what would have happened if Fuks *et al*[5] had included patients within UCSF criteria in LR and primary LT groups. Similarly, we do not have any information about how many of patients who had a recurrence beyond MC after initial LR (n = 30) met the UCSF criteria and what would have been the long-term results if those patients had undergone ST.

Another important point is that the study by Fuks *et al*[5] did not evaluate if it was possible to throw off an unnecessary LR by proceeding directly to LT in the presence of pejorative factors in patients with early stage chronic liver disease. While preoperative imaging by today's state of the art technology is the mainstay of decision making process when planning the treatment of malignant liver tumors, there may yet be valuable information obtained from histological evaluation of tissues taken by minimally invasive techniques. The main concern with regard to fine-needle aspiration cytology or core biopsy is that the intervention may cause significant bleeding and tumor seeding. Although much of the evidence is anecdotal, a few reports have suggested that fine needle aspiration cytology or core biopsy be avoided due to tumor seeding risk up to 5%[12-14]. The risks and benefits of preoperative biopsy may need to be reassessed in the future given newly recognized advantages attributed to histological evaluation. In fact, DuBay *et al*[15] recently proposed "Toronto Criteria" in which preoperative biopsy is used as a guide when deciding exclusion of patients beyond MC from wait list. They reported that outcomes comparable to those of patients meeting MC could be achieved if histological findings demonstrate well-differentiated carcinoma. Cillo *et al*[16] reported that tumor differentiation was one of the strongest predictors of biological aggressiveness and therefore recurrence, suggesting that preoperative detection of tumor grade would be of importance in deciding the type of treatment modality. In the study by Fuks *et al*[5], 30 patients treated with curative-intent LR failed to receive ST due to recurrence outside MC. If this result could have been predicted before LR, those patients likely would have undergone immediate LR. Nonetheless, it has to be stated that the nature of their study was not suitable for such an evaluation.

In light of these data, there should be little argument on treatment of patients with HCC who have no underlying chronic liver disease as well as for those who have severe accompanying cirrhosis. What remains controversial is how to manage the patient with HCC developed on a background of Child Pugh class A disease. In this context, we believe the conclusion drawn in the article by Fuks *et al*[5] should be paid attention. Primary LT may be a more logical modality as it has the capability of treating the disease while reducing the risk of recurrence by eliminating carcinogenic fibrotic liver tissue as well as the underlying condition. Some oncological parameters and unfavorable histological factors such as tumor size, microscopic invasion of vessels, presence of satellite nodules not detected by preoperative imaging, the real severity of cirrhosis, and differentiation of carcinoma should be taken into account if resection is to be selected as the first-line treatment. If a patient presents with tumor within MC, but histological factors, either by resection or biopsy, suggest recurrence may be more aggressive after LR and may ultimately exclude the option of ST, then LT should be the primary consideration.

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BRIEF ARTICLE

Outcomes of elective laparoscopic colorectal operations in octogenarians at a district general hospital in South East England

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Abstract

AIM: To assess the outcomes of laparoscopic colorectal cancer resection in the octogenarian population at our institution.

METHODS: Retrospective analysis of registry data accumulated prospectively were used in conjunction with the data obtained from patient notes to identify outcome data for octogenarians who had undergone elective laparoscopic colorectal cancer resection.

RESULTS: Laparoscopic colorectal cancer resections were performed in 68 octogenarians between 2003 and 2011 at our institution. Four operations (6%) were converted to an open technique. There were twelve cases of morbidity (18%) and two cases of mortality (3%). The overall median hospital stay was 8 d. The median time for a patient to be deemed surgically fit for discharge was 5 d reflecting a delay in provision of social care or stoma education.

CONCLUSION: Our results support the view that laparoscopic surgery in octogenarians is safe, feasible and with a reduced length of stay. This is well reflected in our results which are compatible with United Kingdom national figures.

Key words: Laparoscopic surgery; Colorectal disease; Octogenarian; Mortality; Morbidity

Fernandes R, Shaikh I, Doughan S. Outcomes of elective laparoscopic colorectal operations in octogenarians at a district general hospital in South East England. *World J Gastrointest Surg* 2013; 5(1): 9-11 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i1/9.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i1.9

INTRODUCTION

It is well recognised that as a consequence of socioeconomic and healthcare factors, society is ageing and survival rates are rising. The ageing population can produce challenging clinical dilemmas with regard to appropriate management and in particular surgeons are often left with difficult decisions with regard to operative suitability. It has been reported that age alone, in the absence of other significant co-morbidities is not a prognostic factor in gastrointestinal surgery[1]. However, it is rare that such health is found amongst the octogenarian subgroup.

The rapid advancement of laparoscopic surgery has revolutionised colorectal surgery. Studies have shown that hospitalisation is shortened, post operative pain is reduced and post operative recovery is expedited[2,3]. Nevertheless, reservations about laparoscopic surgery in the elderly exist due to perceived longer operating times, and increased technical difficulty. Recent studies have demonstrated that laparoscopic colorectal surgery in octogenarians is safe, feasible, produces less blood loss and is associated with faster postoperative recovery[4-6]. Controversy

exists with regard to complication rates and overall operating time. Studies demonstrate that operating time is significantly shorter in open colorectal operations[5,6]. There was no statistically significant difference in post operative complications between open or laparoscopic cases. There is a marked variation between reported laparoscopic conversion rates to open surgery with figures ranging from 3%-25%[4,7]. One of the key findings on laparoscopic colorectal surgery in the octogenarian population is the consistent finding of shorter hospital stay[4,6,7].

Our institution is a district general hospital in South East England which has been undertaking laparoscopic colorectal resection since 2003. The study was designed to assess the outcomes of laparoscopic-assisted colorectal cancer resection in the octogenarian population at our institution.

MATERIALS AND METHODS

A prospective registry of all patients undergoing elective laparoscopic colorectal resection has been maintained at our institution since 2003. Demographics, Operative details and American Society of Anesthesiologists (ASA) grade are amongst the variables that are currently recorded. This list was utilised to identify patients > 80 years who had undergone laparoscopic colorectal resection. No patient was excluded. Patient notes were then reviewed to ascertain indication for surgery, intra-operative complications, conversion rate, post-operative complications, length of hospital stay and morbidity and mortality rates. Retrospective analysis of the accumulated prospectively collated registry data were used in conjunction with the data obtained from patient notes.

RESULTS

Laparoscopic colorectal resections were performed in 68 octogenarians between September 2003 and September 2011 at our institution. All cases were elective procedures.

The mean age was 84 years (range 80-91 years) and the male:female ratio was 31:37. Fifty-nine (87%) patients had an operation with a curative intent of malignancy. Other indications included diverticulosis in eight patients and rectal prolapse in one patient. Preoperative assessment revealed that the majority of patients (56%) were classified as American Society of ASA grade Ⅱ, whereas 34% and 10% of patients were classified as ASA grade Ⅲ and ASA grade Ⅳ respectively. Table 1 shows the types of resection performed in these 68 patients.

The operations took a mean operating time of 168 min (range 118-294 min). Of the 68 resections, four (6%) were converted to an open technique. Ureteric injury was the cause in two operations, dense adhesions and iatrogenic small bowel injury was another reason for conversion and the need for enbloc resection was the cause for the final conversion. There were no other intra-operative complications.

There were two cases of morality in our series this producing an overall mortality rate of 3%. The two cases of mortality were as a consequence of cardiovascular instability and severe respiratory sepsis. No association was found between mortality and the ASA grading in this series ($P = 0.52$, Fisher's exact test). Other postoperative morbidities are shown in Table 2. There were 12 postoperative complications giving an overall morbidity rate of 18%. The overall mean hospital stay was 11 d. However, the mean time for a patient to be deemed surgically fit for discharge was 6 d reflecting a delay in provision of social care or stoma education.

Table 1 Types of laparoscopic resection performed

Type of laparoscopic resection	No. of patients
Right or extended right hemicolectomy	13
Left hemicolectomy	8
Sigmoid colectomy	16
Anterior resection	18
Abdominoperineal resection	13
Total	68

Table 2 Postoperative complications

Complication	No. of patients
Chest infection	6
Collections/pelvic abscesses	2
Urinary infection	2
Ileus	2
Total	12

DISCUSSION

Minimally invasive surgery has been reported to produce faster recovery times, reduced post-operative pain and shortened hospital stay in comparison to open surgery[4,5]. Such advantages are especially beneficial for the elderly population in whom often other co-morbidities are found and may have less physiological reserve to cope with the stresses of surgery. However, in order to produce results which reflect these advantages, surgeons need to be well experienced in laparoscopic surgery so that operative progression is achieved and the operation is not unnecessarily prolonged.

There are numerous issues with making accurate comparisons with data for open colorectal resection in the octogenarian population. Obtaining a matched population retrospectively in whom open resection took place is difficult as there is usually a particular reason as to why the operation was not done laparoscopically. For example an en-bloc resection might have been required or anaesthetic concerns may have encouraged an open technique. Consequently, using this group for comparison would have resulted in bias as any difference in morbidity or mortality could have been attributed to increased technical difficulty or more fragile patient population. There have been several studies that have produced data for elective open colorectal procedures in octogenarians. However, many of the studies are prior to the widespread

use of laparoscopic surgery and are thus quite outdated. Isbister in 1997 reported results of 86 patients with a mortality of 11%, respiratory complications in 15% and urinary complications in 36%[8]. Vignali *et al*[5] conducted a case-matched control study in which the results of 61 patients who had undergone laparoscopic resection were compared to 61 patients undergoing open colorectal resection. There was no statistical difference in morbidity rates, 21.5% in the laparoscopic group and 31.1% in the open group. Two percent mortality was reported in the laparoscopic group. The mean hospital stay was 9.8 d in the laparoscopic group and 12.9 d in the open group. Our results are comparable in that our mortality rate is 3%, morbidity rate 18% and our mean hospital stay was 11 d.

Although respiratory complications seem to be consistently found in both laparoscopic and open patients we believe that our results are consistent with others in the literature in providing evidence that the risk of pulmonary complications is reduced by laparoscopic surgery perhaps reflecting the reduced post-operative pain.

In our study we found that although the mean length of hospital stay was 11 d, patients were surgically fit for discharge after a mean of 6 d. The discrepancy reflects time required for social planning or stoma education which is understandable in this patient population.

Our results, in combination with others in the literature provide further evidence to support the view that laparoscopic surgery is safe, feasible and more beneficial to the octogenarian population. In particular, shortened hospital stay and lower pulmonary complications are of especially pertinent. Our results also provide support for early involvement of stoma education and social provision planning.

COMMENTS

Background

It is a current approach in the oldest-old people dealing with the feasibility of laparoscopic colorectal surgery with acceptable results in this group of patients. Nevertheless there is still associated stigma attached to laparoscopic surgery in the octogenarian subgroup due to perceived increased risks.

Research frontiers

The rapid advancement of laparoscopic surgery has revolutionised colorectal cancer surgery. Nevertheless, reservations about laparoscopic surgery in the elderly exist due to perceived longer operating times and special positioning with consequent morbidity. This study was designed to assess the outcomes of laparoscopic colorectal cancer resection in the octogenarian population at the authors' institution.

Innovations and breakthroughs

In this study the authors found that although the mean length of hospital stay was 11 d, patients were surgically fit for discharge after a mean of 6 d. The discrepancy reflects time required for social planning or stoma education which is understandable in this patient population.

Peer review

It is a current approach in the oldest-old people dealing with the feasibility of laparoscopic colorectal surgery with acceptable results in this group of patients.

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Patent (list all authors)

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Statistical data

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Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.

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FIELD OF VISION

Response evaluation following neoadjuvant treatment of pancreatic cancer patients

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human neoplastic entities, with a very poor prognosis characterized by a high mortality rate and short survival. This is due both to its aggressive biological behaviour and the high incidence of locally advanced stages at the time of the initial diagnosis. The limits of resectability and the role of neoadjuvant (radio) chemotherapy for PDAC management are still unclear. A recently published article by Kats *et al* compared the radiological, surgical and histopathological results of 129 patients with borderline resectable tumors undergoing neoadjuvant treatment followed by surgery. Although post-neoadjuvant treatment imaging implied a low response rate, a high rate of complete resections was achieved. This seems to confirm that, though radiology has made a significant progress in defining locally advanced PDAC, there is place for further improvement. In particular, the differentiation between radiotherapy-induced scarring/fibrosis and cancer-associated desmoplasia remains a clinical/radiological challenge. Though selection of patients with occult systemic disease is possible with neoadjuvant treatment, downstaging does not seem to occur frequently. Thus, development of novel, more aggressive (radio) chemotherapy regimens is required to improve prognosis of patients with locally unresectable but not systemically micro-metastasized tumors.

Key words: Pancreatic ductal adenocarcinoma; Borderline resectable tumors; Neoadjuvant chemotherapy

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COMMENTARY ON HOT TOPICS

We read with great interest the recent article by Katz *et al*[1] analysing the correlation between clinical and pathological staging following neoadjuvant treatment in patients suffering from pancreatic ductal adenocarcinoma (PDAC). PDAC accounts for more than 85% of all pancreatic tumours, and though it is the 10th most common cancer in Western countries, it is ranked as the 4th most common cause of cancer-related deaths[2,3]. Less than 5% of the patients survive longer than 5 years after the initial diagnosis and the only chance for cure is resection[4]. The main factor contributing to the prognosis of the disease is the stage[5], which also determines resectability. Only 15%-20% of the patients present with a resectable tumor at the time of diagnosis; at least 40% of the tumors are locally advanced and the remaining 45%-50% are metastasized[6]. While treatment of locally confined and of metastasized tumors is not debated, neoadjuvant (radio) chemotherapy in the management of borderline resectable or locally advanced, primarily un-resectable tumours is still a hot topic in clinical research.

Assessment of PDAC resectability

Resectability of the local tumor depends on whether ad-

Table 1 Borderline resectable tumors have been defined according to the most recent national comprehensive cancer network guidelines (version 2.2012)

Tumor-associated deformity of the SMV or PV
Abutment of the SMV or PV > 180°
Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction
Abutment of the SMA < 180°

SMV: Superior mesenteric artery; PV: Portal vein.

jacent structures (*i.e.*, mostly the vessels) are infiltrated. Multi-detector computed tomography (MDCT) has been widely accepted as the technique of choice for the primary staging of PDAC[7,8]. MDCT and magnetic resonance imaging (MRI) are similarly sensitive and specific[9], but MRI seems to be better in detecting hepatic metastases[10]. Endoscopic ultrasound (EUS) allows EUS-guided fine-needle aspiration, but is technically demanding, and potentially associated with complications. Because preoperative determination of vascular infiltration is important for the assessment of resectability, radiologic criteria have been defined based most importantly on portal/superior mesenteric vein as well as superior mesenteric artery (SMA) and celiac trunk involvement. Borderline resectable tumors have been defined according to the most recent NCCN guidelines (version 2.2012)[11] (Table 1).

Neoadjuvant treatment

Recent studies and meta-analysis have shown that tumor down-staging can be achieved with gemcitabine- or 5-FU-based (radio)chemotherapies in about one third of the patients, with a significantly higher overall survival in resected (compared to non-resected) patients[12-15]. The more aggressive FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) protocol has been shown to be superior to gemcitabine-based regimens in the palliative situation[16] and has also been used in the neoadjuvant setting, demonstrating encouraging results[17].

Comment on the study

In this study Katz *et al*[1] analysed the clinical data of 129 patients with border-line resectable pancreatic cancers who underwent surgery after neoadjuvant therapy. As Katz *et al*[1] point out, there is not yet a general agreement on several topics, such as the definition of resectability and the indication for oncological therapies; the aim of their study was to improve the diagnostic workup and the therapeutic procedure, trying to design simple and sensitive guidelines for the selection of patients who could potentially have an R0 resection.

A review of radiological features (CT) before and after chemotherapy was performed by an experienced gastrointestinal radiologist, according to the MD Anderson and American Hepato-Pancreato-Biliary Association (AHPBA)/Society for Surgical Oncology (SSO)/Society for Surgery of Alimentary Tract (SSAT) criteria in order to determine the clinical response to neoadjuvant treatment. Though only one patient (1%) had a clinical down-staging according both to the AHPBA/SSO/SSAT and MD Anderson criteria, 85 patients (66%) underwent pancreatectomy. The systematic definition of histopathological staging and response to chemotherapy, performed according to the American Joint Committee on Cancer Staging Manual, showed 81 R0 resections (95%) and a histopathologic grade Ⅲ and Ⅳ response in 17% of the resected patients.

Table 2 Some questions towards the aim and the clinical meaning of neoadjuvant treatment in pancreatic cancer

How reliable is traditional imaging assessment of resectability?
Were these tumors resectable even before (radio) chemotherapy administration?
If so, was (radio) chemotherapy useful or did it only delay surgery?
Which exactly is the target of neoadjuvant treatment?

The achievement of R0 resections in a relative high percentage of patients who did not have a significant clinical down-staging reported in this paper raises some questions towards the aim and the clinical meaning of neoadjuvant treatment in pancreatic cancer (Table 2).

Assessment of resectability following neoadjuvant treatment

The most interesting points in the article by Katz *et al*[1] are the use of standard criteria for the indication to resection (AHPBA/SSO/SSAT criteria[11,18] and MD Anderson criteria[19,20]) and the assessment of the clinical and pathological response to chemotherapy (*e.g.*, using RECIST). The authors report a clinical down-staging in only 1% of patients, disease progression in 19% and no change in 80% of the patients according to the AHPBA/SSO/SSAT criteria. Even worse results are reported according to the MD Anderson criteria (1% down staging, 21% progressive disease and 78% no change). Nevertheless, the intraoperative findings showed a much more satisfactory response to chemotherapy: 66% of patients underwent resection and 95% of the resected patients had an R0 resection.

Here, the authors conclude that imaging has a fundamental role in the decision-making phase but still does not seem to be satisfactorily accurate of the actual anatomical situation. Though one imaging modality such as multidector CT is more straight-forward, it seems that additional techniques may be necessary to better judge particularly the presence of vascular infiltration.

Thus, it would be interesting to investigate how to differentiate between chemo- and/or radiotherapy-induced scarring/fibrosis and cancer-associated desmoplasia (following neoadjuvant treatment). Standard descriptive imaging such as CT scans can hardly distinguish between these tissue alterations[21]. Functional imaging modalities such as fluorodeoxyglucose-/fluorothymidine-positron emission tomography-CT may be helpful adjuncts in the

neoadjuvant situation and will have to be analyzed in this particular patient population.

Potential resectability even before administration of neoadjuvant treatment

The radiological results reported by Katz *et al*[1] show no relevant differences between tumor volume and (potential) vascular invasion before and after neoadjuvant treatment. Nevertheless, most of the patients received an R0 resection. The findings may indicate that these tumors could actually have already been resected before administration of chemotherapy. However, because current imaging cannot (easily) distinguish between cancer-associated desmoplasia and (radio) chemotherapy-induced fibrosis or fibrosis due to tumor regression (as described above), it is difficult to retrospectively judge on resectability before neoadjuvant treatment. Refined imaging or rather functional imaging[21,22] seems thus to be necessary to better select patients with truly locally restricted *vs* locally advanced tumors.

Usefulness of neoadjuvant treatment vs delay of surgery

The validity of preoperative (radio) chemotherapy administration in border-line resectable PDAC is still discussed: in fact, neoadjuvant treatment does not induce regression at the same rates in pancreatic cancer as in colo-rectal or esophageal cancers; thus, the relevance of neoadjuvant treatment for downstaging or local control in pancreatic cancer remains unclear. Nevertheless, we agree with the authors that preoperative (radio) chemotherapy is a potentially useful strategy to select patients without occult systemic disease for later surgery. To this end, chemotherapy regimens with better response rates than gemcitabine alone will have to be tested. In this regard, a recent study of advanced and border-line resectable pancreatic cancers[17] reported an R0 resection rate of 44% following treatment with FOLFIRINOX while another study[23] reported resectability in 11 out of 39 patients (15 border-line and 24 primarily unresectable tumors) following neoadjuvant treatment with GEMOX. Survival rates were comparable to patients with resectable tumors in both studies.

Targets of neoadjuvant treatment

The data reported by Katz *et al*[1] suggest that neoadjuvant treatment does not reduce the volume of the tumor, but that it selects tumors with a less aggressive biological behaviour. In fact, only the patients who did not show progression of the disease during neoadjuvant treatment underwent surgery; and these had a survival rate similar to patients with resectable disease at the time of diagnosis. Besides, a good pathological response to neoadjuvant (radio) chemotherapy (in opposite to a disappointing clinical down-staging, as reported in a recent study by Tajima *et al*[24]), seems to confirm the hypothesis that neoadjuvant treatment in PDAC rather acts on the biology of the tumor than on the volume. Thus, the aim of neoadjuvant treatment is not the achievement of a more "permissive" local surgical region, but the selection of patients with less aggressive diseases. However, larger studies using neoadjuvant FOLFIRINOX protocols will be necessary to determinate whether more aggressive chemotherapy results in shrinking of the local tumor.

In conclusion, we support the authors' statement that the development of imaging techniques helps to avoid useless surgery and its associated complications for those patients who would not have any benefit from it (*e.g.*, potential R2 resections)[25]. Though radiology has shown an incredible progression in detection of vessel infiltration, the assessment of resectability is still a delicate, tricky field.

In the absence of an unequivocal definition of the surgical limits, the effort made by Katz *et al*[1] point out the main guidelines in this field is particularly interesting; from these data it seems to emerge that centers with larger clinical volumes have more aggressive surgical standards and potentially also better outcomes, enforcing the conviction that pancreatic surgery should be performed in dedicated centers.

Finally we agree with the authors on the hypothesis that there is a rationale in administrating preoperative neoadjuvant (radio) chemotherapy in locally advanced pancreatic cancers in order to select the patients who would benefit from a resection (*e.g.*, those without occult systemic disease at the time of diagnosis). The question of whether neoadjuvant treatment with more aggressive (radio) chemotherapies will decrease the size of the local tumor and will lead to true downstaging of PDAC remains unanswered.

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BRIEF ARTICLE

Limited resection for duodenal gastrointestinal stromal tumors: Surgical management and clinical outcome

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Abstract

AIM: To analyze our experience in patients with duodenal gastrointestinal stromal tumors (GIST) and review the appropriate surgical approach.

METHODS: We retrospectively reviewed the medical records of all patients with duodenal GIST surgically treated at our medical institution between 2002 and 2011. Patient files, operative reports, radiological charts and pathology were analyzed. For surgical therapy open and laparoscopic wedge resections and segmental resections were performed for limited resection (LR). For extended resection pancreatoduodenectomy was performed. Age, gender, clinical symptoms of the tumor, anatomical localization, tumor size, mitotic count, type of resection resectional status, neoadjuvant therapy, adjuvant therapy, risk classification and follow-up details were investigated in this retrospective study.

RESULTS: Nine patients (5 males/4 females) with a median age of 58 years were surgically treated. The median follow-up period was 45 mo (range 6-111 mo). The initial symptom in 6 of 9 patients was gastrointestinal bleeding (67%). Tumors were found in all four parts of the duodenum, but were predominantly located in the first and second part of the duodenum with each 3 of 9 patients (33%). Two patients received neoadjuvant medical treatment with 400 mg imatinib per day for 12 wk before resection. In one patient, the GIST resection was done by pancreatoduodenectomy. The 8 LRs included a segmental resection of pars 4 of the duodenum, 5 wedge resections with primary closure and a wedge resection with luminal closure by Roux-Y duodeno-jejunostomy. One of these LRs was done minimally invasive; seven were done in open fashion. The median diameter of the tumors was 54 mm (14-110 mm). Using the Fletcher classification scheme, 3/9 (33%) tumors had high risk, 1/9 (11%) had intermediate risk, 4/9 (44%) had low risk, and 1/9 (11%) had very low risk for aggressive behaviour. Seven resections showed microscopically negative transsection margins (R0), two showed positive margins (R1). No patient developed local recurrence during follow-up. The one patient who underwent pancreatoduodenectomy died due to progressive disease with hepatic metastasis but without evidence of local recurrence. Another patient died in complete remission due to cardiac disease. Seven of the nine patients are alive disease-free.

CONCLUSION: In patients with duodenal GIST, limited surgical resection with microscopically negative margins, but also with microscopically positive margins, lead to very good local and systemic disease-free survival.

Key words: Gastrointestinal stromal tumor; Duodenum; Surgery; Limited resection; Survival

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of gastrointestinal tract. GIST arise from interstitial cells of Cajal or Cajal-like precursor cells which are located in the muscular layer of gastrointestinal organs[1]. GIST can be distinguished from other mesenchymal tumors by immunohistochemistry: in contrast to sarcomas, leiomyomas, and myoblastomas, they show a KIT expression (CD117)[2,3]. The most common site where GIST are found is the stomach with 50%-60%. The next frequent locations are the small bowel (25%) and the colo-rectum (10%). GIST with duodenal origin are very rare and represent only about 5% of all GIST.

In the absence of metastatic disease, surgical resection is the primary curative approach to treat GIST. Since longitudinal submucosal spread is very limited and lymph node involvement is rare, margin-negative resection without lymphadenectomy is the commonly accepted surgical treatment[4]. In the stomach, limited resections are technically simple in the majority of cases due to anatomic circumstances. By contrast, local resections in the duodenum are more challenging. The direct proximity to the pancreatic head, the papilla of Vater and the mesenteric root make limited resections technically demanding and thus, clear resection margins are often barely obtainable.

To evaluate the results and outcome of surgical therapy of duodenal GIST, we retrospectively analysed all patients who underwent resection extended by pancreatoduodenectomy or limited to local resections at our institution within the last 10 years.

MATERIALS AND METHODS

Between 01/2002 and 12/2011, 9 patients underwent surgical treatment for duodenal GIST at the Department of Surgery at University of Freiburg in Germany. This review was carried out retrospectively by analyzing the patient files, operative reports, radiological charts and pathology reports. CD117, CD34, Desmin, Smooth Muscle Actin and S100 were stained immunohistochemically. According to our protocols for GIST diagnosis, tumors were classified as GIST either if CD117 was positive, or if typical morphology was present along with CD34 positivity in immunohistochemistry.

Open and laparoscopic wedge resections and segmental resections were performed for limited resection (LR). For extended resection (ER), pancreatoduodenectomy was performed.

Age, gender, clinical symptoms of the tumor, anatomical localization, tumor size, mitotic count, type of resection (LR *vs* ER), resectional status, neoadjuvant therapy, adjuvant therapy, risk classification and follow-up details were analysed in this retrospective study. Risk stratification of the GIST was carried out according to the criteria proposed by Fletcher *et al*[2] (Table 1).

Table 1 Fletcher criteria for risk stratification of gastrointestinal stromal tumors

Risk	Tumor size (cm)	Mitotic count (/50 HPF)
Very low-risk	> 2	< 5
Low-risk	2-5	< 5
Intermediate risk	< 5	6-10
	5 - 10	< 5
High-risk	> 5	> 5
	> 10	any mitotic rate
	any size	> 10

HPF: High-power field.

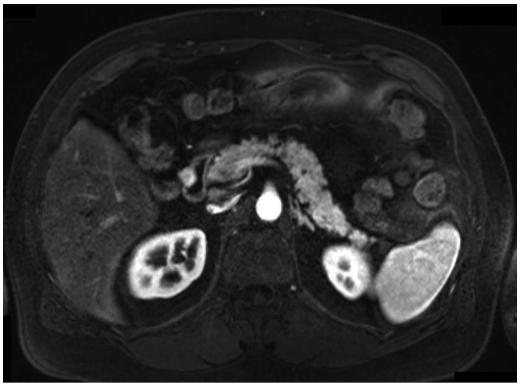

Figure 1 magnetic resonance scan of small gastrointestinal stromal tumors in the second portion of the duodenum resected by laparoscopic wedge resection (Patient 3).

RESULTS

Clinical characteristics

Between 01/2002 and 12/2011, nine patients underwent surgery for duodenal GIST at the Department of Surgery at University of Freiburg. The medium age was 58 years (range 43-75 years) and there were 5 men and 4 women. The tumors were located in all 4 parts of the duodenum. Three tumors were found each in part 1 and 2 of the duodenum. Two tumors were located in the third portion of the duodenum and one in the fourth portion of the duodenum. In one patient, the duodenal GIST was an incidental finding and the other 8 were symptomatic. The most frequent initial symptom was upper gastrointestinal bleeding which was present in 6 patients (Table 2).

Surgical management

All 9 patients underwent curative resection including one ER with pancreatoduodenectomy and 8 LR (Table 3). The 8 LR included 1 segmental resection of pars 4 of the duodenum, 1 laparoscopic wedge resection with primary closure (Figure 1), 4 open wedge resections with primary

Table 2 Clinical, anatomical and surgical characteristics of patients with duodenal gastrointestinal stromal tumors

Patient no.	Age (yr)	Sex	Initial symptom	Location	Surgical procedure	Resectional status
1	51	M	Bleeding	2	Open wedge resection + duodenojejunostomy	R0
2	63	M	Bleeding	3	Open wedge resection	R0
3	52	M	Bleeding	1	Laparoscopic wedge resection	R0
4	62	F	Jaundice	1	Pancreatoduodenectomy	R0
5	58	M	Abdominal pain	1	Open wedge resection	R0
6	69	F	Incidental finding	2	Open wedge resecction	R1
7	43	F	Bleeding	4	Segmental resection	R0
8	75	M	Bleeding	3	Open wedge resection	R0
9	49	F	Bleeding	2	Tumor resection without duodenal resection	R1

M: Male; F: Female.

Table 3 Adjuvant therapy, pathological features and follow-up

Patient no.	c-KIT	Tumor size (mm)	Mitotic count (/50 HPF)	Risk	Neoadj. therapy	Adjuvant therapy	Disease relapse	Status
1	pos.	32	5	Low risk	No	No	No	NED at 6 mo
2	pos.	35	14	High risk	No	Imatinib	No	NED at 7 mo
3	pos.	14	1	Very low risk	No	No	No	NED at 13 mo
4	pos.	110	35	High risk	No	No	Liver	Died of PD at 3 mo
5	pos.	30	0	Low risk	No	No	No	NED at 90 mo
6	pos.	25	0	Low risk	No	No	No	NED at 111 mo
7	pos.	110	4	High risk	No	No	No	NED at 92 mo
8	pos.	50	0	Low risk	Imatinib	No	No	Died with NED at 37 mo
9	pos.	80	1	Intermediate	Imatinib	Imatinib	No	NED at 39 mo

HPF: High-power field; NED: No evidence of disease; pos: Positive; PD: Progressive disease.

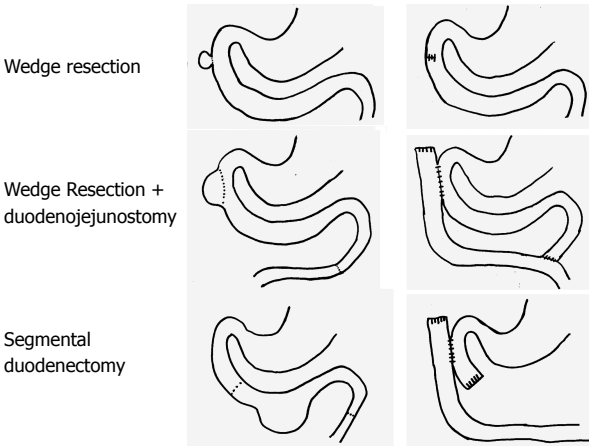

Figure 2 Illustration of the different techniques for limited resection of duodenal gastrointestinal stromal tumors. Wedge resection was performed for small tumors and for larger tumors with only a small-area base at the duodenal wall in all parts of the duodenum. Wedge resection with reconstruction of the defect at the duodenal wall by duodenojejunostomy was performed in patients with larger defects of the second part of the duodenum after tumor resection. Segmental duodenectomy was carried out for larger tumors of the third or fourth part of the duodenum.

closure and 1 open wedge resection with luminal closure by Roux-Y Duodeno-Jejunostomy. Figure 2 illustrates the different surgical procedures applied for LR of duodenal GIST in our study. In one patient, intraoperative exploration and intraoperative examination in frozen section revealed the residual tumor after neoadjuvant imatinib therapy to be strictly periduodenal with no involvement of the duodenal wall. In this patient an extraduodenal tumorectomy was performed. The patient who underwent pancreatoduodenectomy with portal vein resection (Figure 3) had a concomitant small liver metastasis in Segment 2 of the liver which was detected intraoperatively and resected in the same session by atypical liver resection. All patients had macroscopically clear margins after resection of the tumor. However, 2 patients showed microscopically positive transsection margins (R1) (Table 2). Postoperative course after LR and ER in all patients was uneventful. After LR, the patients were discharged medium on the 8th postoperative day (range 5-16 d). The patient after ER left the hospital on the 22nd postoperative day.

Perioperative chemotherapy

In our series, 2 patients received neoadjuvant medical treatment with 400 mg imatinib per day for 12 wk before resection. In both patients, neoadjuvant therapy was started due to large duodenal GIST in which cross-sectional imaging showed infiltration of other organs and complete resectability did not appear possible. In one patient neoadjuvant imatinib therapy was started because of suspected tumor infiltration of the Vena cava in computed tomography (CT). The other patient underwent initial duodenotomy with operative haemostasis of the bleeding GIST in an outside hospital, the resection of the remaining tumor was carried out in our

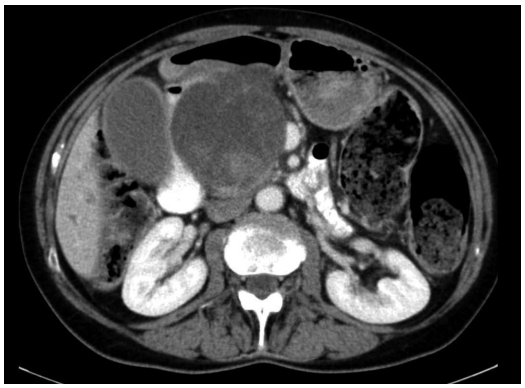

Figure 3 Computed tomography scan of a high-risk large duodenal gastrointestinal stromal tumors which hast been resected by pancreatoduodenectomy including portal vein resection (Patient 4). The origin of the tumor is located in the first part of the duodenum were pathology revealed a 65 mm x 55 mm ulcer.

institute after 12-wk neoadjuvant imatinib therapy by tumorectomy of the remaining tumor. Neoadjuvant treatment was initiated because of a large duodenal GIST infiltrating the liver hilum and the retroperitoneum and a complete resection initially appeared impossible. Due to microscopically margin-positive resectional status in the second procedure, adjuvant chemotherapy with imatinib was continued for 12 mo postoperative. Besides this patient only one other patient-with a high risk tumor-received postoperative adjuvant imatinib therapy for one year (Table 3).

Pathological and immunohistological characteristics

The medium tumor size was 54 mm; diameters ranged from 14 mm to 110 mm. Immunohistochemically, all duodenal GIST were positive for KIT (CD117). Six of nine GIST were also positive for CD34. Using the Fletcher classification scheme[2], 3/9 tumors had high risk, 1/9 had intermediate risk, 4/9 had low risk, and 1/9 had very low risk for aggressive behaviour (Table 3). Microscopically margin-negative resectional status (R0) was achieved in 6 of 8 patients undergoing LR. The final resectional status after LR was margin positive in two patients. The patient with the large, high-risk GIST treated by pancreatoduodenectomy showed negative transsection margins and lymph node status.

Outcome and survival

One patient with a large, high-risk GIST, which was completely resected by pancreatoduodenectomy, died 3 months after surgery due to progressive disease with hepatic metastasis. Another 75-year-old patient died of cardiopulmonary disease 37 mo after surgery without evidence of local or distant tumor recurrence. Both patients with R1 resection are alive 39 and 111 mo after surgery without evidence of local or distant manifestation of GIST disease. All other patients who were surgically treated by LRs are alive without evidence of GIST disease (Table 3).

DISCUSSION

GIST are a distinct group of mesenchymal tumors with predominantly gastrointestinal distribution. They are molecularly characterized by mutations in the KIT proto-oncogene which results in over-expression of the transmembrane tyrosinkinase receptor KIT (CD117). GIST have been described nearly everywhere in the gastrointestinal tract but also rarely affect extragastrointestinal sites such as omentum and mesentery[5].

It is known that GIST of different anatomical sites not only vary in morphology and gene expression but also in clinical presentation and clinical outcome[2,6,7]. For this reason, it is necessary to characterize the different subsets of GIST as precisely as possible and to identify and define tailored diagnostic approaches and surgical strategies for management of GIST. In this retrospective analysis, we have focused on the relatively small subset of duodenal GIST and present our experience in their management over the last decade. In contrast to the relatively common gastric GIST, GIST of the duodenum are rare and represent only 3%-5% of all GIST[3]. We identified nine patients who were surgically treated for duodenal GIST in our institution over the last ten years. Duodenal GIST can be located in all four parts of the duodenum, although our study shows a descending distribution beginning with three GIST each in both the first and the second part of the duodenum, followed by two in the third and one in the fourth part.

In this series, 8 of 9 patients presented with symptoms. According to the literature[3,8] the most common clinical symptom is gastrointestinal bleeding, which was the initial symptom in 6 of our 9 patients. Three of these 6 patients presented with massive gastrointestinal bleeding and endoscopic attempts to stop the bleeding were unsuccessful. In these patients, the GIST resection was performed as an emergency operation. Only one small 25 mm tumor presented as asymptomatic and was incidentally found in endoscopic retrograde cholangiopancreatography for cholecystolithiasis. Since gastrointestinal bleeding was the most frequent initial symptom, gastrointestinal endoscopy was routinely the method for detection and verification of the duodenal GIST, which usually appear as submucosal swelling with or without mucosal ulceration. In our population, tumors located not only in the upper duodenum but also in the third and fourth part of the duodenum could be macroscopically detected in endoscopy and verified as GIST by pathology workup of the biopsy samples from endoscopy. Besides gastrointestinal endoscopy, cross-sectional imaging by CT or magnetic resonance imaging are useful. They can be used not only for examination of the local extension of the primary tumor, but also for the detection of metastasis[9]. However, it is often impossible to obtain histological samples for the verification of diagnosis through cross-sectional imaging-guided biopsy from duodenal GIST. Finally F-fluoro-2-deoxy-D-glucose positron emission tomography-CT seems to be

very promising, especially for early response evaluation within one to two weeks after starting neoadjuvant medical treatment of GIST[9].

Surgical resection with the achievement of microscopically clear resection margins is the therapeutical goal of treatment in cases of primary non-mestastatic GIST-not only of the duodenum[4]. As lymph node involvement is very rare in adult GIST[10-14] and even the largest clinicopathologic series of duodenal GIST[3] did not detect lymphatic spread in 167 patients, routine lymph node dissection is not required in duodenal GIST. Supporting these findings, we did not detect any lymph node recurrence in either LRs or in ER in this study.

We performed LRs of duodenal GIST if the primary tumor showed no infiltration of other organs and lymph node involvement was excluded in cross-sectional imaging and in intraoperative macroscopic examination. This is the same strategy we apply in surgical therapy of GIST of the stomach and the small bowel. In our series, only one patient required pancreatoduodenectomy and atypical liver resection of a small metastasis. This was necessary due to a large, high-risk tumor infiltrating the pancreatic head. Although it was possible to achieve a microscopically margin-negative resection and no lymphatic involvement was seen in the specimen, the patient died due to tumor progression with liver metastasis three months after resection. LRs were carried out in all other patients, independent of tumor location within the duodenum (parts 1-4).

Wedge resections with primary closure, wedge resections with duodenal closure by Roux-Y duodeno-jejunostomy and segmental duodenectomy and extraduodenal tumorectomy for residual GIST after neoadjuvant therapy were performed in this study as LRs. Longitudinal wedge resection usually resulted in only limited defects of the duodenal wall. These limited defects were closed directly by interrupted sutures in transverse direction. This technique was utilized for tumors located in all first three parts of the duodenum. In one patient with larger GIST located in the second part of the duodenum and without involvement of the papilla of Vater, the reconstruction was carried out with a side-to-side duodeno-jejunostomy at the site of the duodenal wall defect and a Roux-Y limb as described by Goh *et al*[13]. Another option for LR of small and large GIST located in the third and fourth part of the duodenum is segmental duodenectomy. In this study, resection using a segmental duodenectomy of the fourth part of the duodenum and reconstruction using a side-to-side Roux-Y duodeno-jejunostomy was performed in one patient with an 11 cm high-risk GIST of the fourth portion of the duodenum.

Intraoperatively, all patients of our study showed macroscopically clear resection margins. However, pathohistological examination of the specimens revealed positive margins in two patients after LR. This fact could be a drawback in LRs of duodenal GIST. Due to the narrow and complex anatomy of the pancreaticoduodenal area with the proximity to the pancreas, the bile duct, the mesenteric root, the portal vein and the papilla of Vater, clear resection margins of LRs of duodenal GIST often measure only a few millimetres. Although the findings above represent a rate of 25% of margin-positive resections in the limited surgical approach of our series, both margin-positive patients are well and without evidence of local or systemic tumor recurrence 111 and 39 mo after surgery.

Although there is no official market authorization for neoadjuvant treatment of GIST with imatinib, it was used for downstaging of the tumors in two of our patients because large duodenal GIST infiltrating adjacent organs or large vessels made the possibility of a complete resection questionable. A pathologic response rate of 86% and a rate of complete resections after treatment with imatinib of 89% have been reported for neoadjuvant therapy of GIST[14]. Different studies were able to demonstrate that adjuvant imatinib treatment was able to significantly increase recurrence-free survival[15,16]. In case of high-risk duodenal GIST with a > 30% risk of recurrence or microscopically margin-positive resection, adjuvant imatinib treatment was also carried out in our patients after 2007. In our series, none of the patients treated with imatinib before or after surgery had recurrent disease. Adjuvant imatinib was planned for the only patient with recurrent tumor after resection PD, but therapy was not started due to rapid worsening of the general state of health in progressive metastatic tumor disease.

In conclusion, LR offers an excellent option for the surgical treatment of duodenal GIST. LR shows good results in terms of tumour-free survival and missing evidence of tumor recurrence in all of our patients treated by LR. Although microscopically positive margins were evident in 2 cases, no local recurrence was detected. Nevertheless, negative resection margins should be achieved in LR. If it is not possible by LR, tumor resection should be performed by ER.

COMMENTS

Background

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. GIST arise from interstitial cells of Cajal which are located in the muscular layer of gastrointestinal organs. GIST of the duodenum are rare tumors and represent only a small subgroup of all GIST.

Research frontiers

Up to now, various surgical procedures have been described for their treatment. Both extended resections (ER) by pancreatoduodenectomy and limited local resections (LR) are performed. The presented study was to evaluate the results of LR and ER in patients with duodenal GIST and to find the appropriate surgical approach in future cases.

Innovations and breakthroughs

This study shows that LR of duodenal GIST promise very good results in terms of local and systemic disease-free survival (DFS). Both margin negative, but also margin positive LR showed good results concerning DFS.

Applications

As LR offers good results concerning DFS it can be advocated as therapy of duodenal GIST. Different techniques of LR for duodenal GIST can be applied for surgical therapy.

Terminology

GIST: Gastrointestinal stromal tumors are mesenchymal tumors of gastroin-

testinal tract. LR: Limited resection means a surgical resection of the tumor without larger tumor-negative resection margins and without regional lymphadenectomy. ER: Extended resection means a surgical resection of the tumor with larger tumor-negative resection margins and regional lymphadenectomy. DFS: Disease-free survival describes the chances of staying free of disease after a particular treatment for cancer.

Peer review

Duodenal GIST is very rare. Surgical treatment is another problem for duodenal GIST because of localization. Therefore, these cases are important.

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CASE REPORT

Laparoscopic hemicolectomy in a patient with situs inversus totalis after open distal gastrectomy

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Abstract

Situs inversus totalis (SIT) is a rare anomaly in which the abdominal and thoracic cavity structures are opposite their usual positions. Occasionally, a few patients with a combination of this condition and malignant tumors have been encountered. Recently, several laparoscopic operations have been reported in patients with SIT. We report a case of an 83-year-old man with situs inversus totalis who developed colon cancer after open distal gastrectomy. Laparoscopic hemicolectomy with radical lymphadenectomy in such a patient was successfully performed by careful consideration of the mirror-image anatomy. Techniques themselves was not different from those in ordinary cases. Thus, curative laparoscopic surgery for colon cancer in the presence of situs inversus totalis is feasible and safe.

Key words: Situs inversus totalis; Laparoscopic surgery; Hemicolectomy; Colon cancer; Radical lymphadenectomy

Sumi Y, Tomono A, Suzuki S, Kuroda D, Kakeji Y. Laparoscopic hemicolectomy in a patient with situs inversus totalis after open distal gastrectomy. *World J Gastrointest Surg* 2013; 5(2): 22-26 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i2/22.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i2.22

INTRODUCTION

Situs inversus totalis (SIT) is a rare congenital anomaly and denotes complete right-left inversion of thoracic and abdominal viscera. Although laparoscopic experience in such patients often has been reported, the majority of reported cases are of laparoscopic cholecystectomy[1]. Reports of advanced laparoscopic surgeries are increasing in accordance with the progression of laparoscopic procedures. However, reports of laparoscopic surgery for colorectal malignancy are very few, and only 2 laparoscopic colorectal surgeries with lymphadenectomy have been reported[2,3]. Here we present a third case and a review of the literature.

CASE REPORT

In a follow-up after open distal gastrectomy performed for gastric cancer at the age of 77 years, an 83-year-old man with a history of SIT visited our department, reporting bloody stool. After colonoscopy yielded a diagnosis of transverse (splenic flexure) colon cancer, the patient was admitted to our hospital for further evaluation and surgical treatment. Abdominal examination revealed an upper midline scar. Laboratory examination confirmed anemia (red blood cell count, $396 \times 10^4/mm^2$; hemoglobin, 11.1 g/dL; hematocrit, 34.6%). Serum carcinoembryonic antigen was not elevated (2.8 ng/mL; reference range, 0-5 ng/mL). Chest radiography showed dextrocardia and a right subphrenic gastric bubble (Figure 1A). Abdominal computed tomography revealed complete transposition of abdominal viscera, confirming SIT (Figure 1B). Barium enema and colonoscopy showed an

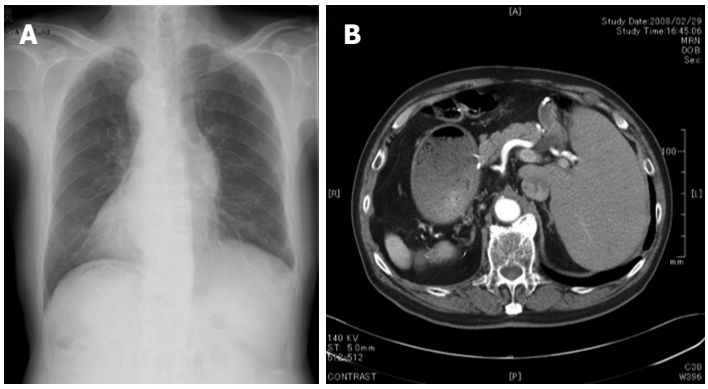

Figure 1 Chest radiography (A) and abdominal computer tomography (B) of the patient. A: Dextrocardia and a right subphrenic gastric bubble are evident; B: Complete transposition of abdominal viscera is shown, confirming situs inversus totalis.

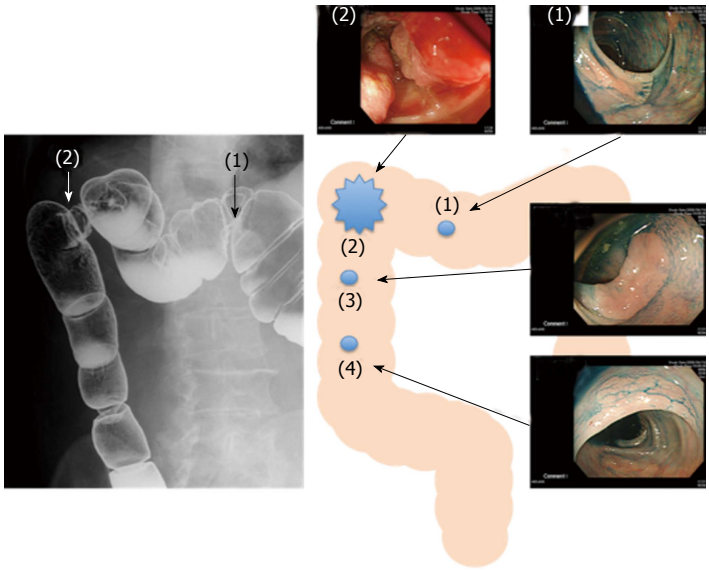

Figure 2 Barium enema and colonoscopy. Barium enema and colonoscopy showed an ulcerated lesion (2) in the splenic flexure of the transverse colon and a polyp (1) in the transverse colon. Polyps (3, 4) in the descending colon were not detected by barium enema, but were detected by colonoscopy.

ulcerated lesion in the splenic flexure of the transverse colon and polyps in the descending and transverse colon (Figure 2). Histologic examination of specimens from colonoscopic biopsy indicated adenocarcinoma. According to the findings described above, laparoscopic hemicolectomy with radical lymphadenectomy was performed.

After general anesthesia was induced, the patient was placed in a modified lithotomy position. The operator was situated on the right because of the need to dissect the adhesion between the liver and the transverse colon, the endoscopist was between the legs, and the first assistant was on the left side. A 12-mm infraumbilical port was placed using the Hasson technique and a 30° telescope was introduced into the peritoneal cavity. In the peritoneal cavity, we recognized the adhesion between the liver and the transverse colon. Additional ports were placed, including a 12-mm trocar in the right lower quadrant and two 5-mm trocars in the right upper quadrant for the operator, and a 12-mm trocar in the left upper quadrant and 5-mm trocar in the left quadrant for the assistant (Figure 3A). After the adhesion between the jejunum and the mesocolon was dissected carefully because the reconstruction in the last distal gastrectomy was a Billroth Ⅱ *via* retrocolic root (Figure 3B), the transverse colon was dissected from the liver. The mesentery was incised from the area dissected between the jejunum and mesocolon to the origin of the middle colic artery. Radical lymphadenectomy was continued up to the root of the middle colic artery and the branch of the splenic flexure was divided (Figure 3C). The incision of the mesentery was extended up to the origin of the right colic artery (the left in an orthotopic patient) and the branch of the right colic artery was divided (Figure 3D). After mobilization up to the descending colon, dissection and reconstruction of the colon were performed extracorporeally through a 5-cm skin incision continued to the right port using a functional end-to-end stapling method. Operating time was 402 min and blood loss was 230 mL. Compared to orthotopic patients, the operating time was longer and the blood loss greater because of the intraabdominal adhesions after open distal gastrectomy. According to the Japanese classification of colorectal carcinoma[4], macroscopically, the tumors were a 51 mm × 41 mm type 3 lesion in the transverse colon, a 38 mm × 17 mm Ⅱc lesion in the transverse colon, and 17 mm × 13 mm and 10 mm × 10 mm Ⅱa lesions in the descending colon. Histological examination of the resected specimens disclosed a moderately-differentiated adenocarcinoma (type 3, pSS, pN0, sH0, sP0, cM0, ly1, v0, Stage Ⅱ) and well-differentiated adenocarcinomas (Ⅱa and Ⅱc lesions, pM, pN0, sH0, sP0, cM0, ly0, v0, stage 0) (Figure 4). After an uneventful postoperative course, the

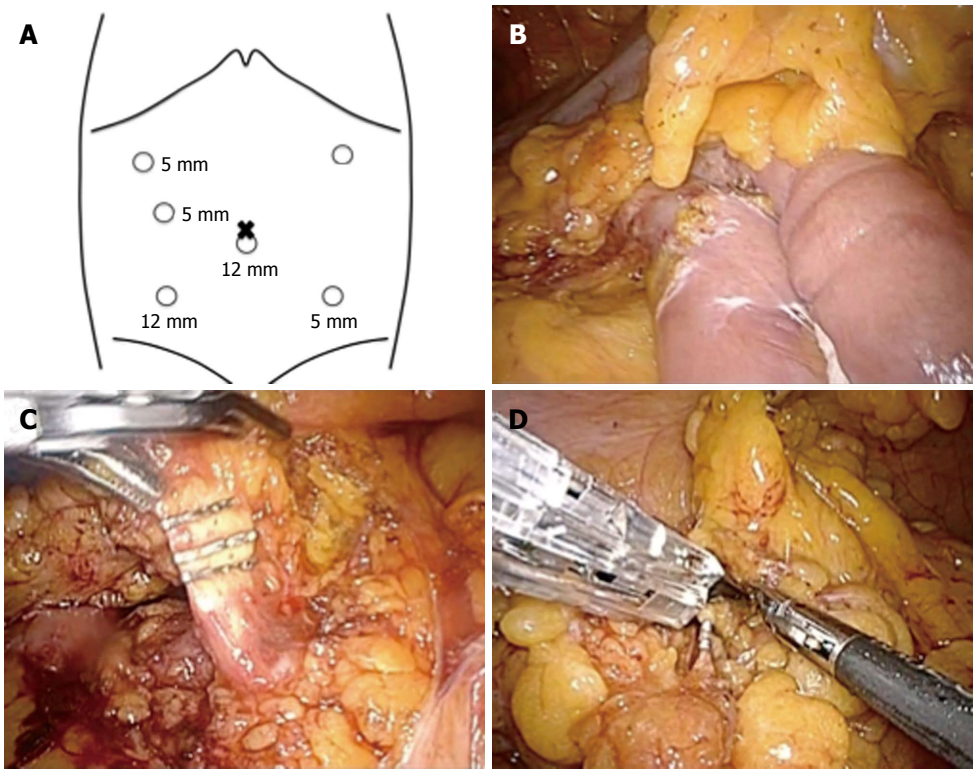

Figure 3 Sites of trocar placement and intraoperative finding. A: A camera was inserted into the subumbilical area through a 12-mm trocar; B: The reconstruction in the last distal gastrectomy was Billroth Ⅱ *via* retrocolic root; C: Radical lymphadenectomy was continued up to the root of the middle colic artery and the branch of the splenic flexure was divided; D: The branch of the right colic artery (the left in an orthotopic patient) was divided.

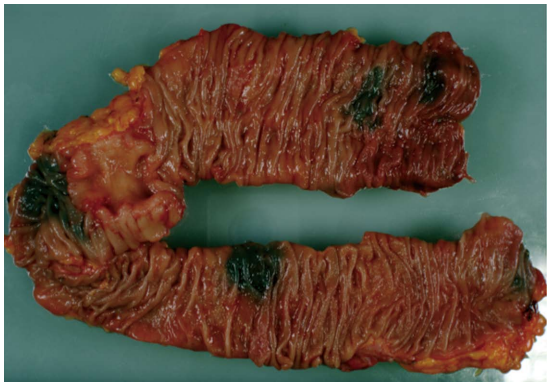

Figure 4 Macroscopic findings. The main tumor was a 51 mm × 41 mm type 3 lesion in the transverse colon. A 38 mm × 17 mm Ⅱc lesion was in the transverse colon and 17 mm × 13 mm and 10 mm × 10 mm Ⅱa lesions were in the descending colon.

patient was started on a clear liquid diet on the 4th postoperative day and was discharged on the 16th postoperative day according to the clinical pathway at our hospital.

DISCUSSION

Situs inversus (SI) is a rare congenital anomaly in which the organs are transposed from their normal site to the opposite side of the body. SI may involve transposition of thoracic or abdominal organs, or both. SIT denotes complete inversion of thoracic and abdominal viscera[5-7]. The incidence is 1 in 5000-20 000[1]. Apart from a genetic predisposition, no etiologies have been established, and SI itself has no pathophysiologic significance[6,7]. Cardiovascular malformations (8%) and bronchiectasis (10%) are often present[8]. With SIT, abnormal vascularization of the arteries and veins is common; therefore, the preoperative confirmation of any abnormal vascularization is very important. Particularly with laparoscopic surgery, it is important to determine the presence of vascular anomalies on preoperative CT or angiography. In the report of Iwamura *et al*[6], several cases having a combination of SIT and malignant tumors, such as cancer of the lung, stomach, liver, colon, and rectum, were described. Including our case, only 7 cases with SIT complicated by colorectal malignancy have been reported in the English literature[2,3,6,7,9,10].

Surgical procedures, especially laparoscopic procedures, are considered more difficult in patients with SIT than in other patients because of the mirror-image anatomy. Thus, because laparoscopic surgery in patients with SIT is a technical challenge for the surgeon, it remains relatively rare. However, it has been performed more often in recent years in such patients, but most of these procedures have been laparoscopic cholecystectomies[1], and only 10 advanced laparoscopic procedures have been described (Table 1)[2,3,5,11-17]. Furthermore, for malignancy, only 4 laparoscopic procedures have been reported[2,3,13,14]. While laparoscopic colorectal surgery has recently become a standard procedure, only 5 (only 2 for colorectal cancer) reports of laparoscopic surgery for colorectal disease with SI have been published[2,3,5,11,12]. The reason

Table 1 Reports of advanced laparoscopic surgery for situs inversus totalis

Operation	Author	Year	Disease	Operation time (min)	Blood loss (mL)
Laparoscope-assisted distal gastrectomy	Futawatari *et al*[14]	2010	Gastric cancer	300	350
	Yamaguchi *et al*[13]	2003	Gastric cancer	280	240
Laparoscopic gastro bypass	Ahmed *et al*[16]	2006	Obesity	160	ND
	Wittgrove *et al*[15]	1998	Obesity	ND	ND
Laparoscopic sleeve gastrectomy	Cateline *et al*[17]	2006	Obesity	ND	ND
Laparoscopic hemicolectomy	Fujiwara *et al*[2]	2007	Colon cancer	191	60
Laparoscopic sigmoidectomy	Jobanputra *et al*[12]	2007	Diverticulitis	ND	ND
	Kobus *et al*[5]	2004	Diverticulitis	180	ND
	Davies *et al*[11]	2002	Diverticulitis	ND	ND
Laparoscopic total mesorectal excision	Huh *et al*[3]	2010	Rectal cancer	250	120

Only 10 advanced laparoscopic procedures have been reported, 4 of which were for malignancies. ND: Not determined.

is considered to be that the number of SI patients is so small, and the anatomic abnormality has made surgeons reluctant to attempt laparoscopic surgery.

The positions of the operator, assistant, and trocar did not differ from those in orthotopic patients. We found no technical difficulties using the laparoscopic procedure because we had acquired images of the anatomy. Attention to the fundamentals of laparoscopic procedures, such as the careful handling of devices and keeping the operating field dry, is very important. Of course, accurate preoperative anatomic assessment and careful preoperative planning of laparoscopic procedures (positions of operator, assistants, and trocar sites as well as instrumentation) are needed to ensure a safe and smooth procedure, as mentioned in previous reports of laparoscopic surgery in patients with SI[5,11]. Although advanced surgical skill is required for radical lymphadenectomy in a patient with SIT, careful recognition of the mirror image anatomy is more important. In the present patient, we had obtained information on vascularization of the arteries and veins from operative records of the previous open distal gastrectomy. Although this operation was after open surgery, we could safely perform the laparoscopic procedure by adhering to the fundamentals of laparoscopic procedures.

In summary, laparoscopic colectomy for colon cancer in a patient with SIT can be performed safely by a skilled surgeon and surgical team after thorough preoperative planning including assessment of the anomaly. This procedure is a feasible option to enable such patients to benefit from minimally invasive surgery.

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FIELD OF VISION

Is there a role for arterial reconstruction in surgery for pancreatic cancer?

Reena Ravikumar, David Holroyd, Giuseppe Fusai

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Abstract

Surgery remains the only potentially curative treatment for patients with pancreatic cancer. Locally advanced pancreatic cancer with vascular involvement remains a surgical challenge because high perioperative risk and the uncertainty of a survival benefit. Whilst portal vein resection has started to gather momentum because the perioperative morbidity and long term survival is comparable to standard pancreatectomy, there isn't yet a consensus on arterial resections. There have been various reports and case series of arterial resections in pancreatic cancer, with mixed survival results. Mollberg *et al* have appraised the heterogeneous published literature available on arterial resection in pancreatic cancer in an attempt to compare this to standard pancreatectomy. In this article, we discuss the results of this systematic review and meta-analysis, and the limitations associated with analysing results from heterogenous data. We have outlined the important features in surgery for pancreatic cancer and specifically to arterial resections, and compared arterial resections to the published literature on venous resections.

Key words: Arterial resection; Pancreatic cancer; Vascular resection; Hepatic artery; Coeliac axis; Pancreatectomy

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COMMENTARY ON HOT TOPICS

The systematic review and meta-analysis on arterial resection during pancreatectomy by Mollberg *et al*[1] is a very timely and current paper. They report perioperative and survival outcomes associated with arterial resection during pancreatectomy for pancreatic cancer, compared to pancreatectomy alone.

Worldwide, pancreatic cancer is the 13th most common cancer, but the eight most common cause of cancer death with little improvement in survival over the last few decades[2]. Surgical resection remains the only hope for cure in these patients. However, many of these patients are diagnosed at a late stage because of the nature of the disease and surgical resection with a curative intent is rarely possible. Fortner[3], first described a "regional pancreatectomy" involving total pancreatectomy, radical lymph node clearance, combined portal vein resection (Type 1) and/or combined arterial resection and reconstruction (Type 2). This was found to be associated with unacceptably high morbidity and mortality rates, and was abandoned. More lately, pancreatectomy with portal vein resection and reconstruction has began to gather momentum as studies demonstrated acceptable morbidity and long term survival rates comparable to standard pancreaticoduodenectomy (PD)[4-6]. In recent years, the morbidity and mortality rates between standard PD and pancreatico-duedenectomy with vascular resection have been similar[4,5,7,8]. Isolated venous involvement

is no longer a contraindication to PD when performed by experienced surgeons at high volume centers as part of a multidisciplinary approach to localized pancreatic cancer[9] arterial resection, however, has remained highly controversial. Current oncological guidelines suggest that pancreatic tumours invading arterial structures render these cancers inoperable[10]. Nevertheless, attempts at resection involving reconstruction of the main arteries such as the coeliac axis, hepatic artery and superior mesenteric artery (SMA) have been reported, albeit in small case series[8,11-16].

The study population for the meta-analysis is the largest in the published literature despite the unsurprising heterogeneity of the 26 studies that met inclusion criteria; a limitation acknowledged by the authors. In total, 366 patients underwent pancreatectomy with concomitant aprtic regurgitation (AR) out of a total of 2609 patients that were included in the study. All data were non-controlled, collected retrospectively, over a prolonged study period (1973-2010), with a high proportion of procedures performed pre-2000, and with a high risk of bias in 22/26 studies. In addition, as the authors point out, the median number of patients per study is 12.5, suggesting a pooled analysis may be a more suitable method of data evaluation[1].

There was considerable heterogeneity in the types of surgical procedures performed across the studies included in Mollberg's systematic review, including cases where arterial resection was performed in combination with venous resection and/or extended lymphadenectomy. Mollberg *et al*[1] found that perioperative morbidity was significantly increased in patients undergoing concomitant AR compared to those undergoing pancreatectomy alone (OR = 2.17, 95%CI: 1.26-3.75, $P = 0.006$; $I^2 = 35\%$), with a significantly higher re-operation rate (OR = 3.28, 95%CI: 1.68-6.41, $P < 0.001$; $I^2 = 33\%$) and with a 5 times greater perioperative mortality risk in the AR group (OR = 5.04, 95%CI: 2.69-9.4, $P < 0.0001$; $I^2 = 24\%$). This can be explained by the complexity and technical challenge associated with an arterial resection including the risk of bowel ischaemia. They also found a greater perioperative mortality rate amongst patients undergoing arterial resection in comparison to venous resection in their subgroup analyses (OR = 8.87, 95%CI: 3.4-23.13, $P < 0.0001$; $I^2 = 5\%$).

There was no significant difference in the incidence of lymph node metastases between patients undergoing pancreatectomy with and without AR (OR = 1.39, 95%CI: 0.85-2.27, $P = 0.19$; $I^2 = 0\%$). There was also no difference found in R0 resection rates between the 2 groups when analysing 209 patients in 15 studies who provided this data. However, the exclusion of a study by Boggi *et al*[14] by sensitivity analysis indicated a lower R0 resection rate in the AR group with low heterogeneity. However, the role of resection margin status as a prognostic indicator remains controversial due to the lack of uniformity of pathology reporting for pancreatic cancer[17,18].

Median survival at 1, 3 and 5 years for patients undergoing AR during pancreatectomy was 49.1%, 8.3% and 0%, respectively. Meta-analysis of survival data demonstrated that there was a significantly lower chance of long term survival for patients undergoing pancreatectomy with concomitant AR compared to pancreatectomy. This is in contrast to survival outcomes for patients with pancreatic cancer involving the portal vein where the overall survival is similar in the resection groups (with and without vein resection) and significantly greater than patients having a palliative bypass[4,5,19,20]. The median 1-, 3- and 5-year survival rates for patients with AR were significantly reduced. This persisted even after excluding the study by Boggi *et al*[14] for heterogeneity following a sensitivity analysis. The authors therefore compared AR to palliative non-surgical therapy, which was reported in 6 studies. This showed a significantly higher 1- and 2-year survival for patients undergoing AR after excluding a study by Wang for heterogeneity. However, as explained by the authors, the non-controlled nature of these studies could have meant that the patients who did not undergo resection could have had an inherently worse prognosis, with more advanced tumours, compared to those undergoing AR.

This study is a very comprehensive analysis of the data that are currently available concerning arterial resection during pancreatectomy. It demonstrates significantly increased peri-operative morbidity and mortality, combined with significantly poorer survival outcomes at 1, 3 and 5 years. The authors conclude that the need for arterial resection in itself is the actual risk factor for increased perioperative death. However, they also suggest that in the absence of other treatment for tumours involving the SMA, with careful patient selection, arterial resection may be justified in a small cohort of patients. In addition, the authors also suggest a prospective registry to allow accurate analysis of outcome data for patients undergoing an arterial resection. We would augment this idea by suggesting a protocol detailing patient eligibility for arterial resection as a first step towards determining the suitability of this highly complex procedure, which may only be relevant to a specific subset of patients.

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BRIEF ARTICLE

Hepatic histopathology and postoperative outcome after preoperative chemotherapy for Chinese patients with colorectal liver metastases

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Abstract

AIM: To assess the effects of preoperative treatment on the hepatic histology of non-tumoral liver and the postoperative outcome.

METHODS: One hundred and six patients underwent hepatic resection for colorectal metastases between 1999 and 2009. The surgical specimens were reviewed with established criteria for diagnosis and grading of pathological hepatic injury. The impact of preoperative therapy on liver injury and postoperative outcome was analyzed.

RESULTS: Fifty-three patients (50%) received surgery alone, whereas 42 patients (39.6%) received neoadjuvant chemotherapy and 11 (10.4%) patients received preoperative hepatic artery infusion (HAI). Chemotherapy included oxaliplatin-based regimens (31.1%) and irinotecan-based regimens (8.5%). On histopathological analysis, 16 patients (15.1%) had steatosis, 31 (29.2%) had sinusoidal dilation and 20 patients (18.9%) had steatohepatitis. Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone (42.4% *vs* 20.8%, $P = 0.03$); however, the perioperative complication rate was not significantly different between the oxaliplatin group and surgery group (27.3% *vs* 13.2%, $P = 0.1$). HAI was associated with more steatosis, sinusoidal dilation and steatohepatitis than the surgery group, with higher perioperative morbidity (36.4% *vs* 13.2%, $P = 0.06$) and mortality (9.1% *vs* 0% $P = 0.02$).

CONCLUSION: Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone. However, the preoperative oxaliplatin had no significant impact on perioperative outcomes. HAI can cause pathological changes and tends to increase perioperative morbidity and mortality.

Key words: Drug liver injury; Preoperative chemotherapy; Hepatic artery infusion; Sinusoidal dilation

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common

causes of cancer death in the Western world, ranking second in Europe and third in the United States[1]. The incidence of CRC in China is lower than that in the West, but has increased in recent years[2,3] and has become a substantial burden in China. Some studies have reported changes in the characteristics of colorectal cancers in China[4,5]. Approximately 50% of patients with colorectal cancer develop liver metastases at some point during the course of their disease[6,7]. Surgical resection remains the first choice of treatment, with a 25%-40% long-term survival rate[8,9]. However, only 15%-20% of patients with colorectal liver metastases are suitable for surgical resection[10]. Chemotherapy is the first choice of treatment for unresectable patients but it is very rare for patients treated with chemotherapy alone to survive longer than 5 years.

Neoadjuvant chemotherapy has been evaluated in patients with initially resectable liver metastases. The rationale for using preoperative chemotherapy in patients with initially resectable disease includes an opportunity to demonstrate regimen-specific efficacy, as well as allowing time to identify those patients who will progress and who therefore may not benefit from liver resection. In addition, preoperative chemotherapy may decrease the magnitude of resection needed[11].

Although the use of new chemotherapeutic agents has a number of theoretical benefits, concern about liver injury after surgery led investigators to examine the impact of chemotherapy[12-16]. In the current study, we analyze the histopathological changes associated with preoperative chemotherapy and report the postoperative outcome.

In addition, hepatic artery infusion (HAI) has been increasingly used in China as a palliative treatment of unresectable colorectal metastases (CRM) or the edge of the liver function in an effort to reduce lesion size and thus make surgery feasible when the remnant liver is insufficient in size, based on cross-sectional imaging volumetrics. Therefore, we also collected data to evaluate whether HAI before surgery can have an impact on hepatic histopathology.

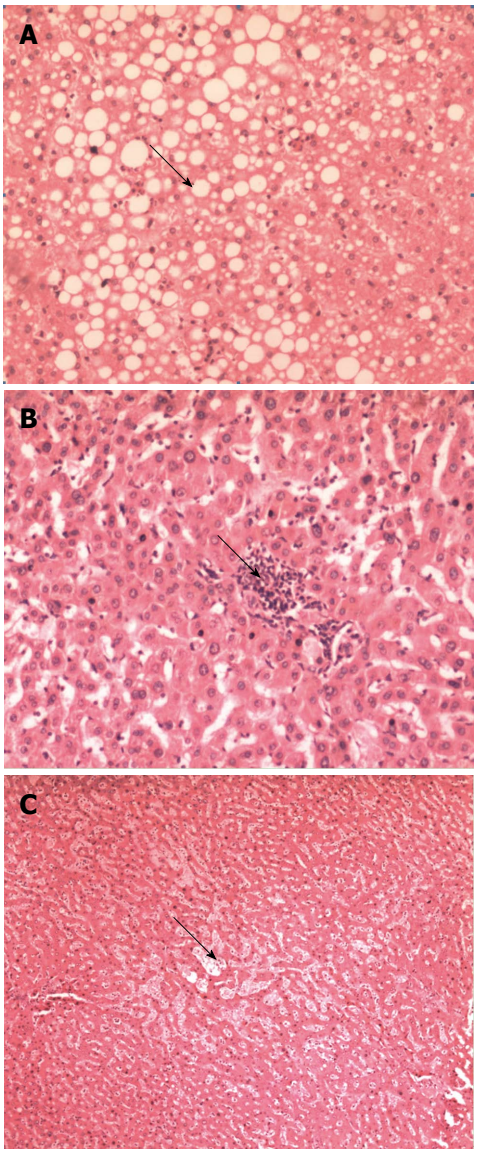

Figure 1 Histopathological findings. A: Severe steatosis. Large drop of fat (arrow) in the majority of hepatocytes, HE, 100 ×; B: Example of steatohepatitis showing the foci (arrow) of inflammation among the hepatocytes, HE, 100 ×; C: Grade 3 sinusoidal dilation involved the complete lobule, HE, 40 ×.

MATERIALS AND METHODS

A retrospective review was undertaken on patients who underwent hepatic surgery for CRM with a curative intent at Peking University Cancer Hospital between January 1999 and April 2009. Hepatic resections were defined according to the Brisbane terminology[17,18]. Patients were divided into the following four groups based on their preoperative therapy: (1) no preoperative therapy; (2) Oxaliplatin-based chemotherapy with fluorouracil (FU) or Xeloda; (3) Irinotecan-based chemotherapy plus FU; and (4) preoperative HAI. Only patients who received regional therapy with HAI were included in the HAI group.

Standard demographic data were collected on all patients, including type and duration of preoperative treatment, details of the resection, estimated blood loss (EBL), characteristics of the resected tumor, postoperative morbidity and 90 d mortality.

The archival slides (original formalin-fixed, paraffin-embedded and HE staining) from those resected hepatic specimens were blindly reviewed by a pathologist (Zhao AL). The histopathological findings in the non-tumoral liver tissue were evaluated semi-quantitatively as follows: (1) degree of steatosis was graded as none, mild (< 30%), moderate (≥ 30% to 50%) or severe (≥ 50%; Figure 1A); (2) steatohepatitis was graded as defined by Kleiner *et al*[19] based on steatosis (score 0: < 5%; 1: 5% to 33%; 2: > 33% to 66%; and 3: > 66%), lobular inflammation (score 0: no foci; 1: one foci; 2: two to four foci; and 3: > four foci per 200 × field) and ballooning (score 0: none; 1: few balloon cells; and 2: many cells/prominent ballooning, Figure 1B); and (3) sinusoidal injury was graded according to an established grading system of sinusoidal dilation (grade 0: absent; grade 1: centrilobular involve-

Table 1 Clinical and pathological features of patients (*n* = 106) *n* (%)

Variable	Patients
Sex	
Female	56 (52.8)
Male	50 (47.2)
Site of primary tumor	
Colon	55 (51.9)
Rectum	51 (48.1)
Hepatic metastases	
Median	3
Solitary	61 (57.5)
Multiple	45 (42.5)
Metastases type	
Synchronous	44 (41.5)
Metachronous	62 (58.5)
Extent of hepatic resection	
Minor (1-2 segment)	81 (76.4)
Major (≥ 3 segment or hemihepatectomy)	25 (23.6)

Median age of patients is 60 yr.

ment limited to one-third of the lobular surface; grade 2: centrilobular involvement extending in two-thirds of the lobular surface; grade 3: complete lobular involvement)[12] (Figure 1C). Hepatic injury was defined as steatosis more than 30%, steatohepatitis Kleiner score ≥ 4 and/or grade 2-3 sinusoidal dilation.

Statistical analysis

Summary statistics were performed using the χ^2 test and Fisher's exact test for comparing categorical variables; the Kruskal-Wallis test was used to compare continuous variables among the treatment groups. The odds ratios (OR) and the 95%CI were estimated and *P* value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS software, version 9.0.

RESULTS

Table 1 presents the clinicopathological features of the 106 patients in the study. A total of 106 patients were included in the analysis. There were 50 (47.2%) men and 56 (52.8%) women and the median patient age was 60 years (range 32-79 years). The presentation of hepatic metastases was metachronous in most patients (*n* = 62; 58.5%), while synchronous metastases accounted for 41.5%. The median number of hepatic metastases was 3 (range 1-5) and the median size of the largest lesion was 4 cm (range 0.7-22 cm).

At the time of the operation, the extent of hepatic resection was less than 3 segments or hemihepatectomy in 81 patients (76.4%) and a hemihepatectomy or more than 3 segments removal in 25 patients (23.6%). The median EBL was 200 mL (range 50-3000 mL). The median EBL in the preoperative chemotherapy arm was 575 mL, which was obviously higher than those without preoperative treatment (200 mL).

A total of 42 patients received neoadjuvant chemotherapy therapy, consisting of oxaliplatin plus FU regimen (33, 31.1%) and irinotecan plus FU regimen (9, 8.5%). While 11 (10.4%) patients received preoperative HAI before surgical treatment of the hepatic metastases, in which 8 patients received Cisplatin plus Epirubicin, three patients received oxaliplatin plus FU/CF. Of the 42 patients who received preoperative chemotherapy, the median duration was 5 cycles with 2-3 wk per cycle (range 2-10 cycles). The median duration of the HAI group was 3 cycles with 1 mo per cycle (range 1-3 mo). In general, the tumor characteristics and surgery details were similar among all preoperative treatment groups (Table 2). There was also no significant difference between groups with regard to age, gender, site of primary tumor, number of hepatic CRM, EBL or hepatic CRM tumor size (all $P > 0.05$). Patients who received HAI before surgery tended to have less EBL than other groups.

The overall perioperative complication rate was 18.9%. Thirteen patients (12.3%) suffered from hepatic complications, including liver failure (*n* = 3), hepatic insufficiency (*n* = 2), bile leaks (*n* = 9) and hepatic abscess (*n* = 1). Non-hepatic complications occurred in 11 patients (10.3%); there were 6 pulmonary complications (5.7%; pleural effusion, *n* = 6), 1 cardiovascular complications (0.94%; rapid atrial fibrillation, *n* = 1), 1 stress ulcer (0.94%) and 1 pancreatic fistula (0.94%), 2 peritoneal effusion (1.8%) and 1 with abdominal infectious complications (0.94%). Overall, the perioperative complication rate was similar between the no-chemotherapy group (13.2%) and the chemotherapy group (21.4%) ($P = 0.29$). In addition, patients who received HAI tended to have more postoperative morbidity (36.4% *vs* 13.2%, $P = 0.06$) and mortality (9.1% *vs* 0% $P = 0.02$) than those who received no preoperative chemotherapy. The complication rate did not differ with a different type of preoperative therapy (HAI 36.4%; irinotecan 0%; oxaliplatin 27.3%) ($P = 0.07$).

During the final pathological analysis of the resected specimen, hepatic injury was shown in 51 patients (48.1%). Steatosis more than 30% was identified in 16 patients (15.1%), grade 2 to 3 sinusoidal dilation in 31 patients (29.2%) and steatohepatitis Kleiner score ≥ 4 in 20 patients (18.9%). Preoperative chemotherapy is associated with pathological liver injury compared with non treatment before surgery (57.1% *vs* 35.8%, $P = 0.038$; OR: 2.39; 95%CI: 1.0-5.4). When patients were stratified according to the duration of chemotherapy (1 to 5, 6 to 10 cycles), the rate of hepatic injury increased over time in patients who received preoperative chemotherapy (76.2% *vs* 38.1%, $P = 0.01$). In Table 3, specifics on hepatic injury stratified by preoperative therapy are listed. Neither oxaliplatin nor irinotecan as neo-adjuvant chemotherapy before liver resection was associated with an increased rate of steatosis. The type of chemotherapy regimen used was associated with distinct patterns of liver injury: oxaliplatin was associated with grade 2 to 3 sinusoidal dilation compared with no chemotherapy (42.4% *vs* 20.8%, respectively, $P = 0.03$; OR = 2.8; 95%CI: 0.97-8.2). Patients receiving irinotecan also tended to have a higher likelihood of steatohepatitis compared with non treatment before surgery (33.3% *vs* 11.3%, $P = 0.08$), although the *P*

Table 2 Patient clinicopathological characteristics stratified by whether they received chemotherapy *n* (%)

Variable	Patients (*n* = 106)	Chemotherapy (*n* = 53)	Oxaliplatin (*n* = 33)	Irinotecan (*n* = 9)	HAI (*n* = 11)	*P* value
Mean age, yr	60	59.8	56.9	56.9	54.2	0.26
Gender						
Female	56 (52.8)	29 (54.7)	16 (48.5)	5 (55.6)	6 (54.5)	0.95
Male	50 (47.2)	24 (45.3)	17 (51.5)	4 (44.4)	5 (45.5)	
Site of primary tumor						
Colon	55 (51.9)	28 (52.8)	16 (48.5)	5 (55.6)	6 (54.5)	0.97
Rectum	51 (48.1)	25 (47.2)	17 (51.5)	4 (44.1)	5 (45.5)	
Timing of hepatic metastases						
Synchronous	44(41.5)	19 (35.8)	20 (60.6)	2 (22.2)	3 (27.3)	0.05
Metachronous	62 (58.5)	34 (64.2)	13 (39.4)	7 (77.8)	8 (72.7)	
Surgery type						
Minor (1-2 segment)	81 (76.4)	42 (79.2)	24(72.7)	9 (100)	6 (54.5)	0.10
Major (≥ 3 segment or hemihepatectomy)	25 (23.6)	11 (20.8)	9 (27.3)	0 (0)	5 (45.5)	
No. of hepatic CRM						
Single	61 (57.5)	34 (64.2)	17 (51.5)	6 (66.7)	4 (36.4)	0.29
Multiple	45 (42.5)	19 (35.8)	16 (48.5)	3 (33.3)	7 (63.6)	
Largest hepatic CRM tumor size, cm	10.4	4.87	4.55	4.73	4.05	0.87
Median estimated blood loss, mL	200	400	350	600	300	0.90
Duration of chemotherapy, wk (median)	4	0	4.8	4.1	0	< 0.0001
Postoperative complication						
Yes	20 (18.9)	7 (13.2)	9 (27.3)	0 (0)	4 (36.4)	0.07
No	86 (81.1)	46 (86.8)	24 (72.7)	9 (100)	7 (63.6)	

CRM: Colorectal metastases; HAI: Hepatic artery infusion.

Table 3 Liver injury characteristics stratified by preoperative therapy *n* (%)

Regimen	Liver toxicity (*n* = 51)			Steatosis > 30% (*n* = 16)			Sinusoidal dilation (*n* =31)			Steatohepatitis (*n* = 20)		
	Yes	No	[1]*P* value	Yes	No	[1]*P* value	Yes	No	[1]*P* value	Yes	No	[1]*P* value
No CTx	19 (35.8)	34 (64.2)		5 (9.4)	48 (90.6)		11 (20.8)	42 (79.2)		6 (11.3)	47 (88.7)	
Oxaliplatin	19 (57.6)	14 (42.4)	0.04	5 (15.2)	28 (84.8)	NS	14 (42.4)	19 (57.6)	0.03	7 (21.2)	26 (78.8)	NS
Irinotecan	5 (55.6)	4 (44.4)	NS	2 (22.2)	7 (77.8)	NS	1 (11.1)	8 (88.9)	NS	3 (33.3)	6 (66.7)	0.08
HAI	8 (72.7)	3 (27.3)	0.02	4 (36.4)	7 (63.6)	0.02	5 (45.5)	6 (54.5)	0.08	4 (36.4)	7 (63.6)	0.03

[1]Presence of liver injury characteristic; each chemotherapy group *vs* no chemotherapy. CTx: Chemotherapy; NS: Not significant; HAI: Hepatic artery infusion.

value was not statistically significant. Specifically, HAI was also associated with more steatosis, sinusoidal dilation and steatohepatitis than no preoperative treatment. HAI was associated with steatosis and steatohepatitis compared with non treatment before surgery (36.4% *vs* 9.4%, $P = 0.02$; 36.4% *vs* 11.3%, $P = 0.03$, respectively) and patients receiving HAI tended to have a higher likelihood of sinusoidal dilation compared with no chemotherapy (45.5% *vs* 20.8%, $P = 0.08$), although the *P* value was not statistically significant.

There were three patients who died within 90 d of surgery, with a perioperative mortality rate of 2.8%. Of those three deaths, one was due to renal failure, one was associated with an abdominal infection and a bile leak and another from acute respiratory distress syndrome (ARDS). There were two deaths among the preoperative chemotherapy (1.8%), all from oxaliplatin preoperative treatment, while another death occurred in the HAI arm (0.9%). There is no association between preoperative chemotherapy and the risk of perioperative mortality ($P = 0.1$). Patients with oxaliplatin ($n = 33$) tended to have a higher risk of death (6.1%) *vs* no preoperative treatment (0%), although the *P* value was not statistically significant ($P = 0.07$). There were 2 deaths (3.9%) in 51 patients with hepatic injury (one death was associated with an abdominal infection and a bile leak, another from ARDS) compared with one death (1.8%) in 55 patients without hepatic injury (one from renal failure).

In our study, there were seven patients with concomitant hepatitis before surgery, six with hepatitis B virus infection and one with hepatitis C virus infection. Two of these received neoadjuvant chemotherapy. However no further liver injury or complication was observed in those two patients.

DISCUSSION

Currently, chemotherapy has been commonly used as a part of an integrated multimodality approach to CRM and sometimes as the first treatment choice. Recently, an increasing number of reports have shown that the administration of preoperative chemotherapy can be associ-

ated with pathological changes in liver parenchyma[12-16]. However, the question remains whether these hepatic injuries have any clinical significance.

In the current study, we performed a retrospective analysis on the result of the use of preoperative treatment, including chemotherapy and HAI, for any impact on pathological liver injury and on clinical outcome, including postoperative complication and mortality.

Our study results show that preoperative treatment with oxaliplatin was significantly associated with a greater likelihood of sinusoidal dilation compared with no chemotherapy (42.4% *vs* 20.8%, $P = 0.03$), which is consistent with other recently published studies[15,20-22].

Interestingly, we observed that the incidence of sinusoidal dilation with oxaliplatin was 42.4%, relatively higher than Vauthey *et al*[16] (18.9%) and Pawlik *et al*[22] reported (9.6%). The reason for the different prevalence of sinusoidal dilation is probably multifactorial. Although progress has been made in this area, cohesive guidelines have yet to be proposed and consensus is lacking on a uniform set of pathological terminology to define chemotherapy-associated liver injury. The subjective variability between expert pathologists can lead to a different incidence rate of pathological changes in liver parenchyma. That is why we decided to have only one pathologist with hepatobiliary expertise assess the degree of liver injury and follow Vauthey's[16] strict definition.

Until now, only a few studies have been able to connect a given chemotherapeutic agent with a specific histopathological injury and a meaningful adverse outcome[16]. In our study, preoperative oxaliplatin was not significantly associated with an increase risk of postoperative complication (27.3% *vs* 13.2%, $P = 0.1$). Similar results were observed in other studies[22-24], indicating that preoperative oxaliplatin had no impact on postoperative morbidity or mortality.

Among previous reports, only Vauthey *et al* linked irinotecan-based chemotherapy with steatohepatitis and increased 90 d postoperative mortality[12-16]; 34 (8.4%) patients had steatohepatitis as defined by the nonalcoholic steatohepatitis score. Irinotecan was associated with steatohepatitis (20.2% incidence in the irinotecan group *vs* 4.4% in the non-chemotherapy group, $P = 0.0001$) and patients with steatohepatitis had an increased 90 d mortality rate compared with patients who did have steatohepatitis. In our study, steatohepatitis (Kleiner score $\geqslant 4$) was observed in 20 patients (18.8%), a higher rate than that Vauthey reported (20.2%). However, no postoperative complication or mortality was observed in patients with irinotecan treatment. We need to closely monitor the patient's status when we use irinotecan before surgery due to a relatively high steatohepatitis incidence rate, although data is not sufficient at present.

HAI has been used extensively in the palliative treatment of unresectable hepatocellular carcinoma. It was observed in several studies that it could improve quality of life, symptomatic control and survival time as a local therapy for CRM[25-28]. HAI is increasingly used in China as a palliative treatment of unresectable CRM as it may increase the possibility of surgery and can be used when surgery is not possible or not successful. However, less attention has been paid to the hepatic histological injures and perioperative complications after HAI, since it is commonly excluded from preoperative studies which observe the impact on hepatic histology and its outcomes for CRM. Until now, limited studies have explored whether HAI can affect the remaining liver for CRM and determine whether it can be used before surgery to improve postoperative recovery. Pulitanò *et al*[29] reported that postoperative morbidity rate were comparable between the HAI group and surgery alone group (14% *vs* 14%). He concluded that HAI of fluorodeoxyuridine does not negatively affect the outcome of subsequent liver resection. However, his article did not evaluate the hepatic pathological changes. In our study, we observed that HAI was associated with a higher risk of steatosis, sinusoidal dilation and steatohepatitis compared with non treatment before surgery. In addition, patients who received HAI tended to have more postoperative morbidity and mortality; those data alerted us to be more careful about its adverse impact on hepatic histology, despite a limited small sample size.

Discussion about the optimum interval between chemotherapy and hepatectomy has been based on the assumption that hepatic side effects of chemotherapy are time-related and reversible. Kopetz *et al*[30] reviewed the data and stated that a limited course of chemotherapy, with an interval of at least 5 wk, might minimize the incidence of surgical complications. Although the optimal timing of hepatic resection after completion of chemotherapy varies among institutions, a consensus is evolving for a minimum interval of 4 wk to allow the liver to recover, in the hope of reducing morbidity and mortality. In our study, almost all recruited patients received hepatic resection after completion of chemotherapy with an interval of 4-6 wk. Based on the clinical practice in our cancer center, the preoperative complication rate is observed at 13.2%, comparable with other reported papers[29].

Given this, the use of preoperative chemotherapy and HAI may need to be more carefully monitored and the choice of regimen and duration of treatment tailored to the particular individual's situation. Future investigations will be needed to clarify the pathogenesis and molecular pathways underlying the cause of chemotherapy-associated liver injury and its relationship to other known pathways. In addition, only through a thorough understanding of the patient's status and the patient's liver condition prior to administration of systemic chemotherapy can potentially confounding variables be accounted for and the true impact of systemic chemotherapy on the liver be determined[22].

Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone. However, the preoperative oxaliplatin had no significant impact on perioperative outcomes. HAI can cause pathological changes and tends to increase perioperative morbidity and mortality.

COMMENTS

Background

Colorectal cancer (CRC) is one of the most common causes of cancer death in the Western world, ranking second in Europe and third in the United States. The incidence of CRC in China is lower than that in the West, but has increased in recent years and become a substantial burden in China. Some studies have reported changes in the characteristics of colorectal cancers in China.

Research frontiers

Preoperative chemotherapy before resection of hepatic colorectal metastases may cause hepatic injury and affect the postoperative outcome. The objective of this study was to assess the effects of preoperative treatment on the hepatic histology of non-tumoral liver and the postoperative outcome.

Terminology

Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone. However, preoperative oxaliplatin had no significant impact on perioperative outcomes. Hepatic artery infusion can cause pathological changes and tends to increase perioperative morbidity and mortality.

Peer review

The data presented in this paper is very interesting, especially the references about the impact of the duration of chemotherapy and the effect of hepatic artery infusion on the liver parenchyma. It is worthy of being published.

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CASE REPORT

Clostridium difficile enteritis: A report of two cases and systematic literature review

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Abstract

Clostridium difficile (*C. difficile*) is the most common cause of healthcare associated infectious diarrhea. In the last decade, the incidence of *C. difficile* infection has increased dramatically. The virulence of *C. difficile* has also increased recently with toxigenic strains developing. *C. difficile* is generally a disease of the colon and presents with abdominal pain and diarrhea due to colitis. However, *C. difficile* enteritis has been reported rarely. The initial reports suggested mortality rates as high as 66%. The incidence of *C. difficile* enteritis appears to be increasing in parallel to the increase in colonic infections. We present two cases of patients who had otherwise uneventful abdominal surgery but subsequently developed *C. difficile* enteritis. Our literature review demonstrates 81 prior cases of *C. difficile* enteritis described in case reports. The mortality of the disease remains high at approximately 25%. Early recognition and intervention may reduce the high mortality associated with this disease process.

Key words: Clostridium difficile; Enteritits; Antibiotics; Colorectal surgery; Nosocomial infection

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INTRODUCTION

Clostridium difficile (*C. difficile*) is a common nosocomial infection caused by a gram-negative spore forming organism that most commonly leads to pseudomembranous colitis[1,2]. The incidence of *C. difficile* infection has been increasing rapidly since the early 2000s[2,3]. The rate of *C. difficile* infection nearly tripled between 1996 and 2005[2]. The number of severe cases of *C. difficile* infection is also rising; the number of fatal cases in England rose from approximately 500 in 1999 to nearly 3400 in 2006[2]. The increasing severity of disease may be due to a rise in an epidemic strain, NAP1/BI/027, which produces toxin A and B in significantly greater quantity compared to the normally occurring strain. *C. difficile* resides in the colon and risk factors for infection, such as antibiotic use, are generally those that alter normal colonic flora. However, we present two cases of patients diagnosed and treated with *C. difficile* enteritis. Due to the rare nature of this disease we reviewed the literature on the subject and present data to suggest increasing recognition of this manifestation of *C. difficile*.

CASE REPORT

Case 1

The first patient is a 54-year-old Caucasian male with ulcerative colitis who underwent a total proctocolectomy with end ileostomy in 1997. He developed a parastomal

hernia that was becoming increasingly symptomatic. Following a discussion with the patient regarding the risks and benefits of parastomal hernia repair, he underwent an exploratory laparotomy with enterolysis, parastomal hernia repair and re-siting of the ileostomy. The hernia defect was repaired primarily with a biologic mesh underlay (Alloderm, Lifecell®). He received one preoperative dose of cefoxitin; consistent with preoperative antibiotic guidelines. The operation was uneventful. His postoperative course was uncomplicated; on postoperative day 4 he was tolerating a regular diet and had normal ileostomy output. He was subsequently discharged home.

Twenty-four hours later, he returned to the hospital emergency department with complaints of abdominal pain and feculent vomiting. Vital signs on arrival were notable for a temperature of 38.5 ℃, heart rate of 130 beats per minute and blood pressure of 150/90 mmHg. On physical exam his abdomen was diffusely tender to palpation without peritoneal signs. The ileostomy was viable and there was gas and a small amount of fluid noted in the ostomy bag. A nasogastric tube was placed and returned 1600 mL of feculent effluent.

Laboratory examination revealed a white blood cell count of 5400 cells/mm^3, hemoglobin of 16 g/dL, and 192 000 platelets/mm^3 and a serum lactate of 2.1 mg/dL. An abdominal and pelvic computed tomography (CT) scan obtained in the emergency department revealed mildly dilated, fluid filled small bowel without a transition point. There was a small amount of free fluid and air which was consistent with the history of recent laparotomy. Blood cultures were obtained in the emergency department.

He was transferred to the intensive care unit for fluid resuscitation and started on broad-spectrum antibiotics. Serial abdominal exams were performed over the course of the next several hours, and he began to stabilize clinically. Notably, his tachycardia began to resolve and his urine output increased. Additionally, during this time, his ileostomy began to produce copious amounts of fluid and gas requiring frequent ostomy bag changes. The following day, his blood cultures returned positive for *Enterococcus* and his stool studies from his stoma output were positive for *C. difficile*.

Treatment for *C. difficile* was initiated with oral metronidazole but was subsequently changed to a combination of intravenous metronidazole and vancomycin enemas as the patient was not tolerating oral intake well. On hospital day 2, the antibiotic regimen used to treat the bacteremia was tailored to intravenous vancomycin alone based on sensitivity information. The patient improved with his antibiotic treatment and was transitioned to oral vancomycin for treatment of *C. difficile*. He was treated for a total of 14 d and he had complete resolution of his symptoms.

Case 2

The second case is a 48-year-old male patient with a history of diverticulitis who presented with left lower quadrant abdominal pain. His vital signs were normal on admission. A CT scan revealed inflammation of the sigmoid colon without evidence of a discrete fluid collection. The patient was initially started on intravenous antibiotics. However, approximately 24 h following admission, the patient developed worsening abdominal pain. His abdominal examination demonstrated worsening tenderness, with diffuse rebound and guarding. After discussion of operative risks he was taken to the operating room for exploration.

The sigmoid colon demonstrated only a focal area of perforation with moderate inflammation. A sigmoidectomy was performed with healthy proximal tissue and normal rectum. A primary anastomosis was performed using an EEA stapling device. A diverting ileostomy was performed to protect the anastomosis. The patient received 24 h of antibiotic treatment prior to operation which included three doses each of ciprofloxacin and metronidazole. Postoperatively, the patient developed an ileus which resolved on postoperative day 6. He was tolerating a diet following this. On postoperative day 8, the patient experienced significantly increased output from his ileostomy (greater than 2 L). A *C. Difficile* toxin sent from the ileostomy returned positive. The patient was started on intravenous metronidazole and improved. He was transitioned to oral medications upon discharge to complete a 14 d course.

Literature review

A systematic literature review was conducted by searching PubMed for the terms "enteritis" and "*Clostridium difficile*". One hundred and ninety-two citations were screened. One-hundred and fifty-eight were excluded based on review of title or abstract. Thirty-four citations were reviewed and the references of individual reports were hand searched to identify any missed reports. Data was extracted from individual case reports. All patients were symptomatic and tested positive for *C. difficile*. There were 34 reports identified from this search (Figure 1). We did not perform a meta-analysis due to the heterogeneity of the data and lack of randomized trials.

There were 81 cases of *C. difficile* enteritis found in the literature[4-37], with the addition of our cases, the total number of cases is now 83. Figure 2 illustrates that the number of cases has increased considerably in the last decade. There were 9 cases reported between the years 1980 and 2000. Since then there have been 73 cases reported. The mortality from the first 9 cases reported was 67% (6/9). The overall mortality of the 83 cases published is 23%. The average age of patients is 54 ± 2.44 years. Male patients constituted 53% of the cohort. Antibiotic use in the prior 4 wk was 71% and the incidence of inflammatory bowel disease was 41%. Twenty-one of 83 patients died resulting in a mortality rate of 23%.

DISCUSSION

C. difficile is the most common cause of health care-associated infectious diarrhea[3]. As first described, *C. difficile*

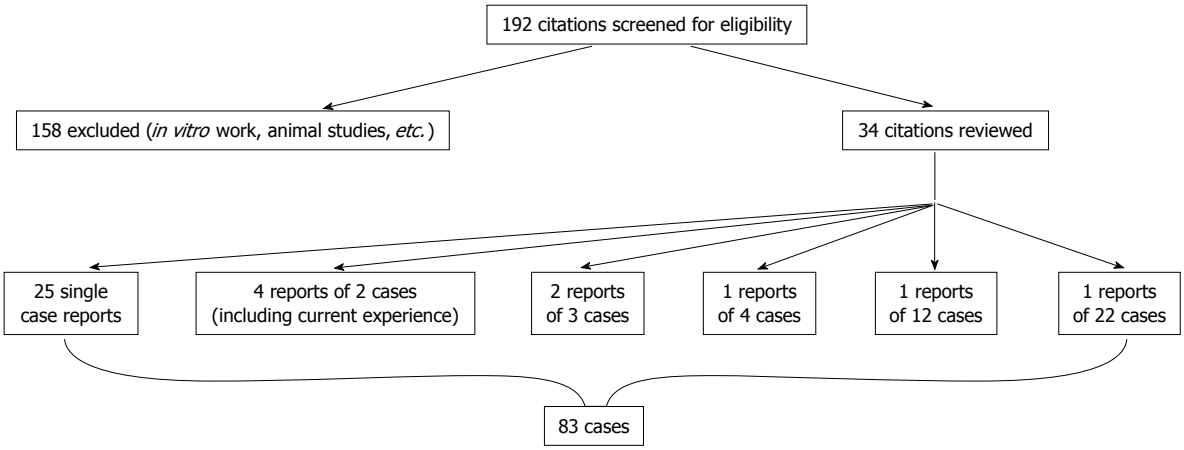

Figure 1 CONSORT diagram indicating the results of the systematic literature review. The results of the systematic review demonstrated 34 citations that met criteria for inclusion. There were a total of 83 patient-cases of *Clostridium difficile* enteritis identified.

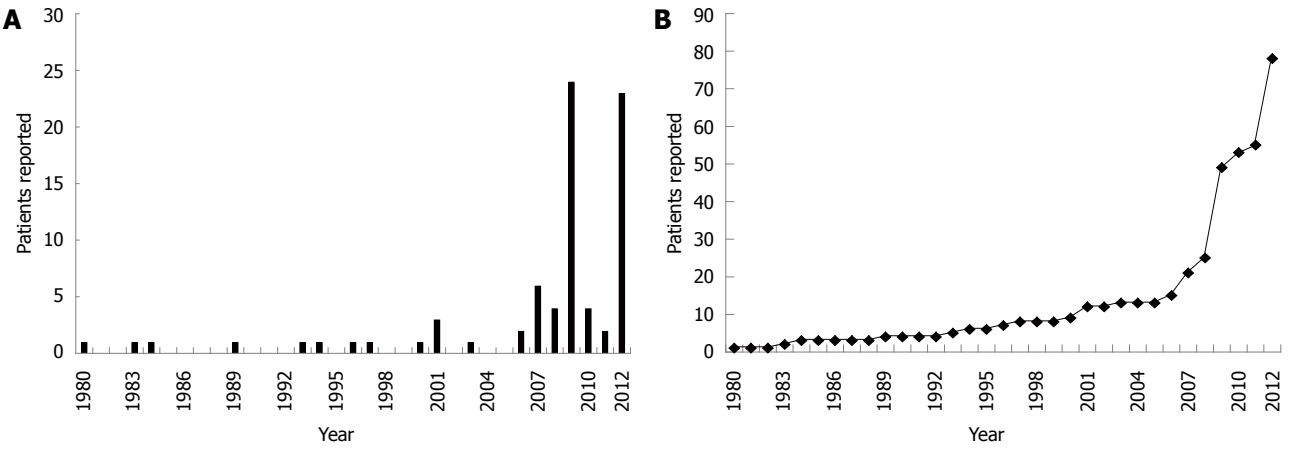

Figure 2 Number of cases has increased considerably in the last decade. A: The number of cases (patients) reported in the literature each year between 1980-2012; B: The cumulative number of cases over the same time period.

colitis was thought to be associated with the exclusive use of clindamycin administration[2]. Ironically, the bacteria that was difficult to grow (thus the *difficile*) is now increasing with dramatic incidence[2,38]. The increase in incidence is due, in part, to the highly virulent NAP1/BI/027 strain of *C. difficile*. In the United States, the frequency of *C. difficile* infection has doubled in the past 10 years[38]. The understanding of *C. difficile* and its pathophysiology has increased substantially over the past few decades. Severe *C. difficile* infection is being reported more frequently in patients not previously thought to be at high risk, including children[38,39]. It is possible that *C. difficile* enteritis is less dependent on alterations in colonic flora to develop. *C difficile* enteritis has previously been considered a rare disease. However, as highlighted in our review, the incidence of this also appears to be increasing.

Predisposing factors to *C. difficile* infection include prior antibiotic use; which is thought to alter the colonic flora, allowing *C. difficile* to proliferate. Many case reports, including ours, would suggest that previous antibiotic use is also associated with *C. difficile* enteritis. Lavallée *et al*[19] report that ten of twelve patients with ileal *C. difficile* had recent antibiotic administration (one did not have recent antibiotic use and one was not documented). Similarly, Lundeen *et al*[20] present 6 cases of *C. difficile* enteritis in which all 6 cases had recent antibiotic exposure. However, Tsiouris *et al*[30] report 22 cases in which the association with prior antibiotic use is less strong. Of the 22 patients in this series, only 22.7% demonstrated recent use of antibiotics. Based on our review, the association is still high, as 71% of patients had received antibiotics within 4 wk of presentation with *C. difficile* enteritis.

It is believed that gastric acid is a key mechanism of defense against ingested pathogens[1]. *C. difficile* has been identified as a pathogen in animals and has been identified in some food products[40]. Therefore, it is possible that transmission from ingested meats may occur[40]. Proton pump inhibitor (PPI) and H2-blockers are frequently used for gastric acid suppression. Acid suppressive therapy has been demonstrated to significantly increase the risk for *C. difficile* infection[1,41]. The patient in Case 1 was

treated preoperatively with a PPI for gastroesophageal reflux disease. Case 2 was not on outpatient therapy, but did receive a PPI postoperatively. This association is not entirely clear, however, as Lundeen *et al*[20] reported six cases, in which only one patient was on acid reducing therapy.

The pathophysiology of *C. difficile* enteritis is not well understood. Patients with an ileostomy may develop a metaplasia of the terminal end, creating an environment more similar to the colonic environment[42]. Additionally, changes in the intestinal flora have been noted after ileostomy[43]. Testore *et al*[44] isolated *C. difficile* from jejunum in asymptomatic human autopsy specimens. This supports the theory that small bowel may act as a reservoir. Kralovich *et al*[15] demonstrated *in vivo* that a patient with a jejunal-ileal bypass developed *C. difficile* infection in the defunctionalized limb. In addition to alterations in the host, changes in the pathogen may also be responsible for the development of *C. difficile* enteritis. Small bowel mucosa requires a higher concentrations of toxin for infection to occur[45]. In this case, the toxigenic NAP1/BI/027 strain may be more capable of causing small bowel infection. This is hypothetical at this point, but the increased recognition of *C. difficile* enteritis is compatible with the timing of the rise in NAP1/BI/027. This strain has been confirmed as the causative agent in one case of *C. difficile* enteritis[19]. We did not specifically test for NAP1/BI/027 strain and, therefore, cannot determine if this was a predisposing factor in our patients.

The diagnosis of *C. difficile* enteritis requires a high index of suspicion. As many patients may not initially be suspected of *C. difficile* infection, CT scan evidence may be useful. Wee *et al*[33] reviewed CT scan findings in four patients with *C. difficile* enteritis. They suggest that ascites and fluid-filled small bowel in the presence of mild mesenteric stranding could be considered consistent with *C. difficile* enteritis. Our patient in Case 1 demonstrated fluid filled loops of small bowel and a moderate amount of ascites. This was initially thought to be due to his recent surgery. However, these findings are consistent with the reported CT findings of small bowel *C. difficile*.

Treatment for *C. difficile* enteritis is generally similar to that for colonic infections. Oral metronidazole is considered standard first line therapy. However, Follmar *et al*[8] report the use of vancomycin for metronidazole resistant *C. difficile*. Severe *C. difficile* infection may be better treated with vancomycin[46,47]. In our patient, due to his ileus and his severe clinical status, we elected to use intravenous metronidazole and vancomycin enemas for his initial treatment.

It should be noted that our review is focused on case reports. There is no prospective data on the incidence of *C. difficile* enteritis. Therefore, it is not possible to know whether the apparent increase in cases is a true increase in incidence or if there is simply more reporting of the disease. However, even in the context of simply more reporting, the mortality remains high and increased recognition will still remain a priority.

The mortality of *C. difficile* enteritis has historically been considered very high as the initial 9 reports demonstrated a mortality of 66%. However, as the experience has steadily accumulated, the mortality rate appears to be decreasing. Our report of a mortality rate of 25.3% is lower than earlier reports, but remains substantial. This clinical entity is still rare and requires a high index of suspicion to initiate treatment early. As the use of antibiotics, immunosuppressive agents, and the age of the patient population will all continue to increase it is likely that *C. difficile* infections, including *C. difficile* enteritis will only continue to increase. Awareness of this process and efforts to determine the optimal treatment will continue to be necessary.

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CASE REPORT

Recurrent intestinal volvulus in midgut malrotation causing acute bowel obstruction: A case report

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Abstract

Intestinal malrotation occurs when there is a disruption in the normal embryological development of the bowel. The majority of patients present with clinical features in childhood, though rarely a first presentation can take place in adulthood. Recurrent bowel obstruction in patients with previous abdominal operation for midgut malrotation is mostly due to adhesions but very few reported cases have been due to recurrent volvulus. We present the case of a 22-year-old gentleman who had laparotomy in childhood for small bowel volvulus and then presented with acute bowel obstruction. Preoperative computerised tomography scan showed small bowel obstruction and features in keeping with midgut malrotation. Emergency laparotomy findings confirmed midgut malrotation with absent appendix, abnormal location of caecum, ascending colon and small bowel. In addition, there were small bowel volvulus and a segment of terminal ileal stricture. Limited right hemicolectomy was performed with excellent postoperative recovery. This case is presented to illustrate a rare occurrence and raise an awareness of the possibility of dreadful recurrent volvulus even several years following an initial Ladd's procedure for midgut malrotation. Therefore, one will need to exercise a high index of suspicion and this becomes very crucial in order to ensure prompt surgical intervention and thereby preventing an attendant bowel ischaemia with its associated high fatality.

Key words: Gut volvulus; Intestinal malrotation; Acute bowel obstruction; Computerised tomography scan; Laparotomy

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INTRODUCTION

Intestinal malrotation occurs when there is a disruption in the normal embryological development of the bowel rotation, elongation and fixation. Normal developmental gut rotation takes place around the superior mesenteric artery (SMA) which supplies the midgut. Disturbance of this process will lead to incomplete or non-rotation of the foetal midgut. This condition affects approximately 1 in 500 live births with the vast majority of the associated complications presenting in the first month of life when its diagnosis is made[1-3]. It has been reported that well over 90% of the affected individuals manifest by the time of their first birthday[1-5].

The diagnosis of midgut malrotation is rarely reported in adults[2,4-9]. A small proportion of the cases go undetected until adulthood when they are incidentally diagnosed in the course of radiological investigations or operative interventions for acute bowel obstruction or other unrelated conditions[3-6]. There is even a lesser

group of patients presenting later in life with intermittent non-specific acute or chronic symptoms where the diagnosis is particularly difficult to make and the condition can go on for life undetected[2,5-9].

This is a report of a young adult who previously underwent a laparotomy three weeks of age for bowel volvulus and represented later with acute small bowel obstruction due to recurrent volvulus in the setting of midgut malrotation. This unique case is reported to illustrate a rare occurrence of recurrent volvulus following Ladd's procedure for midgut malrotation. Therefore, a high index of suspicion is required for early diagnosis and prompt surgical intervention in order to prevent the risk of bowel gangrene and its associated high fatality.

CASE REPORT

A 22-year-old gentleman presented with three days history of an acute onset central abdominal pain, progressive distension and vomiting. Patient has been experiencing intermittent abdominal pain for weeks and erratic bowel habit with scanty pellet-like stool prior to presentation. He had presented 2 wk earlier and underwent an emergency left inguinal hernia repair which was misdiagnosed as the cause of the intermittent abdominal pain. There was a background history of laparotomy for "twisted" bowel when he was 3-wk-old.

Physical examination at this presentation showed dehydration, distended abdomen with tenderness around the umbilicus. There was no peritonitis and bowel sounds were high pitched and hyperactive. Rectum was empty.

Blood tests were unremarkable with normal parameters for full blood count, urea and electrolytes, liver function tests, arterial blood gases, C-reactive protein and lactate. The abdominal radiograph showed features of a small bowel obstruction. This was subsequently confirmed on the abdominal computerised tomography (CT) scan. The caecum was located to the upper left quadrant with the large bowel on the left of the abdomen and most of the small bowel loops were on the right side (Figure 1A). There was failure of progress of the duodenum to the left side of the spines and aorta (Figure 1B). There was also a reversal of the relationship between the mesenteric artery and vein (Figure 1C). A diagnosis of adhesions causing bowel obstruction in the setting of midgut malrotation was made.

The patient was adequately resuscitated and underwent an emergency laparotomy and limited right hemicolectomy with ileocolic anastomosis. The findings at operation were consistent with midgut malrotation, with small bowel on the right side and pelvis, caecum and ascending colon on the left upper abdomen and the duodenal-jejunal flexure on the right side of the ascending colon. The appendix was absent presumably removed at the previous laparotomy. There were minimal intra-abdominal adhesions. The cause of obstruction was small bowel volvulus with dilated, congested but viable bowel and a segment of chronically thickened and strictured terminal ileum presumably the site of previous ileoileal

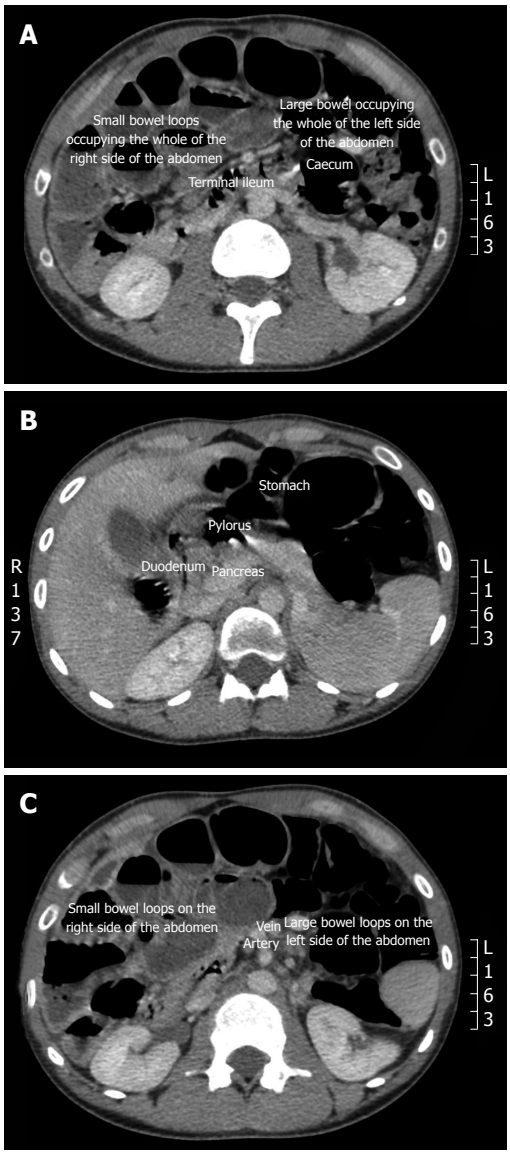

Figure 1 Computerised tomography scan. A: Abnormal location of the caecum and terminal ileum and most of the small bowel to the right side of the abdomen; B: Non-progression of the duodenum across the spines and aorta; C: Reversal of the relationship between mesenteric artery and vein.

anastomosis in childhood (Figure 2). The patient made a good recovery postoperatively and was discharged home a week after the operation. Follow up in the clinic showed no recurrence of symptoms up until 6 mo after surgery.

DISCUSSION

Midgut malrotation is a rare cause of intestinal obstruction in adult life and only few of such cases have been reported in the literature[2,4-11]. Recurrent intestinal obstruction is even rarer in adults who have been previously operated for gut malrotation and few of such cases have been reported. Features of intestinal obstruction in patients who have had previous laparotomy always raise the suspicion of adhesions as the aetiological factor. The other possible causes to consider are either postoperative

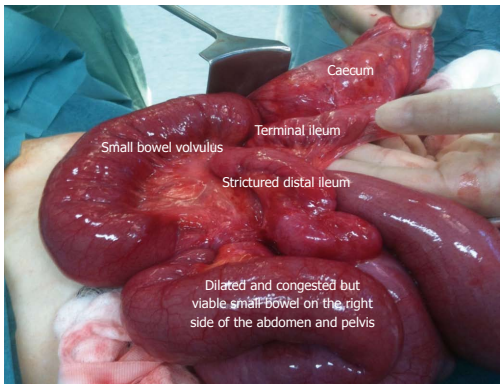

Figure 2 Intraoperative findings showing high riding left upper quadrant caecum, dilated congested but viable small bowel on the right of the abdomen. Terminal ileum entering the caecum on the right side.

midgut volvulus or internal herniation and few of the latter have been reported following laparoscopic appendicectomy, cholecystectomy and gastric banding operations[12-14]. The reason(s) for this rare phenomenon following laparoscopic operations is not well understood. Biko *et al*[15] in their retrospective review of obstructive symptoms in patients post Ladd's procedure showed that adhesive small bowel obstruction was more common than the most dreaded recurrent gut volvulus.

Midgut malrotation is rarely considered as an underlying diagnosis in adults and may present in various ways. Our patient had a history of abdominal surgery as a child for volvulus but there was no knowledge of the aetiological factor at the time of this presentation. He presented initially two weeks earlier with features of subacute obstruction and finding of a left inguinal hernia. He had a presumed diagnosis of an obstructed left inguinal hernia and underwent an emergency hernia operation. However, this treatment did not resolve his symptoms hence necessitating a representation with an acute bowel obstruction. The initial diagnosis of acute adhesive bowel obstruction was made on the background history of previous laparotomy he had as a 3-wk-old child. The clinical diagnosis of midgut malrotation in adolescents and adults is difficult because it is rarely considered on clinical grounds. Beside, many of these patients remain asymptomatic and majority of them are only discovered incidentally during investigations or laparotomy. Dietz *et al*[9] in a series of 10 adults with intestinal malrotation showed that 4 and 5 of them presented with acute and chronic bowel obstructive symptoms respectively and one patient had an acute abdomen due to appendicitis.

Recurrent volvulus as a cause of bowel obstruction following Ladd's operation for midgut malrotation is very rare both in children and adult life and very few of such cases have been reported in literature[15-21] (Table 1). Recurrent symptoms in such cases are usually considered to be due to adhesions and one may be inclined to adopt a non-operative approach. Fu *et al*[16] reported only two recurrences in a series of 12 adults treated for symptomatic malrotation with one of them requiring a reoperation and the other managed conservatively. It is

Table 1 Reported cases of recurrent intestinal volvulus following previous Ladd's procedure for midgut malrotation

Ref.	Year	No of cases	Diagnosis	Management of volvulus
Fu *et al*[16]	2007	3	2-recurrent volvulus 1-adhesive bowel obstruction	1-surgery 1-conservative treatment
Mazeh *et al*[17]	2007	1	Recurrent volvulus	Surgery
Alkan *et al*[18]	2007	1	Recurrent volvulus	Surgery
Tashjian *et al*[19]	2007	3	1-recurrent volvulus 1-adhesive bowel obstruction 1-closed loop obstruction	All had surgery
Panghaal *et al*[20]	2008	1	Recurrent volvulus	Surgery
El-Gohary *et al*[21]	2010	10	1-recurrent volvulus 9-adhesive bowel obstruction	Surgery
Biko *et al*[15]	2011	9	1-recurrent volvulus 8-adhesive bowel obstruction	Surgery
This case	2012	1	Recurrent volvulus	Surgery

believed that the increasing use of CT scan will enable one to make such diagnosis with certainty preoperatively as this has the overall advantage of detecting the abnormal location of the midgut as well as any other intra-abdominal anomalies. The finding of midgut malrotation should make one to suspect a possible diagnosis of intestinal volvulus which may require an early surgical intervention so as to prevent the most dreadful and life threatening bowel ischaemia and infarction.

The standard surgical intervention in patients with obstructive symptoms and gut malrotation is Ladd procedure which was originally described in paediatric population by Ladd[22]. This procedure consists of 4 elements including the division of Ladd's bands overlying the duodenum; widening of the narrowed root of the small bowel mesentery by mobilising the duodenum and division of the adhesions around the SMA to prevent further volvulus; counterclockwise detorsioning of the midgut volvulus if present and appendicectomy to prevent future diagnostic dilemma of an abnormally located inflamed appendix[22]. Most authors are of the opinion that Ladd's procedure is an adequate treatment for intestinal malrotation but various modifications of this operation have been reported. The full components of this procedure may not be required in the adult group to deal with the bowel obstruction[5,8,9,22]. One of the clear objectives of surgical management of midgut malrotation is to prevent recurrent volvulus and there are various techniques used to prevent such complication. This includes re-establishment of the normal gut anatomy by duodenopexy, caecopexy and suture fixation of the ascending colon to the right abdominal wall, in the retroperitoneal position[8,9]. There are reports of increasing use of laparoscopic approach to Ladd's operation in the literature[2,5,7] with excellent outcome.

It was difficult to ascertain the full details of the procedure(s) performed in our patient in childhood as the operation took place in a different hospital with una-

vailable medical records. Our best guess is that he may have had the standard Ladd's procedure at that age as the appendix and the classical Ladd's bands were absent at laparotomy. We presumed he may have also had a bowel resection for ischaemic bowel resulting from volvulus as evident by strictured distal ileum. There was no evidence that a caecopexy and/or fixation of the ascending colon to the right abdominal wall were performed. This patient had a recurrent small bowel volvulus and chronic stricture of the distal ileum causing acute bowel obstruction. Recurrent small bowel volvulus also may have been encouraged by the minimal adhesion formation following the laparotomy he had in childhood. He then underwent a limited right hemicolectomy and ileocolic anastomosis with an uneventful postoperative recovery.

In conclusion, midgut malrotation is rare in adult population but an important factor contributing to bowel obstruction in that group. The most dreadful and life threatening complication of intestinal malrotation both in children and adults is gut volvulus with possible ischaemic changes and associated high mortality. However, recurrent volvulus resulting from intestinal malrotation is uncommon after treatment with Ladd's procedure and only very few of such cases have been reported in the literature. Majority of recurrent bowel obstructive symptoms are due to adhesions from previous laparotomy. Therefore, one will need to exercise a high index of suspicion and an awareness of the possibility of recurrent volvulus even several years following an initial Ladd's procedure. This is crucial to ensure prompt surgical intervention in order to prevent attendant bowel ischaemia and a high fatality rate.

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CASE REPORT

Perforated duodenal diverticulum, a rare complication of a common pathology: A seven-patient case series

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Abstract

Duodenal diverticula (DD) are frequently encountered and are usually asymptomatic, with an incidence at autopsy of 22%. Perforation of DD is a rare complication (around 160 cases reported) with potentially dramatic consequences. However, little evidence regarding its treatment is available in the literature. The aim of this study was to review our experience of perforated DD, with a focus on surgical management. Between January 2001 and June 2011, all perforated DD were retrospectively reviewed at a single centre. Seven cases (5 women and 2 men; median age: 72.4 years old, rang: 48-91 years) were found. The median American Society of Anesthesiologists' score in this population was 3 (range: 3-4). The perforation was located in the second portion of duodenum (D2) in six patients and in the third portion (D3) in one patient. Six of these patients were treated surgically: five patients underwent DD resection with direct closure and one was treated by surgical drainage and laparostomy. One patient was treated conservatively. One patient died and one patient presented a leak that was successfully treated conservatively. The median hospital stay was 21.1 d (range: 15-30 d). Perforated DD is an uncommon presentation of a common pathology. Diverticular excision with direct closure seems to offer the best chance of survival and was associated with a low morbidity, even in fragile patients.

Key words: Duodenal perforation; Duodenum; Duodenal diverticulum; Surgical management

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INTRODUCTION

Duodenal diverticulum (DD) is common, with a reported prevalence of 22% at autopsy[1]. A similar incidence has been reported during endoscopicretrograde cholangiopancreatography (ERCP)[2,3]. The most frequent location is the second and third portions of the duodenum (D2-D3)[4].

Although, DD is rarely symptomatic and only 5% of patients present with symptoms due to the compression of neighbouring organs, cholestasis (in cases of periampullary diverticulum), haemorrhage, inflammation or perforation[4]. One hundred and sixty-two cases of perforated DD have been reported in the literature[5-8]. The supposed cause of perforation in 57% of cases is ischaemic processes due to distension related to food retention in the diverticula[9]. Other reported causes are ulcerations, enterocolitihs, blunt abdominal trauma and perforation due to the ERCP procedure[5,9-12].

However, diagnosis remains a challenge, with many potential differential diagnoses, including perforated duodenal ulcer. Helical computed tomography (CT) has emerged as a useful diagnostic tool and most centers now use CT routinely to confirm the diagnosis. Yet surgical exploration in unstable and septic patients is still considered mandatory, especially if the diagnosis is not clear[13,14].

The appropriate surgical management remains under debate. A surgical approach is usually advocated. However, some groups[5,14,15] have reported using a more conservative approach, and demonstrated that non-operative management is a safe and practical alternative to surgery in selected patients. The aim of this study was to review our 11-year experience with perforated DD at a single centre with a special focus on surgical management.

CASE REPORT

Between January 2001 and June 2011, all perforated DD were retrospectively reviewed at a single center. Only non-traumatic cases were included. Iatrogenic perforations (*e.g.* during endoscopy) were excluded from the study. For all the analyzed patients a CT-scan was performed at the admission. Seven cases (five women and two men; median age: 72.4 years old, range: 48-91 years) were found. The median American Society of Anesthesiologists' (ASA) score in this population was 3 (range: 3-4). Six cases were treated surgically and one with a naso-gastric tube and antibiotics (Taylor's approach for upper digestive perforation).

We report herein a series of seven cases of spontaneous DD perforation (Table 1). The clinical presentation was abdominal pain in six cases and bilateral basithoracic pain in one case. Of note, only one patient was admitted with severe septic shock. All the patients presented elevated leucocyte count and C-reactive protein. Diagnosis was performed by CT scans in 42.8% (3 out of 7) of the cases (Figure 1). Diagnosis of the other cases was made intra-operatively. Six patients underwent surgery (85.7%). Of these, five cases had an ASA score of 3 and one an ASA score of 4. The perforated DD was located at the D2 level in six cases (85.7%) (Figure 2A and B) and at the D3 level in one case. All the patients received endovenous antibiotics therapy for 10 d (ceftriaxone and metronidazole). In five cases surgical treatment (Table 2) involved resection of the DD and direct duodenal suture. A nutritional jejunostomy was also performed in three cases.

A transpapillary bilio-duodenal drain was used in the patient with a D3 perforation due to the proximity of Vater's papilla. Only one patient presented with septic shock, and at laparotomy, a damage control approach was chosen (drainage and laparostomy) given the instability of the patient, and the important bowel edema that did not allowed to close the abdominal wall.

The non-surgically treated case was treated with antibiotics and a naso-gastric tube because presented with only bilateral basithoracic pain, and a diagnosis of a cover DD perforation was performed on CT scan. An image control (Upper passage opacification Rx with gastrographine®) was performed after 7 d after the oral intake. In terms of outcome, a suture leak occurred in one patient at post-operative day-5; this leak did not require surgery and was conservatively treated with success (nasogastric tube and endovenous antibiotics). One patient died (mortality: 14.3%) after a cardiac complication-cardiac failure. This patient was admitted in a critical condition with severe septic shock and the preferred surgical treatment was damage control surgery. Oral intake was restored for all the patients on average seven days after the operation.

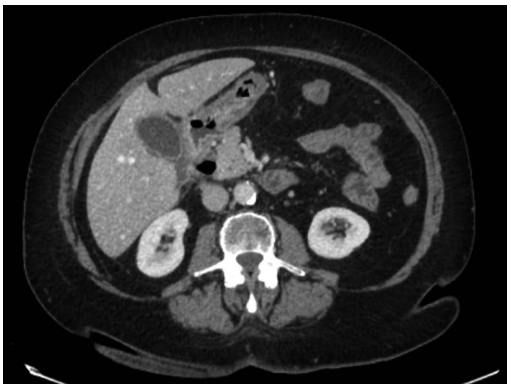

Figure 1 Computed tomography scan of case 5 showing a perforated duodenal diverticula.

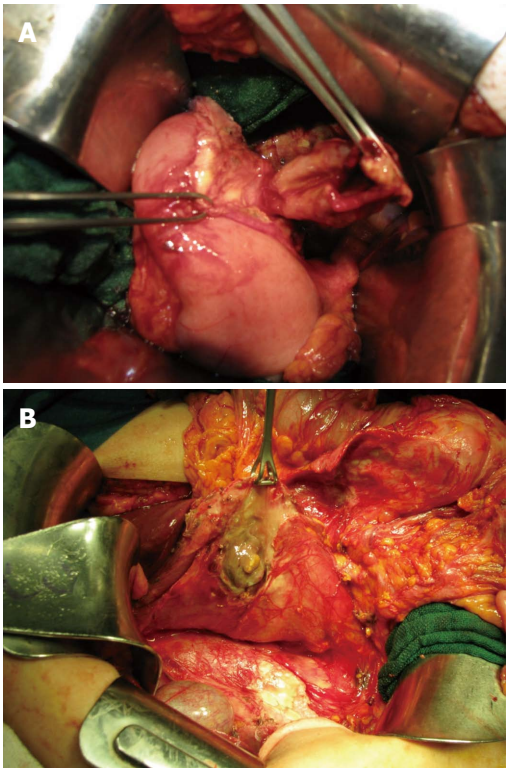

Figure 2 Intraoperative image of case 6 (A) and 7 (B) after a Kocher manoeuvre. A: A perforated duodenal diverticulum was found after performing a Kocher manoeuvre.

Table 1 Results of population characteristics and clinical presentation

Case	Age (yr)	ASA	Symptoms	Shock	Diagnosis	Perforation localization	Follow-up
1	91	3	RUQ acute pain, nausea and vomiting	No	Surgery	D2	Alive at present after 12 yr
2	68	4	Epigastria acute pain, septic shock	Yes	Surgery	D2	Died
3	83	3	RUQ acute pain, nausea and vomiting	No	CT scan	D2	Lost after 5 yr of follow-up
4	78	3	Epigastria acute pain, nausea and vomiting	No	Surgery	D2	Lost after 5 yr of follow-up
5	76	3	Bilateral basithoracic pain	No	CT scan	D2	Lost after 9 yr of follow-up
6	65	3	Epigastria and RUQ acute pain, nausea and vomiting	No	Surgery	D2	Alive after 1 yr of follow-up
7	48	3	RUQ pain irradiating to the back	No	CT scan	D3	Alive after 2 yr of follow-up

ASA: American Society of Anesthesiologists' score; CT: Computed tomography; RUQ: Right upperquadrant.

Table 2 Results of treatment

Case	Localization	Treatment	Morbidity-mortality	Hospital stay (d)
1	D2	Excision, direct duodenal suture and nutritional jejunostomy		26
2	D2	Drain and laparostomy	Died (cardiac comorbidity)	1
3	D2	Excision, direct duodenal suture and nutritional jejunostomy		18
4	D2	Excision and direct duodenal suture	Conservatively treated suture leak on POD day 5	30
5	D2	Gastric tube and antibiotics therapy		16
6	D2	Excision and direct duodenal suture		15
7	D3	Excision, direct duodenal suture, nutritional jejunostomy and bilio-duodenal drain		22

POD: Post-operative day.

The median hospital stay was 21.1 d (range: 15-30 d). No long-term complications were detected (median follow-up of 63 mo).

DISCUSSION

Perforation is an uncommon complication of DD and also one of the most serious[16]. In this paper, we present one of the largest series (seven patients) published to date. The overall outcomes are encouraging, with a low mortality rate and acceptable morbidity. In fact, the most recent review reported rates of morbidity and mortality of 33% and 8%-34% respectively[5]. Our results compare favorably with these data.

Although well known as a possible complication of DD, few reports of perforation can be found in the literature. In fact, Thorson *et al*[5] recently reviewed the available literature and found only 162 cases. The leitmotif remains a difficult preoperative diagnosis. Indeed, the symptoms are often non specific and vague. Yet, one of the most frequent patterns of presentation seems to be right upper abdominal pain associated with nausea and vomiting, as found in our series. Moreover, the differential diagnosis is wide and can be confusing. The most difficult differential diagnosis is a perforated duodenal ulcer, which can show the same pattern in the clinic and on CT scan. Since the wide diffusion of CT, the preoperative diagnosis of perforated DD has increased, and this is currently the best imaging modality available. Although the final diagnosis is often made in the operating room, CT is undeniably helpful and can sometimes differentiate perforated DD from a perforated duodenal ulcer. In addition, perforation may cause retroperitoneal abscesses[16,17]. However, we did not find extended abscesses of the retroperitoneal area in our case series, probably thanks to the early performance of CT scans (maximum delay of 6 h). Therefore, CT is usually the first diagnostic procedure to be performed even though its specificity is below 100%.

In terms of the location of the perforation, the second and third duodenal portions are involved in most cases[5,14], as observed in our series. As a corollary to its rarity, the management of perforated DD remains subject to debate. No surgical guidelines have been published for perforated DD, as only case reports and small series (up to 8 patients) have been reported in the literature[5,16,17]. In general, the surgical approach was considered the treatment of choice. However, several recent cases were treated with bowel rest, a naso-gastric tube and antibiotics, with encouraging results in selected patients[5,15]. If a surgical intervention is highly indicated for unstable patients, the conservative approach deserves consideration since its use appears to be attractive in more stable patients. This option may be particularly useful in a patient of advanced age or in a patient with multiple medical comorbidities who is a prohibitive operative risk[14]. On the other hand, in a patient with mild abdominal symptoms and no evidence of impending sepsis, non-operative management may suffice[14]. Taylor's approach is widely and successfully used for upper digestive perforation and perforated DD could be treated using the same technique. In the present series, the only patient who underwent conservative treatment was selected for such treatment because he presented with mild symptoms and

a clear diagnosis was possible preoperatively. Therefore, in selected patients with a precise CT-scan diagnosis and good clinical condition, conservative treatment can be considered.

In terms of surgical approach, several technical options are available, ranging from local excision to the Whipple procedure, depending on the location of the DD and the inflammatory status[18]. Moreover, laparoscopic diverticulectomy has also been reported to give good results[19]. In their recent review, Thorson *et al*[5] found diverticulectomy to be the most common treatment (49%). In our series, five patients were surgically treated with an almost identical procedure: excision of the DD and direct suture, with a drain placed in the resection area.

Nutritional jejunostomy was performed in three of the five cases and a naso-gastric tube was left in place for at least 7 d. Of note, in one case, a transcystic biliary drain was necessary due to the location of the perforated periampullary DD. This was introduced in order to prevent biliary stenosis in relation to the duodenal suture. Perforation of a DD is a very serious complication and may be fatal. Early CT scan is recommended for diagnosis in suspected cases. Our therapeutic strategy for a perforated DD is resection of the diverticula and direct suture when possible, associated with drainage and placement of a nutritional jejunostomy. A conservative approach is attractive in selected patients.

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CASE REPORT

Liver blood supply after a modified Appleby procedure in classical and aberrant arterial anatomy

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Abstract

Reported here are two cases of a modified Appleby operation for borderline resectable ductal adenocarcinoma of the pancreatic body, in one of which a R0 distal resection was attended to by excision, not only of the celiac axis, but also of the common and left hepatic arteries in the presence of arterial anatomic variation Michels, type Ⅷb. The possibility and avenues of the maintenance of the blood supply to the left hepatic lobe after surgical aggression of this kind are demonstrated employing computed tomography (CT) and 3-D CT angiography. Furthermore, both cases highlight all important worrisome aspects of pancreatic cancer resectability prediction.

Key words: Cancer; Pancreas; Management; Pancreatectomy; Distal pancreatectomy; Vascular invasion; Computed tomography; Blood supply

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INTRODUCTION

Unlike pancreatic head cancer, pancreatic neck or body cancer is commonly diagnosed at the locally advanced stage after the celiac axis branches, among them the common hepatic artery (CHA), having already been involved by the neoplastic process. In terms of current recommendations, celiac axis (CA) and superior mesenteric artery (SMA) invasion presents a contraindication to pancreatectomy for ductal adenocarcinoma[1,2]. However, in certain instances, excision of the CA together with its branches allows a curative procedure to be performed and obviates arterial reconstruction, incurring a high risk of serious complications. In 1953, while carrying out a distal pancreatectomy along with a gastrectomy for locally advanced gastric carcinoma, Appleby pioneered taking advantage of the chance of the re-establishment of the blood supply to the liver after CA and CHA resection by way of

the constantly existent pancreaticoduodenal arcade from the SMA basin[3]. In 1976, Nimura applied Appleby's technique to treat locally advanced pancreatic body-tail carcinoma[4] and in 1991, Nagino *et al*[5] and Hishinuma *et al*[6] succeeded in preserving the stomach in the absence of its invasion from pancreatic tumor by means of sparing the gastroduodenal and right gastroepiploic arteries (GDA and RGEA), thereby modifying Appleby's operation. By the year 2003, two dozen such operative interventions had been accomplished[5,7-15], at most, but refinements in diagnosis and surgical technique have progressively promoted their growing in number[5,11,15-24]. The modified Appleby procedure case reviews in the literature tend to say nothing about the pattern of the celiac-mesenteric arterial vasculature encountered, in as much as, when dealing with variant arteries and the classical arterial architecture, this sort of surgery can be successfully performed without vascular reconstruction. We give an account of two cases of the modified Appleby operation for pancreatic body borderline resectable cancer, in one of which (as yet not described) a R0 distal resection was accompanied by excision, not only of the CA and the CHA, but left gastric arteries as well in the context of aberrant arteries Michels, type VIIIb.

CASE REPORT

Case 1

On the 12th October, 2011, a 64-year-old woman presented with complaints of constant severe upper abdominal pain relievable with Tramadol administration (four times daily), fatigue and a weight loss of 4 kg in a month. According to the past history, back pain had started 5 mo earlier and had been extending into the lower abdomen. The patient had endured the pain for quite a long time and it was not until October that she sought medical attention and was examined. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed cancer of the pancreatic body and tail with affected CA branches. No evidence of dissemination was observed. Performance status was Eastern Cooperative Oncology Group score of 2, Karnofsky index 70%. On admission, the patient was in a moderately grave condition due to the pain experienced and was asthenic with skin pallor. Pulse was 72/min, regular and good volume. Blood pressure was 110/70 mmHg. Breath sounds were vesicular. The abdomen was soft with tenderness in the epigastrium through the thinned anterior wall of which a solid mass was palpable.

Instrumentally derived findings: Abdominal ultrasound (US) showed evidence of pancreatic body tumor extending to the CA, CHA, splenic artery (SA), superior mesenteric vein (SMV) and confluence of the portal vein (PV). The GDA showed close tumor contact over 1 cm, suspicious for ingrowth. Extrinsic compression of the SMV, PV confluence and CHA was documented.

The CT showed that the liver structure appeared unchanged with no focal lesions. A space occupying mass 25 mm in diameter was visualized in the neck and body of the pancreas. Pancreatic hypertension and atrophy of the pancreas' tail were noted. The duct of Wirsung was shown to be dilated up to 7 mm in the tail portion with a blunt cutoff (interrupted duct sign) at the level of the body of the gland, where tiny 2-3 mm cystic entities were discernable. The SMA was apparently traveling just along the left contour of the growth. The GDA was found to be circumferentially encased by the tumor over a length of 1 cm. An accessory renal artery was visible on the right. The lymph nodes in the pancreatic head and paraaortic regions and along the course of the SMA measured up to 17, 10 and 7-9 mm respectively. The conclusion was adenocarcinoma of the pancreatic neck and body with involvement of the CA, CHA and, probably, GDA and confluence of the PV (Figure 1).

A perivaterian diverticulum, simple left kidney cysts, a splenic cyst, lung emphysema and aortal, coronary and iliac atherosclerosis were identified, classical celiaco-mesenterial arterial anatomy (Michels, type 1) (Figure 2).

Esophagogastroduodenoscopy (EGDS) showed focal gastritis and Paquet's stage 1 upper third esophageal varices.

Endoscopic ultrasound (EUS) showed a tumor of the pancreatic body, presumably adenocarcinoma, with neoplastic process spreading to the CHA, distal third of the CA and confluence of the PV. The new growth was seen to be intimately in contact with the left wall of the GDA over a run of 1 cm. Regional lymph node enlargement, most likely related to their being metastatic, was defined (Figure 3).

Abdominal MRI showed a tumor of the neck-body of the pancreas, atrophy of the parenchyma of the pancreas' tail and pancreatic hypertension in the tail portion of the gland. Infiltration of the retroperitoneal fat with extension encircling the CA, SMA and PV confluence was depicted.

Preoperative concept was of a 64-year-old female diagnosed with a T4NxM0 ductal adenocarcinoma of the pancreatic body with invasion of the CA branches and PV and no evidence for distant metastases. She was deemed to have borderline resectable disease because of suspected tumor encroachment on the GDA. Distal pancreatectomy with resection of the CA and PV was planned. The final extent of the procedure was intended to be decided after intraoperative exploration.

The operation was carried out on the 5th December, 2012. At surgery, no distant metastases were found. A whitish solid tumor taking up the whole of the pancreatic body and growing into the CA trifurcation and CHA with adherence to the left 180° of the uninvolved GDA was discovered. On duplex ultrasound with a clamp across the CHA there was a sufficient arterial blood flow in the liver and the hepatic arterial pulsation was present as before. The lesion was judged resectable. A corpo-caudal pancreatectomy with resection of the CA and its branches was completed (Figure 4). At that, the RGEA was not sacrificed, which provided the gastric blood sup-

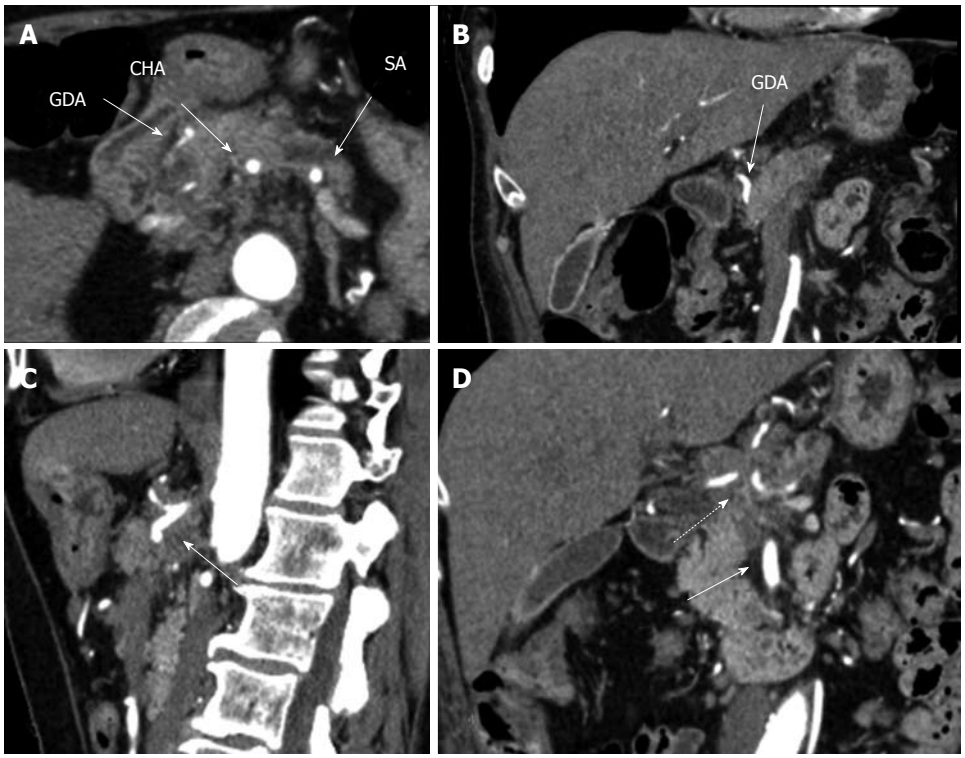

Figure 1 Preoperative computed tomography. Arterial phase. A: Axial image. The common hepatic (CHA) and splenic (SA) arteries present circumferential adjacency to pancreatic body ductal adenocarcinoma. The gastroduodenal artery (GDA) appears to be completely encircled by tumor; B: Frontal view. Computed tomography (CT) evidences circumferential infiltration of GDA; C: The celiac artery (CA) along with CHA springing from it, are completely circumscribed by tumor (arrow); D. All three CA branches (dashed arrow) show circumferential tumor contact. The superior mesenteric artery is unaffected (arrow).

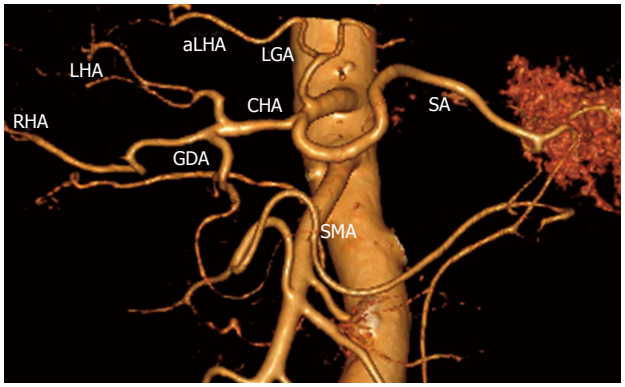

Figure 2 Three-dimensional computed tomography-angiography before surgery. Classical arterial architecture (Michels, type I). Tumor-induced common hepatic (CHA) stenosis is noted. Anatomical variation of type I is observed: CHA trifurcation in the absence of proper hepatic artery. RHA: Right hepatic artery; LHA: Left hepatic artery; GDA: Gastroduodenal artery; LGA: Left gastric artery; SMA: Superior mesenteric artery; SA: Splenic artery; aLHA: Accessory left hepatic artery.

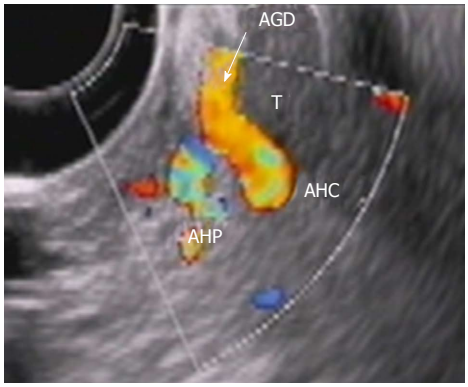

Figure 3 Endoscopic ultrasound. Tumor (T) abutment to gastroduodenal artery (AGD and arrow) without its encasement. HAC: Common hepatic, HAP: Proper hepatic artery.

ply, with the stomach and liver's color remaining unaltered throughout the operative time period.

Post surgery, the patient developed a retroperitoneal pancreatic fluid collection in the projection of the cut edge of the gland with an amylase of 60 000 (pancreatic fistula Class B), which was drained on postoperative day 5. Nine days after the surgery, EGDS recognized areas of gastric mucosa ischemia of mixed (portal and arterial) genesis, ischemic gastropathy. Recurrent hydrothorax was repeatedly addressed with pleural tapping (G3, Dindo-Clavien). After management with antibiotics, antisecretory and anti-ulcer therapy and treatment for diabetes mellitus, the patient's condition stabilized, body temperature returned to normal and complete pain abolition was achieved. The glycemic profile was stable with a blood sugar level of 7-9 mmol/L under insulin therapy and the patient was discharged to receive adjuvant gemcitabine chemotherapy.

Microscopic examination and pathological diagnosis showed a moderately-differentiated pancreatic body-tail adenocarcinoma (pT3N1b, G2) with CA branches and

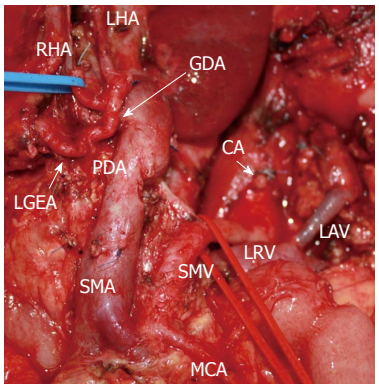

Figure 4 Photograph. View of operating field after distal pancreatectomy with excision of celiac artery (CA) and its branches. Liver and stomach are fed with blood from the superior mesenteric artery (SMA) *via* pancreaticoduodenal arcade (PDA) and, thereafter, through the gastroduodenal artery (GDA). Full-blown right gastro-epiploic artery is found. Superior mesenteric vein (SMV) was resected at the site of confluence with splenic vein. LAV: Left adrenal vein; MCA: Medial colic; RHA: Right hepatic; LHA: Left hepatic arteries; LRV: Left renal vein; LGEA: Left gastro-epiploic artery.

PV involvement. The patient had a R1 distal resection owing to the vascular specimen margin from the sites contacting with the SMV and GDA (Figure 5). The 6 month follow-up CT yielded no evidence for disease recurrence and CT angiography displayed an ample blood flow in the liver and stomach (Figure 6).

Case 2

In May, 2010, a 65-year-old woman consulted a doctor about pain in her right upper abdominal quadrant. On examination, a diagnosis of chronic pancreatitis was made and she was given conservative therapy which was of no benefit. In November 2010, abdominal CT invited by the pain worsening was undertaken and revealed a mass in the pancreatic body.

She entered the Moscow Herzen Institute of Oncology. CT detected an up to 5.6 cm pancreatic body tumor spreading to the CA branches and superior mesenteric arteries. On fine-needle aspiration biopsy, a well-differentiated adenocarcinoma was identified. The neoplasm was considered not to be amenable to resection. 8 courses of a palliative combination chemotherapeutic regimen consisting of 200 mg of eloxatin + 3600 mg of gemzar were instituted.

In July, 2011, the follow-up CT showed no drastic evolution in the disease course with persistent infiltration of the CA, its branches, superior mesenteric and splenic veins and no distant metastases (Figure 7). On CT angiography, variant arterial architecture Michels, type ⅧIb, with a replaced right hepatic artery (rRHA) coming from the SMA and an accessory left hepatic artery (LHA) given off by the left gastric artery (LGA) was determined (Figure 8).

Reasoning from the absence of interval neoplastic progression, we opted for an attempt at a radical procedure. Preoperative diagnosis was a ductal pancreatic body adenocarcinoma, cT4NxM0. Upon abdominal inspection, a pancreatic body solid whitish knobby tumor, up to 3-4 cm in diameter, involving the splenic and CHAs, proximal segment of the CA and LHA with peritumoral fibrosis and contraction in the center was disclosed. On table US demonstrated the blood flow in the left hepatic lobe to be sustained subsequent to briefly clamping the LHA, which encouraged us to undertake a subtotal pancreatectomy with CA excision and resection of the common and left hepatic arteries. As we did so, the GDA was also resected and ligated, that is to say, the pancreaticoduodenal arcade was unlocked (Figure 9). She was discharged on postoperative day 12 after uneventful postoperative recovery to be continued on neoadjuvant gemcitabine chemotherapy.

Conclusion on histological examination was a well-differentiated adenocarcinoma of the pancreatic body, pT2N0M0, G1. Tumor structures, measuring up to 1.2 cm in their greatest dimension, were found throughout an immense fibrotic bulk harboring remnants of pancreatic tissue composed of ductules and atrophic islets (Figure 10). The shortest margin-to-margin distance between the tumor and the specimen was 3 mm and a R0 resection was achieved. No features of post chemotherapeutic changes were identified.

The 12-mo follow-up CT evidenced no disease recurrence, the patient feels well and goes on working as a doctor. There is an adequate arterial blood supply to the liver and stomach on CT angiography. Sufficient arterial nutrition of the left hepatic lobe is afforded by the engagement of the interlobar artery having an extraparenchymal hilar course (Figures 11 and 12).

DISCUSSION

The observations under review might be dually instructive. In the first place, they illustrate the feasibility of the maintenance of the blood flow in the left hepatic lobe after the modified Appleby operation with CHA and LHA resection in the presence of the RHA departing from the SMA. Secondly, both cases pinpoint key bothersome aspects of preoperative determination of pancreatic cancer resectability.

The modified Appleby technique has rightly gained acceptance as an effective approach to the management of pancreatic body cancer in cases of CHA involvement by tumor. We have performed 11 modified Appleby procedures, at 10 of which the classical arterial anatomy, identical to that encountered in Case 1, was found. An aberrant arterial pattern was present only in Case 2. Theoretically, when dealing with most variants in the celiac-mesenteric arterial architecture, this operation is quite safe with regard to the re-establishment of the arterial blood supply to the liver and stomach. Yet, cases with the replaced LHA (Michels, types Ⅳ and ⅧIa) or the CHA (Michels, type X) arising from the LGA[25], as well as the described above situation, when the tumor involvement requires resection of either of the hepatic arteries (more often the LHA), present a real challenge secondary to CA excision. With all the patterns men-

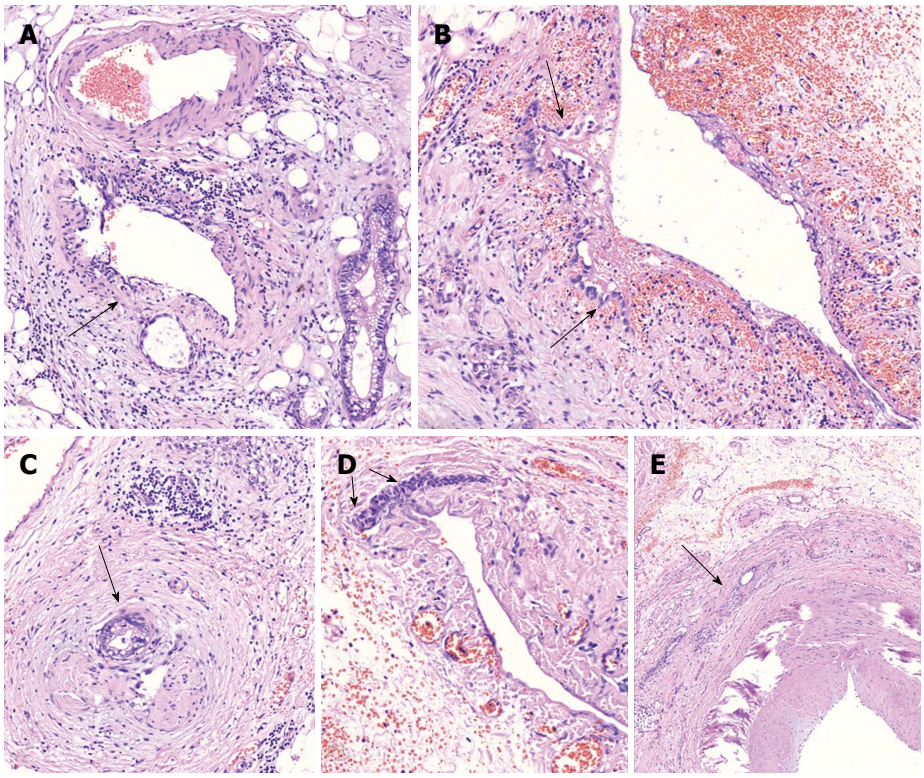

Figure 5 On microscopic examination. A: Perivascular tumor growth (complexes of malignant cells in adventitia of small artery of peripancreatic fat (arrow), HE, × 200; B: Tumor incursion into vein wall (arrow), HE, x 200; C. invasion of the nerve by the tumor (arrow), HE, x 50; D: Vein wall involvement (complexes of malignant cells in media of 2-mm diameter vein (arrows), HE, × 50; E: Tumor complexes in the common hepatic artery adventitia (arrow), HE, × 50.

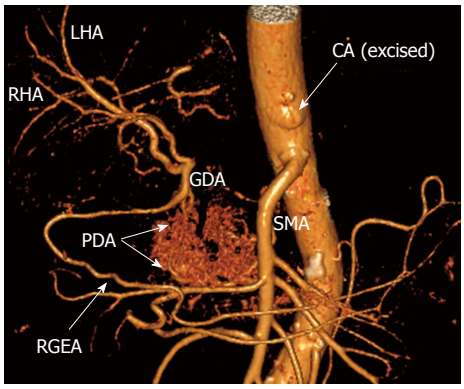

Figure 6 Three-dimensional computed tomography-angiography following distal pancreatectomy with excision of celiac artery and its branches. Blood supply to liver and stomach is delivered from superior mesenteric artery (SMA) *via* pancreaticoduodenal arcade (PDA) and then through gastroduodenal artery (GDA). There is robust right gastro-epiploic artery (RGEA) appearing in its entirety. RHA: Right hepatic artery; LHA: Left hepatic artery; CA: Celiac axis; GDA: Gastroduodenal artery.

tioned above, except variation Michels, type X, in the instance of which Appleby's operation is not feasible without recourse to vascular repair, it is vital to know the sources of the collateral blood supply to the liver to avoid unnecessary arterioplasty.

Investigations of collateral circulation during temporary balloon occlusion of either of the hepatic arteries have first of all been spurred by both the needs of hepatopancreatobiliary surgery and advancements in interventional radiology for hepatopancreatobiliary diseases. The development of collateral blood flow with one of the hepatic arteries being occluded was shown to be a possibility and to depend heavily on the site of vascular obstruction[26,27]. Hepatic interlobar arterial collaterals were exhaustively analyzed in autopsied specimens and corrosion casts[26-30], as well as with radiological studies[31-37] called into being by the evolution of hepatic surgery, transplantation, interventional radiology, endovascular chemotherapy and embolization. Angiography demonstrated the interlobar branch-relayed collateral blood flow between the hepatic arteries[31-37] to be readily noted at the occlusion of either of the hepatic arteries[32,33,37], which was demonstrated by computerized tomographic angiography in our Case 2 (Figure 11). The interlobar arterial collaterals may be responsible for the poor distribution of a chemotherapeutic agent at its selective intraarterial infusion[32]. Injuries to these collateral pathways, participating in the blood supply of the hilar bile ducts, may induce ischemia of the biliary tract after liver resections and biliary surgery[28,29]. The majority of investigators are in agreement that the interlobar collateral is extraparenchymal, passes cranial to the bifurcation of the PVs in the hepatic hilum in close proximity to the bile ducts[32,33,37-40] and makes the crucial contribution of the blood supply to the biliary tract, as well as one of the hepatic lobes in the event of liver major route interruption[29,36,37,41]. So far it has not been clear whether there are transparenchymal branches to connect the hepatic lobes[31,33,36,42].

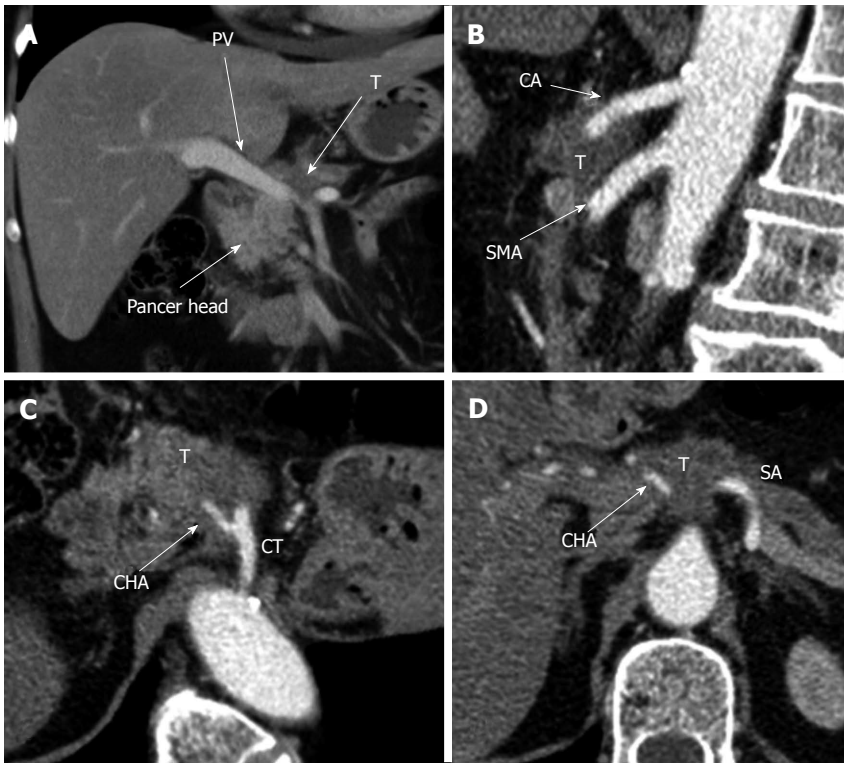

Figure 7 Computed tomography prior to operation. A: Axial view. Venous phase. Hypovascular tumor of pancreatic neck (T) is shown to abut portal vein (PV) trunk. Pancreatic head is demonstrated to be intact; B: Sagittal view. Arterial phase. Circumferential encasement of celiac artery (CA) by hypovascular tumor of pancreatic body and the latter's adherence to anterior aspect of superior mesenteric artery (SMA); C, D: Axial image. Arterial phase. Circumferential contiguity of tumor to CA along with common hepatic (CHA) and splenic (SA), both arising from the former, is visualized. CT: Celiac trunk.

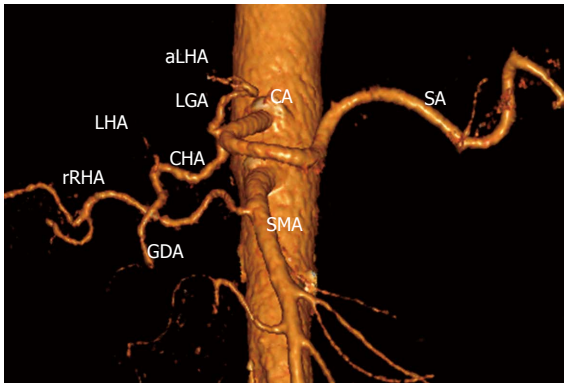

Figure 8 Three-dimensional computed tomography angiography before surgery. Variant arterial anatomy: replaced right hepatic artery (rRHA) originating from superior mesenteric artery (SMA), accessory left hepatic (aLHA) - from left gastric (LGA) (Michels, type Ⅷb). CA: Celiac artery; LHA: Left hepatic artery; SA: Splenic artery; GDA: Gastroduodenal artery; CHA: Common hepatic.

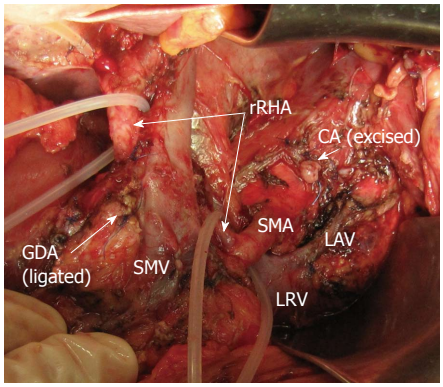

Figure 9 Photograph. View of operating field after distal pancreatectomy with excision of celiac artery (CA), left gastric, common hepatic and left hepatic arteries. Superior mesenteric artery (SMA)-derived blood feeding of right hepatic lobe carried *via* the replaced right hepatic artery (rRHA). Blood supply to stomach is routed from SMA *via* pancreaticoduodenal arcades and then through gastroduodenal artery (GDA) with the latter's proximal segment being resected and ligated. CA: Celiac artery; LAV: Left adrenal vein; LRV: Left renal vein; SMV: Superior mesenteric vein.

Case 2 demonstrates that LHA excision at a distal pancreatectomy with resection of CA and its branches is permissible by virtue of the fact that an arterial blood supply keeps coming to the left hepatic lobe thanks to the availability of the interlobar collateral. In this case, the arterial blood supply to the left hepatic lobe and segment 1 kept being furnished through the interlobar collateral, originating from the rRHA and running in the liver hilum (Figure 12). The evidence for the functioning of the interlobar collateral emerges quite frequently on angiography at chemoembolization of the hepatic arteries or for control of external hemorrhage and/or hemobilia (Figures 13 and 14).

Pancreatic cancer remains one of the most aggressive neoplastic processes and the ways of its management are in the development stage[43,44]. Despite impressive progress attained in the diagnosis and treatment of otherwise sited malignances, the resectability and 5 year

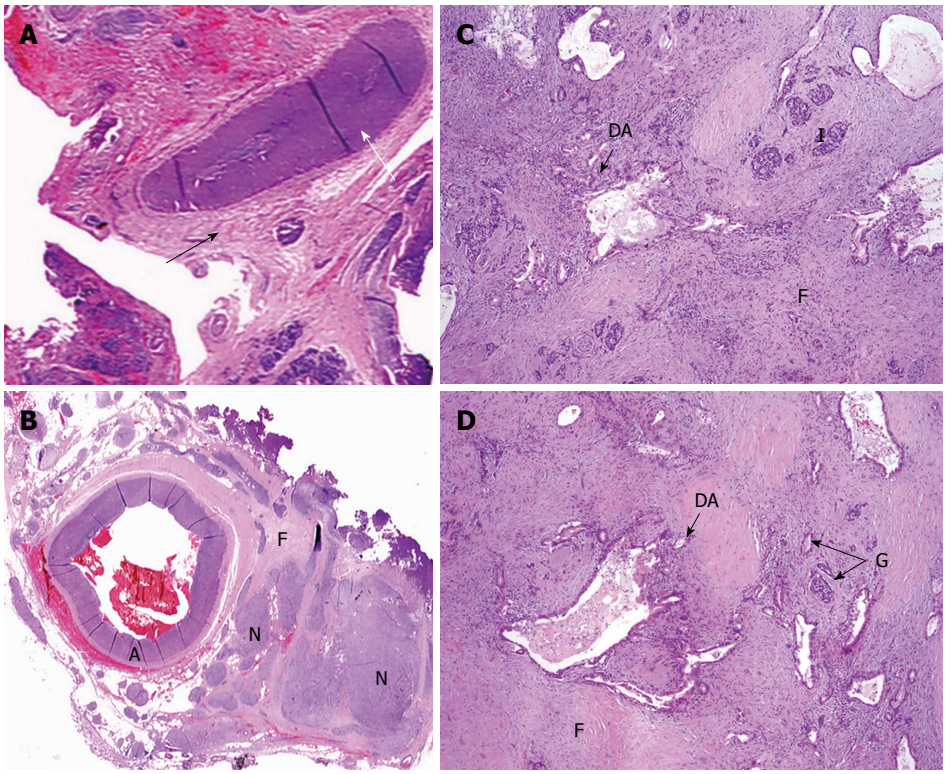

Figure 10 Under microscope. A: Common hepatic (CHA) section obtained from close to the point of its transection (white arrow) amid fibrotic zone (black arrow) along pancreas margin. No evidence of tumor growth (× 5); B: Celiac plexus and trunk area of diffuse fibrosis (F) (× 5); C: Pancreatic tissue with apparent diffuse fibrosis (F), groups of islets left (I) and that of glandular formations of ductal adenocarcinoma of pancreas (DA) (× 50); D: Structures of DA throughout fibrotic tissue (F) containing remnants of pancreatic tissue (atrophic islets and ductules) (HE, × 5). A: Artery; N: Nerve plexus with large ganglion (G).

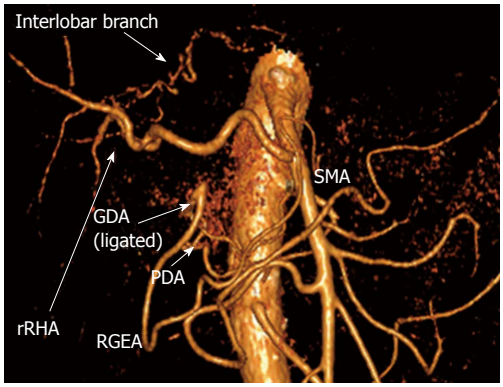

Figure 11 Three-dimensional computed tomography angiography subsequent to distal pancreatectomy with excision of celiac artery, left gastric, common hepatic and left hepatic arteries. Blood supply to right hepatic lobe is provided by superior mesenteric artery (SMA) through the replaced right hepatic artery (rRHA) and that to left hepatic lobe - *via* interlobar collateral anastomosing with rRHA. Stomach is supplied from SMA *via* pancreaticoduodenal artery (PDA) and, thereafter, through gastroduodenal artery (GDA) and right gastro-epiploic artery (RGEA).

survival rates for pancreatic cancer are still very poor with those for pancreatic body and tail of 10% and 10%[45-47] in North America and the Western Europe and of 34% and 18% in Japan respectively[48]. Compared to pancreatic head cancer, typically manifesting itself in jaundice, and for lack of specific symptoms, carcinoma of the pancreatic body is generally recognized at more advanced stages, presenting with rather a sizable tumor, distant metastases and back pain.

The pancreatic body is a fairly modest size across and tumor advancement to the retroperitoneal organs, nerve plexuses, SA, CHA and CA does not take long, which potentially causes the neoplasm to be interpreted as unresectable in compliance with the adopted Jakarta International Community Center classification[1]. Just the same, not only does radical removal of pancreatic body carcinoma with the use of Appleby's technique improve patient life quality, it also significantly prolongs survival, which was attested to, not only in cases of arterial resection necessitating no reconstruction[5,11,13-21], but in those resorting to repair as well[16,23-25].

Completeness (radicality) of resection is one of the dominant independent prognostic factors for pancreatic cancer[46-53]. A curative resection of tumor is the only means of treatment that will hold out a hope of long-term survival for pancreatic cancer patients, although only 10%-15% of them would be eligible for a radical procedure[54]. Preoperative resectability estimation is an outstanding problem of great concern resulting primarily from the intricacies of the involvement evaluation of the major peripancreatic arteries in so far as their actual invasion is regarded as a contraindication to a curative procedure[55-57]. Since CT is invariably rated the gold standard for the diagnosis of pancreatic cancer, it is of critical importance that patients with a resectable tumor

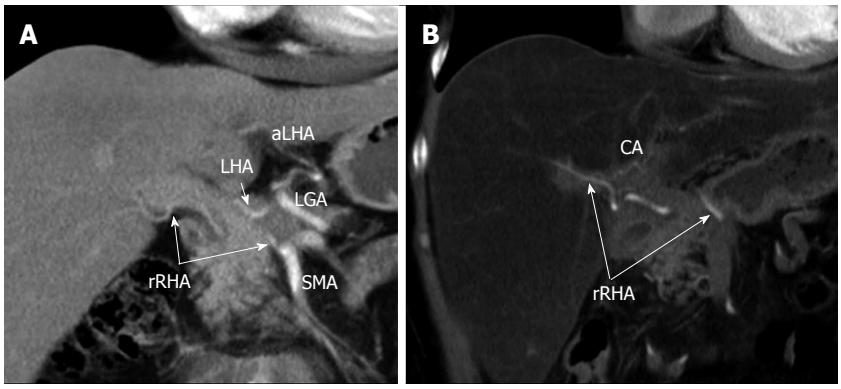

Figure 12 Coronal image. Arterial phase. A: Previous to surgery. Aberrant arterial vasculature (Michels, type Ⅷb): replaced right hepatic artery (rRHA) stemming from superior mesenteric artery (SMA), the left gastric artery (LGA) giving rise to accessorial left hepatic artery (aLHA). No interlobar collateral is detectable; B: Distal pancreatectomy with excision of celiac artery (CA), LGA, common hepatic (CHA) and left hepatic (LHA) arteries. Increased blood flow *via* rRHA is displayed and extra-parenchymal hilar interlobar collateral transmitting blood supply to left hepatic lobe became visible.

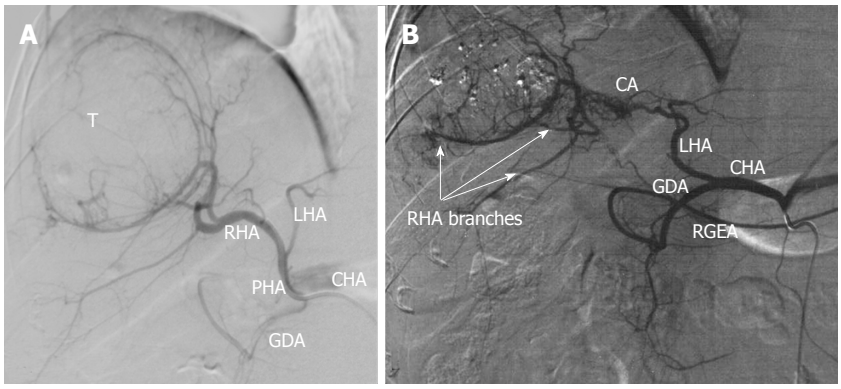

Figure 13 Selective celiacography in a 37-year-old man with firearm (machine gun shots) liver wounds, false aneurysms of left hepatic lobe and hemobilia. A: Classical arterial architecture (Michels, type 1). There is communicating interlobar artery (CA) connecting right and left hepatic arteries (RHA and LHA). Turbulent blood flow is seen in areas of pulsative hematomas (H); B: Control of hemorrhage was achieved with RHA occlusion but arterial branches of right hepatic lobe keep being filled owing to CA-conveyed blood transit from the left hepatic artery (LHA). GDA: Gastroduodenal artery; PHA: Proper hepatic artery; CHA: Common hepatic artery; RGEA: Right gastroepiploic artery; T: Tumor.

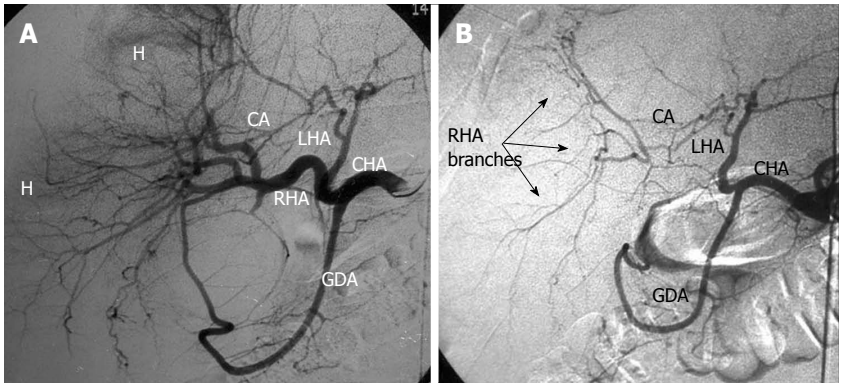

Figure 14 Selective celiacography in a 64-year-old man with hepatocellular cancer. A: Before and after chemoembolization through the right hepatic artery; B: Arterial branches of right hepatic lobe keep being filled owing to communicating interlobar artery (CA)-conveyed blood transit from the left hepatic artery (LHA). GDA: Gastroduodenal artery; CHA: Common hepatic artery; RHA: Right hepatic artery; H: Hematoma.

should not be denied surgery on account of a false-positive CT finding (*i.e.*, when a neoplasm is misinterpreted as nonresectable at CT). On the other hand, what counts for no less is the prevention of an unneeded cumbersome procedure, fraught with devastating morbidity, for an unresectable lesion, keeping in mind that a R2 resection is associated with poor survival.

In the historical series of studies conducted by different authors prior to 2000, from 15% to 70% pancreatic cancer cases thought of as resectable from CT data

turned out to be nonresectable at operation[58-61]. As of now, the sensitivity and specificity of the assessment of vascular involvement, even with a > 90° circular contact and marked vascular deformity (D or E according to Phoa), are reported at 60% and 90% correspondingly[62,63], which indicates that the accuracy of pancreatic cancer resectability appraisal is an elusive troublesome question. Based on the findings reported by various researchers, Li *et al*[64] defined the following CT criteria for major vascular invasion with an exhibited sensitivity of the method of 79% and a specificity of 99%: embedment of the arterial trunk in tumor, encasement by tumor > 180° or > 50% of the vessel circumference coupled with either irregularity of the wall contour or arterial narrowing. Loyer *et al*[65] established that with type A (a fat plane between tumor and vessel) or type B (a normal pancreatic parenchyma separating the tumor from the vessel), the accuracy of the resectability prediction was 95% and Phoa *et al*[62] showed type D (a vascular wall concavity against the tumor to be consistent with a 88% risk for invasion and a 7% predicted resectability) and type E (complete vascular encirclement by tumor) to correlate with a 0% resectability, depending on tumor surface irregularity and vascular deformity. Nevertheless, there is presently no consensus of opinion as to the modality of choice for the assessment of pancreatic cancer extension previous to surgery, since studies that would offer sufficient accuracy are lacking[66,67].

Both our cases demonstrate the unresolved problem of pancreatic cancer resectability determination to be currently pressing, among other reasons, as a consequence of CT being employed for this purpose in the majority of clinics (and quite routinely as a single option). The basic guide to the accuracy of resectability estimation is the ability of a diagnostic technique to identify the presence or absence of invasion of the major peripancreatic arteries. In Case 1, circumferential encasement of the GDA was found on CT and in Case 2, CHA, LHA and CA bifurcation was recognized. At surgery and subsequently under the microscope, the finding in Case 1 proved to be a mere close tumor-artery contact free of ingrowth (which ensured a R1-resection level). In observation 2, the bulk of the tissue misdiagnosed as tumor at CT turned out to be fibrosis with no features of post-therapeutic changes, which in great part enabled a R0 resection level. From strict considerations relying on the belief that the larger is the tumor-vessel contact area, the higher is the likelihood of vascular invasion[68], both cases might have been judged unresectable, as concluded from the CT interpretation[69]. Nonetheless, in both cases, the tumor was found to be resectable, which suggests that it is desirable that CT evidence-based conclusion in favor of unresectability should be confirmed with further clarifying adjunct modalities, such as EUS.

We feel that the salient features of the reported cases might be of equal interest to hepatopancreatobiliary surgeons as well as diagnostic radiologists engaged in this challenging line.

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CASE REPORT

Mesenteric paraganglioma: Report of a case

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Abstract

We report a rare case of paraganglioma that developed in the mesentery of terminal ileum. A 78-year-old woman complained of right-sided abdominal pain. Abdominal computed tomography revealed a solid heterogeneously enhanced mass in the right lower abdomen. The tumor was laparoscopically excised. The mesenteric tumor was well circumscribed, ovoid, and encapsulated and measured 3 cm × 1.5 cm × 1.5 cm. Histological examination showed a cellular neoplasm comprised of nests and groups of tumor cells separated by fibrovascular connective tissue, giving a characteristic nested Zellballen pattern. Immunohistochemically, the tumor cells were positive for chromogranin, synaptophysin, CD56, and vimentin and negative for cytokeratins, SMA, CD34, CD117/c-kit and S100. On the basis of histologic and immunohistochemical features, a diagnosis of mesenteric paraganglioma was made. The operative and postoperative courses were unremarkable, and the patient was discharged on postoperative day 7. She was doing well 1 year after the surgery with no signs of recurrence. Extra-adrenal paragangliomas most commonly develop adjacent to the aorta, particularly the area corresponding to the organ of Zuckerkandl. Mesenteric paraganglioma, as in our case, is extremely rare; only 11 cases have been reported in the literature. We herein discuss the clinical findings of these cases.

Key words: Mesenteric tumor; Extra-adrenal paraganglioma; Pheochromocytoma; Surgical management; Preoperative diagnosis

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INTRODUCTION

Paraganglia are groups of morphologically and cytochemically similar cells derived from the neural crest. They include such tissues as the adrenal medulla, carotid and aortic bodies, organs of Zuckerkandl, and other unnamed paraganglia in the distribution of sympathetic and parasympathetic nerves.

Paragangliomas are uncommon tumors arising from the neuroendocrine elements (chief cells) of the paraganglia. However, they have been described in virtually every site in which normal paraganglia are known to occur; only 5%-10% of sporadic paragangliomas are extra-adrenal[1-3]. Paraganglioma as a mesenteric mass is extremely rare, and only occasional reports have been published. The present case report describes a quite rare mesenteric paraganglioma, including its imaging features and histopathological characteristics. In addition, a review of the current literature summarizes the clinical findings associated with mesenteric paragangliomas.

CASE REPORT

A 78-year-old woman, who underwent distal gastrectomy for early gastric cancer in 1994 and total thyroidectomy for papillary thyroid carcinoma in 2000 was followed up at our hospital. In June 2010, she complained of right-sided abdominal pain. Abdominal computed tomography (CT) revealed a solid mass, 16 mm × 22 mm × 25 mm in size, in the right lower abdomen. Contrast-enhanced CT showed a smoothly marginated, heterogeneously enhanced hypervascular tumor adjacent to the right major psoas muscle (Figure 1A and B). Magnetic resonance imaging (MRI) showed that the lesion was hypointense on T1-weighted images and hyperintense on T2-weighted images. After the bolus infusion of gadolinium chelate, the lesion had marked contrast enhancement on T1-weighted images (Figure 1C-E). Whole-body ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) was negative (Figure 1F), and subsequent upper gastrointestinal endoscopy and colonoscopy were not remarkable. Laboratory studies yielded normal blood chemistry and hematology results. The carcinoembryonic antigen and carbohydrate antigen 19-9 levels were both within normal limits. In retrospect, follow-up CT after gastrectomy in 2002 already showed the tumor, which was 16 mm × 13 mm × 15 mm in size and was not pointed out at that time. For 8 years, the tumor had been slowly but definitely growing.

For a definitive diagnosis, surgical resection was recommended to the patient, and she was admitted to our hospital. Physical examination showed a blood pressure of 118/80 mmHg and a regular pulse of 68 bpm. On angiography, the tumor appeared as a hypervascular lesion fed by the superior mesenteric artery (Figure 1G and H). Before surgery, although the differential diagnosis included gastrointestinal stromal tumors, leiomyoma and Castleman's disease, we could not definitively diagnose this tumor.

In March 2011, exploratory laparoscopy confirmed a solid, brownish-red mass in the mesentery of the terminal ileum. There was no lymph node swelling or ascites. Throughout the exploration, there was no remarkable fall or rise in blood pressure. The mass was excised under laparoscopy without ileum resection. Grossly, the mesenteric mass was well circumscribed, ovoid, and encapsulated and measured 3 cm × 1.5 cm × 1.5 cm (Figure 2A). Histological examination showed a cellular neoplasm comprised of nests and groups of tumor cells separated by fibrovascular connective tissue, giving a characteristic nested Zellballen pattern (Figure 2B). Immunohistochemically, the tumor cells were positive for chromogranin, synaptophysin, CD56, and vimentin and negative for cytokeratins, SMA, CD34, CD117/c-kit, and S100. The proportion of Ki-67-positive cells was low (Figure 2C-E).

On the basis of histologic and immunohistochemical features, a diagnosis of mesenteric paraganglioma was made. The operative and postoperative courses were unremarkable, and the patient was discharged on postoperative day 7. She was doing well 1year after the surgery with no signs of recurrence.

DISCUSSION

Paraganglioma is a rare tumor of neural crest cell origin that arises from sympathetic or parasympathetic neural paraganglia. While the most common location of paragangliomas is the adrenal medulla, where they give rise to pheochromocytomas, approximately 5%-10% of sporadic paragangliomas occur in extra-adrenal sites[1-4]. Although extra-adrenal paragangliomas may develop in every site in which normal paraganglia exist, 70%-85% of cases actually occur intra-abdominally, most commonly adjacent to the aorta and particularly the area corresponding to the organ of Zuckerkandl[3,4]. Paragangliomas that develop in the mesentery, as in our case, are extremely rare, with only 11 cases in the literature[3] (Table 1).

As shown in Table 1, there appears to be a marked predilection for females (9:3), which contrasts with the slight male predominance (1.3:1) reported for retroperitoneal paraganglioma[5,6]. At the time of diagnosis, most patients are older (median, 57.5 years of age) than those with retroperitoneal paraganglioma (median, 39-43 years of age[4-6]). No significant difference was noted in the size of mesenteric (average, 9.3 cm) and retroperitoneal tumors (average, 7.4-10.5 cm[4-6]).

The pathogenesis of paragangliomas is not fully understood. They may be either sporadic or hereditary. Overall, as many as 10%-50% of paragangliomas are considered to be hereditary[7]. Hereditary paragangliomas are multicentric in 20%-50% of cases[8,9], whereas sporadic paragangliomas are multicentric in 10% of cases. In hereditary cases, they may be associated with multiple endocrine neoplasia type 2, von Hippel-Lindau disease, familial paraganglioma, Carney triad and neurofibromatosis type 1[10]. For this reason, especially in patients diagnosed before 50 years of age and in those who present with bilateral, multifocal, and malignant paragangliomas, genetic testing may be beneficial[11]. In the present case, the tumor was solitary and the patient was a 78-year-old woman with no history of genetic disorders; thus, genetic screening was not performed.

From a diagnostic viewpoint, functional tumors are easier to diagnose. Most patients undergo paroxysmal episodic hypertension and the typical triad of symptoms associated with pheochromocytoma: palpitations, headache, and profuse sweating. When functional paraganglioma is suspected, biochemical analysis of catecholamine hypersecretion should precede any form of imaging.

However, a majority of extra-adrenal paraganglioma is nonfunctional[11], as in our case. A large proportion of these tumors are incidentally discovered in normotensive patients during imaging evaluation for other reasons. In addition, the CT features of extra-adrenal paraganglioma include a nonspecific soft tissue density and overlap those of other neoplasms. Specifically, tumors of neural or mesodermal origin and those of metastatic

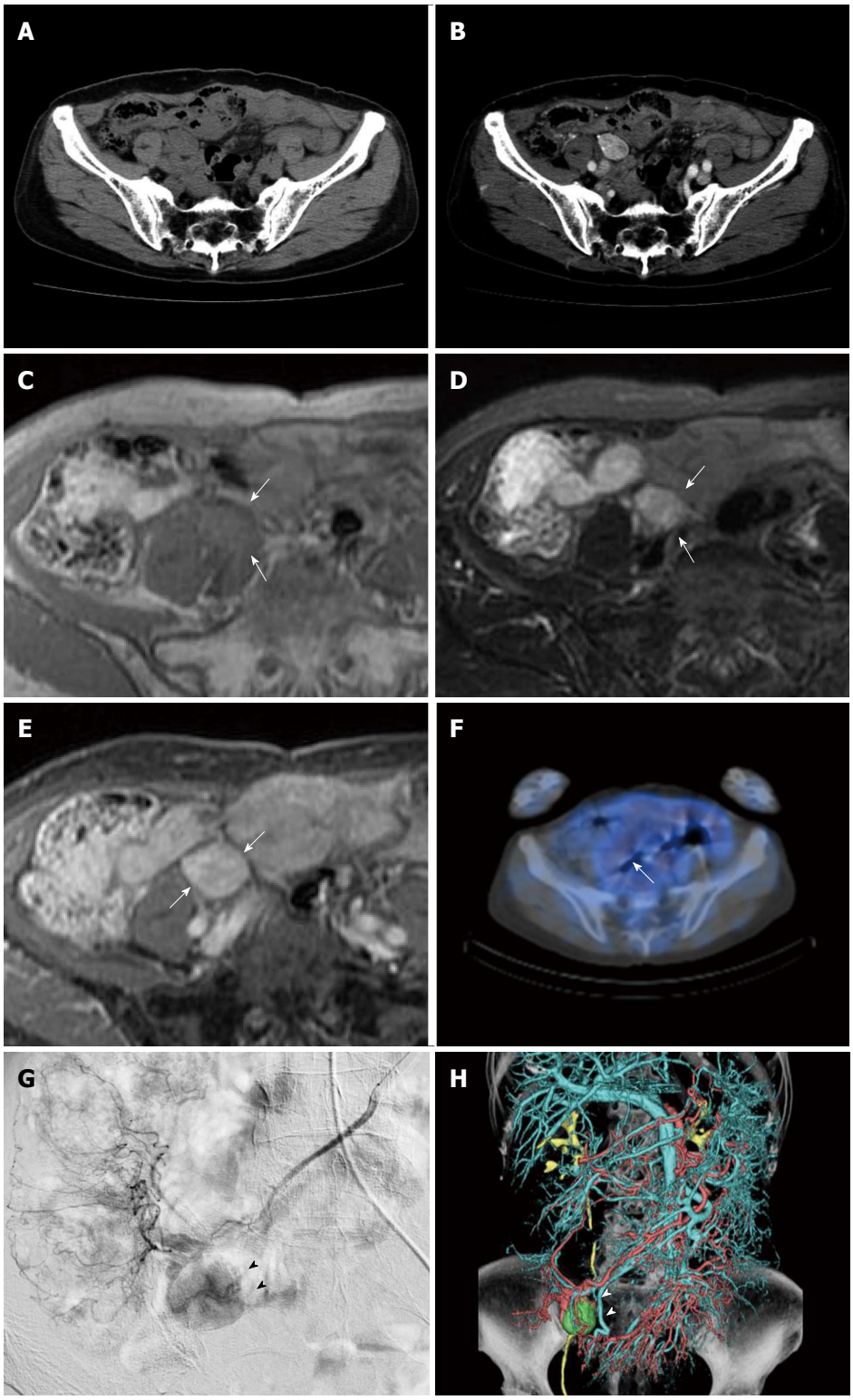

Figure 1 Imaging features of tumor (white arrows) before treatment. A: Axial plain; B: contrast-enhanced computed tomography (CT), CT shows a smoothly marginated, heterogeneously enhanced tumor adjacent to the right major psoas muscle, 16 mm × 22 mm × 25 mm in size; C: T1-weighted magnetic resonance image shows a well defined, isointense mass; D: On T2-weighted images, the mass shows heterogeneous high intensity; E: On T1-weighted images after a bolus infusion of gadolinium chelate, the mass had marked contrast enhancement; F: Positron emission tomography-CT scan was negative; G: Superior mesenteric arteriography displays a markedly hypervascular mass (black arrow heads) adjacent to the terminal ileum; H: Volume rendering image acquired from angio-CT (white arrow heads).

disease must be considered[1]. Thus, because of their clinical manifestation and the overlap with other tumors in terms of medical imaging findings, the preoperative diagnosis of extra-adrenal paraganglioma is usually difficult. Especially when extra-adrenal paragangliomas arise from unusual sites, as in the present case, accurate diagnosis is seldom made preoperatively (Table 1).

The MRI characteristics of our case are quite typi-

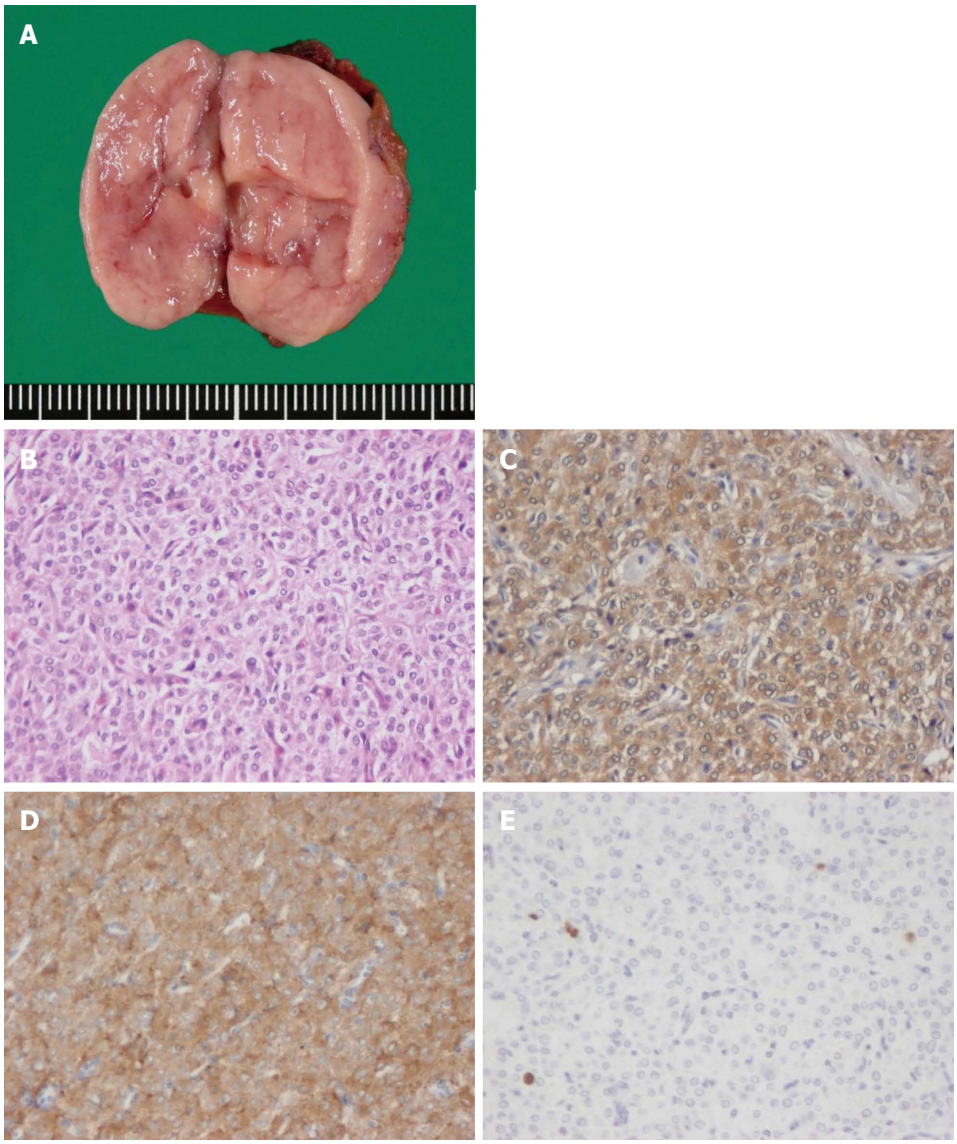

Figure 2 Macroscopic findings and pathological features of the resected tumor. A: Gross findings of the resected specimen. The tumor was encapsulated and measured 3 cm × 1.5 cm × 1.5 cm; B: The paraganglioma comprised a dual cell population arranged in a characteristic nested Zellballen pattern (HE stain, × 400); C: Immunohistochemistory of Chromogranin A, × 400; D: Synaptophysin were strongly positive and confirmed a neuroendocrine origin, supporting the diagnosis of paraganglioma, × 400; E: The MIB-1 labeling index, × 400.

cal for paraganglioma. Paragangliomas have low signal intensity on T1-weighted images and enhance strongly after administration of contrast material. On T2-weighted images, they appear hyper intense. In addition, a speckled appearance with multiple flow voids is typical in tumors > 2 cm in diameter[12]. Angiography was thus useful to outline the location and vascular supply of the tumor in our case; theoretically, however, clinically silent functional tumors should be ruled out by urine analysis before manipulation.

In functional paraganglioma, ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy is the best imaging study for a preoperative diagnosis. MIBG scintigraphy may also be helpful to rule out clinically silent cases, but the specificity for diagnosis of nonfunctional paraganglioma is unclear[13]. In certain cases, FDG-PET may be indicated to investigate metastatic disease[7]. It was recently reported that the newest technique using fluorine-18-dihydroxyphenylalanine-PET imaging offers even higher accuracy than MIBG scintigraphy in the localization of paragangliomas[14].

In the case described here, diagnostic imaging played a very important role preoperatively to determine tumor localization, vascularity, and extent of disease. Differential diagnosis including gastrointestinal stromal tumors, leiomyoma, malignant lymphoma, Castleman's disease and other metastatic tumor could be made preoperatively. However, pitfall for misdiagnosis in our case was tumor location. Because of the tumor location away from the para-aortic area, a preoperative diagnosis of paraganglioma could not be made. Although rare, paraganglioma should be included in the preoperative differential diagnosis of solid hypervascular mesenteric tumors.

The treatment of choice for paraganglioma is surgi-

Table 1 Clinical characteristics of the 12 reported cases of mesenteric paraganglioma

No. of cases	Ref.	Age (yr)	Sex	Location	Symptoms	Size (cm)	Hyperten-sion	Preoperative diagnosis	Surgical procedures	Prognosis
1	Arean *et al*[18]	32	M	Mesentery of the small intestine	Nausea, vomiting, diarrhea	10 × 7 × 6	-	Abdominal mass	Resection of the intestine and its mesentery along with mass	8 mo: Alive without recurrence
2	Carmichael *et al*[20]	62	F	Mesentery of the small intestine	Nausea, vomiting, back pain	3.2	+	Abdominal mass	Resection of the intestine and its mesentery along with mass	Not documented
3	Tanaka *et al*[20]	29	F	Descending colon	Nausea, vomiting	10 × 9 × 7	-	Retroperitoneal mass	Resection of themass	32 mo: Alive without recurrence
4	Ishikura *et al*[21]	33	F	Sigmoid colon	Lower abdominal pain, dysuria	15 × 15 × 15	-	Ovarian tumor	Resection of the sigmoid colon and its mesentery along with mass	Not documented
5	Onoue *et al*[22]	38	F	Mesentery of the small intestine	None	4.5 × 3.2	-	Mesenteric tumor	Resection of the intestine and its mesentery along with mass	24 mo: Alive without recurrence
6	Jaffer *et al*[3]	76	M	Mesentery of the small intestine	Abdominal mass, vomiting, diarrhea	8.5 × 8	+	Abdominal mass	Resection of the intestine and its mesentery along with mass	Not documented
7	Muzaffar *et al*[23]	76	F	Mesentery of the small intestine	Abdominal mass	20 × 15	-	Abdominal mass	Not documented	15 mo: Alive without recurrence
8	Ponsky *et al*[24]	35	F	Mesentery of the small intestine	Abdominal mass, headache	5.5	+	Abdominal mass	Resection of the intestine and its mesentery along with mass	24 mo: Alive without recurrence
9	Kudoh *et al*[25]	72	F	Mesentery of the small intestine (ileum)	Abdominal pain and mass	10 × 9 × 9	-	Mesenteric tumor	Resection of segment of ileum and mesentery containing mass	12 mo: Alive without recurrence
10	Nobeyama *et al*[26]	53	M	Mesentery of the small intestine (ileum)	Abdominal mass	15 × 10 × 7	-	Abdominal mass	Resection of segment of ileum and mesentery containing mass	Not documented
11	Matsumoto *et al*[27]	77	F	Mesentery of the small intestine (near Bauhin's valve)	Abdominal mass	7 × 5.5	-	Mesenteric tumor	Resection of segment of ileum and mesentery containing mass	9 mo: Alive without recurrence
12	Present case	78	F	Mesentery of the small intestine (near Bauhin's valve)	None	3 × 1.5 × 1.5	-	Mesenteric tumor	Resection of themass	8 mo: Alive without recurrence

M: Male; F: Female.

cal resection. As shown in Table 1, most tumors were excised along with a segment of small bowel, probably because of the large tumor size and intestinal vascularity. From the viewpoint of lymph node dissection, however, recurrence in cervical lymph node was reported for retroperitoneal paraganglioma[5], neither local nor distant lymph node metastasis was reported for mesenteric paragangliomas.

With regard to malignant potential, the incidence of malignant change reportedly ranges from 14% to 50%[15,16]. In these reports, the clinical and histological distinction between benign and malignant tumors was unclear, and the definitive diagnosis of malignancy was based solely on the presence of metastases. The distinction of endocrine tumors was recently well defined according to the World Health Organization classification[17]. In particular, mitotic counts and the Ki-67 labeling index are of considerable significance in grading its malignant potential.

In the present case, the Ki-67 labeling index was low and mitoses were rare. The tumor presented as a well circumscribed mass with no metastases. The patient was considered to be at low risk of malignancy. However, in retroperitoneal paraganglioma, the 5- and 10-year disease-free survival rates were 75% and 45% even after successful resection, indicating that more than half of these patients will experience a relapse if followed long enough after resection[5]. Although recurrence of mesenteric paraganglioma has not been reported, long-term follow-up after surgical excision is likely to be necessary.

In conclusion, mesenteric paraganglioma is a very rare entity with a limited number of cases reported. Preoperative diagnosis of extra-adrenal paraganglioma in asymptomatic patients is usually difficult. Although rare, paraganglioma should be included in the preoperative differential diagnosis of solid mesenteric tumors. Even after complete resection, patients should continue to be followed up carefully.

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CASE REPORT

Pancreatic insulinoma combined with glucagon positive cell: A case report

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Abstract

We present a 70-year-old man who was referred for surgery with uncontrollable hypoglycemia. Ultrasonography and abdominal contrast computed tomography revealed a hypervascular tumor of 1 cm in diameter in the pancreatic tail. With a diagnosis of insulinoma, we performed a distal pancreatectomy. The patient showed a good postoperative course without any complications. The patient's early morning fasting hypoglycemia disappeared. The respective levels of C-peptide and insulin dropped from 14.9 ng/mL and 4860 μIU/mL preoperatively to 5.3 ng/mL and 553 μIU/mL after surgery. A histopathological examination demonstrated that the tumor was a pancreatic neuroendocrine tumor, grade 1. Immunostaining was negative for insulin and positive for CD56, chromogranin A, synaptophysin and glucagon. These findings suggested that the tumor was clinically an insulinoma but histopathologically a glucagonoma. Among all insulinoma cases reported between 1985 and 2010, only 5 cases were associated with independent glucagonoma. In this report, we characterize and discuss this rare type of insulinoma by describing the case we experienced in detail.

Key words: Hypoglycemia; Insulinoma; Pancreas; Neuroendocrine tumor; Glucagon

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INTRODUCTION

Gastrointestinal and pancreatic neuroendocrine tumors (PNETs) comprise a group of rare neoplasms arising from the neuroendocrine system of the gut. The annual incidence is estimated at 1-4 in 100 000, showing a trend toward a higher incidence over recent decades[1-5]. Advancing diagnostic techniques have enabled the early detection of both functional and nonfunctional PNETs in recent years and, as a result, these tumors are more likely to be cured by radical operation. Most of these tumors are sporadic and completely cured by enucleation, but cases of high-grade malignancy, those accompanied by independent tumor(s) that secrete other hormone(s) and those with multiple tumors require careful attention.

CASE REPORT

The case was a 70-year-old man diagnosed with diabetes mellitus 15 years prior to the current presentation who

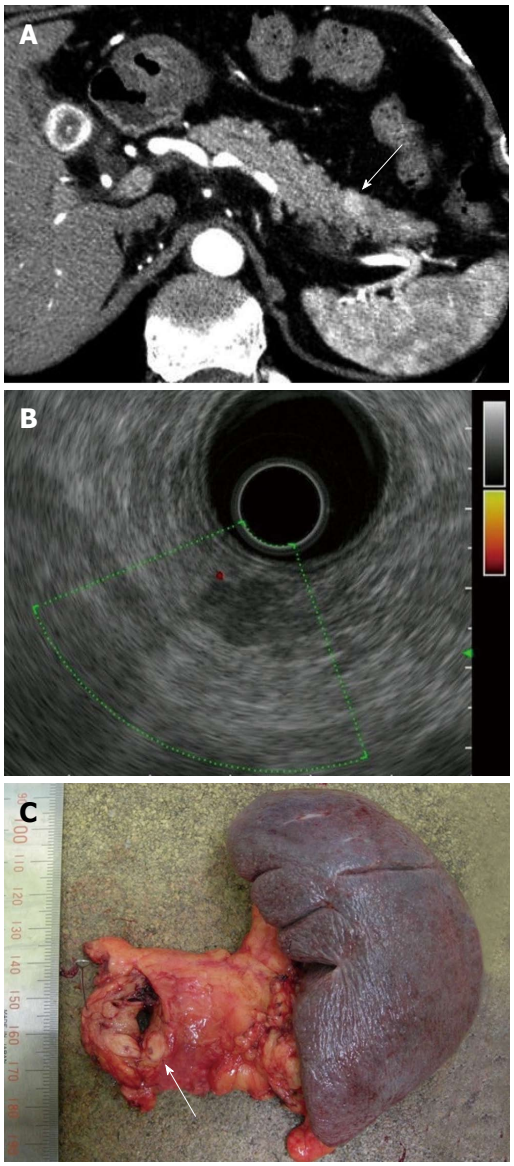

Figure 1 Removal of tumor. A: Enhanced abdominal computed tomography showed a tumor of 1 centimeter in diameter in the tail of the pancreas which was highly contrasted in the arterial phase (arrow); B: Endoscopic ultrasonography identified a uniformly hypoechoic tumor which measured 11 mm × 6 mm with a smooth surface in the tail of the pancreas; C: The resected specimen obtained from distal pancreatectomy and splenectomy included a solid whitish nodule (arrow).

was started on insulin self-injections in 2011. In 2012 he was placed under observation by the hospital due to worsening nephropathy. Two months ago, he presented with overhydration and started dialysis; he developed fasting hypoglycemia that did not improve after discontinuing the insulin injections. Careful examinations suggested that he had an insulinoma in the tail of the pancreas. He was given diazoxide and referred for surgery. The examinations on admission showed the following results: level of consciousness, lucid; blood pressure, 136/91 mmHg; pulse, 82 bpm; temperature, 36.6 ℃; overall status, stable. The patient had renal anemia and hypoalbuminemia (Table 1). The renal function test results and fasting blood glucose level before starting dialysis are shown in Table 1.

Table 1 Blood test findings on admission

Albumin, g/dL	3.0 (3.9-4.9)
Total bilirubin, mg/dL	0.3 (0.2-1.0)
Aspartate aminotransferase, IU/L	7 (10-40)
Alanine aminotransferase, IU/L	7 (5-45)
Blood urea nitrogen, mg/dL	54 (7.2-20.0)
Creatinine, mg/dL	8.2 (0.5-1.1)
Sodium, mmol/L	131 (136-145)
Potassium, mmol/L	4.1 (3.6-4.8)
Chlorine, mmol/L	101 (99-109)
White blood cell, μL	8000 (3100-9500)
Hemoglobin, g/dL	9.9 (13.5-16.9)
Platelet /μL	23.6×10^4 (15.1-34.9)
Fasting blood sugar, mg/dL	290 (70-109)
Hemoglobin A1c	7.6% (4.3%-5.8%)
Insulin, μIU/mL	4860 (1.8-12.2)
C-peptide, ng/mL	14.87 (0.61-2.09)
Binding rate of anti-insulin antibodies	76.2% (< 0.4%)
Carcinoembryonic, ng/mL	7.8 (< 5.0)
Pancreatic cancer-associated antigen-2, U/mL	190 (< 150)

Renal function test results and fasting blood glucose level before starting dialysis. Values in parentheses are normal ranges in our institution. All data were collected during the fasting state.

The blood levels of insulin and C-peptide were remarkably high, and those of carcinoembryonic antigen and duke pancreatic monoclonal antigen type 2 were slightly high. The levels of thyroid hormone and pituitary hormone were normal. The binding rate of anti-insulin antibodies was high, and we therefore could not deny insulin autoimmune syndrome.

Abdominal contrast computed tomography revealed a tumor 1 cm in diameter in the tail of the pancreas that was highly contrasted in the arterial phase (Figure 1A). The main pancreatic duct was not expanded, and the tumor was a suspected islet tumor. Endoscopic ultrasonography identified a uniformly hypoechoic tumor in the tail of the pancreas that measured 11 mm × 6 mm and had a smooth surface. Doppler ultrasonography demonstrated blood flow in the marginal regions of the tumor (Figure 1B). No other tumors were observed in the pancreas. We performed a distal pancreatectomy because intraoperative ultrasonography (IOUS) revealed that the tumor was close to the main pancreatic duct, making enucleation difficult. A cross-section of the surgical specimen showed a solid whitish nodule (Figure 1C). The tumor was preoperatively suspected as an insulinoma, but immunostaining showed that the main lesion was negative for insulin and positive for glucagon (Figure 2A and B). Additionally, the tumor was positive for CD56, chromogranin A and synaptophysin and negative for somatostatin. With an MIB-1 index of 1.6% and mild venous invasion, the tumor was identified as an NET, grade 1 (G1). At the slightly tail side of the main lesion, one hyperplastic nodule 3 mm in diameter was observed. Immunostaining demonstrated that the microadenoma was positive for insulin and glucagon (Figure 2C and D). After surgery, the blood levels of insulin and C-peptide significantly decreased, but the binding rates of anti-insulin antibodies were unchanged (Table 2). The patient resumed insulin self-injections and

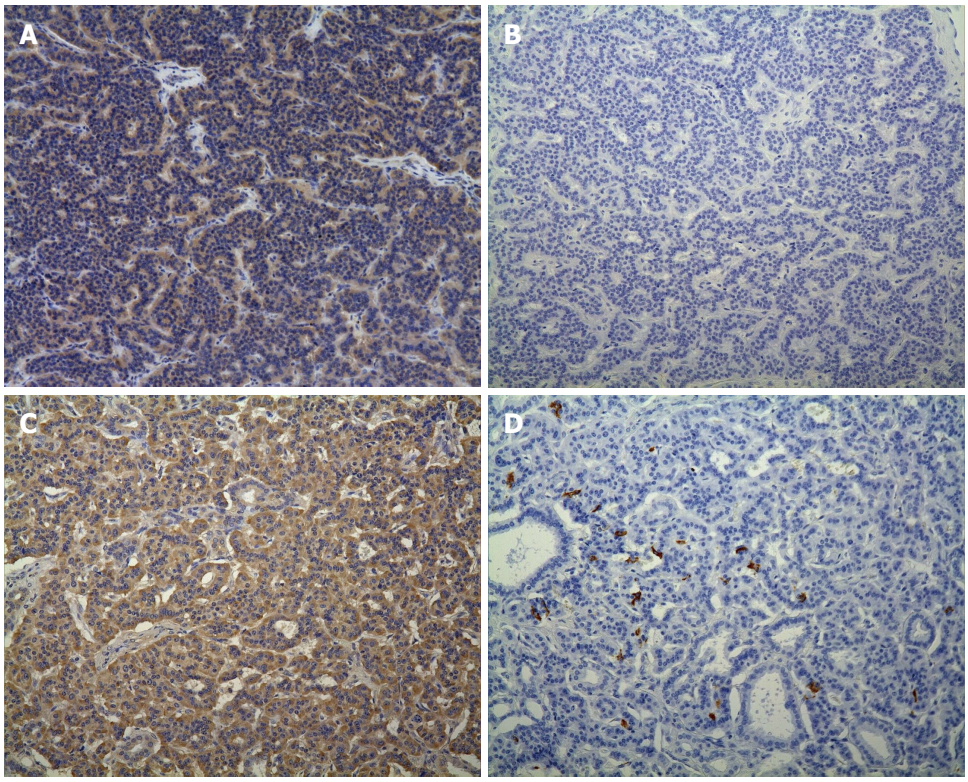

Figure 2 Immunostaining histological findings for the main lesion and the microadenoma (× 100). A: The main lesion revealed positive for glucagon; B: The main lesion revealed negative for insulin; C: The microadenoma revealed most positive for glucagon; D: The microadenoma revealed weakly positive for insulin.

Table 2 Changes of three parameters around distal pancreatectomy

	Before the operation	After the operation (POD 14)
Serum insulin level (1.8-12.2 μIU/mL)	4860	553
Serum C-peptide level (0.61-2.09 ng/mL)	14.87	5.28
Binding rate of anti-insulin antibodies (< 0.4%)	76.2	70.3

Values in parentheses are normal ranges in our institution. POD: Postoperative day.

achieved good glycemic control without taking diazoxide. He was discharged without complications on postoperative day 14.

DISCUSSION

Neuroendocrine tumors (NETs) originate from the pancreas or gastrointestinal tract and are histologically divided into NET G1, NET G2 and neuroendocrine carcinoma, including small cell type, large cell type, and mixed adenoneuroendocrine carcinoma, according to the World Health Organization classification[6]. Our case was ultimately diagnosed as an NET G1. Endocrinologically, functional tumors account for 41%-48%, and most are insulinomas[7,8]. The symptoms of insulinoma generally include hypoglycemia resulting in neuroglycopenic symptoms and hyperadrenalism because of a vicarious increase in adrenalin[9]. While blood examinations are useful for identifying insulinoma, imaging studies are helpful for localizing tumors. In recent years, surgeons have had to guess the locations of some microscopic tumors by observing the hormones flowing back to the hepatic vein after an intraarterial injection of calcium and then resecting the tumors under IOUS[10,11]. Most insulinomas are sporadic and completely cured by enucleation. After surgical therapy, patients with insulinomas generally have excellent long-term survival. A large patient cohort from the Mayo Clinic in Rochester demonstrated that cure was achieved in 98% of patients after surgical resection[12,13]. However, some cases, including high-grade malignant tumors with a poor expected prognosis, those accompanied by independent tumor(s) that secrete other hormone(s) and patients with multiple insulinomas, require careful attention[14]. Specifically, the percentage of patients with concomitant insulinoma and glucagonoma among all insulinoma cases reported in Japan between 1991 and 2000 was 1.7% (6/358)[15]. Many were mixed tumors, which can produce more than one type of hormone. Mixed endocrine pancreatic tumors producing several peptide hormones have also been reported in the West[16,17]. However, our patient had 2 independent lesions, and it is therefore highly likely that we could not achieve good glycemic control only by simple enucleation of the main lesion. To our knowledge, only 6 cases including our case, which had both insulinoma and glucagonoma, have been reported since 1985 in Japan (Table 3)[18-22]. There were no particular correlations with age or gender among the 6 patients, and in all cases, only the insulinoma was responsible for their chief complaints.

Table 3 Reports of coexistent cases of pancreatic insulinoma and glucagonoma in Japan

Case	Age (yr)	Gender	Chief compliant	Definitive diagnostic procedure	Preoperative diagnosis	Operative procedure	Postoperative diagnosis
1[18]	24	M	Consciousness disturbance	ASVS + AG	Six insulinoma at pancreatic tail	DP	Five insulinomas and two glucagonomas
2[19]	73	F	Consciousness disturbance	ASVS	One insulinoma at the region of GDA perfusion	enucleation	One insulinoma and one glucagonoma
3[20]	21	M	Consciousness disturbance	ASVS	One insulinoma at the region of SpA perfusion	1st enucleation, 2nd DP	One insulinoma and one glucagonoma
4[21]	60	F	Consciousness disturbance	AG	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma
5[22]	59	F	Consciousness disturbance	CT	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma
6 (our case)	70	M	Fasting hypoglycemia	CT + EUS	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma

ASVS: Arterial stimulation and venous sampling; AG: Angiography; CT: Computed tomography; EUS: Endoscopic ultrasound; GDA: Gastroduodenal artery; SpA: Splenic artery; DP: Distal pancreatectomy; M: Male; F: Female.

Glucagonoma was postoperatively diagnosed in most cases by examining additional tumors that were perioperatively identified by IOUS and resected. In 1 case (Case 3), the surgeons postoperatively identified an enucleated tumor as a glucagonoma and performed further surgery to improve persisting hypoglycemia; the patient later underwent distal pancreatectomy. Some PNETs secrete multiple hormones or are accompanied by independent hormone-positive cells that secrete other hormone(s). In this case, a small hyperplasic nodule secreting insulin incidentally coexisted with a glucagonoma. Some have reported that pancreatic islet cell hyperplasia could cause hyperinsulinemic hypoglycemia[23-27]. It is not necessarily easy to clinically and preoperatively diagnose such rare cases, even with advancing localization techniques. Careful attention is thus required to identify possible multiple lesions and monitor patients for the postoperative recurrence of tumors secreting the same or other hormone(s).

In this report, we characterized and discussed a rare insulinoma case that was preoperatively diagnosed as pancreatic insulinoma and postoperatively shown to be accompanied by glucagon-positive cells.

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ORIGINAL ARTICLE

Systemic inflammation and immune response after laparotomy *vs* laparoscopy in patients with acute cholecystitis, complicated by peritonitis

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Abstract

AIM: To evaluate acute cholecystitis, complicated by peritonitis, acute phase response and immunological status in patients treated by laparoscopic or open approach.

METHODS: From January 2002 to May 2012, we conducted a prospective randomized study on 45 consecutive patients (27 women, 18 men; mean age 58 years). These subjects were taken from a total of 681 patients who were hospitalised presenting similar preoperative findings: acute upper abdominal pain with tenderness, involuntary guarding under the right hypochondrium and/or in the flank; fever higher than 38 ℃, leukocytosis greater than 10 × 10^9/L or both, and ultrasonographic evidence of calculous cholecystitis possibly complicated by peritonitis. These patients had undergone cholecystectomy for acute calculous cholecystitis, complicated by bile peritonitis. Randomly, 23 patients were assigned to laparoscopic cholecystectomy (LC), and 22 patients to open cholecystectomy (OC). Blood samples were collected from all patients before operation and at days 1, 3 and 6 after surgery. Serum bacteraemia, endotoxaemia, white blood cells (WBCs), WBC subpopulations, human leukocyte antigen-DR (HLA-DR), neutrophil elastase, interleukin-1 (IL-1) and IL-6, and C-reactive protein (CRP) were measured at 0, 30, 60, 90, 120 and 180 min, at 4, 6, 12, 24 h, and then daily (8 A.M.) until post-operative day 6.

RESULTS: The two groups were comparable in the severity of peritoneal contamination as indicated by the viable bacterial count (open group = 90% of positive cultures *vs* laparoscopic group = 87%) and endotoxin level (open group = 33.21 ± 6.32 pg/mL *vs* laparoscopic group = 35.02 ± 7.23 pg/mL). Four subjects in the OC group (18.1%) and 1 subject (4.3%) in the LC group ($P < 0.05$) developed intra-abdominal abscess. Severe leukocytosis (range 15.8-19.6/mL) was observed only after OC but not after LC, mostly due to an increase in neutrophils (days 1 and 3, $P < 0.05$). This value returned to the normal range within 3-4 d after LC and 5-7 d after OC. Other WBC types and lymphocyte subpopulations showed no significant variation. On the first day after surgery, a statistically significant difference was observed in HLA-DR expression between LC (13.0 ± 5.2) and OC (6.0 ± 4.2) ($P < 0.05$). A statistically significant change in plasma elastase concentration was recorded post-operatively at days 1, 3, and 6 in patients from the OC group when compared to the LC group ($P < 0.05$). In the OC group, the serum levels of IL-1 and IL-6 began to increase considerably from the first to the sixth hour after surgery. In the LC group, the increase of serum IL-1 and IL-6 levels was delayed and the peak values were notably lower than those in the OC group. Significant differences between

the groups, for these two cytokines, were observed from the second to the twenty-fourth hour ($P < 0.05$) after surgery. The mean values of serum CRP in the LC group on post-operative days (1 and 3) were also lower than those in the OC group ($P < 0.05$). Systemic concentration of endotoxin was higher in the OC group at all intra-operative sampling times, but reached significance only when the gallbladder was removed (OC group = 36.81 ± 6.4 pg/mL *vs* LC group = 16.74 ± 4.1 pg/mL, $P < 0.05$). One hour after surgery, microbiological analysis of blood cultures detected 7 different bacterial species after laparotomy, and 4 species after laparoscopy ($P < 0.05$).

CONCLUSION: OC increased the incidence of bacteraemia, endotoxaemia and systemic inflammation compared with LC and caused lower transient immunological defense, leading to enhanced sepsis in the patients examined.

Key words: Systemic inflammation; Immune response; Laparoscopy; Cholecystectomy; Bile peritonitis

Core Tip: Laparoscopic techniques are being increasingly used in diffuse or localised peritonitis. However, a possible concern is that increased intra-abdominal pressure may promote bacteraemia and the systemic inflammatory response during laparoscopic surgery. The majority of reports in the literature are on experimental studies made using animal models. This study, instead, is a prospective randomized study conducted on human subjects. Experimental studies on peritonitis showed that the inflammatory response was significantly higher in the open cholecystectomy (OC) group than in the laparoscopic cholecystectomy (LC) group in the animal models, suggesting that carbon dioxide pneumoperitoneum has a protective effect against bacterial peritonitis. This study, in contrast to the previous ones, is the first work demonstrating that OC after biliary peritonitis increases the incidence of bacteraemia, endotoxaemia and systemic inflammation, compared with the LC group. The authors also demonstrated that early enhanced post-operative systemic inflammation may cause lower transient immunologic defense after laparotomy (decrease of human leukocyte antigen-DR), leading to increased sepsis in these patients.

Sista F, Schietroma M, De Santis G, Mattei A, Cecilia EM, Piccione F, Leardi S, Carlei F, Amicucci G. Systemic inflammation and immune response after laparotomy *vs* laparoscopy in patients with acute cholecystitis, complicated by peritonitis. *World J Gastrointest Surg* 2013; 5(4): 73-82 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i4/73.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i4.73

INTRODUCTION

Laparoscopic techniques are increasingly used in surgical conditions complicated by diffuse or localised peritonitis. Successful treatment of acute appendicitis, acute cholecystitis, perforated peptic ulcers and acute diverticulitis has been reported with low morbidity[1-3]. However, a possible concern is that the increased intra-abdominal pressure during laparoscopic surgery may promote bacteraemia and systemic inflammatory response. Data regarding the effects of pneumoperitoneum on physiological changes and systemic inflammation during sepsis are contradictory[4,5]. Furthermore, only the early effects of pneumoperitoneum during peritonitis have been assessed, and the differences between conventional and laparoscopic surgery have been compared only in animal models[6,7].

Therefore, the influence of laparotomy and laparoscopy on bacteraemia and endotoxaemia, peripheral leukocytic subpopulations (neutrophils, total lymphocytes, lymphocyte subpopulations), human leukocyte antigen-DR (HLA-DR), neutrophil elastase, interleukin-1 (IL-1), IL-6, and C-reactive protein (CRP) were investigated in a prospective, randomized study in subjects with acute calculous cholecystitis, complicated by bile peritonitis, who randomly underwent open or laparoscopic cholecystectomy.

MATERIALS AND METHODS

Study design

From January 2002 to May 2012, we conducted a prospective randomized study on 45 consecutive patients (27 women, 18 men; mean age 58 years), who showed intra-operatively bile peritonitis with acute calculous cholecystitis. Bile peritonitis is an inflammatory, irritative response to the abnormal presence of bile and bacteria in the peritoneal cavity[8]. These patients were taken from a total of 681 subjects who were admitted presenting similar preoperative findings: acute upper abdominal pain with tenderness, involuntary guarding under the right hypochondrium and/or in the flank; fever higher than 38 ℃, leukocytosis greater than 10×10^9/L or both, and ultrasonographic symptoms (thickened gallbladder wall, edematous gallbladder wall, presence of gallstones, ultrasonographic Murphy's sign and pericholecystitis and/or Douglas space fluid collection). These diagnostic criteria suggested acute calculous cholecystitis possibly complicated by peritonitis. All the subjects were randomly assigned to be treated by laparoscopic or open approach, according to a computer-generated table of random numbers. Randomization was performed by an independent computer consultant. The patient and the surgeon were informed of the type of approach just before the intervention.

The diagnosis of bile peritonitis was confirmed in 45 patients (6.6%), intraoperatively. Thirty-one patients had rupture of the gallbladder, 11 gangrenous gallbladder and three bile peritonitis without perforation. In Figure 1 the randomization is described in detail.

Exclusion criteria were as follows: acute cholangitis;

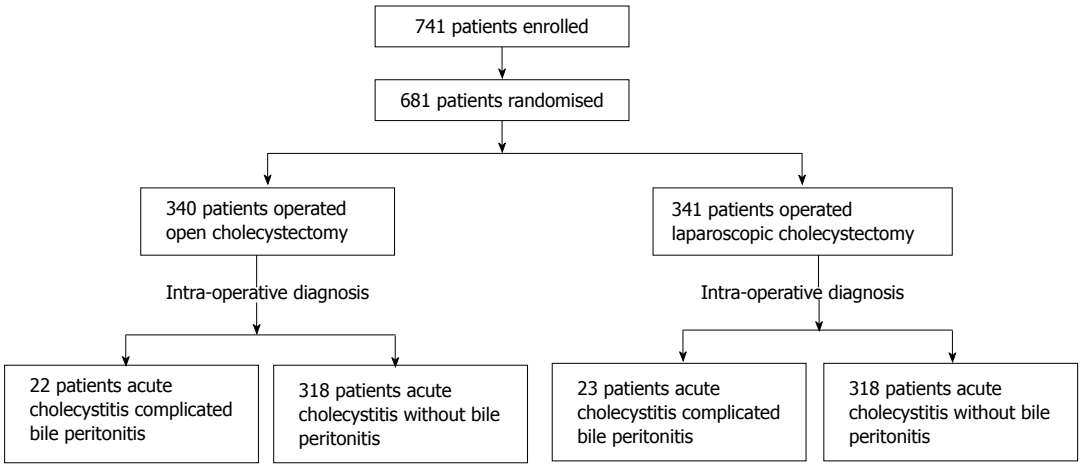

Figure 1 Randomization of diagnosis of bile peritonitis.

Table 1 Demographics and clinical characteristics of patients and type of operation performed

Parameter	Open cholecystectomy *n* = 22	Laparoscopic cholecystectomY *n* = 23[1]	*P* value
Age (yr)	58.3 (36-84)	56.9 (32-83)	NS
Sex (F/M)	14/8	13/10	NS
ASA grade			
I	3	3	NS
II	12	13	NS
III	5	6	NS
IV	2	1	NS
APACHE			
score < 15	12	13	NS
score > 15	10	10	NS
MPI			
score < 20	13	14	NS
score > 20	10	9	NS
Anaesthesia (min)	51.6 (46-72)	61.8 (51-81)	0.01
Operative time (min)	46.7 (40-62)	51.2 (42-64)	NS
Post-operative complications[2]	4 (18.1%)	1 (4.3%)	0.01
Mortality	5 (22.7%)	1 (4.3%)	0.02
Post-operative hospitalization (d)	10.2 (6-18)	5.4 (2-13)	0.02
Adjusted length of stay (d)	6.8 (6-9)	4.6 (2-6)	0.004

[1]Three patients (8.1%) were converted to open surgery; [2]Intra-abdominal abscess. NS: No significant; F: Female; M: Male; ASA: American Society of Anesthesiologists; APACHE: Acute Physiologic and Chronic Health Evaluation; MPI: Message passing interface.

other acute inflammation; current or recent (6 mo) acute pancreatitis; hematological disorder; anticoagulant treatment; current or recent (6 mo) thromboembolic disorders; renal, hepatic, rheumatic or vascular disease; pregnancy; recent (6 mo) surgery; current or recent (3 years) malignancy; immunosuppressive therapy. Five of the selected patients with clinical suspicion of common bile duct stones were subjected to pre-operative endoscopic retrograde cholangiopancreatography. When common bile duct stones were discovered (3 cases), endoscopic sphincterotomy was performed and ductal clearance achieved before operation. All five patients were excluded by the study. Therefore, there were no indications for intra-operative cholangiography in either group.

Twenty-two patients (14 women, 8 men; mean age 58 years, Table 1) underwent open cholecystectomy (OC) using a right subcostal incision. The remaining 23 patients (13 women, 10 men; mean age 57 years, Table 1) were subjected to laparoscopic cholecystectomy (LC) using the standard technique with four trocar incisions and 14 mmHg CO_2 pneumoperitoneum. All procedures were performed by surgeons experienced in hepatobiliary surgery and advanced laparoscopic surgery (Carlei F, Amicucci G).

The severity of sepsis was evaluated by Acute Physiologic and Chronic Health Evaluation (APACHE) II Score and by message passing interface (MPI) Score (Mannheim Peritonitis Index) (Table 1)[9,10]. Peritoneal lavage was performed with at least 4 washes with warm normal saline solution or until the recovered fluid was clear.

This trial was conducted according to the principles of good clinical practice and received ethics committee approval. Informed consent was obtained from every subject. The patients were classified as grade I, II, III, or IV according to the American Society of Anesthesiologists (ASA) grading system[11].

The initial supportive care during the acute phase was the same for both groups of patients. All subjects received intravenous fluid infusion, intravenous antibiotics (cefotaxime: 2 g per 8 h, tobramicine: 100 mg per 12 h), a proton pump inhibitor (omeprazole: 40 mg *iv* per 24 h) and pain relief (ketorolac trometamine: 30 mg *im* per 6 h). There were no indications for blood transfusions.

Anaesthesia was achieved in both groups using the same procedure. Preanaesthesia was accomplished using atropine (0.01 mg/kg), plus promethazine (0.5 mg/kg); induction was conducted using sodium thiopental (5 mg/kg) and atracurium (0.5 mg/kg); tracheal intubation and assisted ventilation were performed using NO_2/O_2 2:1. After intubation, anaesthesia was maintained with oxygen in air, sevoflurane and remifentanil (0.25 μg/kg per minute). LC and OC were performed as soon as possible, within 12 h of admission.

Wound infections were graded using a classification described elsewhere[12]. Infections were considered grade Ⅰ in the case of erythema, indurations, and pain; grade Ⅱ as grade Ⅰ but with serous fluid; grade Ⅲ, in the presence of contaminated fluid in less than half the wound; grade Ⅳ as grade Ⅲ but contaminated fluid was in more than half the wound. Wound dehiscence was considered to be present when surgical closure of the cutaneous or subcutaneous tissue (superficial) or the fascia and muscular plane (deep) was necessary in the early post-operative period.

Laboratory analysis

Blood samples were collected from all patients before operation and at days 1, 3 and 6 after surgery. Serum concentration of interleukin-1 (IL-1), IL-6 and endotoxin were measured at 0, 30, 60, 90, 120 and 180 min, at 4, 6, 12, 24 h, and then daily (8 A.M.) until post-op day 6.

Bacterial assay was performed immediately before (within 60 min) and then after operation (within 60 min and within 7 d). Blood was collected in pyrogen-free tubes and centrifuged at 4 ℃ at 2000 rpm for 10 min, aliquoted into sterile cryotubes (NUNC 36341, Intermed, Denmark) and stored at -80 ℃ until analysis for the subsequent determination of endotoxin. To determine the severity of peritoneal contamination, undiluted peritoneal fluid was aspirated from the Douglas space during surgery for quantitative bacterial and endotoxin assays. All samples were tested for total white blood cell (WBC) count, and WBC populations, T-helper lymphocytes (CD4), T-suppressor lymphocytes (CD8), natural killer lymphocytes (CD16 and CD56), pan-B cell antigen (CD20), TCR gamma/delta and the T-helper/T-suppressor ratio (CD4/CD8).

Human leukocyte antigen-DR (HLA-DR) in peripheral monocytes was measured by a cytofluorimetric method. All blood samples (10 mL) were collected with ethylenediaminetetraacetic acid (EDTA) (0.5 mL). A FITC (Fluorescein Isothiocyanate)-conjugated (10 μL) monoclonal antibody for the HLA-DR antigen was added. Whole blood (100 μL) from each patient was then added, and the tubes were vortex mixed and stored at 4 ℃ for 30 min. Two mL of lysis solution were added to each sample. All samples were stirred and then incubated for 15 min at room temperature. Finally, an Ortho cytofluorimeter was used for the assay.

Elastase concentration was photometrically determined, using an immune-activation immunoassay (Merck, Damstadt, Germany), as a complex with 1-proteinase inhibitor, according to the method described by Hafner *et al*[13].

The plasma concentration of CRP was measured using a competitive CRP Elisa Kit. Serum IL-1 and IL-6 concentrations were measured using a quantitative "sandwich" enzyme-linked immunosorbent assay (ELISA) kit (R and D Systems, Minneapolis, United States), according to the manufacturer's description (range IL-β 3.9-250 pg/mL; IL-6 3.13-300 pg/mL). Samples of serum (100 μL) were dispensed into wells of 96-well microlitre plates which had been coated with the relevant monoclonal cytokine antibody. After a 2-h incubation at room temperature, unbound proteins were washed away from the wells. An enzyme-linked antibody directed against the relevant cytokine was then added and plates were incubated for 2 more hours at room temperature. After further rinsing to remove unbound antibody, a substrate solution was added to each well and the mixture was incubated for 20 min at 37 ℃. The reaction was terminated with the addition of a stop solution. Adsorbance was determined by using an ELISA plate reader at 450 nm. Serial dilution of the relevant recombinant cytokine provided the standard curve. Assays were performed on duplicate samples. Samples were appropriately diluted with the diluent provided in the kit if the levels of neat samples were beyond the linear measuring range.

The microorganisms were grown on chocolate agar (tryptic soy agar supplemented with 10% defibrinated sheep blood, heated for 10 min to 80 ℃), blood agar (Columbia agar supplemented with 5% defibrinated sheep blood), Endo agar, and Sabouraud agar in both an aerobic and anaerobic atmosphere. The phenotypic identification of all strains was carried out by testing the carbohydrate fermentation reactions or by using commercially available enzyme activity and fermentation test (API, Bio Mérieux, Nürtingen, Germany).

Microbiological analysis of blood was performed immediately before the operation, 1 h after and 3 d after surgery. The initial blood cultures were drawn prior to antibiotic administration. Endotoxin was quantified in duplicates using a modified chromogenic Limulus amoebocyte lysate assay (Quadratech, Epsom, United Kingdom). Test plasma samples and standards were diluted 1:10 in pyrogen-free water and heated to 75 ℃ for 10 min to remove plasma inhibitors. The concentration of endotoxin in the sample was taken as the average of the duplicates calculated from a standard curve. The assay had a sensitivity of 8 g/mL and was linear in the range 8-100 pg/mL. Each aliquot was assayed for endotoxin only once. If the assay gave poor duplicates or very high values, indicating possible contamination, a fresh aliquot of the same sample was retested.

Statistical analysis

The sample size of the study was calculated *a priori* on the assumption that it would have been clinically relevant to have a 15% reduction in the parameter (hypothesis of IL-1 and IL-6 reduction between laparoscopy and laparotomy) with a 10% standard deviation. Furthermore, a power (1-β) of 80% was computed for the two-sided null hypothesis. A sample size of at least 20 patients was needed in each group to have a type Ⅰ error of less than 5% and a type Ⅱ error of less than 20%, using a two-tailed test. Comparisons between groups were on an intention-to treat basis.

The primary efficacy variable was the proportion of patients with immunological status improvement at the evaluation performed 1 d, 3 d and 6 d after the end of

either of the treatments. The normality distribution of the data was checked with the Shapiro-Wilk test. Data were analyzed using non-parametric statistics, which are more powerful when the data show a skewed distribution. Since the data were not normally distributed, an analysis of variance (non-parametric Friedman's repeated measures comparisons) was performed in both groups to determine differences between post-operative values and baseline. In the presence of significant difference, *post-hoc* analysis were made using the Mann-Whitney *U* test, to compare the values between the two groups Thus, all continuous variables were expressed as mean and standard deviation and compared using the Mann-Whitney *U* test. χ^2 test and Fisher's exact test were used to compare nominal data. Statistical calculations were performed with the help of Stata/MP 12.1, and a *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Clinical data

There was no difference between the two groups of patients in terms of co-morbidity, pre-operative clinical features (severity and duration of symptoms, involuntary guarding), biochemical (WBCs count) and radiological (ultrasounds, computed tomography) features of acute calculous cholecystitis possibly complicated by peritonitis. Three subjects (8%) in the laparoscopic group were converted to open surgery and were excluded from the study. As shown in Table 1, no significant differences were observed between the two groups with respect to age, sex, ASA grades, APACHE Ⅱ Score, MPI score and operation time ($P > 0.05$), while considerably shorter hospitalization and time of anaesthesia were observed in the LC group ($P < 0.05$).

LC required almost the same operative time as OC, but it required shorter hospitalization ($P < 0.05$; Table 1). The two groups were comparable with respect to the severity of peritoneal contamination, as indicated by the viable bacterial count (OC group = 90% of positive cultures *vs* LC group = 87%) and endotoxin level (open group = 33.21 ± 6.32 pg/mL *vs* laparoscopic group = 35.02 ± 7.23 pg/mL). Four patients who had undergone OC (18.1%) developed intra-abdominal abscess (Table 1). Clinical and ultrasonographic findings demonstrated a subphrenic abscess in all cases. The characteristics of these subjects are reported in Table 2. Monocyte expression antigen (HLA-DR), which was low one day after operation, remained low even 7 d after surgery and normalised 8-10 d after operation. In patients number 2 and 4, HLA-DR normalised 13 d after surgery (Table 2). The patients were discharged from hospital as a mean 13.8 d after their admission (range 9-18 d). The patient of the LC group with a subphrenic abscess was discharged from after hospital 13 d.

Largely because of the five patients who developed post-operative abscess, the unadjusted median length of stay was rather long for both groups. In fact, the OC group's unadjusted length of stay (10.2 d) was significantly longer than that of the LC group (5.4 d, $P < 0.05$). However, if these 5 patients are counted out the calculation, the median length of stay for the OC group falls to 6.8 d and to 4.6 d ($P = 0.004$) for the LC group (Table 1).

The rate of overall wound infections was 23.8% (10 out of 42). Seven patients (31.8%) in the OC group and 3 (15%) in the LC group had a wound infection ($P < 0.05$). Two infections of the laparotomy wound appeared at between 1 and 6 mo after surgery. Wound infection was consistently lower in the LC group than in the OC group ($P < 0.05$). No wound dehiscence was observed in any patient. No subject required surgical revision or re-operation for this complication and all wound infections were successfully managed with secondary closure.

The overall mortality rate was 13.3% (6/45); five in the OC group (22.7%) and one (4.3%) in the LC group ($P < 0.05$). The mortality rate associated with intra-abdominal abscess was 50% (3/6), all in patients who underwent OC. The remaining 3 subjects died from myocardial infarction (1 patient in the OC group and 1 patient in the LC group) and pulmonary embolism (1 patient in the OC group).

Laboratory data

Severe leukocytosis was observed after OC (range 15.8-19.6/mL) but not after LC (range 12.1-14.4/mL), mostly due to an increment of neutrophils (Figure 2) on days 1 and 3 ($P < 0.05$). Values returned to the normal range within 3-4 d after LC and 5-7 d after OC. Other WBC types showed no significant variation. There were no differences between the two groups of patients before and after operation in relation to lymphocyte populations. A statistically significant change in HLA-DR expression was recorded post-operatively at day 1 as a reduction of this antigen expressed on the monocyte surface in patients from the OC group; no changes were noted in LC patients (Figure 3; $P < 0.05$). In this case HLA-DR expression returned to normal levels within 7 d after surgery.

A statistically significant change in plasma elastase concentration was recorded post-operatively at days 1, 3, and 6: the increase of plasma elastase in the OC group patients was higher than in the LC group patients (Figure 4; $P < 0.05$). In the OC group, plasma elastase concentration returned to normal values within 10 d after operation.

Before the operation, the serum levels of neither IL-1 nor IL-6 were significantly different between the two groups. Figure 5 shows the chronological change in the serum level of IL-1β and IL-6β after surgery. In the OC group, the serum levels of IL-1β and IL-6β began to increase consistently 1 h from the beginning of the operation, reaching a peak at the sixth hour (approximately 4 h after surgery) and, thereafter, declining to pre-operative levels by 7 d. On the other hand, in LC group patients, the increase in the serum levels of IL-1β and IL-6β was delayed and the peak values were significantly lower than those in the OC group. The differences between baseline

Table 2 Demographics and clinical characteristics of four patients who developed intra-abdominal abscess

Patients (*n*)	1	2	3	4
Age (yr)	46	71	62	48
ASA	I	III	II	II
WBC count[1] (mL)	14.800	13.600	19.200	13.200
HLA-DR[2]	7%	4%	7.80%	4.10%
PMN-elastase[3] (mg/L)	69.6	70.2	70.6	78.2
IL-1[4] (pg/mL)	42.6	48.1	36.9	41.3
IL-6[5] (pg/mL)	415.16	381.8	402.25	408.4
Blood cultures[6]	Positive	Positive	Negative	Positive
Systemic endotoxin[7] (pg/mL)	18.4	19.6	18.2	19.2

[1]WBC count normalized 7-12 d after surgery; [2]HLA-DR normalized 8-10 d after surgery; [3]PMN-elastase normalized 8-12 d after surgery; [4]IL-1 normalized 10-13 d after surgery; [5]IL-6 normalized 11-13 d after surgery; [6]Blood cultures normalized 3-4 d after surgery; [7]Systemic endotoxin concentration normalized 5-6 d after surgery. ASA: American society of anesthesiologists; WBC: White blood cells; HLA-DR: Human leukocyte antigen-DR; PMN: Polymorphonuclear; IL-1: Interleukin-1.

values and post-operative levels of IL-1β and IL-6β values were significant in both groups (using the Friedman test, $P < 0.05$). In addition , the Mann-Whitney *U* test indicated significant differences between values for the groups at 2, 3, 4, 5, 6 and 24 h after the operation (Figure 5; $P < 0.05$).

Moreover, the mean values of the serum CRP on post-operative days (1 and 3) were lower in the LC group than in the OC group. The differences between baseline values and postoperative values for CRP were significant in both groups (using the Friedman test, $P < 0.05$). Besides, significance was obtained by comparing values between the groups at days 1, 2 and 3 after surgery, using the Mann-Whitney *U* test (Figure 6; $P < 0.05$). In this case CRP concentration returned to normal values within 7 d after operation.

The number of blood cultures positive for organisms was higher in the OC group than in the LC group (Table 3; $P < 0.05$). There was no difference in bacteraemia between the groups one week after intervention.

One hour after surgery, microbiological analysis of blood cultures detected 7 different bacterial species after laparotomy and 4 species after laparoscopy. Aerobic bacteria were not found in the LC group. The systemic endotoxin concentration significantly increased during the course of surgery but returned to near baseline by day 2 (Figure 7). Systemic concentrations of endotoxin were higher in the OC group at all intra-operative sampling times, but reached significance only when the gallbladder was removed (OC group = 36.81 ± 6.4 pg/mL *vs* LC group = 16.74 ± 4.1 pg/mL, $P < 0.05$) (Figure 7).

DISCUSSION

Laparoscopic surgery is increasingly used treatment of for intra-abdominal disease complicated by inflammatory processes and peritonitis. In literature there are no studies on stress response after LC or OC for acute calculous cholecystitis complicated by biliary peritonitis. In a recent review[3] it was demonstrated that laparoscopy is superior to conventional open appendectomy in terms of post-operative complications and recovery. Furthermore, laparoscopic management of perforated peptic ulcers has been reported to be simple and followed by a short recovery time, albeit with some limitations[2,14].

Experimental studies on rats showed that the inflammatory response in peritonitis models was significantly higher in the OC group than in the LC group[7,15]. On the other hand, other studies failed to find relevant differences[4,5]. Finally, other authors showed that carbon dioxide pneumoperitoneum has a protective effect against bacterial peritonitis induced in rats[16].

Studying subjects with peritonitis from perforated peptic ulcers, Lau *et al*[17] compared acute stress responses, endotoxaemia and bacteraemia between laparoscopy and open surgery. They concluded that endotoxaemia and bacteraemia are insignificant in most patients with perforated peptic ulcers. In these cases, laparoscopic patch repair does not reduce acute stress response if compared with open surgery.

Our study shows no difference in the pre-operative clinical parameters (age, ASA grade, Apache II and MPI scores, *etc.*) between the studied groups. Our results prove that colecystectomy in patients with acute cholecystitis complicated by peritonitis, whether performed by laparoscopic or open approach, is associated with significant stress response and with an increase in the biochemical markers measured. Nonetheless, the LC group was superior to the OC group in terms of post-operative systemic inflammation as well as intra-peritoneal abscess formation. In fact, the immunological status was better preserved and systemic inflammatory response was lower in the laparoscopic group than in the open group.

The number of positive blood cultures for organisms was significantly higher after laparotomy than in the laparoscopic group 1 h after surgery. Moreover, aerobic bacteria were not found after 1 h in the laparoscopic group. Since carbon dioxide is bacteriostatic on aerobic bacteria[16,18], this may explain why aerobic bacteria were only detected in blood cultures after laparotomy at this time.

Unlike laparoscopy, laparotomy caused a significant increase of systemic inflammation in the early post-operative course[19,20]. This difference was found in cytokine and cell-mediated immune responses not only in animal experiments but also in clinical trials[21,22].

In our study, while leukocyte counts recovered on day 2 in the laparoscopic group, they did not recover after laparotomy. Moreover, in the OC group we observed a post-operative decrease in HLA-DR of peripheral monocytes. Patients who underwent LC showed normal levels of HLA-DR expression[23]. Previous studies had demonstrated the crucial role of this antigen in assessing the activity of the immune system[24]. The HLA-DR antigen expression on monocytes plays an important role in antigen presentation to lymphocytes, particularly T-helper lymphocytes[24]. In fact, these cells require both HLA-DR and exogenic antigens on the macrophage surface to initiate proliferation. Moreover, studies have shown that

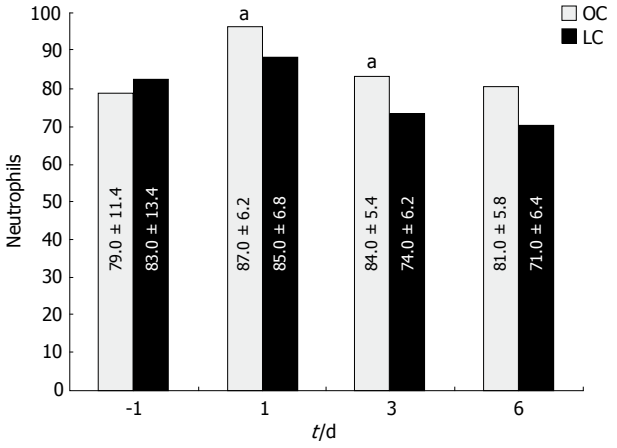

Figure 2 Severe leukocytosis was observed only after open cholecystectomy, but not after aparoscopic cholecystectomy, mostly due to an increment of neutrophils on day 1 and 3. Regarding Neutrophilis values, the difference between baseline values and post-operative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$). LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy.

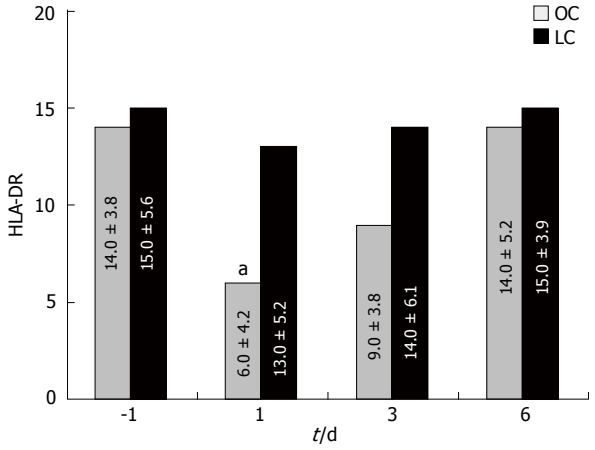

Figure 3 Change in human leukocyte antigen-DR expression in the open cholecystectomy group and laparoscopic cholecystectomy group. Regarding human leukocyte antigen-DR values, the difference between baseline values and post-operative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$). LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy.

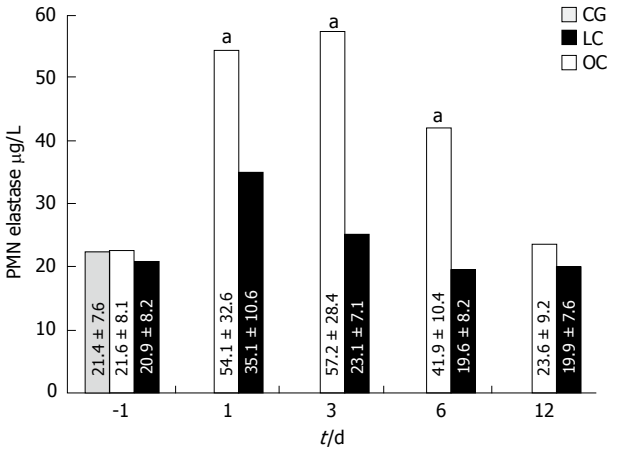

Figure 4 Change in plasma elastase concentration in the open cholecystectomy group and laparoscopic cholecystectomy group. Regarding polymorphonuclear (PMN)-elastase values, the difference between baseline values and post-operative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$). Concerning significance between baseline values and post-operative values, they were significant at day 1, 3 and 6 after surgery ($P = 0.047$) using the Mann-Whitney *U* test; $P < 0.05$. LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy.

Table 3 The number of blood cultures positive for organism was increased in the open cholecystectomy group as compared with the laparoscopic cholecystectomy group *n* (%)

Time intervention	Open cholecystectomy (*n* = 22)	Laparoscopic cholecystectomy (*n* = 20)	*P* value
Within 60 min before	10 (45.4)	8 (40)	NS
Within 60 min after[1]	10 (45.4)	4 (20)	0.001
Within 7 d after	1 (4.5)	0	NS

[1]Significant difference between groups, using Fisher's exact tests, $P < 0.05$; NS: No significant difference between groups, using χ^2 o Fisher's exact tests, $P > 0.05$.

HLA-DR is related to the surgical trauma and the occurrence of post-operative sepsis is strongly correlated with a minor expression of the human leukocyte antigen-DR of peripheral monocytes[22]. Given that HLA-DR expression is not significantly affected by age, sex, or race, this antigen can be considered meaningfull in the post-operative monitoring of surgical patients[24].

Neutrophil function has been examined by measuring neutrophil elastase (PMN-elastase). Neutrophil elastase is one of the major enzymes in neutrophils and is upregulated during activation[25]. During surgical procedures there is a massive release from the neutrophils of elastase [25,26], along with other proteinases. Therefore, the measurement of the elastase-α1-protease inhibitor complex might be a useful indicator of the degree of surgical trauma[26,27]. Varga *et al*[28] noted an elevation of PMN-elastase on the first postoperative day in both groups (OC and LC). However, in the laparoscopic patients it considerably decreased on the post-operative day 3 while in the OC group it remained high. The same discrepancy was present between the two groups on the 5th day. In the OC group a post-operative increase of plasma elastase concentration has been observed. Patients who underwent LC showed normal activity of leukocyte elastase. Therefore, it is conceivable that they maintain an adequate immune response even during the early post-operative phase, when the risk of infection is higher.

In relation to other serologic parameters (B and T lymphocytes, lymphocyte subpopulations), we observed no significant differences in pre- and postoperative values between the two groups of patients or between patients within each group.

IL-1, IL-6 and CRP showed significantly higher values in the OC group one hour after intervention. It may be that an abdominal incision causes a greater tissue trauma, leading to an increase of inflammatory cytokines and enhancing post-operative systemic inflammation[29,30]. In

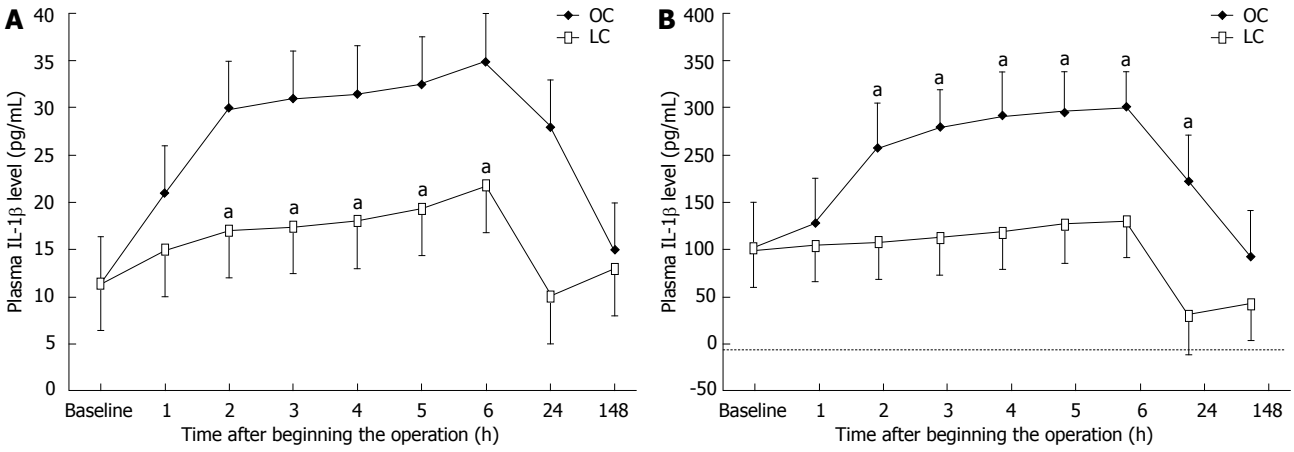

Figure 5 Chronological change in the serum level of interleukin-1β and interleukin-6β after surgery. A: The chronological change in the serum level of interleukin-1β (IL-1β) after surgery. Regarding IL-1β values, the difference between baseline values and post-operative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$); B: The chronological change in the serum level of interleukin-6β after surgery. Regarding IL-6β values, the difference between baseline values and post-operative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$). LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy.

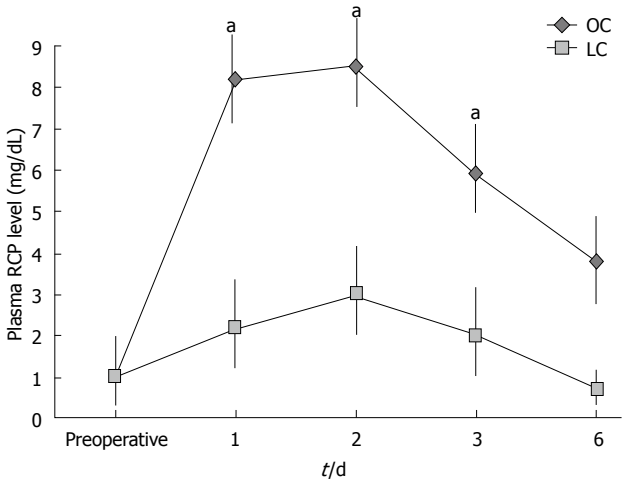

Figure 6 Change of values of the serum C-reactive protein on post-operative days. Regarding C-reactive protein values, the difference between baseline values and post-operative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$).

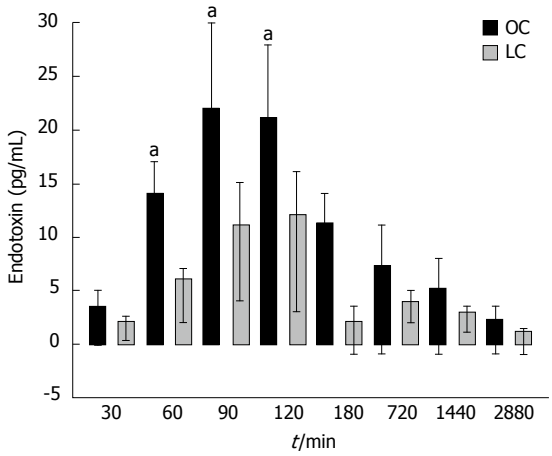

Figure 7 Systemic endotoxin concentration significantly increased during the course of surgery but returned to near baseline by day 2. Regarding endotoxin values, the difference between baseline values and postoperative values were significant in both groups (using the Friedman test, $^{a}P < 0.05$). Besides, significance was obtained by comparing values between groups 60, 90 and 120 min after surgery, using the Mann-Whitney *U* test, $P < 0.05$.

patients undergoing colectomy, systemic inflammation was significantly higher after an open approach than after a laparoscopic procedure, which is due to less trauma in the LC group[31-34]. Endotoxin is a potent stimulator of the release of cytokines such as IL-6 and tumor necrosis factor (TNF)[33,35,36]. These inflammatory mediators play an important role in the pathogenesis of systemic inflammatory response syndrome and multiple organ dysfunction syndrome[37]. In our study, a systemic concentration of endotoxin was higher in the open group, supporting the clinical findings. Intra-peritoneal abscess formation was detected in 5 patients after laparotomy and was significantly higher in this group than in the laparoscopic group. Therefore, it is conceivable that the patients who undergo LC maintain an adequate immune response even during the early post-operative phase, when the risk of infection is higher.

In conclusion, OC after biliary peritonitis increases the incidence of bacteraemia, endotoxaemia and systemic inflammation, compared with LC. Early enhanced post-operative systemic inflammation may cause lower transient immunological defense after laparotomy (decrease of HLA-DR), leading to enhanced sepsis in these patients.

COMMENTS

Background

Laparoscopic techniques are being increasingly used in diffuse or localised peritonitis. However, a possible concern is that increased intra-abdominal pressure may promote bacteraemia and the systemic inflammatory response during laparoscopic surgery. Data regarding the effects of pneumoperitoneum on physiologic changes and systemic inflammation during sepsis are controversial.

Furthermore, only early effects of pneumoperitoneum during peritonitis have been evaluated, and the differences between conventional and laparoscopic surgery have been compared only in animal models. The influence of laparotomy and laparoscopy on bacteraemia and endotoxaemia, peripheral leukocytic subpopulations (neutrophils, total lymphocytes, lymphocyte subpopulation), human leukocyte antigen-DR (HLA-DR), neutrophil elastase, interleukin-1 (IL-1), IL-6, C-reactive protein and skin Multitest was investigated in a prospective, randomized study in patients with acute calculous cholecystitis, complicated by biliary peritonitis, undergoing a random open or laparoscopic cholecystectomy. The results showed that open cholecystectomy (OC) increased the incidence of bacteraemia, endotoxaemia and systemic inflammation compared with the laparoscopic cholecystectomy (LC). It also caused lower transient immunologic defense, leading to enhanced sepsis in these patients. Few studies in the literature show a detailed evaluation of these parameters by prospective randomized study and there are no studies on stress response after LC or OC for acute calculous cholecystitis, complicated by biliary peritonitis.

Research frontiers

The study of inflammation biomarkers such as IL-1 and IL-6 allows us to directly quantify the response of the immune system since these interleukins are the basis of the activation of the cell-mediated immune system. The evidence of a faster normalization of the leukocyte count at post-operative day 2 in the LC group compared to the OC group is a further demonstration of this. Another substantial piece of evidence, not showed in any related study in the literature, can be inferred from the study of HLA-DR in both groups, given the crucial role of this antigen in the activation of the T-helper cell-mediated response of the immune-system. In the OC group we observed a post-operative decrease in the HLA-DR of peripheral monocyte. Patients who undergone LC showed a normal level of HLA-DR expression. The study of serum concentrations of neutrophils and of the enzymes produced by them (PNM-elastase) in the two groups allowed us to optimize the study with the evaluation of the polymorphic-nucleated component of the immune system.By these means, the study has demonstrated how the immune status has been better preserved and the inflammation response has been less in the LC group than in the OC group.

Innovations and breakthroughs

The majority of studies presented in the literature are experimental studies using animal models. This study is, instead, a prospective randomized study conducted on human subjects. Experimental studies on peritonitis showed that the inflammatory response was significantly higher in the OC group than in the LC group in the animal models, suggesting that carbon dioxide pneumoperitoneum has a protective effect against bacterial peritonitis. This study, in contrast to the previous ones, is the first demonstrating that OC after biliary peritonitis increases the incidence of bacteraemia, endotoxaemia and systemic inflammation more than LC The authors also demonstrated that early enhanced post-operative systemic inflammation may cause lower transient immunological defense after laparotomy (decrease of HLA-DR), leading to enhanced sepsis in these patients.

Applications

This study lays the foundations for future applications of laparoscopy in emergency surgery. The immunologic implications of laparoscopic surgery shown in this study on acute cholecystitis, complicated by bile peritonitis indicate a new management for peritoneal sepsis. However, this study has been limited to the observance of bile peritonitis. This means that further random prospective studies on immunologic responses in other forms of peritonitis (chemical and stercoraceous) treated by laparoscopy may be useful to detect new guidelines on the laparoscopic or open approach to colic perforations, such as diverticular perforations generating diffuse peritonitis (Hincey > 2). Moreover, further studies comparing the two methods when applied to the variations of peritoneal bacterial charges during stercoraceous or chemical peritonitis may give useful indications on the surgical approach to prefer. New studies of this type may foster the replacement of explorative laparotomy with the laparoscopic approach in case of peritonitis, as it presents the undeniable advantages of lower invasiveness and shorter recovery in patients.

Terminology

Bile peritonitis is an inflammatory, irritative response to the abnormal presence of bile and bacteria in the peritoneum. It may occur in up to 15% of patients with acute cholecystitis, even in the absence of gallbladder perforation. During bile peritonitis some chemical mediators of inflammation playing specific roles are studied: IL-1 is a cytokine excreted by various types of immune system cells including macrophages and monocytes in response to bacterial infections. The role of this molecule is to recruit macrophages and lymphocytes to the site of infection promoting the maturation and clonal expansion of T-helper lymphocytes and B lymphocytes. IL-6 acts as a cytokine with a pro- and anti-inflammatory effect. It is secreted by T-lymphocytes and macrophages to stimulate the immune response to specific microbial molecules. IL-6 is one of the main mediators of fever and responses in the acute phase. It can cross the hemato-cephalic barrier and start prostaglandin E2 synthesis in the hypothalamus, thus provoking the increase of body temperature. Another mechanism through which IL-6 causes the increase of body temperature is the stimulation of the catabolism of energetic substrates in muscles and adipose tissue. HLA-DR is a major histocompatibility complex class II cell surface receptor. The HLA-DR molecules are upregulated in response to signaling. During an infection, the peptide is bound into a DR molecule and presented to a few of the many great T-cell receptors found on T-helper cells. These cells then bind to antigens on the surface of B-cells, stimulating B-cell proliferation. The HLA-DR antigen expression on monocytes plays an important role in antigen presentation to lymphocytes, particularly T-helper lymphocytes. In fact, these cells require both HLA-DR and exogenous antigens on the macrophage surface to initiate proliferation. Neutrophil elastase is an enzyme of the serine protease family, released by neutrophils during the inflammatory process. It coordinates the destruction of bacteria and extraneous cells.

Peer review

The authors evaluated the systemic inflammation and immune response after laparotomy *vs* laparoscopy in patients with bile peritonitis caused by acute cholecystitis. The study design is unclear making interpretation of the data difficult.

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ORIGINAL ARTICLE

Computed tomography-based diagnostics might be insufficient in the determination of pancreatic cancer unresectability

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Abstract

AIM: To inquire into a question of an overestimation of arterial involvement in patients with pancreatic cancer (PC).

METHODS: Radiology data were compared with the findings from 51 standard, 58 extended and 17 total pancreaticoduodenectomies; 9 distal resections with celiac artery (CA) excision; and 28 palliations for PC. The survival of 11 patients with controversial computed tomography (CT) and endoscopic ultrasound data with regard to arterial invasion, after R0/R1 procedures (false-positive CT results, Group A), was compared to survival after eight R2 resections (false-negative CT results, Group B) and after 12 bypass procedures for locally advanced cancer (true-positive CT results, Group C).

RESULTS: In all of the cases in group A, operative exploration revealed no arterial invasion, which was predicted by CT. The one-year survival in Group A was 88.9%, and the two-year survival was 26.7%, with a median follow-up of 22 mo. One-year survival was not attained in groups B and C, with a significant difference in survival ($P_{a\text{-}b}$ = 0.0029, $P_{b\text{-}c}$ = 0.003).

CONCLUSION: Arterial encasement on CT does not necessarily indicate arterial invasion. Whenever PC is considered unresectable, endoUS should be used. In patients with controversial CT an EUS data for peripancreatic arteries involvement radical resection might be possible, providing survival benefits as compared to R2-resections or palliative surgery.

Key words: Vascular invasion; Cancer; Pancreas; Management; Pancreaticoduodenectomy; Distal pancreatectomy; Computed tomography; Endoscopic ultrasound; Arteries; Resectability

Core Tip: Pancreatic cancer remains one of the most aggressive neoplastic processes, and the methods to manage it are constantly evolving. Resection remains the only potential cure for pancreatic cancer, and it can prolong survival in patients compared to those who do not undergo resection. However, only a minority of patients are candidates for surgery at diagnosis, and

only a minority of patients who undergo surgery survive beyond 5 years. The most important cause of an inacurate assessment of resectability is underestimation of vascular invasion. This study attempted to address the other side of the problem: overestimation of arterial involvement in patients with pancreatic cancer.

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INTRODUCTION

Pancreatic cancer remains one of the most aggressive neoplastic processes, and the methods to manage it are constantly evolving[1,2]. Despite impressive progress in the diagnosis and treatment of other-sited malignances, the resectability and 5-year survival rates for pancreatic cancer are still very poor, with survival rates for cancers of the pancreatic body and tail of 10% and 10% in North America and Western Europe, respectively, and of 34% and 18% in Japan, as well as approximately 19% for the pancreatic head[3,4]. Resection remains the only potential cure for pancreatic cancer, and it can prolong survival in patients compared to those who do not undergo resection. However, only a minority of patients are candidates for surgery at diagnosis, and only a minority of patients who undergo surgery survive beyond 5 years[5-9].

The decision "to resect or to palliate" depends on the clinical staging system, which is based on the results of pre-surgical imaging studies. In the absence of metastatic disease, assessment of vascular invasion is a key aspect in the evaluation of resectability for pancreatic cancer[4,5,10-15]. Obviously, surgical exploration with pathological examination remains the "gold standard" in terms of evaluation of resectability, especially from the point of view of vascular involvement[6,7,9]. The salient sign of unresectability in pancreatic ductal adenocarcinoma (PDAC) is encasement of the superior mesenteric and celiac arteries, indicating vascular invasion. Computed tomography (CT) is the "gold standard" for preoperative PDAC detection and for evaluation of its resectability[4,5,10-15]. Efforts have typically been focused on accurately assessing tumor resectability based on CT criteria to avoid non-therapeutic laparotomy. It is equally important, however, to ensure that no patient with a resectable tumor is denied surgery because of a false-positive evaluation of arterial invasion[10-26]. The degree of arterial involvement has been assessed by CT, with accuracy in the evaluation of pancreatic cancer (PC) resectability for single-detector row machines varying between 70% and 80%[16-18]. For modern multi-detector row computed tomography (MDCT) scanners, the accuracy of 85%-93% (sensitivity of 80%-90%, specificity of 89%-100%) is only slightly better[19-26]. The most important cause of an inaccurate assessment of resectability is underestimation of vascular invasion. This study attempted to address the other side of the problem: overestimation of arterial involvement in patients with PC.

In this study, we compared the following: (1) the instrumentally derived evidence with the findings during surgery from patients with CT-predicted circumferential tumor apposition to the peripancreatic arteries (judged unresectable in compliance with current recommendations), which proved to be uninvaded intraoperatively; and (2) these patients' survival with that of patients treated with R2 resections and palliative procedures for locally advanced pancreatic cancer.

MATERIALS AND METHODS

Patients

The institutional review board approved this retrospective study, and special patient informed consent, other than standard consent for surgery, was not required.

Data from preoperative CT and endoscopic ultrasound (EUS) reports of 163 patients consecutively operated on for ductal adenocarcinoma were compared with the findings of 51 standard, 58 extended and 17 total pancreatoduodenectomies (PDs), 9 distal resections with CA excision (DPCA) and 28 palliative bypasses for PDAC, performed between June 2005 and June 2012 (EUS-between 2008 and 2012). From all of these cases, 11 borderline-resectable patients were found who had controversial data on CT and EUS with regard to peripancreatic arterial tumor invasion (group A). They all had CT signs of arterial involvement, but curative R0/R1 procedures, with or without excision of the arteries, were performed. Survival in the above-mentioned group was compared to the survival of 8 patients who underwent R2 resections (group B) and of 12 patients with locally advanced cancer, in whom palliative bypass surgeries were performed (group C). Sixteen patients who underwent bypass procedures were not included in the study due to the presence of distant metastases. In the remaining patients, no distant metastases were detected during surgery.

The patients' historical data, including the stage of disease, level of resection, age, sex, diagnosis and site of tumor, affected vessels, mode of adjuvant chemotherapy, recurrence-free time interval (when possible) and survival, were obtained.

Methods

CT: All of the patients underwent preoperative, native and contrast-enhanced triphasic 64-slice and 256-slice multi-detector computed tomography (Phillips Brilliance). Five hundred milliliters of water was routinely administered 5-10 min before the examination to demarcate the duodenum and delineate the pancreatic head region. Each patient received 100 mL of non-ionic contrast ma-

terial with 370 mg of iodine/mL (omnipaque 350, ultravist 370, optiray 350) *via* intravenous injection at the rate of 3-5 mL/s, using an automatic power injector (OptiVantage DH (Mallinckrodt, Inc.) through an 18-gauge or 20-gauge intravenous catheter inserted into an antecubital vein. Unenhanced and triphasic (arterial phase, portal venous phase) enhanced scans were obtained. Unenhanced and enhanced scan images were obtained from the top of the diaphragm through the pelvis. Monitoring of the contrast media bolus was performed on the level of the aortic arch in all cases. The trigger threshold of density was set at 150 HU for the aortic ROI, which was placed at the center of the vessel lumen. The delay after the start of the injection was 10 s for the arterial phase and 35 s for the portal venous phase. The levels of the tracker and the starting position were the same. To estimate individual vascular trees pre-surgically, three-dimensional reconstructions of CT angiograms were acquired with the software used during routine CT examinations. All of the CT angiographic images were read by the radiologist and attending surgeon, and the arterial diameters and variants of celiaco-mesenteric arterial anatomy (according to Michels[27] criteria) were recorded.

EUS: Patients underwent EUS of the pancreato-biliary system, performed by experienced endoscopists using electronic echoendoscopes EG 530 UR for radial scanning and EG 530 UT for linear scanning, supplied by an SU-7000 ultrasound processor (Fujinon, Japan) with color Doppler function. Evaluation of the superior mesenteric, portal and splenic veins and the celiac trunk could be performed with high accuracy by radial echoendoscopy. A limitation of radial scanning was incomplete visualization of the superior mesenteric artery. In such cases, we resorted to linear scanning. Endoscopy was performed under conscious sedation using intravenous midazolam. The EUS criteria for vascular invasion were: loss of the hyperechoic vessel wall/tumor interface; an irregular tumor/vessel interface; a tumor within the vessel lumen; irregularity of the vascular wall; vessel encasement; and collaterals with associated arterial narrowing or occlusion (non-visualization of major vessels)[11-13,28].

Procedures

A standard PD included the removal of the lymph nodes of the anterior and posterior pancreatoduodenal, pyloric, hepatoduodenal ligament and of the superior and inferior pancreatic head and body lymph node stations. An extended in our institution consisted of the additional removal of all of the lymph nodes from the hepatic hilum, along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to both the renal hila, as well as clearance of the circumference of the origin of the celiac trunk and the superior mesenteric artery, with total resection of the nerve plexus around the superior mesenteric artery and the portal vein. The procedure included removal of perivascular lymphatics and nerves and retroperitoneal connective tissue.

An extended distal pancreatectomy, which we usually perform "from the right to the left", consisted of removal of the spleen and the pancreatic neck, body and tail with the splenic vessels, as well as all of the lymph nodes from the hepatic hilum, along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery, and clearance of the circumference of the origin of the celiac trunk and the superior mesenteric artery, with resection of the nerve plexus to the left and right of the superior mesenteric artery. The procedure included removal of perivascular lymphatics and nerves and retroperitoneal connective tissue. If malignancy was suspected during frozen section examination of the posterior border of the specimen, a left adrenalectomy with periglandular tissue was performed. In cases of involvement of the common hepatic or celiac artery by pancreatic body cancer, a modified Appleby procedure (extended distal pancreatectomy with excision of the celiac and common hepatic arteries) was performed. The resection was considered radical if there were no tumor cells on frozen section examination, in the left resection margins for PD and in the right margins for distal pancreatectomy.

For histopathological examination of PD specimens, an axial slicing technique and circumferential resection margins studying were used. The definitions of R0 and R1 resection were based on the "1 mm clearance" rule, including lymph node assessment in case of tumor spreading beyond the lymph node capsule. We considered resection to be R0 if there were no tumor cells found within a 1 mm distance from the specimen's circumferential margins, except for the anterior surface evaluation, in which we applied the "0 mm clearance" rule[29].

Statistical analysis

Statistica software (data analysis software system, version 6.0 StatSoft, Inc. 2001; MedCalc version 11.6.0.0 of MedCalc) was used for the statistical analysis. The distributions of age at operation, postoperative hospital stays, and follow-up periods are described as medians with interquartile ranges. The numbers of the complications in the groups are expressed as integers without percentages in light of the small number of subjects. Fisher's exact test was used to analyze morbidity and mortality between the subgroups of patients. Data values are presented on a continuous scale, but distributions different from normal (*e.g.*, patient age, duration of postoperative treatment) were compared using the nonparametric analogue ANOVA and the Kruskal-Wallis test. For consistent distinction comparison, the Mann-Whitney method with Bonferroni's correction for multiple comparisons was used. Overall survival from the date of resection was estimated using the Kaplan-Meier method. The 1-and 2-year actuarial survival rates and the median survival time, with corresponding 95%CI, are presented. Disease-free survival could not be calculated in all of the patients because of the retrospective nature of the study. The end of the follow-up period for the patients who survived was in December 2012. Patients alive at the last follow-up were censored and are

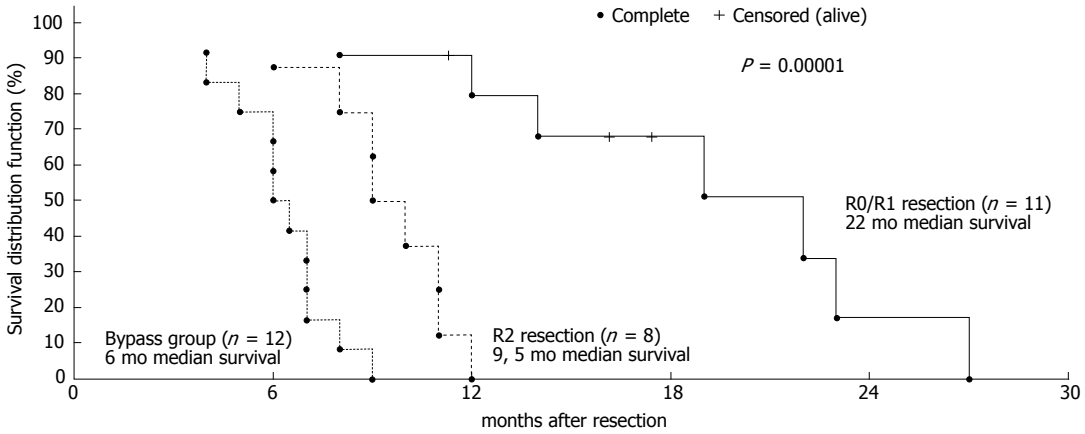

Figure 1 Differences in survival between the groups were significant. The explanation is in the text.

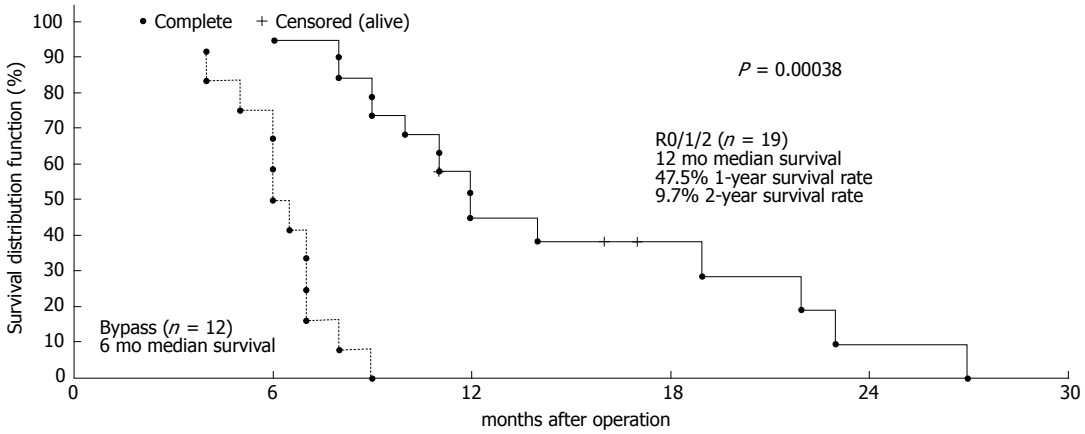

Figure 2 Median survival following palliative operations was 6 mo (95%CI: 5-7 mo) and there was a significant difference in survival between the palliative group (C) and the united resection group (group A + group B).

marked in Figures 1 and 2. The log-rank test was used to compare survival curves. Two-sided *P* values were always computed, and an effect at a *P* value <0.05 was considered statistically significant.

RESULTS

The diagnosis of ductal adenocarcinoma of the pancreas was histologically proved in all of the cases. In all of the cases in group A, the arteries involved on CT were considered intact during surgery (Figures 3-7). There were no differences between the groups regarding age or sex. The tumor size was significantly larger in the bypass group (Table 1), although real tumor size in these patients could not be measured because the tumors were not removed, and they were assessed during surgery only approximately.

Attempts at PD or distal pancreatectomy in Group A were chosen as a result of the obvious discrepancies between the CT evidence and EUS findings: in each of these cases, the CT imaging features displayed were consistent with the peripancreatic arteries (Table 2) being completely encased by the tumor, while the EUS appearance was suggestive of the tumor merely abutting the arteries. In group B, palliative PDs were performed as motivated by the equivocal CT findings regarding tumor resectability and surgeon-disclosed superior mesenteric artery (SMA) and/or CA tumoral involvement after gland transection, that is, after having crossed "the point of no return".

In group A (Table 2), the tumor was located in the pancreatic head and body in 5 and 5 cases, respectively, and in 1 case, the pancreas was completely involved. No CT-presumed encasement of the peripancreatic arteries by the tumor was noted in the surgical records to have been discovered during surgery in group A (Figures 3-7). Under microscopy, in cases 2, 3, 7, 9 and 10, tumor cells were detected in the periarterial nerve plexus to the left of the artery of interest, while the right side of the plexus was free of tumor. In cases 1, 5, 6, 8 and 11, tumor cells were detected in the periarterial nerve plexus to the right of the artery of interest, and the left side of the plexus was free of tumor. In case 4, tumor cells were detected in the periarterial nerve plexus to the right and to the left of the SMA. In all of the cases, the artery of interest was definitely uninvolved (Figures 3-7).

In all but one of the cases, the level of an R1 resec-

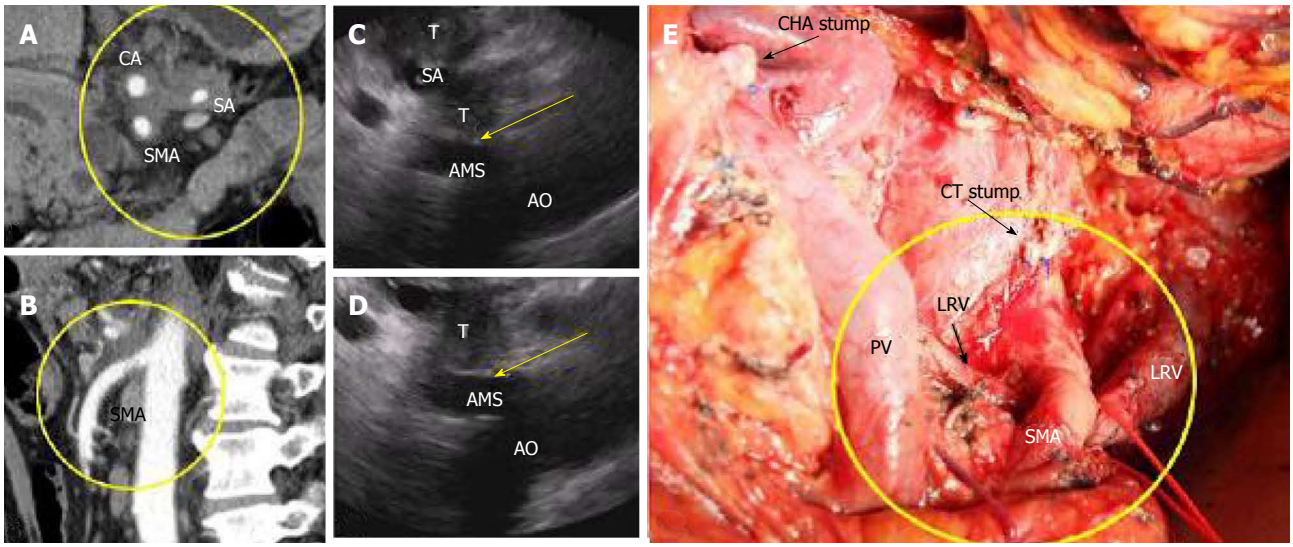

Figure 3 In this 65-year-old man (case #10), pancreatic body DAC with 360° celiac (CA), splenic (SA) and superior mesenteric artery (SMA) encasement was established on CT (A, B), but endoUS data did not confirm this conclusion, finding a plane between the tumor and the SMA (C, D, arrows). AMS: Arteria mesenterica superior, AO: Aorta, T: Tumor. Distal pancreatectomy with excision of the celiac artery (CA) and left adrenalectomy were performed, and no SMA involvement was identified during surgery (E). The level of resection was R1 because of the contact of the SMA with the tumor. CHA: Common hepatic artery; CT: Celiac trunk; LRV: Left renal vein; PV: Portal vein.

Table 1 The demographic findings and tumor size in groups

	R0/R1 resection (*n* = 11)	R2 resection (*n* = 8)	Bypass (*n* = 12)	$P_{Kruskal-Wallis}$
Age (yr)	61 (59-65)	69 (65-72)	62 (60-68)	0.122
Male/female	5/6	4/4	3/9	-
Tumor size (cm)	4 (4-4.5)	4 (3.9-4.2)	5 (4.5-5.5)[1]	0.001

[1]Tumor size was measured without tumor removal.

tion was secured as required by the artery-tumor contact; in 1 case an R0 resection was achieved. The status of a negative resection margin of the pancreas and clear soft tissues to the left of the SMA during PD and to the right of the SMA during distal pancreatectomy were histologically confirmed during surgery in each of these cases. In three cases a classical PD was performed, in two cases - pylorus-preserving PD, in one case - a pylorus-preserving total duodenopancreatectomy, and in five cases we performed distal PD with CA excision (the modified Appleby procedure). Three PDs were added by pancreatic body resection and portal vein (PV) or superior mesenteric vein (SMV) resection. Based on the CT data in all the cases, the tumor extents were clinically staged as T4, with regional spread suspected in five cases. In all the cases, CT revealed the unresectable tumors: in six cases it was caused by involvement of the SMA, in one case - of the SMA and CA, in one case - of the CA and left hepatic artery (LHA), in one case - of the common hepatic artery (CHA), and in the last two cases the unresectability on CT were caused by replaced right hepatic artery (rRHA) and gastroduodenal artery (GDA) involvement respectively.

In the R2 group (B, Table 3), the neoplasm was observed in the pancreatic head in 7 cases and in the body of the pancreas in 1 case. In 2 cases, the classical version of standard PD was performed, and in 6 cases, its pylorus-preserving variation was performed. In one case, the modified Appleby operation was performed. In all of the cases, the tumor extent was intraoperatively assigned as T4, owing to SMA invasion, and all of the patients were found to have regional metastases (Table 3). Five patients in this group were examined by endoUS, which showed SMA involvement in one case and CA involvement in one case, and in three cases, the report was equivocal because of technical difficulties.

In the bypass group (C, Table 4), the tumor was located in the pancreatic head and body in 9 and 2 cases, respectively, and in 1 case, the entire gland was affected. In all of the cases, CT identified the spread of the malignancy as T4 due to SMA alone or both the SMA and CA together being involved in 7 and 5 cases, respectively. Regional spread was proved in 5 cases. In the other patient, pancreas biopsy was performed, while biopsy of the lymph nodes was not performed.

Gemcitabine chemotherapy is a standard postsurgery treatment in pancreatic cancer, and it was performed in 23 cases. Eight patients in group A, 6 in group B and 8 in group C received and/or are receiving gemcitabine chemotherapy. One patient with pancreatic body cancer from group A was administered gemcitabine and eloxatin neoadjuvant chemotherapy. Five patients (1 from group A, 1 from group B and 3 from group C) refused chemotherapy, and in three cases (1 case from each group), chemotherapy was canceled because of bad physical performance.

Perioperative characteristics were only compared in groups A and B because there was no significant blood loss or ICU stays in the bypass group (C). There were no differences between operating time (P_{MW} = 0.368),

Table 2 The characteristics of patients who underwent radical (R0-1) surgery for pancreatic ductal adenocarcinoma with circular arterial involvement on computed tomography (group A)

Stage	R factor	PDAC location	Artery involved on CT	ChT	DFS (mo)	Survival (mo)
cT4NxM0	pT3N1M0(R1)	Head	rRHA	+	17	19
cT4NxM0	pT3N1M0(R1)	Body	SMA	+	20	27
cT4NxM0	pT3N1M0(R1)	Body	SMA	+	19	22
cT4N1M0	pT3N1M0(R1)	Head	SMA	+	17	23
cT4NxM0	pT3N0M0 (R1)	Total	CHA	-	12	14
cT4NxM0	pT3N1M0(R1)	Head	SMA + SMA[2]	+	NA	17[1]
cT4N1M0	pT2N0M0 (R0)	Body	CA and LHA	+	16	16[1]
cT4N1M0	pT3N1M0(R1)	Head	SMA	+	10	12
cT4N1M0	pT3N1M0(R1)	Body	GDA	-	6	8
cT4NxM0	pT4N1M0(R1)	Body	SMA	+	NA	11[1]
cT4N1M0	pT3N1M0(R1)	Head	SMA and CA	+	10	11[1]

[1]Alive; [2]In case 6 there were two SMA segments involved on CT. SMA: Superior mesenteric artery; rRHA: Replaced right hepatic; LHA: Left hepatic; CA: Celiac artery; GDA: Gastroduodenal artery; PDAC: Pancreatic ductal adenocarcinoma.

Table 3 The characteristics of patients who underwent R2 resections for pancreatic ductal adenocarcinoma (group B)

Stage		PDAC location	Artery involved	ChT	Distant mets (mo)	Survival (mo)
cT3NxM0	pT4N1M0	Head	SMA	+	7	10
cT3NxM0	pT4N1M0	Body	SMA	-	3	6
cT3N1M0	pT4N1M0	Head	SMA	+	NA	11
cT3NxM0	pT4N1M0	Head	SMA	+	8	12
cT3N1M0	pT4N1M0	Head	SMA	+	7	11
cT3NxM0	pT3N1M0	Head	SMA	+	NA	9
cT3NxM0	pT4N0M0	Head	SMA	-	NA	9
cT3NxM0	pT4N1M0	Head	SMA	+	6	8

SMA: Superior mesenteric artery; PDAC: Pancreatic ductal adenocarcinoma; NA: Not available; ChT: Chemotherapy.

Table 4 The characteristics of patients who underwent bypass procedures for locally advanced pancreatic ductal adenocarcinoma (group C)

Stage	PDAC location	Artery involved	ChT	DFS (mo)	Survival (mo)
cT4N1M0	Head	SMA and CA	-	3	4
cT4NxM0	Head	SMA	-	NA	7
cT4NxM0	Head	SMA	+	4	7
cT4NxM0	Head	SMA	+	4	6,5
cT4NxM0	Head	SMA	+	NA	6
cT4N1M0	Body	SMA and CA	+	2	5
cT4NxM0	Total	SMA and CA	-	NA	4
cT4NxM0	Head	SMA	+	5	7
cT4NxM0	Head	SMA	+	5	9
cT4N1M0	Head	SMA and CA	+	NA	6
pT4N1M0	Body	SMA and CA	-	NA	6
pT4N1M0	Head	SMA	+	4	8

ChT: Chemotherapy; SMA: Superior mesenteric artery; CA: Celiac artery; GDA: Gastroduodenal artery; LHA: Left hepatc artery; CHA: Common hepatic artery; rRHA: Replaced right hepatic artery; DFS: Disease-free survival.

blood loss (P_{MW} = 0.47) and length of ICU stay (P_{MW} = 0.409) between groups A and B. The overall hospital stay time was approximately the same (P_{KW} = 0.165) in all three groups (Table 5). Postoperative complications are shown in Table 6. Three pancreatic fistulas appeared after Appleby procedures, as well as one after a Whipple procedure.

There were significant differences in survival among the groups (P = 0.0001). One-year survival was not attained in groups B and C, notwithstanding the difference in survival between groups B and C being considerable (P = 0.003). The median survival for group B was 9.5 mo (95%CI: 8.5-11 mo). The one-year survival rate in group A was 79.5% (95%CI: 54.5%-100%), and the two-year survival rate was 17% (95%CI: 0.00%-47.5%), with a median follow-up period of 16 mo (95%CI: 11-22 mo) and median survival of 22 mo (95%CI: 14-23 mo). The difference in survival between groups A and B was significant ($P_{log\text{-}rank}$ = 0.00001) (Figure 1). The actuarial one-year survival in the united resection group (group A + group B), *i.e.*, in resections with non-mettering factor R, was as high as 45% (95%CI: 21%-68%), while two-year survival was 9.7% (95%CI: 0.00%-27.5%), with median survival of 12 mo (95%CI: 10-22 mo). The median survival following palliative operations was 6 mo (95%CI: 5-7 mo), and there were significant differences in survival among the groups (Figure 2).

The sensitivities of CT (147 patients) and EUS (87 patients) for the detection of arterial involvement were 60% and 78.5%, respectively, with specificities of 78.5% and 98.6%, respectively. Sixteen patients were excluded because of distant spread confirmed by CT and during surgery.

DISCUSSION

Vascular involvement was found in 21%-64% of patients with pancreatic carcinoma, most often with involvement of the superior mesenteric artery, due to its location, and errors associated with evaluation of arterial invasion were frequent[19-26]. Currently, it is believed that involvement of the PV or SMV is not a criterion of unresectability for pancreatic carcinoma[4,5,8,9,30,31]. In half of the cases, only fibrotic changes were found during the histologic

Table 5 The perioperative characteristics in groups

ME (25%-75%)	R0/R1 resection (*n* = 11)	R2 resection (*n* = 8)	Bypass (*n* = 12)
Operation time, min	570 (470-630)	540 (390-600)	Ne
Blood loss, mL	700 (450-1500)	1000 (600-1500)	Ne
ICU, d	2 (2-3)	3 (2-8)	Ne
Postoperative hospital stay, d	16 (13-26)	13 (12-19)	12 (11-17)

Ne: Not evaluated; ICU: Intensive care unit.

Table 6 The postoperative complications in groups (according to Clavien-Dindo classification)

	R0/R1 resection (*n* = 11)	R2 resection (*n* = 8)	Bypass (*n* = 12)
Grade 2	3	2	3
Lymphorrhea	3	2	-
Diarrhea	2	-	-
Delayed gastric emptying Grade 3a	-	-	3
Pancreatic fistula[1]	3 (grade B)	1 (grade B)	-

[1]According to ISGPF classification.

evaluation of resected veins due to a suspicion of tumor intergrowth[30,31]. According to the existing TNM classification, involvement of the main peripancreatic arteries by pancreatic adenocarcinoma is considered a contraindication for pancreatic resection[4,5]. Nevertheless, the concept of arterial invasion remains a matter for discussion and gradual changes, which is supported by recently adopted National Comprehensive Cancer Network guidelines for borderline resectable pancreatic adenocarcinoma[5]. In particular, it happens because reconstruction of arteries is not a technical problem anymore[32-34], and resection of the celiac and common hepatic arteries during distal pancreatectomy usually does not require reconstruction[35,36]. Histologic results, similar to those for veins, have shown that invasion of resected arteries occurs in only half of cases[37-39].

The criteria for assessing the accuracy of resectability prior to surgery and, in particular, vascular involvement remain surgical exploration with pathohistological evaluation, although intraoperative diagnostics for arterial invasion can require aggressive actions, resulting in incomplete resection and remains subjective[37-40]. Frequently, invasion of the arteries is found when the pancreas has already been cut and the "point of no return" passed[40]. Palpation of the superior mesenteric artery and celiac artery, even after mobilization and cutting of the pancreas, cannot be considered an accurate method of detection of arterial invasion, especially after radiotherapy, during reoperations, or in cases of large tumors and accompanying pancreatitis[2,6,7,37-40]. For example, in our research, according to data on only intraoperative revisions, none of the tumors was considered resectable in group A, and none of the tumors was considered unresectable in group B before transection of the pancreas.

Today, CT scanning is considered the method of choice for suspected pancreatic carcinoma, allowing for diagnosis and for determining the localization, size, dissemination and staging of tumors during one noninvasive examination[10-15]. The adoption of CT criteria for arterial involvement in pancreatic cancer (absence of a fat plane between the tumor and vessels, vessels surrounding the tumor by more than 50% of its circumference, occlusion of vessels with development of collaterals) can be significantly aided by 3D and multiplanar reconstructions[22-24], 3D CT-angiography[41,42] and the technique of thin pancreatic slices, which reveals fine details of the vessel walls[10,19,43-45].

Two meta-analyses of CT's ability to reveal arterial involvement in pancreatic carcinoma showed sensitivities of 91% and 68% and specificities of 85% and 93%[25,26]. Loyer *et al*[46] noted that the presence of a fat plane (type A) or normal pancreatic tissue between the tumor and vessels (type B) is a good prognostic sign, as resectability in these situations reached 95%. Phoa *et al*[15] discovered that in vessel embedment into the tumor (type D) or the vessel's circular encasement (type E), the rate of vessel invasion was nearly 88%, and potential resectability was 7% for type D and 0% for type E. It was noted that the sensitivity of CT for the detection of unresectability of pancreatic carcinoma reached 60%, and specificity reached 90% if contact of a vessel with tumors of type D or E was noted over at least 90° degrees of its circumference[15]. A relatively reliable sign of vein intergrowth by a tumor is contact of more than 5 mm in length (78% for PV and 81% for SMV). This sign was not proved for arteries; however, it was shown that surrounding of the vascular wall by more than 180° of the tumor's circumference was correlated with unresectability, with a sensitivity of 84%, specificity of 98%, positive predictive value (PPV) of 95%, and negative predictive value (NPV) of 93%[23]. A high risk of invasion has been recognized by several authors due to pronounced narrowing of the arteries on CT, although involvement of the arterial wall is possible, even if its diameter is normal[15,19,47].

The criteria developed by Li *et al*[47] for arterial invasion during pancreatic carcinoma are embedment of vessels in the tumor or a combination of the tumor surrounding no less than a half of a vessel's circumference with stenosis of the artery (sensitivity of 79%, specificity of 99%) or with irregularity of the arterial wall (sensitivity of 45%, specificity of 99%). House *et al*[48], using 3D CT for detection of arterial invasion, showed sensitivity of 86%-87% and specificity of 97%-99%. The accuracy of CT for the detection of arterial invasion by pancreatic carcinoma is shown in Table 7.

The accuracy of MRT for the detection of arterial invasion in pancreatic carcinoma was equal to the accuracy of CT[25,26,49,50] and EUS[51], while the accuracy of angiography was relatively low (sensitivity of 21%-84%[11,14,52], specificity of 50%-100%[14,52], PPV of > 60%[11,52] and NPV 50% of 83%[52]) compared to other diagnostic modalities. The capability of CT angiography to delineate the celiaco-mesenteric architecture with high accuracy

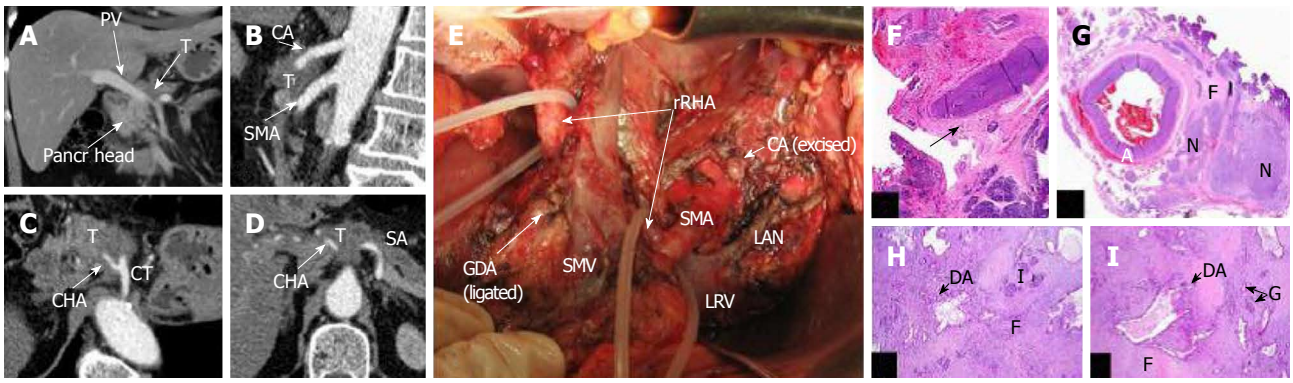

Figure 4 In this 64-year-old woman (case 7), circular encasement of the celiac, common hepatic, left gastric, left hepatic and splenic arteries by PDA on the background of aberrant arterial anatomy; a replaced right hepatic artery (rRHA, Michels, type VIIIb) was identified on CT (A-D). E. Photograph of operating field after distal pancreatectomy (R0 resection), with excision of the celiac, common, left gastric, left hepatic arteries and gastroduodenal artery resection in the absence of any evidence for major arterial invasion, either during surgery or on histopathology; the blood supply to the stomach was routed from the SMA *via* pancreaticodudenal arcades and then through the GDA with the latter's proximal segment being resected and ligated. F-I: Removed specimen under microscope. The tumor (DA) was smaller than 2 cm and was surrounded by a thick layer of fibrotic tissue (H,I). There were no signs of involvement of the major peripancreatic (CHA, GDA, LHA) arteries; H: CHA section obtained from close to the point of its transection (white arrow) in the fibrotic zone (black arrow) along the pancreas margin. No evidence of tumor growth x 5. G: Celiac plexus and trunk area of diffuse fibrosis (F) x 5; A: Artery; N: Nerve plexus with large ganglion; H: Pancreatic tissue with apparent diffuse fibrosis (F), groups of islets remaining (I) and groups of glandular formations of ductal adenocarcinoma (DA) of the pancreas x 50. d: Structures of DA throughout the fibrotic tissue (F) containing remnants of pancreatic tissue (atrophic islets and ductules) x 50, hematoxylin + eosin. PV: Portal vein; T: Tumor; CA: CT-celiac artery (celiac trunk); SMA: Superior mesenteric artery; GDA: Gastroduodenal artery; rRHA: Replaced right hepatic artery; PDA: Pancreato-duodenal arcade; LRV: Left renal vein; PV: Portal vein; SMV: Superior mesenteric vein; LAV: Left adrenal vein.

has practically excluded angiography from the diagnostic algorithm for patients with pancreatic tumors[41,42].

EUS is an operator-dependent (especially in the hepatopancreatobilliary zone) and expensive method[11-13,28,53-61], the sensitivity of which for staging of pancreatic carcinoma (with fine-needle aspiration) is 96.6%, with accuracy of 99.0%, NPV of 96.2% and PPV of up to 100%[11-13,28,56-61]. It was shown that endoscopic ultrasound is a more accurate method for the diagnosis of venous invasion, compared to CT, conventional ultrasound and angiography[54,57]. Evaluation of arterial involvement is a more complicated task for EUS: sensitivity is from 50% to 100%, with specificity from 58 to 100%, PPV from 28% to 100% and NPV between 18% and 93%[28,53,55,56-61].

A comparison of EUS, MDCT, magnetic resonance imaging (MRI) and selective angiography for the evaluation of periampullary tumors showed that EUS was more accurate than CT and MRI for the evaluation of local tumor spread, although this accuracy decreased from 84% to 72% in the presence of transpapillary biliary stents[62]. The accuracy of resectability evaluations by laparoscopic ultrasound is close to that as with endoUS[63]. Transvenous ultrasound is only used for the evaluation of venous invasion, and there are no data on arterial invasion assessments using this method[64].

The low accuracy of CT in the evaluation of the resectability of pancreatic carcinoma was shown by the results of pathohistological evaluations of resected peripancreatic arteries[37-39] as without previous treatment, so as after neoadjuvant radio- and chemoradiotherapy[65,66]. Our observations showed that none of described arterial invasion CT criteria[15,47-49], or even their combination, was absolutely reliable (Figures 3-7). At the same time, combined use of radial and convex EUS transducers allowed for the detection of a space between the tumor and artery (Figure 3), despite the pressing of previously accepted CT data showing circular artery involvement.

It is possible that peritumoral desmoplasia or an inflammatory reaction is indistinguishable from tumor infiltration on CT evaluation. These histopathological findings appear to be a reason for CT false-positive conclusions regarding arterial involvement in pancreatic carcinoma. When considering the accuracy of CT and other diagnostic modalities in assessing arterial invasion by pancreatic cancer, it is noteworthy that the problem of false-positive results of CT in the evaluation of arterial involvement is discussed very little. As mentioned previously, it is accepted now that without distant spread, the resectability of pancreatic carcinoma can be determined by the involvement of the SMA and CA[4,5]. At the same time, according to the literature, patients who underwent pancreatic resection, even with positive margins, lived significantly longer than patients after palliative surgery[67-71], especially taking into consideration recent data that most pancreatic cancer resections are R1 resections[72]. Considering that the tactics for pancreatic carcinoma treatment are based primarily (and often only) on data from CT, the long-term survival rates and patients' fates are extremely CT-dependent. With this connection, cases of CT false positivity regarding arterial invasion (when involvement of the artery, predicted by CT, is not confirmed during surgery) acquire a special meaning. There are only two ways to confirm or refute arterial invasion: to resect and examine a specimen or to perform circular skeletonization and determine that there is no involvement. The mystery is that neither one nor the other is recommended by existing guidelines[4,5], and most HPB departments follow these recommendations. Nevertheless, many pub-

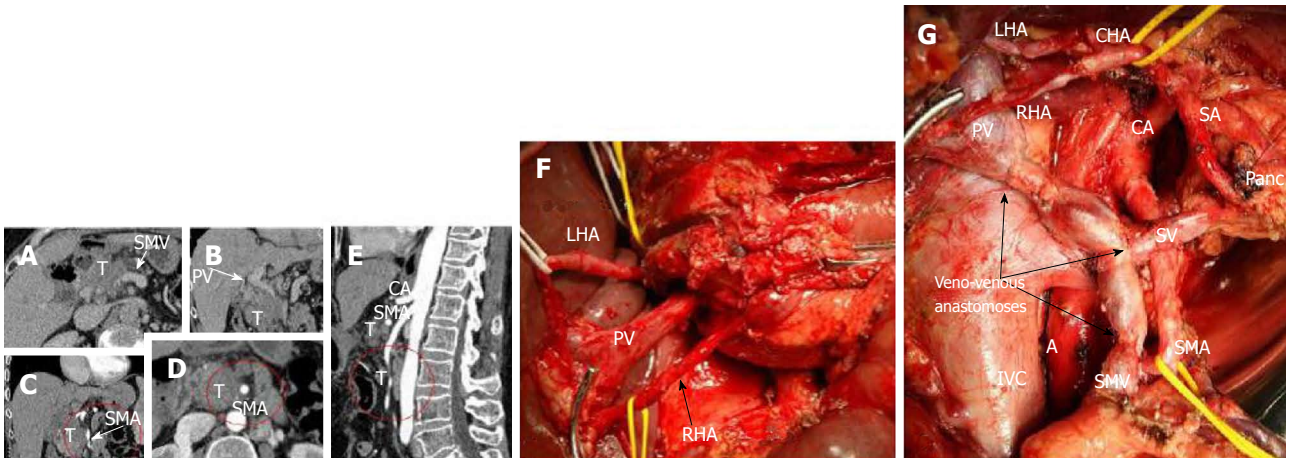

Figure 5 In this 61-year-old woman (case 6), 260° and 360° pancreatic ductal adenocarcinoma encasement of SMA segments was diagnosed on computed tomography (A-E), while endoUS data described only tumor abutment with the superior mesenteric artery. A, B: Venous phase. Sagittal view. Computed tomography provided evidence of circumferential involvement of the SMV and PV; C, E: Arterial phase. Sagittal view. The distal SMA segment (6-7 cm from the origin) presented circumferential adjacency to pancreatic head ductal adenocarcinoma. The celiac artery (CA) was unaffected; D: Arterial phase. Axial image. At least 260° of the proximal SMA segment (2.5-3 cm from the origin) was circumscribed by tumor. An extended Whipple procedure with pancreatic body, portal, splenic and superior mesenteric vein resection was performed with the use of a superficial femoral vein autograft (F, G). Notwithstanding "organoleptic" signs of unresectability (both hepatic arteries were embedded in the tumor) (F), there were no signs of superior mesenteric artery (SMA) or hepatic artery involvement during surgery (G). The level of resection was R1 because of the contact of the SMA with the tumor. A: Aorta; CHA: Common hepatic artery; RHA: Right hepatic artery; LHA: Left hepatic artery; SA: Splenic artery; SMV: Superior mesenteric; PV: Portal vein; LRV: Left renal veins; T: Tumor; Pancr: Pancreatic tail stump.

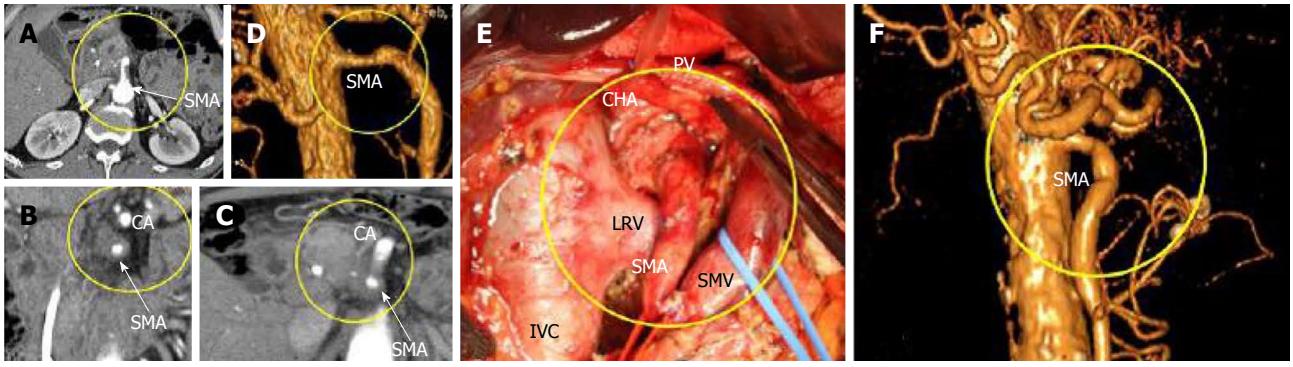

Figure 6 In this 59-year-old man (case 4), 360°pancreatic ductal adenocarcinoma encasement of the superior mesenteric artery was diagnosed on computed tomography (A-D), while endoUS data described only tumor abutment with the superior mesenteric artery. A-C: Computed tomography (CT), Arterial phase, Axial images. CT showed circumferential infiltration of the SMV. The CA was intact; D: CTA. Local narrowing of the SMA at the site at which it was circumscribed by the tumor; E: Intraoperative photograph. An extended Whipple procedure was performed. There were no signs of SMA involvement during surgery. The level of resection was R1 because of the contact of the SMA with the tumor; F: CT angiography. Three months postsurgery. No relapse and no narrowing of the SMA. SMA: Superior mesenteric artery; SMV: Superior mesenteric; PV: Portal; IVC: Inferior caval; LRV: Left renal veins; CA: Celiac artery.

lications comparing different methods of detection of arterial invasion in carcinoma have reported a number of false-positive results different from zero and, accordingly, a PPV different from 100% (Table 7).

This problem generates a number of questions: (1) What is/are the culprit/s in false-positive CT results of arterial invasion assessment in pancreatic cancer? How can surgeons appraise these results intraoperatively? Would mere palpation suffice for the surgeon to determine? (2) What makes a surgeon revise the arteries (primarily the CA and SMA, which are rather tedious to revise) after CT has shown them to be involved? (3) How can the surgeon ascertain that the artery (especially the SMA and CA) is intact, if he/she does not resect it or does not perform extended pancreatectomy, implying circumferential skeletonization of the CA and SMA? (This question is of greater concern in light of it being most hospitals' (including high-volume hospitals) policy not to resort to extended pancreatic resection because they are considered oncologically unwarranted[1,73,74].

The standard answer to these questions is "We do not perform pancreatic resections if CT discovers circular arterial infiltration, indicating arterial and/or periarterial neural invasion, which is associated with poor prognosis. That is why we do not have false-positive results." However, lack of research on this subject, data from a number of authors regarding the long-term survival of patients after pancreatic resections compared to a palliative surgery, the existence of false-positive results on CT (Table 7), and data from our work indicate that not all is

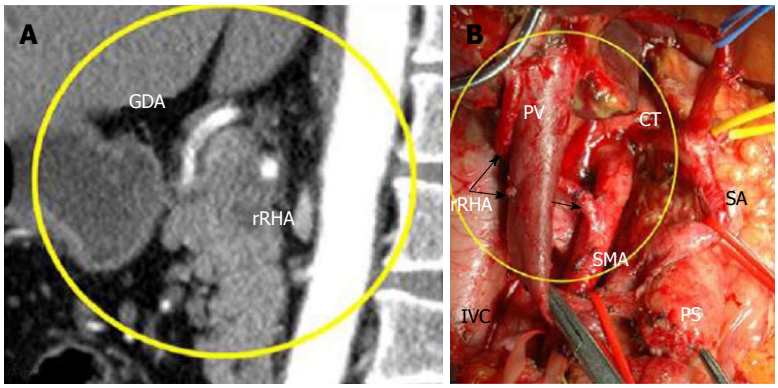

Figure 7 In 75-year-old woman (case 1), 360° PDAC encasement of the replaced right hepatic artery was diagnosed on computed tomography (A), while endoUS data described only tumor abutment with the artery. Arterial phase, Sagittal images: CT showed circumferential infiltration of the rRHA, B: Intraoperative photograph. An extended Whipple procedure was performed. There were no signs of rRHA or SMA involvement during surgery (arrows). The level of resection was R1 because of the contact of the rRHA with the tumor. SMA: Superior mesenteric artery; rRHA: Replaced right hepatic; LHA: Left hepatic; RGEA: Right gastro-epiploic arteries; CT: Celiac trunk; SMV: Superior mesenteric; PV: Portal; LRV: Left renal vein; T: Tumor; PS: Pancreatic stump.

Table 7 The celiac trunk accuracy for assessment of arterial invasion in pancreatic cancer

Reference	*n*	Sensitivity	Specificity	PPV	NPV
Soriano *et al*[14]	62	67%	94%	89%	80%
Li *et al*[47]	54	79%	99%	-	-
House *et al*[48]	115	86% SMA, 87% CA	97% SMA, 99% CA	83% SMA ,93% CA	98% SMA, CA
Squillaci *et al*[52]	50	97%	100%	100%	95%
Gress *et al*[53]	151	15%	100%	100%	60%
Buchs *et al*[57]	153	54.5%	91.2%	66.7%	86.1%
Tellez-Avila *et al*[59]	50	66.7%	90%	60%	92.3%
Pietrabissa *et al*[63]	50	82%	53%	-	-

SMA: Superior mesenteric artery; CA: Celiac artery; PPV: positive predictive value; NPV: Negative predictive value.

clear. In particular, our research showed the following: (1) Diagnostics for arterial invasion in pancreatic carcinoma remains a complex problem requiring a complex approach; (2) There is a group of patients in which pancreatic carcinoma can be considered unresectable according to the CT criteria for arterial invasion, while during surgery (group A), the tumor is found to be resectable. The detection of such patients is also important because after chemoradiation and restaging, they can remain in the group of unresectable locally advanced tumors due to insignificant changes on CT images[59,60]. If a surgeon has results of EUS that disagree with CT data with regard to local tumor extent, then this disagreement can justify pancreatic resection as an initial attempt, as well as an attempt of surgery with curative intent after neoadjuvant therapy. Our retrospective analysis showed that long-term survival after pancreatic resection, regardless of surgical radicalism, is significantly better than that after palliative surgery. Herewith, patients lived significantly longer after R0-R1 resection than after R2 resection, which is consistent with the findings of other authors[36,65,66]; (3) According to our results, EUS has advantages over CT in the detection of local tumor spread, even in large tumors, which is in agreement with the findings of some authors[59] and in disagreement with those of others[60]. CT should be aided by endoscopic ultrasound if unresectability of pancreatic carcinoma as a result of arterial involvement is suspected. In some cases, it allows for the exclusion of arterial invasion, which is important because in cases of rejection of pancreatectomy, patients move to palliative treatment, with a significantly lower survival rate; (4) In our research, intraoperative exploration, including visualization, palpation and even transection of the pancreas, was not a reliable method of evaluation of arterial intergrowth. Out of 19 observations, described in groups A and B, 100% of the cases of operative revision only led or would have led to tactical mistakes, and this finding is reflected in publications[6,7,37-39]. That is, preoperative diagnosis of arterial involvement by pancreatic carcinoma must include not only CT but also endoscopic ultrasound, and a decision regarding the unresectability of a tumor cannot be based only on the results of operative revision and palpation. Such an approach, in our opinion, will allow for the reduction of the number of false-positive and false-negative observations. With regard to the latter aspect, knowing that the detection of arterial involvement in large tumors by palpation is unreliable and considering the difficulties of forthcoming resection, one must bear in mind that it is easier for a surgeon (especially one with a lack of experience) to say "no", that is, to recognize arteries as involved and a tumor as unresectable, even if CT shows the opposite; (5) In light of CT-dependent tactics and the survival prognosis of patients with nonmetastatic large pancreatic carcinomas, it is interesting to analyze the dependence of CT accuracy on arterial involvement from the standpoint of surgical aggressiveness. Aggressiveness leads to an increased number of false-positive results (the artery is involved on CT but not involved during surgery), decreasing specificity, decreasing the number of false-negative results (when the artery is not involved on CT but is considered involved at surgery), and increasing the sensitivity

of the method. This fact means that in every surgical department, the value of CT for the detection of arterial involvement is unique and depends on that department's surgical ideology.

Despite the limitations of this research, including its retrospective nature and small number of patients, we believe that it has demonstrated the need for combined use of CT and EUS for the detection of arterial involvement by pancreatic cancer. This combination allows for the expansion of the group of patients with borderline resectable tumors who could benefit from pancreatic resection. False positivity on CT in the diagnosis of arterial invasion in pancreatic cancer remains a problem for surgeons, radiologists and gastroenterologists, and it requires further research.

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COMMENTS

Background

Decision "to resect or to palliate" pancreatic cancer depends on clinical staging system, which is based on the results of pre-surgical imaging studies. In the absence of metastatic disease, assessment of vascular invasion is a key aspect in the evaluation of resectability for pancreatic cancer. The salient sign of pancreatic ductal adenocarcinoma (PDAC) unresectability is the superior mesenteric and celiac arteries encasement, signaling vascular invasion and computed tomography is the "gold standard" for preoperative evaluation of arteries involvement. Efforts have typically been focused on accurately assessing tumor resectability based on computed tomography (CT) criteria in order to avoid non-therapeutic laparotomy and it is equally important to ensure that no patient with resectable tumor is denied surgery because of a false-positive evaluation of arterial invasion. The most important reason for inaccurate assessment of resectability is underestimation of the vascular invasion. In contrast, this study addresses the overestimation of arterial involvement in patient with pancreatic cancer.

Research frontiers

Diagnostics of arterial invasion in pancreatic carcinoma remains a complex problem requiring a complex approach. There is a group of patients in which pancreatic carcinoma can be considered unresectable according to CT criteria of arterial invasion, while at surgery a tumor is resectable. The detection of such patients is also important because after chemoradiation and restaging they can remain in a group of irresectable locally advanced tumors due to insignificant postradiation changes of CT picture. If surgeon has results of endoscopic ultrasound controversial to CT data in regards to local tumor extent, this can justify pancreatic resection as an initial attempt, as well as an attempt of surgery with curative intent after neoadjuvant therapy. The authors retrospective analysis showed that long-term survival after pancreatic resection, regardless of surgical radicalism, significantly better than that after palliative surgery. Herewith, patients lived significantly longer after R0-R1 resection than after R2 resection which is consistent with other authors. According to the results, EUS has advantages over CT in detection of local tumor spread even in large tumors. CT should be aided by endoscopic ultrasound if irresectability of pancreatic carcinoma as a result of arterial involvement is suspected. In some cases it allows to exclude arterial invasion, which is important because in case of rejection of pancreatectomy patients move to a group of palliative treatment with significantly lower survival rate. In the research, intraoperative exploration, including visualization, palpation and even transection of the pancreas were not reliable methods of evaluation of arterial intergrowth. Out of 19 observations described in 100% of cases operative revision only has led or would have led to tactical mistakes. That is, preoperative diagnostics of arterial involvement by pancreatic carcinoma must include not only CT, but endoscopic ultrasound as well, and a decision regarding irresectability of tumor cannot be based only on results of operative revision and palpation. Such an approach, in our opinion, will allow to reduce a number of false-positive as well as false-negative observations. As regards to the last aspect, knowing that detection of arterial involvement in large tumors by palpation is unreliable and, considering difficulties of forthcoming resection, one has to have in mind that it is easier for surgeon (especially with the lack of experience) to say "no", that is, recognize arteries as involved and a tumor as irresectable even if CT shows the opposite.

Innovations and breakthroughs

The study of CT and EUS accuracy for assessment of arteries involvement in borderline-resectable pancreatic cancer by comparison their conclusions with intraoperative findings shows that we have to double-check CT data if they say about unresectability of pancreatic cancer.

Applications

The research shows the possibility of extraction of patients with pancreatic cancer Stage II (who benefit from radical surgery) from Stage III group (treated by palliation) in which they have to be included according to present regulations if we use only CT (and this is general practice) for diagnostics of arterial involvement. Further application of the tactics introduced by authors may prolong survival of the patients with pancreatic cancer. The authors believe that the topic of false-positivity in CT diagnostics of vascular involvement in pancreatic cancer is of special interest because it was discussed very little.

Terminology

Pancreatic cancer: one of the most deadly cancers which treatment is still experimental and mainly palliative; arterial encasement - involvement by tumor of more than 180° or more than 50% of the vessel circumference; arterial abutment - involvement by tumor of less than 180° or les than 50% of the vessel circumference. Resectability-possibility to remove tumor and regional lymphatics (as potential site of tumor spread) within the borders of uninvolved tissues.

Peer review

This paper is informative and interesting, describing important and contradictory points for surgery of pancreatic cancer.

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ORIGINAL ARTICLE

Predictors of malignancy in chronic calcific pancreatitis with head mass

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Abstract

AIM: To prospectively analyse the clinical, biochemical and radiological characteristics of the mass lesions arising in a background of chronic calcific pancreatitis (CCP).

METHODS: Eighty three patients, who presented with chronic pancreatitis (CP) and a mass lesion in the head of pancreas between February 2005 and December 2011, were included in the study. Patients who were identified to have malignancy underwent Whipple's procedure and patients whose investigations were suggestive of a benign lesion underwent Frey's procedure. Student *t*-test was used to compare the mean values of imaging findings [common bile duct (CBD), main pancreatic duct (MPD) size] and laboratory data [Serum bilirubin, carbohydrate antigen 19-9 (CA 19-9)] between the groups. Receiver operating characteristic curve (ROC curve) analysis was done to calculate the cutoff valves of serum bilirubin, CA 19-9, MPD and CBD size. The sensitivity, specificity, positive predictive valve (PPV) and negative predictive value (NPV) were calculated using these cut off points. Multivariate analysis was performed using logistic regression model.

RESULTS: The study included 56 men (67.5%) and 27 women (32.5%). Sixty (72.3%) patients had tropical calcific pancreatitis and 23 (27.7%) had alcohol related CCP. Histologically, it was confirmed that 55 (66.3%) of the 83 patients had an inflammatory head mass and 28 (33.7%) had a malignant head mass. The mean age of individuals with benign inflammatory mass and those with malignant mass was 38.4 years and 45 years respectively. Significant clinical features that predicted a malignant head mass in CP were presence of a head mass in CCP of tropics, old age, jaundice, sudden worsening abdominal pain, gastric outlet obstruction and significant weight loss ($P \leqslant 0.05$). The ROC curve analysis showed a cut off value of 5.8 mg/dL for serum bilirubin, 127 U/mL for CA 19-9, 11.5 mm for MPD size and 14.5 mm for CBD size.

CONCLUSION: Elevated Serum bilirubin and CA 19-9, and dilated MPD and CBD were useful in predicting malignancy in patients with CCP and head mass.

Key words: Chronic calcific pancreatitis; Pancreatic head mass; Carcinoma head of pancreas; Risk factors of malignancy

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INTRODUCTION

Chronic pancreatitis (CP) is characterized by irreversible destruction and fibrosis of exocrine parenchyma, leading to exocrine insufficiency and progressive endocrine failure resulting in diabetes. Alcoholic chronic pancreatitis (ACP) is the commonest type in the western world accounting for 80% of patients[1], whereas in the tropics there is a distinct form of non alcoholic type of CP called tropical calcific pancreatitis (TCP). The features of TCP include younger age of onset, presence of large intraductal calculi, an accelerated course of disease leading to end points of diabetes or steatorrhea and a high susceptibility to pancreatic cancer[2].

The most common cause of a head mass in CP is inflammatory and occurs as a result of defective restitution after recurrent attacks of acute pancreatitis[3]. Inflammatory mass in the head of pancreas is observed in approximately 30%-75% of all surgical patients suffering from CP[4,5].

The two key issues in the evaluation of focal pancreatic masses in the background of CP are the inability to differentiate between carcinoma and CP mimicking carcinoma, and the impact of this differentiation on subsequent surgical triage and management. The majority of pancreatic tumors (70%) are located in the head of the pancreas and inflammatory masses in CP also seem to prefer the head region[6]. This awareness is widespread in clinical practice but not extensively highlighted in the literature.

In two large series of patients who underwent resection for CP, carcinoma was present in 6 out of 64 cases[7] and 4 out of 250 cases[8] respectively. Similar information is not available from the Indian subcontinent. Furthermore, not much information is available on the outcome of patients who were suspected to have pancreatic carcinoma, but where the pathological diagnosis turned out to be benign.

For patients clinically suspected to harbor malignancy without accompanying definitive documentation of disease, the decision to undergo a major operation may be difficult because of the inherent morbidity and mortality associated with the procedure.

This study aims to prospectively analyse the clinical, biochemical and radiological characteristics of the mass lesions arising in a background of chronic calcific pancreatitis (CCP).

MATERIALS AND METHODS

Eighty three patients, who presented with CP and mass lesion in the head of the pancreas between February 2005 and December 2011, were included in the study. Amongst these, 23 patients had ACP and 60 had TCP. ACP was defined as CP associated with the consumption of alcohol greater than 80 gms/d for at least 5 years with history of recurrent acute CP and features of CP on ultrasonogram (USG) or contrast enhanced computed tomography (CECT) abdomen[9]. A diagnosis of TCP was considered in individuals belonging to younger age[2,10], teetotaler with the presence of large intraductal calculi, with or without diabetes and/or steatorrhea.

A detailed history and clinical examination was recorded. The variables analysed from history included details of smoking, family history of CP/pancreatic malignancy, details of abdominal pain (duration/sudden increase), jaundice, significant weight loss, persistent vomiting (due to gastric outlet obstruction), diabetes (recent onset/sudden worsening) and steatorrhea.

The diagnostic workup included liver function tests, serum carbohydrate antigen 19-9 (CA 19-9), USG of the abdomen and CECT abdomen. In CECT, the following parameters were noted: (1) Head mass: The size and its characteristics, *e.g.*, presence of cystic areas. Head mass was defined as focal enlargement of the head more than 35 mm on USG or CECT scan[11,12]; (2) Calcification-Distribution and type: Alcoholic chronic calcific pancreatitis is characterized by small, speckled, irregular calcification usually in small ducts[13] where as in TCP the calculi are large and dense with discrete margins and most often located in the large ducts that may even reach to a size of up to 4.5 cm in diameter[14,15]; (3) Size of the common bile duct (CBD); and (4) Size of the main pancreatic duct (MPD) in the head, body and tail regions.

Magnetic resonance cholangio pancreatography was performed in selected cases. Only individuals with the typical features of chronic calcific pancreatitis on CECT mentioned above were included in the study. Pre-operative USG/CT guided fine needle aspiration cytology (FNAC) of the head mass was carried out in selected patients in whom malignancy was highly suspected. These included patients above the age of 55 years[16], elevated and rapidly rising serum bilirubin levels[16,17], elevated serum CA 19-9 levels more than 120 U/mL[18], sudden worsening of abdominal pain[19], significant weight loss[19], and worsening diabetes mellitus[20].

In patients where the FNAC was positive and the lesion operable, Whipple's procedure[21] was considered. If inoperable, surgical or endoscopic palliative procedures were considered. In patients where FNAC was negative, per-operative trucut biopsy with frozen section from the head mass was carried out. When frozen sections were negative for malignancy, Frey's procedure[22] with or without choledochoduodenostomy (CDD) was performed and Whipple's procedure or a bypass was performed if the trucut biopsy was positive for malignancy. Patients without high suspicion of malignancy did not undergo pre-operative FNAC and Frey's procedure with or without CDD was carried out. The cored pancreatic tissue was sent for histopathological examination. Details of surgery, radiological intervention, complications and the final pathological diagnosis were recorded. All the patients were followed up either in the outpatient department, or by telephone interviews until the end of the study.

Statistical analysis

Simple descriptive statistics were used. Data were re-

Table 1 Univariable analysis of demographic and clinical presentation of pancreatic lesions in chronic pancreatitis patients with inflammatory and malignant mass *n* (%)

Variables	Benign (*n* = 55)	Malignant (*n* = 28)	*P* value
Mean age (yr)	38.4	45	0.02
Gender			0.35
Male	39 (47)	17 (20.5)	
Female	16 (19.3)	11 (13.3)	
Etiology			0.05
Tropical	36 (43.4)	24 (28.9)	
Alcoholic	19 (22.9)	4 (4.8)	
Smoking	24 (28.9)	7 (8.4)	0.14
Symptoms			
Jaundice	10 (12)	21 (25.3)	0.001
Abdominal pain (sudden worsening)	10 (12)	23 (27.7)	0.001
Persistent vomiting (GOO)	2 (2.4)	9 (10.8)	0.001
Significant wt. Loss	22 (26.5)	25 (13.1)	0.001
Steatorrhea	10 (12)	5 (6)	0.97
Diabetes (Recent onset/ sudden worsening)	20 (24.1)	14 (16.9)	0.23

GOO: Gastric outlet obstruction.

ported as mean ± SD. The Pearson χ^2 test and the Fisher exact probability test were used to compare categorical variables. Student *t*-test was used to compare the mean values of imaging findings (CBD, MPD size) and laboratory data (Serum bilirubin, CA 19-9) between the groups. Receiver operating characteristic curve (ROC curve) analysis was performed to calculate the cutoff valves of serum bilirubin, CA 19-9, MPD and CBD size. The sensitivity, specificity, positive predictive valve (PPV) and negative predictive value (NPV) were calculated using these cut off points. Multivariate analysis was performed using logistic regression model. *P* value of less than or equal to 0.05 was considered statistically significant. All the statistical analyses were performed using software package, SPSS version 15 for Windows.

RESULTS

Eighty three patients with pancreatic head mass in the setting of CP were enrolled in the study. The study included 56 men (67.5%) and 27 women (32.5%). Sixty patients had TCP (72.3%) and 23 (27.7%) had alcohol related CCP. Histologically, it was confirmed that 55 of the 83 patients had an inflammatory head mass (66.3%) and 28 (33.7%) had a malignant head mass. The mean age of individuals with benign inflammatory mass and those with malignant mass was 38.4 years and 45 years, respectively.

Table 1 shows the demographic characteristics of the two groups of patients. Significant clinical features that predicted a malignant head mass in CP were presence of a head mass in CCP of the tropics, age, jaundice, sudden worsening abdominal pain, gastric outlet obstruction and significant weight loss ($P \leq 0.05$). Gender, smoking, steatorrhoea, and diabetes mellitus (recent/worsening diabetes) did not influence the presence of a malignant head mass in CCP.

Table 2 Surgical details in patients without fine needle aspiration cytology

Sl.no	Procedures	*n* = 40
1	Frey's procedure	34
2	Frey's + CDD	4
3	Whipple's procedure	1
4	Bypass for liver metastasis	1

CDD: Choledochoduodenostomy.

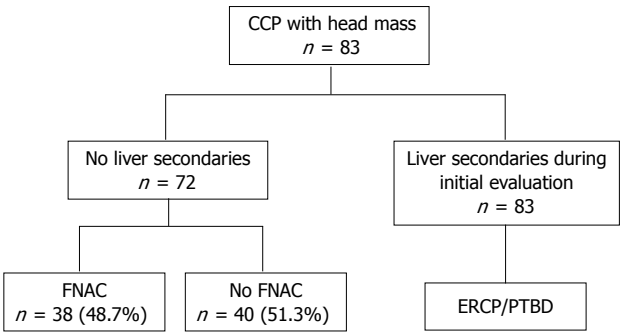

Figure 1 Flow chart for evaluation of patients with chronic calcific pancreatitis and head mass. FNAC: Fine needle aspiration cytology; ERCP: Endoscopic retrograde cholangiopancreatogram; PTBD:Percutaneous transhepatic biliary drainage; CCP: Chronic calcific pancreatitis.

Of the 83 patients studied, 5 were found to have malignant head mass with liver secondaries, malignancy being confirmed by tissue biopsy. Pre-operative USG/CT guided FNAC was performed in 38 (48.7%) of the 78 patients without liver secondaries who were strongly suspected of having malignant head mass (Figure 1).

Malignancy was confirmed by FNAC or tissue biopsy. Out of the 18 patients who underwent intra-operative trucut frozen section biopsy, one was positive for malignancy and Whipple's procedure was carried out on this patient. Patients with negative intra-operative trucut biopsy underwent Frey's procedure, with or without CDD. The histopathology of the cored-out tissue was benign in 16 patients and malignant in one patient who died 6 mo later.

Whipple's procedure was erfprmed on one patient in whom the head mass appeared malignant intraoperatively although the histopathology in this patient was negative for malignancy (Table 2). One patient in this group, who was found to have a malignant head mass with liver secondaries on laparotomy, underwent bypass surgery. All the others in this group had benign mass, confirmed by histopathological examination.

Comparison of the laboratory parameters and radiological features between these two groups of patients with benign and malignant head mass show that serum bilirubin, CA 19-9, MPD size and CBD size were the factors significantly predicting malignant mass in CP ($P \leq 0.05$) (Table 3).

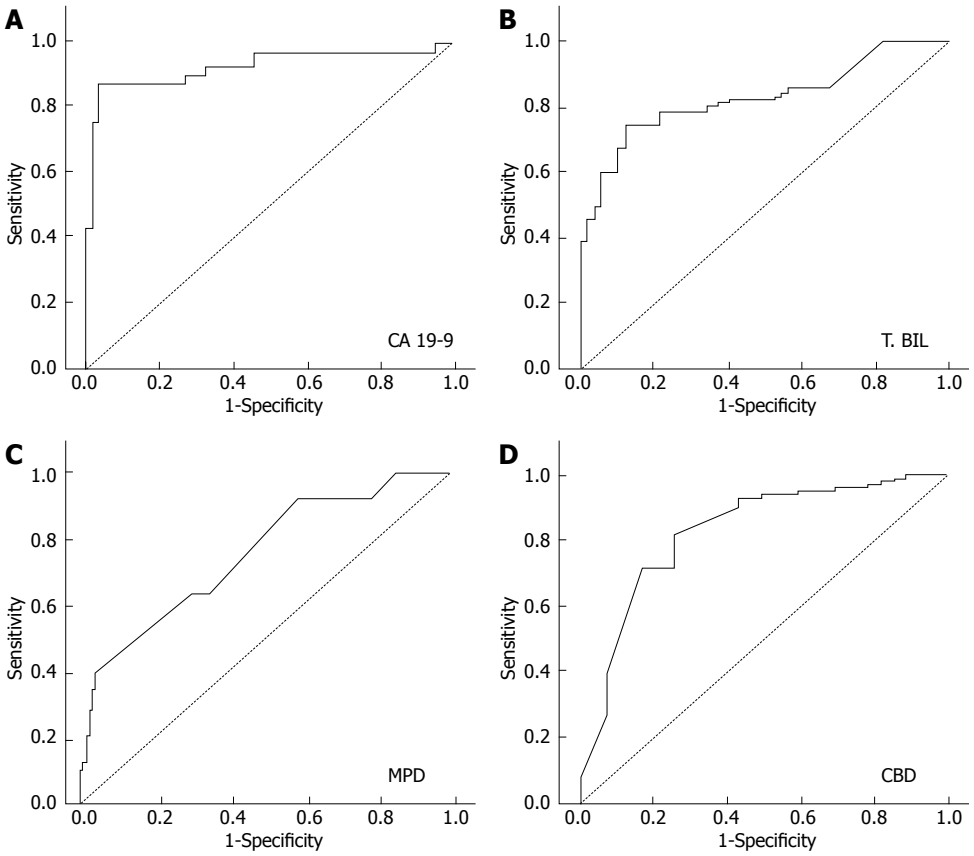

Figure 2 Receiver operating characteristic curve analysis for predicting malignancy by laboratory and radiological parameters. A: CA 19-9 cut off 127 U/mL; B: T. BIL cut off 5.8 U/mL; C: MPD size 11.5 mm; D: CBD size 14.5 mm. MPD: Main pancreatic duct; CBD: Common bile duct.

Table 3 Relationship among ERCC1 genotypes, mRNA expression and clinical characteristics of gastric cancer

Variables	*n*	Mean ± SD	*t*-test	*P* value
Serum Bilirubin (mg%)			5.7	< 0.001
Benign	55	2.06 ± 2.76		
Malignant	28	9.58 ± 6.67		
CA19-9 (U/mL)			6.2	< 0.001
Benign	55	55.3 ± 126.2		
Malignant	28	955 ± 751.9		
MPD Diameter (mm)			3.5	0.001
Benign	55	7.7 ± 3.2		
Malignant	28	12.7 ± 6.9		
CBD Size (mm)			4.7	< 0.001
Benign	55	8.7 ± 5.1		
Malignant	28	15.5 ± 6.6		

MPD: Main pancreatic duct; CBD: Common bile duct.

The receiver operating characteristic curve (ROC) analysis was performed and the cut off value of 5.8 mg/dL for serum bilirubin, 127 U/mL for CA 19-9, 11.5 mm for MPD size and 14.5 mm for CBD size was reached (Figure 2). The sensitivity, specificity, PPV and NPV were calculated using these cut off points and depicted in Table 4.

On multivariate analysis, CA 19-9 was the single most significant factor in predicting malignancy in patients with CCP and head mass (Table 5). The sensitivity and specificity were 100% when a combination of serum bilirubin > 5.8 mg/dL, CA 19-9 > 127 U/mL, MPD > 11.5 mm and CBD > 14.5 mm was taken into consideration.

There was no operative mortality. Major post operative complications occurred in 12 patients (15.8%). These included pulmonary complications, wound infection, intra peritoneal abscess, intra abdominal bleed and pancreatic leak. All the complications were managed conservatively. The mean follow up period was in the range of 6-60 mo. Four patients were lost to follow up. Eleven patients died during the follow up period due to advanced malignancy or cardiac causes. Twenty patients required hospitalisation and the details are shown in Table 6.

During the follow up, the one patient who had Whipple's procedure for benign head mass developed tuberculous cervical lymphadenopathy with severe exocrine and endocrine insufficiency. Three patients died post Whipple's during the follow up period; two of liver secondaries and one of myocardial infarction (Table 6).

DISCUSSION

A sub group of patients with CP suffer from an inflammatory mass in the head of the pancreas[23,24]. These mass lesions present great diagnostic and therapeutic dilemas and malignancy needs to be ruled out with certainty. While a positive biopsy is useful, a negative biopsy does

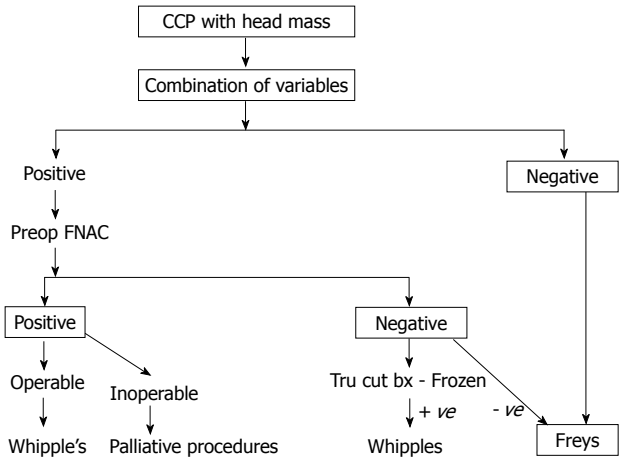

Figure 3 Management protocol for chronic calcific pancreatitis with head mass. CCP: Chronic calcific pancreatitis. FNAC: Fine needle aspiration cytology.

Table 4 Sensitivity, specificity, positive predictive value and negative predictive value of the parameters

Parameters	Cut off value	Sensitivity	Specificity	PPV	NPV
CA 19-9	127 U/mL	85.7%	96.5%	92.3%	93.2%
T.Bilirubin	5.80 mg%	67.9%	89.1%	75.0%	83.1%
MPD	11.5 cms	46.4%	90.9%	72.2%	76.9%
CBD	14.5 cms	71.4%	83.6%	69.0%	85.2%

PPV: Positive predictive value; NPV: Negative predictive value; MPD: Main pancreatic duct; CBD: Common bile duct.

not rule out malignancy. Patients with inflammatory head mass and those with malignancy may present with the similar symptoms of jaundice, gastric outlet obstruction, back ache and weight loss. In both the conditions the patients are lean and emaciated[25].

Diagnosis is difficult even during surgery, because the features of malignant head mass such as presence of a hard mass, presence of vascular invasion, adjacent organ invasion, are also seen in CCP with inflammatory head mass. The definitive evidence of malignancy in these patients is the presence of metastasis or a positive tissue biopsy.

Inflammatory head mass in CP may be operated upon with Beger's or Frey's procedures[26], while malignant pancreatic head mass would require a Whipple's procedure[27]. When the diagnosis is in doubt a radical approach is ideal. Epidemiological studies have shown that the risk of development of ductal pancreatic cancer is increased in a patient with CP[28-33]. Furthermore the risk of pancreatic cancer was independent of the underlying cause of CP[28].

The incidence of malignancy in patients with head mass in the background of CP is 33.7% in our study. The major etiology for malignant mass was TCP (85.7%) and only 14.3% of malignant masses were due to alcoholic pancreatitis. Ramesh *et al*[10], in a series of 91 patients with TCP, showed that 19 (21%) had associated malignancy. However this study included all patients with tropical pancreatitis, irrespective of the head mass.

Table 5 Logistic regression analysis of factors associated with malignancy in patients with chronic calcific pancreatitis and head mass

Variables	β	SE	Wald	*df*	Sig.	Exp(β)
Jaundice	-0.768	2.112	0.132	1	0.716	0.464
Worsening pain	-1.109	1.128	0.967	1	0.325	0.330
GOO	-1.090	1.217	0.803	1	0.370	0.336
Wt loss	-1.755	1.226	2.049	1	0.152	0.173
Cause	-0.980	1.173	0.698	1	0.403	0.375
Total. Bil	-0.254	0.213	1.428	1	0.232	0.776
CA19.9	-0.005	0.002	4.085	1	0.043	0.995
MPD	-0.128	0.148	0.756	1	0.385	0.879
CBD	0.072	0.139	0.272	1	0.602	1.075
Constant	5.956	2.103	8.020	1	0.005	386.147

β: Regression coefficient; SE: Standard error; Wald: Wald statistics; df: Degree of freedom; Sig.: Significance; Exp (β): Exponential β (odds ratio); GOO: Gastric outlet obstruction; MPD: Main pancreatic duct; CBD: Common bile duct.

Table 6 Details of Readmission after surgery in patients with chronic calcific pancreatitis and head mass

Readmission	No. of patients
Post Frey's	10
Pain	6
Acute pancreatitis	3
DKA	1
Post Whipple's	4
Recurrence	1
Liver secondaries	2
Others (cardiac)	1
Post bypass	
Celiac ganglion block	6

DKA: Diabetic keto-acidosis.

Biochemical analysis of patients with CP and inflammatory head mass has shown that 1/3rd of the patients exhibit cholestasis and about 15% have clinical jaundice[34]. The bilirubin level was much higher with malignancy than in CP[16]. Perhaps, more important than the absolute rise of bilirubin was the pattern of elevation. In patients with malignancy, bilirubin increased progressively until the biliary tree was decompressed, while with CP bilirubin rose to a peak and then fell as the attack subsided.

In our study only 10 out of 55 patients with inflammatory head mass (18.2%) presented with jaundice. Among these 10 patients, jaundice subsided in 6 within 3 wk. Seventy five percent of patients with malignant head mass presented with jaundice. The mean serum bilirubin value in our study was 2.06 mg% in inflammatory masses and 9.58 mg% in malignant masses. Frey and coworkers found that serum bilirubin was seldom higher than 10 mg% in CP and usually diminishes in 7-10 d as inflammation subsides[17].

The "duct penetrating sign" seen in 85% of CP and in only 4% of patients with cancer, helps to distinguish an inflammatory from malignant head mass. It refers to a non-obstructed MPD penetrating an inflammatory mass,

unlike obstruction caused by pancreatic carcinoma[35]. Hence gross dilatation of MPD occurs proximal to an obstruction in malignancy. In our study dilatation of MPD more than 11.5 mm predicted malignancy with a specificity of 90.9%.

The CBD may be dilated even in CP and studies have shown that CBD dilatation is not specific for malignancy[36]. Our study shows that a CBD diameter of more than 14.5 mm was predictive of malignancy with a sensitivity and specificity of 71.4% and 83.6%, respectively.

Multivariate analyses of risk factors in our study have shown CA 19-9 as the only significant risk factor predicting malignancy in patients with CCP and head mass. CA 19-9 is useful in establishing the diagnosis of pancreatic cancer[18] with a sensitivity of 80%-85% and specificity of 85%-90%[37,38]. However, in patients with obstructive jaundice, serum CA 19-9 may be elevated even in the absence of malignancy although levels seldom exceed 100-120 U/mL[18]. So, caution needs to be exercised in the interpretation of CA 19-9 as a marker for differentiating carcinoma from pancreatitis, especially in patients with biliary obstruction. The CA 19-9 values in our study show a cut off of 127 U/mL to predict malignancy in patients with CP and head mass, with a sensitivity of 85.7% and specificity of 96.5%. In a similar study by Bedi *et al*[39], which aimed to assess the value of CA 19-9 in patients with CP and a head mass lesion, levels in excess of 300 U/mL suggested malignancy with 100% specificity.

Though pancreaticoduodenectomy has been described as a procedure for patients with CP, most of the evidence comes from the western literature where alcohol is the common etiology. In the Indian scenario, where TCP is very common, pancreaticoduodenectomy is associated with considerable post operative morbidity because these patients are nutritionally depleted with exocrine and endocrine deficiency. So, the need to differentiate benign from malignant is felt more strongly in our part of the world. After analysing this study, we proposed a management algorithm for patients with chronic calcific pancreatitis and head mass (Figure 3).

In conclusion, according to this study, a serum bilirubin more than 5.8 mg/dL, CA 19-9 more than 127 U/mL, MPD more than 11.5 mm and CBD more than 14.5 mm are associated with high sensitivity and specificity for predicting malignancy in patients with chronic calcific pancreatitis and head mass. Multivariate analysis revealed CA 19-9 to be the single most significant factor in predicting malignancy in patients with CCP and head mass.

COMMENTS

Background

Pancreatic head mass in chronic pancreatitis (CP) is most often inflammatory and malignancy needs to be ruled out. Differentiating inflammatory from malignant head mass in the background of chronic calcific pancreatitis is difficult and there is a need to establish the correct diagnosis for proper treatment.

Research frontiers

There is no investigation which can reliably identify malignancy in a patient with chronic calcific pancreatitis with pancreatic head mass. The surgical procedure is different for the two cases and failure to identify malignancy before surgery is disasterous. The authors aim to identify clinical and biochemical factors which can predict malignancy in chronic calcific pancreatitis with head mass.

Innovations and breakthroughs

This study has not only tried to identify the factors, but has also identified the cutoff values of the significant radiological and biochemical factors to help differentiate malignant from benign. This could be the first step in devising a scoring system to increase the specificity and sensitivity of differentiation.

Applications

This study would help in the vital identification of malignancy in a patient with chronic calcific pancreatitis with head mass and thereby in advocating appropriate treatment.

Terminology

CP, a disease characterized by irreversible destruction and fibrosis of exocrine parenchyma, leads to exocrine insufficiency and progressive endocrine failure, resulting in diabetes. In the tropics there is a distinct form of non alcoholic type of CP called tropical calcific pancreatitis (TCP). The features of TCP include younger age of onset, presence of large intraductal calculi, an accelerated course of disease leading to end points of diabetes or steatorrhea, and a high susceptibility to pancreatic cancer.

Peer review

The authors have identified the clinical and biochemical factors which can predict malignancy in chronic calcific pancreatitis with pancreatic head mass. They have also defined the cutoff values for those significant factors. This can help predict malignancy in an otherwise difficult to diagnose situation.

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BRIEF ARTICLE

Clinical presentation predicts the outcome of patients with colon cancer

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Abstract

AIM: To elucidate the relationship between clinical presentation and outcome.

METHODS: A single institution retrospective chart review of patients admitted with the diagnosis of colon cancer. We used univariate and a multivariate analysis to identify symptoms association with mortality. An odds ratio based clinical score was created to evaluate the contribution of the quality of symptoms to outcome. Primary measure of outcome was survival.

RESULTS: During the study period, 236 patients met the inclusion criteria. Overall survival was 60.6%, mean follow-up 3.0 years. A bivariate analysis showed that increasing number of symptoms is not associated with mortality. However, a symptom-specific analysis performed using a logistic regression model controlling for age, stage and the duration of complaints revealed that the presence of melena was independently associated with mortality [P = 0.04, odds ratio (OR) 7.4], while rectal bleeding was associated with survival (P = 0.004, OR 3.9). Applying the proposed clinical score to an receiver operating characteristic curve showed that score > 1 had a strong association with mortality. The same logistic regression model was applied. The results showed that a score > 1 was an independent predictor of mortality (P < 0.001) and associated with node-positive disease (P = 0.008).

CONCLUSION: The quality of symptoms rather than quantity is correlated with outcome among patients with colon cancer. The proposed clinical scoring system may correctly predict the patient's outcome.

Key words: Colon cancer; Symptoms; Mortality

Core tip: Clinical presentation and its association with outcome among patients with colon cancer, although poorly studied in the past, may have an important role in predicting the outcomes among this important cohort of patients. Clinical scoring as proved in other areas in the past may have an important role in outcome prediction.

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INTRODUCTION

Colon cancer is the third most common tumor worldwide and continues to cause significant mortality[1]. To date, pathological staging is the single most important independent predictor of outcome[2-6]. Other factors such as vascular invasion[2,7-9], residual tumor[10-13], serum carcino-embryogenic antigen levels[7,14-19], tumor grade[2,5,7],

histologic type[5,20], perineural invasion[10-11] and radial margins are also linearly associated with outcome. Tumor DNA content, *K-ras* mutations, microvessel density and proliferative activity (Ki-67) are also associated with the prognosis of colon cancer. The clinical presentation of patients diagnosed with colon cancer and its association with outcome has not been studied extensively. The current study was performed to elucidate this association.

MATERIALS AND METHODS

We retrospectively reviewed the electronic charts of all patients admitted to the department of surgery at the Rambam Health Care Campus (RHCC) in Haifa, Israel, from January 2000 through December 2009. Patients with the diagnosis of colon cancer were identified and further scrutinized. Electronic charts were reviewed for age, symptoms at presentation, the duration of complaints, location of the tumor and post-operative TNM staging, according to Union for International Cancer Control. Follow-up and survival were also recorded. Symptoms were collected as described by the admitting physician in the patient's electronic charts (preset menu).

The primary end point of the study was to seek an association between clinical presentation and outcome. The secondary end point was to examine whether various symptoms have different impacts on outcome and whether the quality and combination of complaints may predict the outcome. The primary measure of outcome was mortality.

Only patients who had undergone their index operation at RHCC were included. Patients presenting with sigmoid and rectal cancer were excluded. Mortality was adjusted for peri-operative mortality and patients who died within 30 d from the index operation where eliminated from the secondary analysis.

A logistic regression model controlling for age, stage and the duration of complaints was used to analyze the clinical symptoms and their association with mortality. The odds ratio and the event probability (mortality rate) predicted by this model were used to create a scoring system that incorporates the relative association of each symptom with mortality and/or patient survival. Points were given for each symptom according to a standardized legend (Table 1). The sum of all points for each patient was used to create a new variable with the corresponding score.

The Institutional Review Board of RHCC approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity.

Statistical analysis

Continuous parametric variables were analyzed using Student's *t*-test. The Mann-Whitney *U* test was used to analyze non-parametric variables. The chi-square test was applied to analyze the association between frequencies. A stepwise logistic regression model and a likelihood ratio test were applied to identify positive predictors of mortality among symptoms. The odds ratio and the event probability predicted by that model (mortality) were used to create a clinical scoring system. A receiver operating characteristic (ROC) curve was used to identify the score above which mortality was most likely. The results were applied to the same stepwise logistic regression model and likelihood ratio test, controlling again for age, stage and the duration of complaints. JMP Pro for Mac (Version 9.0.0) was used to analyze the data. $P < 0.05$ (2-sided) was considered to indicate statistical significance.

Table 1 Estimates and scores used for creation of the clinical score

Symptom	Odds ratio	Points
Pain	1.2	1
Diarrhea	1.2	1
Constipation	0.91	-1
Vomiting	1.3	2
Weight loss	1.1	1
Rectal bleeding	0.65	-3
Melena	2.5	5
Change in BH	1.1	1
Legend		
	0.5-0.7	-3
	0.7-0.9	-2
	0.9-1.0	-1
	1.0-1.2	1
	1.2-1.4	2
	1.4-1.6	3
	1.6-1.8	4
	>1.8	5

BH: Bowel habits.

RESULTS

Over a period of ten years, 236 patients met the inclusion criteria for the study. The mean age was 71.5 ± 14.3 years; 124 (52.5%) patients were male, and 140 (59.3%) suffered from left-sided colon cancer. The mean duration of complaints prior to diagnosis was 1.8 mo. The median follow-up time was 36 mo (IQR 24-60 mo). The overall mortality was 39.4%. Adjusted mortality (overall-peri-operative mortality) was 33.9%. The most common symptom, abdominal pain, was present in 51.3% of patients, followed by a change in bowel habits in 41.5% and weight loss in 32.6%. Table 2 depicts the distribution of patient symptoms among the different TNM stages (Union for International Cancer Control) and shows significant differences in the manifestation of symptoms with an increased incidence of abdominal pain ($P = 0.01$), weight loss ($P = 0.04$) and a change in bowel habits ($P = 0.03$) within the node-positive stages.

When comparing the distribution of symptoms with respect to tumor location, rectal bleeding and changes in bowel habits occurred in significantly higher rates in patients with tumors of the left colon ($P = 0.002$ and 0.006, respectively) (Table 3).

A univariate analysis comparing the symptoms among survivors and non-survivors showed that abdominal pain ($P = 0.05$) was the only symptom that was significantly associated with mortality; however, rectal bleeding was

Table 2 Distribution of symptoms among patients, divided according to the Union for International Cancer Control TNM staging system *n* (%)

Stage	Abdominal pain	Diarrhea	Constipation	Vomit	Weight loss	Rectal bleeding	Melena	Change in BH[1]
1	10 (30.3)	3 (9.0)	11 (33.3)	1 (3.0)	11 (33.3)	8 (24.2)	1 (3.0)	11 (33.3)
2a	44 (62.8)	11 (15.7)	20 (28.6)	11 (15.7)	22 (31.4)	11 (15.7)	2 (2.8)	34 (48.6)
2b	2 (66.6)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3a	5 (45.4)	1 (9.0)	2 (18.2)	1 (9.0)	3 (27.3)	0 (0.0)	0 (0.0)	1 (9.0)
3b	15 (44.1)	3 (8.8)	8 (23.5)	3 (2.9)	6 (17.6)	5 (14.7)	1 (2.9)	10 (29.4)
3c	10 (37.0)	1 (3.7)	10 (37.0)	3 (11.1)	7 (25.9)	10 (37)	0 (0.0)	15 (55.5)
4	35 (60.3)	7 (12.1)	18 (31.3)	7 (12.1)	28 (48.3)	13 (22.4)	3 (5.2)	27 (46.5)
Total	121 (51.3)	26 (11)	69 (29.2)	27 (11.4)	77 (32.6)	47 (19.9)	7 (2.9)	98 (41.5)
P value	0.01	0.78	0.79	0.35	0.04	0.14	0.95	0.03

[1]Staging system according to the Union for International Cancer Control. BH: Bowel habits.

Table 3 Comparison of symptoms with respect to tumor location *n* (%)

Symptom	Left colon *n* = 139	Right colon *n* = 97	*P* value
Pain	73 (52.5)	48 (49.5)	0.7
Diarrhea	12 (8.6)	14 (14.4)	0.2
Constipation	47 (33.8)	22 (22.7)	0.08
Vomiting	16 (11.5)	11 (11.3)	1
Weight loss	48 (34.5)	29 (29.9)	0.48
Rectal bleeding	37 (26.6)	10 (10.3)	0.002
Melena	5 (3.6)	2 (2.1)	0.7[1]
Change in BH	68 (48.9)	30 (30.9)	0.006

[1]Fisher's exact test. BH: Bowel habits.

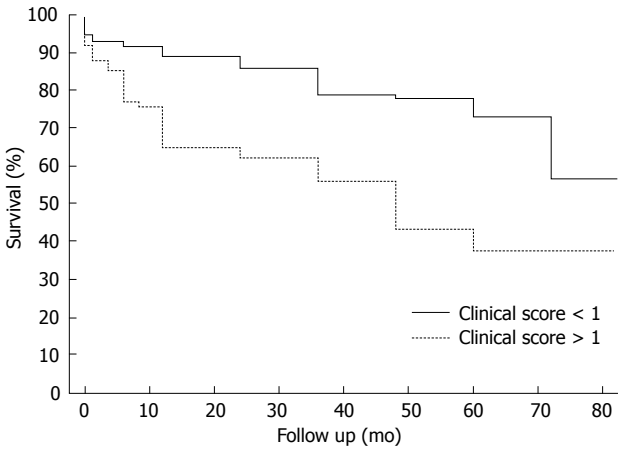

Figure 1 Kaplan-Meier survival curve comparing the survival of patients with clinical scores higher and lower than one.

slightly associated with survival (0.06) (Table 4). A stepwise logistic regression model controlling for age, stage and the duration of complaints was applied. Our analysis showed that the presence of melena was associated with mortality ($P = 0.04$), whereas rectal bleeding was associated with survival (0.004), both independently of the controlled factors. Age ($P = 0.005$), stage ($P < 0.001$) and the duration of complaints ($P = 0.03$) were found to be independent predictors of mortality, as expected. We have applied the same logistic regression model on the adjusted mortality, melena was no longer associated with the adjusted mortality and rectal bleeding was ($P = 0.01$). Interestingly age was no longer an independent predictor, while duration of complaints ($P = 0.04$) and pathological stage ($P < 0.001$) remained strongly significant.

A quantitative analysis of numeric combinations of symptoms indicated that the number of symptoms present had no positive or negative association with mortality. Patients who presented with any numeric combination shared the same outcome on univariate or multivariate analysis when controlled for age, stage and the duration of complaints.

To perform a symptom-specific analysis with regard to mortality, we created a clinical scoring system according to the odds ratios and probability of an event (mortality) predicted by the logistic regression model and the likelihood ratio test applied previously. Each symptom had points assigned according to the legend depicted in Table 1. We summarized the total points assigned to each patient into one variable by creating the new scoring system. The new score showed a normal distribution among patients and a graded association with mortality.

The new clinical scoring system is an independent predictor of mortality ($P < 0.001$) when age ($P = 0.02$), stage ($P < 0.001$) and the duration of complaints ($P = 0.05$) are controlled. When applied to an ROC curve, scores higher than 1 had the highest likelihood of mortality with area under the curve (AUC) of 65%. In a multivariate analysis, scores higher than 1 proved to be a significant predictor of mortality ($P = 0.001$) independently of age ($P = 0.003$), stage ($P < 0.001$) and the duration of complaints ($P = 0.05$) (Table 5).

We have applied the described scoring system on the adjusted mortality, clinical score higher than 1 remained a significant independent predictor of mortality ($P = 0.01$) independently of duration of complaints ($P = 0.04$), stage ($P < 0.001$). Age was no longer an independent predictor of outcome.

A survival analysis was performed using the Kaplan Meier method and the survival curves of both groups (clinical scores < 1 and > 1) are depicted in Figure 1. The mean survival of patients with scores lower than 1 at 48 mo was 78%, whereas patients with scores higher than 1 presented with 43% survival at 48 mo. The curves

Table 4 Crude univariate analysis comparing the presentation of symptoms among survivors and non-survivors *n* (%)

Symptom	Survivors *n* = 142	Non-survivors *n* = 93	Univariate *P* value	Multivariate *P* value	OR (95%CI)
Pain	66 (46.2)	55 (59.1)	0.05	0.38	1.4 (0.7-2.8)
Diarrhea	13 (9.1)	13 (14)	0.24	0.51	1.5 (0.4-5.6)
Constipation	41 (28.7)	28 (30.1)	0.81	0.91	0.94 (0.3-2.7)
Vomiting	12 (8.4)	15 (16.1)	0.07	0.24	1.9 (0.6-5.6)
Weight loss	43 (30)	34 (36.6)	0.32	0.63	0.8 (0.4-1.7)
Rectal bleeding	34 (23.8)	13 (14)	0.06	0.004	0.25 (0.1-0.7)
Melena	2 (1.4)	5 (5.4)	0.1	0.04	7.4 (1.1-72.7)
Change in BH	56 (39.2)	42 (45.2)	0.36	0.96	1 (0.4-2.9)

A stepwise logistic regression model utilizing a likelihood ratio test was applied controlling for, age, stage and the duration of complaints. BH: Bowel habits.

Table 5 Clinical score predicts mortality independently of age, stage and the duration of complaints

	Mortality	OR (95%CI)
Clinical score > 1	0.001	3.1 (1.5-6.1)
Age	0.003	0.96 (0.94-0.99)
Stage	< 0.001	35 (5.3-703.7)
Duration of complaints	0.05	0.6 (0.26-1.0)

Stepwise logistic regression analysis with the application of a likelihood ratio test. OR: Odds ratio.

shown in Figure 1 also indicate the significant differences between the groups in terms of survival, the log-rank test result was $P < 0.001$.

The clinical score was also associated with the TNM stage when patients with scores higher than 1 presented with later TNM stages ($P = 0.008$). However, the score was not associated with age, gender, location of the tumor or the duration of complaints.

DISCUSSION

Although colon cancer is the third most common cancer worldwide[1], studies on the clinical presentation and its association with outcome are limited. Previous studies have shown that rectal bleeding is associated with early TNM stages of disease. Changes in bowel habits and abdominal pain are associated with advanced TNM stages[21-24]. Stapley *et al*[25] reported rectal bleeding to be associated with reduced mortality. The current study investigated the correlation between the number and the quality of symptoms and the outcome among patients with colon cancer, and created a clinical score that may be able to predict outcome based on the clinical presentation prior to diagnosis.

The characteristics of this cohort of 236 patients are comparable to those of other reported cohorts with respect to gender distribution, mean age and tumor location[1,26]. The rates of symptoms reported and the distribution of stages are also comparable to those reported in the English literature.

A univariate analysis of our sample indicated that patients in the late TNM stages presented with significantly more abdominal pain ($P = 0.01$), more weight loss ($P = 0.04$) and more drastic changes in bowel habits (0.03). Rectal bleeding was previously reported to be associated with early TNM stages[21], although this trend was not observed among the patients in our sample.

The comparison of symptoms with respect to laterality showed that patients with left-sided colonic tumors manifested significantly more rectal bleeding ($P = 0.002$) and more drastic changes in bowel habits ($P = 0.006$) than patients with right-sided tumors (Table 2).

Univariate analysis indicated that the number of symptoms regardless of their quality was not associated with mortality or with TNM staging. A multivariate analysis controlling for factors such as age, stage and the duration of complaints did not yield significant differences for any possible numeric combination. These results, although poorly reported in the past, are similar to those reported by Stapley *et al*[25].

Univariate analysis, of the quality of all symptoms showed that except for abdominal pain (0.05) no other symptom was associated with mortality. However, a multivariate analysis controlling for age, stage and the duration of complaints showed that melena was strongly associated with mortality ($P = 0.04$, OR 7.4), and rectal bleeding was strongly associated with survival ($P = 0.004$, OR 0.25). Applying the same univariate analysis on the adjusted mortality did not change the results and abdominal pain remained significantly associated with mortality ($P = 0.05$), while on a multivariate analysis rectal bleeding was associated mortality and no longer with survival ($P = 0.02$, OR 2.5)

Melena is typically not a symptom of colon cancer and was reported in only 2.9% ($n = 7$) of patients. Interestingly, the presentation of melena was not associated with tumor location, age, stage, duration of complaints or any of the other reported symptoms. The association of rectal bleeding with survival was previously reported[26], and the current study was able to validate this observation for overall mortality but the adjusted mortality did not replicate the same results.

We believe that although melena and rectal bleeding were the only symptoms associated with positive or negative outcomes, the clinical presentation prior to diagnosis may play a role in predicting outcomes among patients

with colon cancer. In view of this belief, we developed a clinical scoring system based on the estimates of event probability yielded by the logistic regression model. We assigned points to each symptom according to its relative contribution to outcome, and the sum of these points for each patient allowed us to create a variable that incorporates all symptoms to quantify the relative event probability contributed by the combination of symptoms presented in each patient.

The new clinical score had a normal distribution among patients and a graded association with mortality. To validate the new score, we performed a univariate analysis that revealed a significant association with mortality ($P < 0.001$). A multivariate analysis controlling for age, stage and the duration of complaints showed that the score is an independent predictor of mortality ($P < 0.001$). We placed the various patient scores on a ROC curve and found that scores higher than one were associated with the highest event probability. By applying the same multivariate analysis, we confirmed that when controlled for age, stage and the duration of complaints, a score higher than one is an independent predictor of outcome ($P = 0.001$, OR 3.1) (Table 5).

The Kaplan-Meier survival curve (Figure 1) also demonstrates the negative impact of a score higher than one on survival.

The main limitation of this study is its retrospective nature; it is possible that the patients neglected to report symptoms and that the physicians neglected to document reported symptoms. However, the agreement of the reported symptoms and their distribution with what was previously reported in the literature encourages us to believe that the data accurately represent the symptoms present. The study is novel in its approach to clinical presentation and the predictive model proposed.

In conclusion, clinical presentation and its association with outcome among patients with colon cancer, although poorly studied in the past, may have an important role in predicting the outcomes among this important cohort of patients. The proposed clinical scoring system seems to be able to reliably predict outcome. Further large-scale, population-based studies should be applied to validate the proposed clinical scoring system.

COMMENTS

Background

Although colon cancer is third most common cancer world wide and research regarding it prognosis and outcome is held universally. The clinical presentation of patients diagnosed with colon cancer and its association with outcome has not been studies extensively. The current study was initiated to elucidate on this association.

Research frontiers

Very limited studies were published regarding the reported association between clinical presentation and outcome and prospective evaluation should be considered.

Innovations and breakthroughs

Clinical presentation is of utmost importance and its association with outcome should be further investigated prospectively. Preoperative clinical scoring may provide the clinicians with a toold.

Applications

The current clinical score may predict outcome preoperatively in patients with colon cancer and may imply as to how severe the disease is.

Peer review

This is an interesting work searching for correlation between the number and the quality of symptoms and the outcome among patients with colon cancer. The study has also clinical utility since authors explain how a clinical score can be created to predict outcome based on the clinical presentation prior to diagnosis.

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BRIEF ARTICLE

Efficacy of subcutaneous penrose drains for surgical site infections in colorectal surgery

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Abstract

AIM: To investigate whether a subcutaneous penrose drain would decrease the superficial surgical site infection (s-SSI) rate in elective colorectal surgery.

METHODS: This is a comparative study of the historical control type. Intervention consisted of the use of penrose drain in elective open colorectal surgical wounds. The outcome was an incidence of s-SSI. The patients were risk stratified according to the depth of subcutaneous tissue.

RESULTS: There were 131 patients (40 patients with high s-SSI risk) in the prior period (from July 2008 to June 2009, when no penrose drains were inserted) and 151 patients (75 patients with high s-SSI risk) in the latter period (from June 2010 to November 2011, when penrose drains were inserted). The overall s-SSI rate was 6.1% and 5.3% during the two periods (P = 0.770), and the s-SSI rate in the high s-SSI risk group was 15.0% and 8.0% (P = 0.242).

CONCLUSION: Although penrose drain was not observed to significantly reduce s-SSI, there tended to be a reduced risk of s-SSI in the high s-SSI risk group.

Key words: Surgical site infections; Subcutaneous penrose drains; Colorectal surgery; Open surgery; Subcutaneous tissue

Core tip: In this article, the authors investigated whether a subcutaneous penrose drain would decrease the superficial surgical site infection rate in elective colorectal surgery. Although penrose drain were not observed to significantly reduce superficial surgical site infection, there tended to be a reduced risk of superficial surgical site infection in the high superficial surgical site infection risk group(depth of subcutaneous tissue was over 20 mm).

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INTRODUCTION

Surgical site infections (SSI) are still a major problem in general surgery, because they are responsible for significant discomfort for patients and excess morbidity and mortality, which also translates into a financial burden on the health system[1]. Superficial SSI (s-SSI) account for about 60% of SSI, and the occurrence is associated with wound separation, ventral hernia, and so on[2].

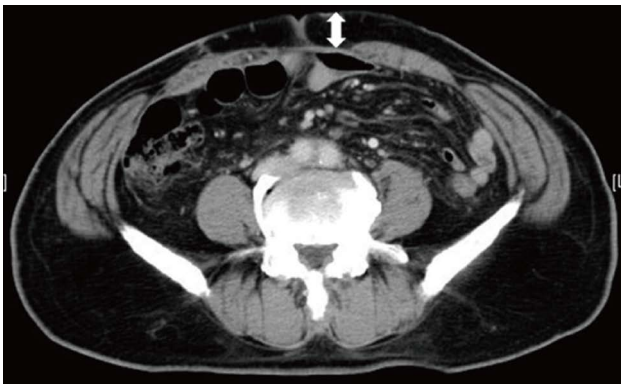

Figure 1 Depth of subcutaneous tissue at the level of the umbilicus.

SSI surveillance by an infection control team (ICT) started in September 2003 at this hospital. The incidence of s-SSI in colorectal surgery decreased from 12% to about 5% by the intervention of the ICT[3]. However, s-SSI still occurs at a low rate yet, and we therefore need further interventions to decrease the incidence of s-SSI. One consideration is to remove the blood and serous fluids from the wound by drains before fluids can get infected[4]. This concept is frequently implemented in clinics. However, a meta-analysis showed that prophylactic subcutaneous drainage to prevent wound complications is not efficient in gynecology[5]. On the other hand, there have so far been few reports on the efficacy of prophylactic subcutaneous drain for the prevention of s-SSI following digestive surgery. Recently one study described a systematic randomized evaluation in patients undergoing laparotomy in digestive surgery while clarifying whether subcutaneous closed suction drains affect wound infection, and the authors concluded that there were no indications for prophylactic subcutaneous suction drain[4]. Furthermore, there is no evidence about the use of prophylactic subcutaneous penrose drains (PD) which are likely to be used more widely than suction drains in digestive surgery due to the fact that they are cheaper. Moreover, there is no evidence about the effect of PD following elective colorectal surgery, in which the incidence of s-SSI is usually higher than other fields.

This study analyzed the efficacy of PD for the prevention of s-SSI in elective colorectal surgery.

MATERIALS AND METHODS

This study was a prospective cohort with historic controls in order to assess the use of PD. Patients undergoing elective open colorectal surgery were included in this study. Patients who underwent emergency surgery, laparoscopic surgery, and re-do operations were excluded. The study classified two periods, the prior period and the latter period. The prior period was from July 2008 to June 2009, in which no PD was inserted subcutaneously in patients that underwent elective colorectal surgery. The latter period was from June 2010 to November 2011, and PDs (an open drain, 8 mm; Fuji Systems Corporation, Japan) were inserted subcutaneously in patients that underwent elective colorectal surgery for prevention of s-SSI. The data of the prior period were collected retrospectively from the medical records, and PDs were prospectively inserted in cases that met the eligibility criteria during the latter period. Moreover, the patients from each period were divided into two groups, the low s-SSI risk group and the high s-SSI risk group. The two groups were based on whether the depth of subcutaneous tissue was over 20 mm, because Soper *et al*[6] reported that the depth of subcutaneous tissue is the most significant risk factor associated abdominal wound infection after hysterectomy. The depth of subcutaneous tissue was measured preoperatively at the level of the umbilicus based on abdominal computed tomography (Figure 1).

Every patient received the same preparations, that is, sennoside and magnesium citrate were administered following fasting 1 d before surgery and followed by a glycerin enema in the morning of the day of surgery. No patient underwent chemical bowel preparation. The patients took showers 1 d before surgery, and underwent body hair removal just before the operation. Moreover, the surgical field was disinfected by the use of iodine and the patients received antibiotic prophylaxis with cefmetazole just before the initial skin incision, every 3 h during the operation, and twice per day on the first and second postoperative days.

The skin incision was performed with a scalpel; subcutaneous fat was dissected by electrocautery. Wound protection was achieved during the operation by a ring drape device. The surgical instruments were exchanged just before the peritoneal-muscle closure, and the wound was irrigated with 1000 mL of saline solution just before skin closure. The fascia/muscle layer was closed by interrupted VICRYL® sutures (Ethicon, Somerville, NJ, United States) and the skin was closed by stapling. There were no differences in the surgical procedures between the latter an prior period, except that a PD was inserted along the entire length of the subcutaneous tissue. The exit of the drain was separated from the incisions. The PD was removed on postoperative day three.

SSI cases were diagnosed within 30 postoperative day by ICT according to the Centers for Disease Control and Prevention (CDC) criteria: (1) purulent drainage with or without laboratory confirmation from the superficial incision; (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (3) at least one of the following signs or symptoms of infection: Pain or tenderness, localized swelling, redness, or heat and superficial incision were deliberately opened by surgeon, unless the incision was culture-negative; and (4) diagnosis of s-SSI by the surgeon or ICT.

Statistical analysis

Numerical data are given as the mean ± SD, and they conformed to the normal distribution. Discrete data were tested for significance by means of the χ^2 test or Fisher's exact test. Continuous data were tested for significance with

Table 1 Demographic characteristics of the patients in the two periods

	Prior period (n = 131)	Latter period (n = 151)	P value
Age (yr, mean ± SD)	62.7 ± 10.4	63.0 ± 12.4	0.847
Sex (male/female)	68/63	91/60	0.158
Diabetes mellitus (yes/no)	17/114	20/131	0.947
Smoking history (yes/no)	24/107	32/119	0.547
ASA classification (ASA score ≤ 2/3 ≤)	124/7	146/5	0.399
Body mass index (kg/m^2)	22.4 ± 3.3	22.5 ± 3.5	0.802
Subcutaneous fat (mm, mean ± SD)	18.2 ± 7.8	19.7 ± 7.1	0.081
Site (colon/rectum)	73/58	95/56	0.220
Operation time (min, median)	206	219	0.864
Blood loss(mL, median)	205	200	0.169
Stoma (yes/no)	32/99	31/120	0.433
Patients with high risk[1]	40	75	0.001
Patiens with PD	0	151	

[1]High risk patients whose depth of subcutaneous tissue are over 20 mm. ASA: American Society of Anesthesiologists; PD: Penrose drains.

Student's t-test. $P < 0.05$ was considered to be significant.

RESULTS

One hundred thirty-one patients underwent surgery during the prior period, and 151 patients during the latter period. The PD was usually removed on postoperative day 3, but the physician in charge removed it depending on properties and amount of drainage. The median times of removal of PD were postoperative day three (range 2-12). There were no severe complications associated with the insertion of the PD. The characteristics of patients during the two periods are shown in Table 1. There was no significant difference between the two periods with regard to the characteristics, such as age, sex, diabetes mellitus, smoking history, American Society of Anesthesiologists classification, body mass index, operation time, blood loss, and presence of stoma. However, the proportion of high s-SSI patients was different between the two periods (30.5% *vs* 49.7%, $P = 0.001$). The types of surgery of all of the patients and the high s-SSI group patients are shown in Table 2, and there was no significant difference between each group during the two periods (overall $P = 0.440$, high risk group $P = 0.190$). The characteristics of the high s-SSI risk patients in the two periods are shown in Table 3. No significant differences were noted with regard to characteristics between the two periods.

The incidences of s-SSI in the two periods are shown in Table 4. The overall s-SSI rate was 6.1% (8/131) in the prior period, and 5.3% (8/151) in the latter period. The s-SSI rate in the high risk group during the two periods was 15.0% and 8.0% ($P = 0.242$). The s-SSI rate was reduced by half. However, there was no significant difference between two the periods. In contrast, the s-SSI rate of the low risk group during the two periods was 2.2% and 2.6% ($P = 0.855$). There was no significant difference between the two periods. Moreover, 6 s-SSI cases of the high risk group in the latter period are presented in Table 5. There were 4 culture-positive cases among in the latter period. Three of 4 cultures showed bacteria in the intestines, and only one culture was skin bacteria.

DISCUSSION

SSI is one of the most serious infectious complications of surgery. The occurrence is associated with a high incidence of reoperation, a long duration of hospitalization, and a large increase in the cost of any postoperative surgery complication. In addition, patient discomfort and the inconvenience of caring for a healing open wound at home make the prevention of this complication a high priority[6]. s-SSI has a high incidence among SSI, and it is generally thought that the incidence of s-SSI is related to amount of bacterium of the wound, formation of hematoma, pool of effusion, potential subcutaneous dead space, disturbance of the local circulation, and the amount of bacterium in the surgical organ[7].

A subcutaneous drain might reduce the amount of bacterium around the wound and remove residual effusion and blood from the wound that could serve as a medium for bacterial growth. This study selected a PD, which is an open drain, because of its convenience and inexpensiveness. Generally, a PD or closed suction drain is used as a subcutaneous drain. A closed drain is an active drain that employs the power of suction. The luminal obstruction of such drains increase with time, and drainage becomes poor 48 h after insertion[7]. On the other hand, long term insertion of a PD is associated with retrograde infection. Moro *et al*[8] pointed out that the insertion of an opened drain for more than 3 d increases the risk of SSI. In addition, Numata *et al*[9] reported that 25% of cultures of discharge from subcutaneous PDs that was inserted over 3 d postoperatively, were positive for skin bacteria. Therefore, the PD was removed on postoperative day three. Table 5 shows the s-SSI cases in the latter period. There were 5 culture positive cases among the 8 s-SSI cases in the latter period. Four cultures of the 5 cases showed bacteria in the intestines, and only one culture was skin bacteria. Moreover, the cost of PD

Table 2 Types of surgery during the two periods

	Prior period (n = 131)		Latter period (n = 151)	
	Overall	High risk group	Overall	High risk group
Resection of the colon	73	18	95	46
Resection of the rectum with the stoma	31	10	28	16
Resection of the rectum without the stoma	27	12	28	13
Total	131	40	151	75

Table 3 Demographic characteristics of the high risk patients

	Prior period (n = 40)	Later period (n = 75)	P value
Age (yr, mean ± SD)	61.8 ± 9.7	62.5 ± 11.0	0.743
Sex (male/female)	15/25	36/39	0.280
Diabetes mellitus (yes/no)	5/35	10/65	0.899
Smoking history (yes/no)	8/32	15/60	> 0.999
ASA classification (ASA score ≤ 2/3 ≤)	40/0	75/0	> 0.999
Body mass index (kg/m^2)	24.2	24	0.767
Site (colon/rectum)	18/22	46/29	0.093
Operation time (min, median)	245	239	0.588
Blood loss (mL, median)	275	205	0.110
Stoma (yes/no)	9/31	18/57	0.857

ASA: American Society of Anesthesiologists.

Table 4 Incidence of superficial surgical site infections during the two periods n (%)

	Prior period (n = 40)	Later period (n = 75)	P value
Patients with s-SSI (high s-SSI risk group)	6/40 (15.0)	6/75 (8.0)	0.242
Patients with s-SSI (low s-SSI risk group)	2/91 (2.2)	2/76 (2.6)	0.855
Patients with s-SSI (overall)	8/131 (6.1)	8/151 (5.3)	0.770

s-SSI: Superficial surgical site infections.

Table 5 Superficial surgical site infections cases in the later period

Case	Age	Sex	ASA	Fat tissue (mm)	s-SSI risk	Operation	Daysof drainage	Culture
1	72	M	2	23	High	Resection of the rectum with the stoma	4	Not done
4	71	F	2	24	High	Resection of the colon	4	Not detected
2	55	M	2	27	High	Resection of the colon	3	Staphylococcus aureus (skin bacteria)
3	73	M	2	27	High	Resection of the colon	3	Enterococcus facium (intestine bacteria)
5	56	F	2	22	High	Resection of the rectum with the stoma	3	Pseudomonus aeruginosa (intestine bacteria)
6	81	F	2	21	High	Resection of the colon	3	Bacteroides fragilis (intestine bacteria)
7	64	M	2	18	Low	Resection of the colon	4	Enterococcus facium (intestine bacteria)
8	62	M	2	16	Low	Resection of the colon	4	Not detected

ASA: American Society of Anesthesiologists; M: Male; F: Female; s-SSI: Superficial surgical site infections.

is less expensive than that of a closed drain. Each type of drain has specific advantages and disadvantages.

Numata *et al*[7] reported that PD is an effective means for preventing s-SSI in high s-SSI risk patients following digestive tract surgery. However, they classified contaminated operations and dirty-infected operations, or clean-contaminated operations accompanied by at least 20 mm thick subcutaneous fat into the high s-SSI risk group, and they reported that PD was more efficient in contaminated surgery, such as a perforation of the colon. However, the cases in the current study were restricted to elective colorectal surgeries, and the amount of bacteria was found to be small. As a result, a potential risk of bias in the intervention population may have existed. Moreover, the current protocol exchanged the surgical instruments just before peritoneal-muscle closure, and performed wound irrigation with 1000 mL of saline solution just before skin closure. So, the decrease of s-SSI has a possibility of limit from the aspect of drainage in elective colorectal surgeries.

In regard to suture choice, we always closed the fascia/muscle layer with VICRYL® sutures in clean-contaminated surgery. However, multifilament sutures, such as VICRYL®, are more prone to develop SSI than monofilament wire, such as PDS®. On the other hand, one recent study reported that antibacterial-coated multifilament (VICRYL PLUS®) was more effective than monofilament (PDS-Ⅱ®)[10]. We therefore need to examine the suture choice to prevent s-SSI from now on.

The current study failed to demonstrate the efficacy of PD. However, dead space in the subcutaneous layer is a risk factor of s-SSI, and Inotsume-Kojima *et al*[11] reported that a combination of subcuticular sutures and a drain for the skin closure reduces wound complications in obese females undergoing surgery using vertical incisions in gynecology. Furthermore, interventions associated with subcuticular sutures may be necessary in elective colorectal surgery.

In conclusion, a PD was inserted subcutaneously to reduce s-SSI following colorectal surgery. However, the results failed to demonstrate that PD reduced the incidence of s-SSI (6.1% *vs* 5.3%). Although the difference was not significant, there was a trend toward a reduced risk of s-SSI (15.0% *vs* 8.0%) in the high s-SSI risk group.

COMMENTS

Background

Surgical site infections (s-SSI) are still a major problem in general surgery, because they are responsible for significant discomfort for patients and excess morbidity and mortality, which also translates into a financial burden on the health system. The major parts of surgical site infections are superficial surgical site infections, and it account for about 60% of surgical site infection.

Research frontiers

The incidence of superficial s-SSI is related to amount of bacterium of the wound, formation of hematoma, pool of effusion, potential subcutaneous dead space, disturbance of the local circulation, and the amount of bacterium in the surgical organ. A subcutaneous drain might reduce the amount of bacterium around the wound and remove residual effusion and blood from the wound that could serve as a medium for bacterial growth. In this study, the authors investigate whether a subcutaneous penrose drain would decrease the superficial surgical site infection rate in elective colorectal surgery.

Innovations and breakthroughs

Some surgeons use subcutaneous drains to prevent surgical site infection. But there is no evidence of the efficacy of prophylactic subcutaneous drain for the prevention of superficial surgical site infection following digestive surgery, including colorectal surgery. This study analyzed the efficacy of penrose drains for the prevention of s-SSI in elective colorectal surgery.

Applications

The current study failed to demonstrate the efficacy of penrose drains. But dead space in the subcutaneous layer is a risk factor of s-SSI, and there are some suture choices and some subcutaneous drains. So, the authors therefore need to examine the combinations of suture and drain to prevent s-SSI.

Terminology

SSI is one of the most serious infectious complications of surgery. The occurrence is associated with a high incidence of reoperation, a long duration of hospitalization, and a large increase in the cost of any postoperative surgery complication.

Peer review

This study compares a prospective cohort with historic controls in order to assess the use of Penrose drains in median laparotomies in patients undergoing colorectal resection in order to reduce superficial surgical site infections. It is a retrospective case control study on a simple but important question.

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BRIEF ARTICLE

Effect of Daikenchuto (TJ-100) on abdominal bloating in hepatectomized patients

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Abstract

AIM: To evaluate the clinical usefulness of Daikenchuto (DKT) in hepatecomized patients.

METHODS: Twenty patients were enrolled with informed consent. Two patients were excluded because of cancelled operations. The remaining 18 patients were randomly chosen for treatment with DKT alone or combination therapy of DKT and lactulose (n = 9, each group). Data were prospectively collected. Primary end points were Visual Analogue Scale (VAS) score for abdominal bloating, total Gastrointestinal Symptoms Rating Scale (GSRS) score for abdominal symptoms, and GSRS score for abdominal bloating.

RESULTS: The VAS score for abdominal bloating and total GSRS score for abdominal symptoms recovered to levels that were not significantly different to preoperative levels by 10 d postoperation. Combination therapy of DKT and lactulose was associated with a significantly poorer outcome in terms of VAS and GSRS scores for abdominal bloating, total GSRS score, and total daily calorie intake, when compared with DKT alone therapy.

CONCLUSION: DKT is a potentially effective drug for postoperative management of hepatectomized patients, not only to ameliorate abdominal bloating, but also to promote nutritional support by increasing postoperative dietary intake.

Key words: Daikenchuto; Hepatic resection; Abdominal bloating; Visual analogue scale score; Gastrointestinal symptoms rating scale score

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INTRODUCTION

Despite developments in surgical skills and perioperative management, uncomfortable abdominal symptoms such as bloating and pain are unavoidable after abdominal surgery. A combination of stool softeners, laxatives, antispasmodics, antidepressants, and diet changes are often used in postoperative management; however, the full effects of the above drugs and diet changes remain unclear, and stimulant laxatives may themselves induce abdominal bloating and pain[1].

Daikenchuto (TJ-100, DKT) is a frequently prescribed traditional Japanese herbal (or Kampo) medicine

in Japan, comprising extract granules of Japanese pepper, processed ginger, ginseng radix, and maltose powder derived from rice. DKT extract powder (Tsumura and Co., Tokyo, Japan) is manufactured as an aqueous extract containing 2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng radix, and 88.9% maltose syrup powder. The standard dosage of DKT is 15 g/d[2].

The effects of DKT in the gastrointestinal (GI) tract are mediated mainly by cholinergic and serotonergic nerves. DKT enhances GI motility both *in vitro* and *in vivo*[3]. Clinically, DKT plays pivotal roles in the management of gastroenterological disorder after surgery by improving bowel blood flow and bowel movement[4].

Hepatectomy is an effective method for treating various liver diseases, such as hepatocellular carcinoma (HCC), metastatic liver cancer (MLC), and cholangiocarcinoma (CCC). Recent advances in surgical techniques and perioperative care have made hepatectomy a safer therapeutic option than previously observed, with less morbidity and mortality. However, postoperative liver failure remains an unsolved problem, especially in patients who have undergone major liver resection and have limited hepatic functional reserve. Bacterial translocation (BT) is a key factor in liver failure after hepatic resection, and leads to high rates of morbidity and mortality[5]. To prevent BT, we have routinely used drugs such as lactulose to promote release of flatus and defecation after hepatic resection. DKT is often used for the same purpose as lactulose in many Japanese institutes[6].

DKT has been used to treat patients following GI surgery, and has been shown to prevent postoperative ileus in these patients. In Japan, many surgeons have successfully used DKT to promote release of flatus and defecation after GI surgery[3-6]. However, there have been few scientific studies of DKT in hepatectomized patients, and the effects of DKT in such patients remain unclear. Therefore, this study sought to evaluate the clinical usefulness of DKT in hepatectomized patients.

Abdominal bloating and pain can be accurately and quantitatively evaluated by using the Visual Analogue Scale (VAS) score, and various abdominal symptoms can be evaluated by using the Gastrointestinal Symptoms Rating Scale (GSRS) score[1]. Here, we used VAS and GSRS scores to evaluate abdominal symptoms in hepatectomized patients. To the best of our knowledge, this is the first study to evaluate the effects of DKT using VAS and GSRS scores in hepatectomized patients.

MATERIALS AND METHODS

Patients

From November 2009 to June 2011, 20 patients with liver malignancy were enrolled in this study. Informed consent was obtained from each patient according to the guidelines for clinical studies established by Kochi Medical School. Two patients were eliminated from the study because their operation was cancelled. Data for the remaining 18 patients were prospectively collected.

Three primary end points were used to assess the severity of abdominal symptoms. First, patients subjectively evaluated their abdominal bloating by using VAS[7], which is a 10 cm horizontal line scoring system ranging between 0 (no abdominal bloating) and 10 (extremely strong or frequent). VAS evaluations were performed the day before the operation, prior to administration of DKT, and 2, 4, 6, 8 and 10 d after the operation. Second, the patients subjectively evaluated their abdominal symptoms by using the GSRS, Japanese edition[8], which comprises 15 items that are each rated according to severity on a scale of 1 (absence of the symptom) to 7 (maximal intensity of the symptom); thus, higher GSRS scores indicate more severe symptoms. The GSRS questionnaire was administered twice to each patient on the day before the operation, prior to administration of DKT, and 10 d after the operation. We used the total GSRS score for all 15 GI symptoms to evaluate abdominal symptoms. Third, in a sub-analysis, we used the GSRS score for abdominal bloating to evaluate abdominal bloating specifically.

Secondary end points were levels of serum ammonia, C-reactive protein (CRP), and interleukin-6 (IL-6), the length of time from the end of general anesthesia until the first release of flatus or defecation, and the presence or absence of postoperative adhesive ileus.

DKT treatment with or without lactulose

Each of the 18 patients was treated orally with a 15 g/d dosage of DKT from 3 d before the operation to 10 d after the operation. Nine of these patients were selected at random, and cotreated with at least 16 g of lactulose 3 times a day ($\geqslant$ 48 g/d) over the same period. Thus, the 18 patients were divided equally into 2 groups: DKT alone therapy group (D group; n = 9) and combination therapy of DKT and lactulose group (D + L group; n = 9).

Statistical analysis

Results are expressed as mean ± SD unless stated otherwise. The treatment responses in the D and D + L groups were evaluated based on the changes in the VAS and GSRS scores between before and after treatment by using the Wilcoxon signed rank test. Background factors with a continuous distribution, such as patient age and body mass index (BMI), were compared between X and Y by using the Wilcoxon rank sum test. The distributions of various categorical factors, such as gender, diagnosis, and Child-Pugh score[9,10] were compared between X and Y by using the Fisher's exact test. The incidences of morbidity were compared between the D and D + L groups by using the χ^2 test. P values less than 0.05 were considered statistically significant.

RESULTS

Effects of DKT therapy in hepatectomized patients

The patient characteristics are listed in Table 1. The 18 patients comprised 15 men and 3 women, with 12 cases of HCC, 5 cases of MLC, and 1 case of CCC. There was no

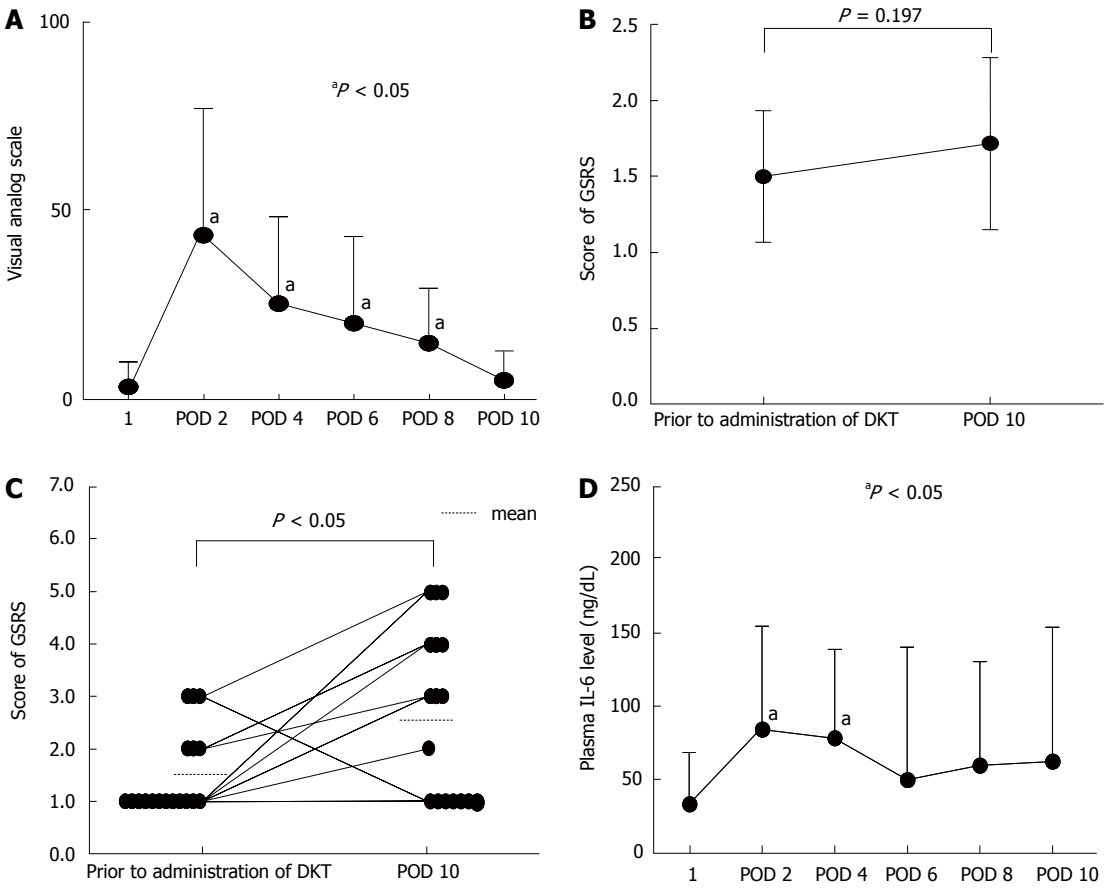

Figure 1 Changes in severity of abdominal symptoms and plasma interleukin-6 level following hepatic resection. A: Visual analogue scale (VAS) score for abdominal bloating; B: Total gastrointestinal symptoms rating scale (GSRS) score for abdominal symptoms; C: GSRS score for abdominal bloating were measured before and after hepatic resection in all patients; D: Plasma interleukin-6 level. In panels (A) and (B), data represent means ± SD (n = 18). In panel (C), data are presented as individual patient scores. Data obtained prior to administration of Daikenchuto (DKT) were measured before hepatic resection. POD: Postoperative day. $^aP < 0.05$ *vs* prior to administration of DKT. 1: Prior to administration of DKT.

Table 1 Patient characteristics *n* (%)

Variable	
Age (yr)	64.9 ± 6.7
Male/female	15/3
Height (cm)	161.4 ± 10.5
Weight (kg)	60.6 ± 9.9
BMI (%)	23.3 ± 3.7
Diagnosis	
HCC	12 (67)
MLT	5 (28)
CCC	1 (5)
Child-Pugh score	
A	18 (100)
B	0 (0)
C	0 (0)

Data are presented as mean ± SD. BMI: Body-mass index; HCC: Hepatocellular carcinoma; MLT: Metastatic liver tumor; CCC: Cholangiocarcinoma.

mortality and no side effects after treatment with DKT. Six patients (33%) had morbidity in the form of minor bile leakage (5 cases) and slight cholangitis (1 case), but all affected patients recovered with conservative therapy.

The VAS score for abdominal bloating peaked at postoperative day 2, and then decreased gradually to a level similar to the preoperative level by postoperative day 10 (Figure 1A). The scores measured on postoperative days 2 to 8 were significantly higher than the preoperative score measured prior to administration of DKT.

Although total GSRS score for abdominal symptoms was slightly elevated at postoperative day 10 (1.72) compared with the level before surgery and prior to administration of DKT (1.51), the difference was not statistically significant (Figure 1B). In contrast, the GSRS score subanalysis showed a significantly elevated GSRS score for abdominal bloating at postoperative day 10 compared with the level prior to surgery (Figure 1C). The use of lactulose in combination with DKT was a significant risk factor for a reduced (*i.e.*, worse) GSRS score after hepatic resection, compared with the preoperative score (Table 2). Other factors such as intraoperative blood loss, operative method, and tumor marker levels were not significant risk factors (Table 2).

Although plasma IL-6 levels increased significantly at postoperative days 1 and 2 after hepatic resection com-

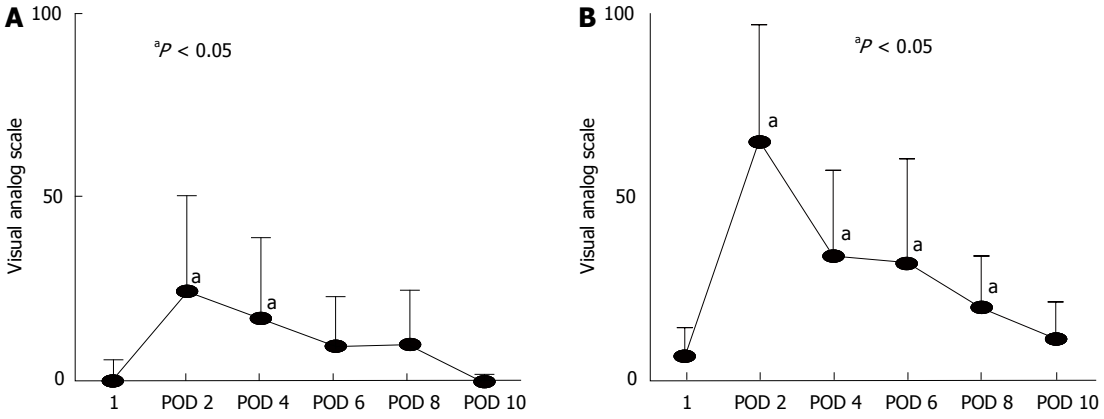

Figure 2 Comparison of visual analogue scale score for abdominal bloating in patients treated with Daikenchuto alone and those treated with combination therapy of Daikenchuto and lactulose. Visual analogue scale (VAS) scores for abdominal bloating were measured in (A) Daikenchuto (DKT) alone group and (B) combination therapy group before and after hepatic resection. Data obtained prior to administration of DKT were measured before hepatic resection. POD: Postoperative day. Data represent means ± SD (n = 9, in each group). [a]P < 0.05 *vs* prior to administration of DKT. 1: Prior to administration of DKT.

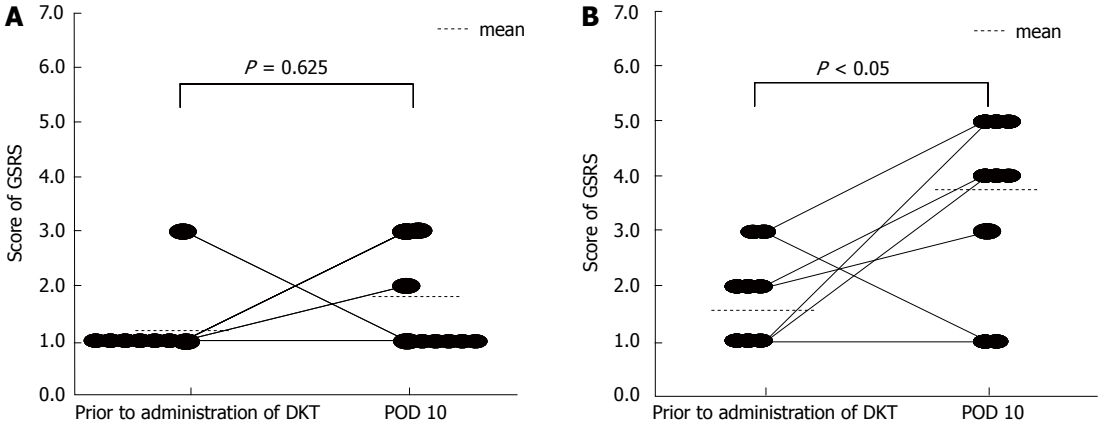

Figure 3 Comparison of gastrointestinal symptoms rating scale score for abdominal bloating in patients treated with Daikenchuto alone and those treated with combination therapy of Daikenchuto and lactulose. Gastrointestinal symptoms rating scale (GSRS) scores for abdominal bloating in (A) Daikenchuto (DKT) alone group (n = 9) and (B) combination therapy group (n = 9) were measured before and after hepatic resection. Data obtained prior to administration of DKT were measured before hepatic resection. Data for individual patients are shown. POD: Postoperative day.

pared with the level before the operation and prior to DKT administration, they recovered to a level that was not significantly different from the preoperative level by postoperative day 4 (Figure 1D).

Comparison between DKT alone therapy and combination therapy of DKT and lactulose

The characteristics of patients treated with DKT (15 g/d) alone (D group; n = 9) and patients subjected to combination therapy of DKT (15 g/d) and lactulose (48 g/d) (D + L group; n = 9) are listed in Table 3. Between the two groups, there were no significant differences in preoperative data such as Child-Pugh score[9,10], CLIP score[11], and liver damage score[12] or intraoperative data such as type of hepatic resection, blood loss, and operation time.

By postoperative day 6, the VAS scores for abdominal bloating in D group had recovered to levels that were not significantly different from the preoperative levels prior to administration of DKT (Figure 2A). In contrast, the VAS scores of the D + L group did not return to preoperative levels until postoperative day 10 (Figure 2B). At postoperative days 2 and 10, the VAS scores for abdominal bloating in D group were significantly lower than those in the D + L group (Figure 2).

The total GSRS score at postoperative day 10 was significantly lower in D group than in D + L group (P < 0.05), whereas there was no significant difference in this score between the groups before the operation. Also, in the sub-analysis, although there was no significant difference between preoperative and postoperative GSRS scores for abdominal bloating in D group (Figure 3A), and the postoperative GSRS score for abdominal bloating was significantly higher than the preoperative score in the D + L group (Figure 3B). Regarding the secondary end points, there were no significant differences in postoperative serum ammonia or CRP values between the two groups. The median times from the end of general anesthesia until the first release of flatus or defecation in

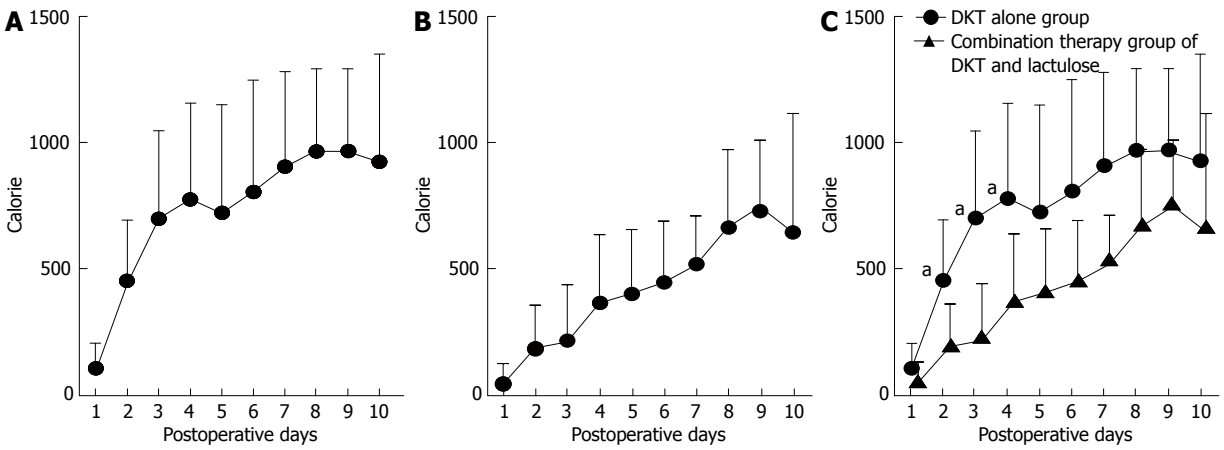

Figure 4 Comparison of nutritional intake between patients treated with (A) Daikenchuto alone and those treated with (B) combination therapy of DKT and lactulose. Mean total calorie intake was measured in the Daikenchuto (DKT) alone group and combination therapy group after hepatic resection. Data represent means ± SD (n = 9, in each group). [a]$P < 0.05$ *vs* combination therapy group (C).

Table 2 Risk factors for worse gastrointestinal symptoms rating scale score after hepatic resection in patients treated with Daikenchuto

Variable	*P* value
Use of lactulose (yes/no)	0.001
Preserved liver function (ChE)	0.115
Marker of liver fibrosis (hyarulonic acid)	0.553
Intraoperative blood loss (mL)	0.080
Type of hepatic resection[1]	0.093
BMI	0.192
Operation time (min)	0.466
Anesthesia time (min)	0.556

[1]Right lobectomy, left lobectomy, segmentectomy, or wedge resection. BMI: Body-mass index; ChE: Choline esterase.

D *vs* D + L groups were 39.7 *vs* 29.3 h (release of flatus) and 77.7 *vs* 42.7 h (defecation), respectively. Although the time until the first release of flatus did not differ significantly between the two groups, the time until the first defecation was significantly smaller in the D + L group than that in the D group ($P < 0.05$). No patients experienced postoperative adhesive ileus.

In terms of patient nutrition, the mean total calorie intake over the period from postoperative day 1 to day 10 (7305.0 kcal, Figure 4A) was significantly higher in the D group than in the D + L group (4201.6 kcal, $P = 0.027$, Figure 4B) and the mean total calorie intake at each of postoperative days 2, 3, and 4 was significantly higher in the D group than in the D + L group ($P < 0.05$, Figure 4C).

The incidence of morbidity after hepatic resection in the D group (1/9 patients experienced cholangitis) was lower than that in the D + L group (5/9 patients experienced bile leakage); however, this difference was not statistically significant ($P = 0.34$). Also, between the groups, there was no significant difference in the mean or median period of hospital stay after hepatic resection ($P = 0.30$, $P = 0.29$, respectively), although D group patients showed a tendency for shorter postoperative hospital stays compared with the D + L group.

DISCUSSION

In this prospective study, we found that DKT therapy produced an effective surgical outcome for hepatic resection in that the VAS score for abdominal bloating in patients treated with DKT returned to close to the preoperative level by postoperative day 10, and the preoperative level of the total GSRS score for abdominal symptoms was well preserved after the operation. We also found that combination therapy of DKT and lactulose produced a significantly poorer outcome, not only in terms of total GSRS score for abdominal symptoms, but also in VAS and GSRS scores for abdominal bloating, compared with DKT alone therapy. As a result, DKT alone therapy was superior to the combination therapy as a perioperative nutritional support by enabling higher postoperative dietary intake.

Horiuchi *et al*[11] suggested that both the VAS and GSRS scores of patients treated with DKT for chronic constipation were superior for dosages of 15 g/d compared with 7.5 g/d. In that study, DKT showed a dose-dependent effect on abdominal bloating and abdominal pain. Therefore, in our study, every patient was treated orally with a dosage of 15 g/d, and we recommend that DKT should be administered to hepatectomized patients with abdominal bloating or pain by using a standard dose of 15 g/d.

Lactulose is an artificially synthesized disaccharide (1, 4-β galactosido-fructose). Following oral administration, lactulose reaches the colon in intact form, where it is split by lactobaccili into lower molecular-weight organic acids such as lactic acid and acetic acid. As a result, gram-negative rods, which are the main cause of ammonia production in the GI tract, reduce in number and lactobaccili increase in number. Diminished ammonia production after lactulose treatment has been explained by alteration of bacterial flora in the gut, changes in bacterial metabolism, and an effect of lactulose on the metabolism of crypt and villus cells of the bowel wall. Lactulose also inhibits the production of tumor necrotizing factor in

Table 3 Patient characteristics of Daikenchuto group and Daikenchuto + lactulose group (mean ± SD)

Variable	DKT group	DKT + lactulose group	*P* value
Age (yr)	65.9 ± 6.1	64.0 ± 7.6	0.567
Male/female	7/2	8/1	1.000
Height (cm)	164.6 ± 7.3	158.2 ± 12.6	0.206
Weight (kg)	65.1 ± 7.4	56.1 ± 10.5	0.052
BMI (%)	24.0 ± 1.7	22.6 ± 5.0	0.455
Child-Pugh score	Grade A: 9	Grade A: 9	0.585
CLIP score	Score 0: 8 and Score 1: 1	Score 0: 7 and Score 1: 2	1.000
Liver damage score	Grade A: 9	Grade A: 7 and Grade B: 2	0.166
Type of hepatic resection			0.188
	Right lobectomy: 1 Segmentectomy: 1 Wedge resection: 7	Left lobectomy: 1 Segmentectomy: 3 Wedge resection: 5	
Intraoperative blood loss (mL)	428.9 ± 294.0	852.2 ± 928.4	0.211
Operation time (min)	307.8 ± 107.5	347.2 ± 125.0	0.483
Anesthesia time (min)	392.8 ± 118.0	420.6 ± 128.4	0.639

BMI: Body-mass index; DKT: Daikenchuto.

endotoxin-stimulated monocytes and binds endotoxin[6]. In our study, if lactulose was used in combination with DKT, the first release of flatus and first defecation after hepatic resection occurred earlier than when DKT was used alone; this effect was statistically significant for defecation, but not for release of flatus; however, we do not recommend combination therapy of DKT and lactulose for patients with uncomfortable abdominal symptoms after hepatic resection because of significantly worse VAS and GSRS scores for abdominal bloating compared with those observed for DKT alone therapy.

Kaiho *et al*[6] reported that levels of postoperative serum ammonia in hepatectomized patients in a DKT-treatment (15 g/d) group were significantly lower than those in the control group (no DKT or lactulose treatment) or the lactulose-treatment (48 g/d) group. These results, albeit from a retrospective study, suggested that DKT might be a more effective and safe agent than lactulose in postoperative management of hepatic resection. The lack of a significant difference in postoperative serum ammonia levels between the D and D + L groups in our study suggests that prevention of increased levels of ammonia and associated hepatic coma after hepatic resection does not require lactulose treatment if DKT is used.

Kono *et al*[2,3] reported that DKT activates the endogenous adrenomedullin (ADM)/calcitonin gene-related peptide (CGRP) system. ADM and CGRP belong to the calcitonin family and are potent endogenous vasodilators. ADM plays important roles in the regulation of microcirculation, angiogenesis, anti-fibrosis, antibiosis, and down-regulation of proinflammatory cytokines. CGRP is present in most sensory neurons supplying the GI tract and plays important roles in the regulation of microcirculation and immune suppression; moreover, CGRP has anti-inflammatory effects. Therefore, DKT has a substantial anti-inflammatory effect through its activation of ADM and CGRP. We also observed that DKT increased the serum CGRP level and contributed to the early recovery of abdominal symptoms in patients with adhesive ileus (data not shown).

Previously we performed absorption, distribution, metabolism, and excretion studies of DKT[13, 14]. In the first study[13], after oral administration of 15 g of DKT in healthy volunteers, 6 ingredients of DKT (*i.e.*, hydroxy-α- and hydroxy-β-sanshool derived from Japanese pepper, 6- and 10-shogaol derived from ginger, and ginsenoside Rb1 and Rg1 derived from ginseng) were detected in intravenous blood. In the second study[14], four of these compounds (*i.e.*, hydroxy-α and hydroxyl-β-sanshool, and 6- and 10-shogaol) were dose-dependently detected in venous blood[14]. Of note, CGRP and ADM are known to be activated by hydroxy-α and hydroxy-β-sanshool and/or 6-shogaol[14].

The increase of inflammatory cytokines after surgery is responsible for a substantial portion of the loss of epithelial barrier function observed. Impaired integrity of the intestine can cause BT, which is a key factor leading to high morbidity and mortality by causing conditions such as sepsis and multiple organ failure[5]. Thus, to improve surgical outcomes, it is important to prevent BT after surgery. Yoshikawa *et al*[5] reported that DKT prevents BT in rats through the morphological preservation of microvilli and the suppression of various inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, and interferon-γ (IFN-γ). These experimental data support our clinical finding that, in patients treated with DKT, the significant elevation of IL-6 observed immediately after hepatic resection recovered by postoperative 4 day to a level that was not significantly different to the preoperative level (Figure 1D). Recently, we found that DKT played important roles in the suppression of inflammatory cytokines such as IL-6 and INF-γ in patients with adhesive ileus (data not shown). In addition, a recent clinical report demonstrated that postoperative DKT therapy (7.5 g/d for 7 d) significantly suppressed the

CRP level correlating to IL-6 in general, and shortened the time until first release of flatus following laparoscopic colorectal resection[15]. Infection control plays pivotal roles in the prevention of liver failure after hepatic resection. Our finding that DKT has anti-inflammatory effects by reducing the elevation of plasma IL-6 after hepatic resection (Figure 1D) suggests that DKT may be a useful drug for infection control and the prevention of BT.

Enhanced recovery after surgery (ERAS) is a novel concept of perioperative management derived from Western countries[16-18]. Briefly, the ERAS protocol, which consists of appropriate nutritional support and good infection control including prevention of hyperglycemia and/or insulin resistance, aims to shorten hospital stays, improve quality of life in patients, and reduce costs to the hospital[16-19]. In our study, treatment with DKT alone was more effective in improving VAS and GSRS scores for abdominal bloating than was treatment with DKT combined with lactulose. Furthermore, the results of our comparison of total calorie intake between patients treated with DKT alone and those treated with combination therapy, suggest that DKT alone therapy is the more effective regimen to promote early recovery associated with dietary nutrition. Also, although it was not a statistically significant difference, patients treated with DKT alone showed a lower morbidity rate and had a tendency towards a shorter hospital stay compared with those subjected to the combination therapy. Furthermore, Ogasawara *et al*[20] found that DKT increased portal blood flow in the early phase after oral administration (2.5 g dose) without any significant changes in the blood pressure and heart rate in the healthy volunteers, cirrhotic patients and liver transplant patients, suggesting that DKT therapy might improve liver function by increasing portal blood flow in patients after hepatic resection. Therefore, in terms of ERAS, DKT alone therapy after hepatic resection may be useful not only for improvement of postoperative abdominal symptoms, and enhanced dietary nutrition, but also for preservation of hepatic function through increasing portal blood flow. Further examinations with larger series of patients will be required to address these issues regarding ERAS.

Besides the small sample size, a limitation of our study is the absence of a control group that was not subjected to DKT treatment. Placebos of Kampo medicine such as DKT are difficult to prepare[4-7], but even if a placebo could be prepared successfully, we consider that the use of such a placebo might give rise to ethical problems, for the following reasons. Almost all hepatectomized patients suffer from abdominal bloating and pain associated with delayed release of flatus and defecation; therefore, if no drugs such as DKT and/or lactulose were used, the situation might grow more serious, especially in patients with chronic hepatitis and cirrhosis. Ammonia levels and the incidence of postoperative BT might increase, and infection control might become poor. In the worst situation, this may lead to high morbidity and mortality caused by hepatic encephalopathy and acute liver failure. At all events, the setting of control group with no DKT and no lactulose group might be needed for more strict evaluation in this study. However, the superior effectiveness of DKT for post-hepatectomy abdominal discomfort compared with lactulose alone group or no DKT and no lactulose group has been already established by previous clinical study[6].

In conclusion, DKT is a potentially effective drug for hepatectomized patients, not only to ameliorate VAS and GSRS scores for abdominal bloating, but also to promote ERAS by increasing postoperative dietary intake. Additional studies of DKT in prospective randomized clinical trials with a large patient series are warranted to further evaluate the effects of DKT against uncomfortable abdominal symptoms such as bloating and pain after hepatic resection.

COMMENTS

Background

Daikenchuto (DKT) has been used to treat patients following gastrointestinal (GI) surgery, and has been shown to prevent postoperative ileus in these patients. In Japan, many surgeons have successfully used DKT to promote release of flatus and defecation after GI surgery. However, there have been few scientific evidences of DKT in hepatectomized patients, and the effects of DKT in such patients remain unclear. This study evaluates the clinical usefulness of DKT in hepatectomized patients.

Research frontiers

Abdominal bloating and pain can be accurately and quantitatively evaluated by using the Visual Analogue Scale (VAS) score, and various abdominal symptoms can be evaluated by using the Gastrointestinal Symptoms Rating Scale (GSRS) score. VAS and GSRS scores are used to evaluate abdominal symptoms.

Innovation and breakthroughs

In hepatectomized patients, combination therapy of DKT and lactulose was associated with a significantly poorer outcome in terms of VAS and GSRS scores for abdominal bloating, total GSRS score, and total daily calorie intake, when compared with DKT alone therapy.

Applications

To promote enhanced recovery after surgery (ERAS), perioperative DKT treatment may play an important role in the improvement of abdominal symptoms and nutritional status after hepatic resection. Therefore DKT may contribute to reduce morbidity, mortality due to liver failure, and hospital staying after hepatectomy.

Terminology

ERAS is a novel concept of perioperative management. The ERAS protocol, which consists of appropriate nutritional support and good infection control, aims to shorten hospital stays, improve quality of life in patients, and reduce costs to the hospital. VAS and GSRS are useful scores to objectively evaluate abdominal symptoms in surgical patients.

Peer review

This is an early study to evaluate the effects of DKT using VAS and GSRS scores in hepatectomized patients. The results suggest that perioperative DKT treatment for surgical patients may have a potential effect to ameliorate abdominal symptoms and contribute to nutrition support and ERAS protocol.

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BRIEF ARTICLE

Ligation of intersphincteric fistula tract and its modification: Results from treatment of complex fistula

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Abstract

AIM: To compare healing rates between intersphincteric fistula tract (LIFT) and LIFT plus partial fistulectomy procedures.

METHODS: A study of complex fistula-in-ano patients was carried out from 1st March 2010 to 31th January 2012. All operations were done by colorectal surgeons at a referral center in a Ministry of Public Health hospital. Data collected included patients' demographic details, fistula type determined by endorectal-ultrasonography, preoperative and postoperative continence status, previous operations, time between diagnosis of fistula-in-ano and operation, type of surgery, healing rates, recurrence rates, and types of failure examined by endorectal-ultrasosnography, re-operation in recurrence or failure cases, and complications.

RESULTS: The study involved 41 patients whose average age was 40.78 ± 11.84 years (range: 21-71 years). The major fistula type was high-transsphincteric type fistula. The median follow-up period was 24 wk. The overall success rate was 83%: in the LIFT (Ligation intersphincteric fistula tract) group the success rate was 81% and in the LIFT plus (LIFT with partial coreout fistulectomy) group it was 85% (P = 0.529). The median wound-healing time was 4 wk in both groups (P = 0.262). The median time to recurrence was 12 wk. Neither group had incontinence (Wexner incontinence score-0) and the difference in healing rates between the two groups was not statistically significant.

CONCLUSION: There was no difference in results between LIFT and LIFT plus operations. The LIFT procedure is a good option for maintaining continence in management of fistula-in-ano.

Key words: Fistula-in-ano; Complex fistula; Intersphincteric fistula tract; Perianal disease; Incontinence

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INTRODUCTION

The ideal way to treat anal fistula is to cure the disease without any risk of fecal incontinence. The many surgical techniques used in treating anal fistula can be divided into 2 groups: sphincter-sacrificing and sphincter-sparing methods. The sphincter-sacrificing techniques, with or without immediate repair, have a high healing rate but also a high post-operative incontinence rate, while the sphincter-sparing methods have varied healing rates but little or no resultant incontinence. The impairment of continence has an effect on quality of life, so the sphincter-sparing methods are now popular. There are a number of sphincter-sparing methods such as fibrin or cyanoacrylate glue injection[1,2], anal fistula plug[3], endorectal

Table 1 Assessment of clinical continence grading

Category	Description
A	Continent of solid and liquid stools and flatus (*i.e.*, normal continence)
B	Continent of solid and usually liquid stools but not flatus (no fecal leakage)
C	Acceptable continence for solid stool but no control over liquid stool or flatus (intermittent fecal leakage)
D	Continued fecal leakage

Reproduced from Browning *et al*[26].

muscular or mucosal advancement flap[4,5], core-out fistulectomy[6,7], radiofrequency ablation[8], ayurvedic seton[9], ligation of intersphincteric fistula tract (LIFT)[10,11], and finally, video-assisted anal fistula treatment (VAAFT)[12].

Several sphincter-sparing methods carry their own risk of recurrence and some degree of incontinence. Most of these are complicated and difficult procedures, and require expertise, highly-experienced surgeons, or high-technology equipment. The ligation of LIFT procedure was presented by Rojanasakul *et al*[10] with a healing rate of 94%. This procedure was a simple, safe, minimally-invasive technique. It was also effective, with a high and rapid healing rate without any resultant incontinence. However, later reports showed healing rates varying between 57% and 83%[13-21]. The treatment failure or recurrence might have been related to inadequate management of sources of infection or remnant fistula tract as proposed by Rojanasakul *et al*[22] and Mitalas *et al*[23]. The aim of this prospective study was to compare the success rates between treating complex anal fistula with the original LIFT and LIFT with partial coreout fistulectomy (LIFT plus).

MATERIALS AND METHODS

The study was conducted from 1st March 2010 to 31st January 2012 in Rajavithi Hospital. All of the patients were diagnosed with fistula-in-ano from their medical history and physical examination. All patients underwent endoanal ultrasonography (Hitachi, EUB 7500) combined with hydrogen-peroxide for classification into simple and complex fistula-in-ano. The ultrasonography study was performed by a colorectal surgeon. The patients' continence was evaluated at the preoperative and postoperative phases by Wexner incontinence score (WIS)[24,25] and clinical continence grading (Table 1)[26] was recorded at every visit. Written informed consent was obtained from all the patients after they were given a full explanation of the procedure, and they agreed to participate in regular follow-up assessments. This study was approved by the Rajavithi Hospital Medical Ethics Committee.

Inclusion criteria were: (1) age more than 18 years; (2) complex cryptoglandular anal fistulas in patients with newly-diagnosed fistula-in-ano; and (3) no sinus abscess confirmed by endoanal ultrasonography.

Exclusion criteria were: (1) superficial fistulas that could be treated by simple fistulotomy; (2) Crohn's perianal disease; and (3) other inflammatory bowel disease or malignancy.

A database was created to collect information pertaining to this study. The unit recorded data on patient demographics, past surgical treatments, fistula characteristics, Endorectal ultrasonographic findings, operative data and follow-up findings. The database also included information on operative findings, postoperative morbidity and length of follow-up.

Patients with complex fistula-in-ano were divided into 2 groups. The first group (the LIFT group) underwent ordinary LIFT, as described by Rojanasakul[22], and the second group (the LIFT plus group) had LIFT combined with partial core-out fistulectomy.

Definitions

Simple fistulas: Low transsphincteric and intersphincteric fistulas that cross 30% of the external sphincter[27].

Complex fistulas: High transsphincteric fistulas with or without a high blind tract; suprasphincteric and extrasphincteric fistulas; horseshoe fistulas; and those associated with inflammatory bowel disease, radiation, malignancy, pre-existing incontinence, or chronic diarrhea[27].

Treatment failure or recurrence: Persistent discharge (purulent stool) more than 4 wk after surgery or recurrent drainage; air leakage from external opening and/or intersphincteric incision wound after the wound had healed.

Healing wound or success: Defined as healing of the external opening and intersphincteric incision wound.

Partial core-out fistulectomy: Excision of fistula tract from the external opening to the outer rim of the anal sphincter muscle.

Operative technique

All patients were admitted 1 d before surgery with no bowel preparation. A wide- spectrum antibiotic was given for 1 wk. Regional anesthesia was performed by anesthesiologists. The Prone-Jacknife position was used. An internal opening was identified by injecting methylene blue or povidine iodine from an external opening, and an incision was made parallel to the anal verge about 2 centimetres above the intersphincteric groove. Dissection deep down into intersphincteric space was carried out with scissors and electric cautery to identify the fistula tract. This tract was then ligated on the internal opening site by polyglactin 3/0 (Vicryl 3/0) before being transected. In order to confirm that it was the correct tract, normal saline, methylene blue or povidine solution was injected, after which the tract was ligated on the external site with polyglactin 3/0.

The first group of patients had the tract curretted

Table 2 Patient demographic data

	LIFT	LIFT plus	*P* vaule
Patients	21	20	
Age average	43.95 ± 12.35	37.45 ± 10.58	
(mean ± SD, yr) (range)	(23-71)	(21-54)	0.650
Sex			
Male	17	14	0.326
Female	4	6	
Underlying disease	0	0	
BMI (kg/m^2, mean ± SD)	24.20 ± 4.62	23.08 ± 5.38	0.480
Prior fistula operation	0	0	
Fistula type			0.365
High-transsphincteric	19	14	
Horseshoe-transsphincteric	1	3	
Suprasphincteric	0	1	
Low-transsphincteric	1	2	
Preoperative incontinence			
Clinical	A	A	
WIS	0	0	
Timing from diagnosis of fistula-in-ano to operation (median, wk) (range)	16 (4-52)	18 (4-150)	0.547

BMI: Body mass index; WIS: Wexner incontinence score; LIFT: Ligation of intersphincteric fistula tract.

from the external opening while patients in the second group had partial core-out fistulectomy performed from the external opening to the external sphincter. The fistula tracts of both groups were sent for pathological examination.

All of the patients were discharged the following day with analgesia and stool softeners. Before being discharged, they were shown how to cleanse their wounds with tap water.

All patients were scheduled for follow-up at 2, 4, 8 and 12 wk postoperatively, and at 4-weekly intervals thereafter. At each visit the patient's clinical continence status[26] was evaluated, and incontinence rates were recorded using WIS [24,25]. Wound examination was carried out at both the internal and external openings of the wound, and other morbidity was also assessed.

Statistical analysis

The authors used χ^2 analysis and the Fisher-exact test to compare factors of recurrence, and the student *t*-test and Mann-Whitney *U* test were used to compare basic characteristics of the patients such as age and underlying diseases in the two groups (SPSS version 17, Microsoft Corp).

RESULTS

From 1st March 2010 to 31st January 2012, 45 complex fistula-in-ano patients were treated in Rajavithi Hospital. We excluded 4 patients from the study: 2 of them did not complete all follow-up visits, 1 had a fistula caused by tuberculosis, and 1 patient had a fistula associated with carcinoma of the anal canal. The remaining 41 complex fistula-in-ano patients were included. There were 31 male and 10 female cases whose average age was 40.78 ± 11.84 years (range: 21-71 years). Classification by type of fistula showed that 33 patients had high-transsphincteric type fistula, 4 had horseshoe-transsphincteric type, 1 had suprasphincteric type, and 3 female patients had anterior low-transsphincteric type. The average healing rate was 83%, the median wound healing time was 4 wk and the time to recurrence was 12 wk (range: 6-16 wk). None of the patients had incontinence. Of the 41 patients, 21 had the LIFT operation, and 20 had the LIFT + partial coreout fistulectomy. Table 2 shows a comparison of the demographic data of the two groups.

In the postoperative period, we had 1 minor bleeding complication from a core-out wound, and 2 anal fissures (one in each group). The fissures were healed by conservative treatment. None of the patients had recurrence of fistula, and none of their complications was associated with recurrence.

In all, there was treatment failure of the fistula in 7 cases. Re-examination by endoanal ultrasonography was carried out before re-operation (by other colorectal surgeons or endoscopists). In the LIFT group, there were 4 cases of recurrence, which was defined as non-healing of the external opening after a second visit or one month after the operation. One case had a sinus abscess due to fistula tract remnants (presented as perianal abscess) while another 3 cases were caused by failure of the ligation of the intersphincteric fistula tract in the intraoperative stage. In the LIFT PLUS group there were three instances of recurrence: 2 were due to failure to ligate the fistula tract and another was due to a new abscess appearing near the operation site, and fistula-in-ano occurred after incision and drainage with a new internal opening. All 6 fistula recurrence cases underwent re-operation: 4 by the LIFT procedure, and 2 by the LIFT PLUS. The patient with the sinus abscess was managed by incision and drainage and curettage. All of the recurrence cases healed after the second operation with no incontinence. Univariate analysis of factors of recurrence showed that body mass index (BMI) was a significant factor for recurrence (Tables 3 and 4).

DISCUSSION

The success rates of sphincter-sparing methods in treating anal fistula have varied considerably. Fibrin glue injection is simple but the results have been disappointing, with success rates as low as 16%-25%[28-30]. Similarly, anal plug studies reported success rates of 29%-87%[31-33]. Draining seton is also a simple technique, but has a long healing time, varying from about 3-9 mo[34,35]. Endoanal advancement flaps and coreout fistulectomy are complicated procedures with high success rates of 86%-97% and with minimal change in continence[6,7] due to stretching or tearing of the anal sphincter (Table 5).

Currently, there is a growing interest in ligation of LIFT because the procedure is minimally invasive, easy to learn and perform, and can be used on recurrent cases. The early results of the LIFT procedure were quite im-

Table 3 Results

	LIFT	LIFT PLUS	*P* vaule
Operative time (mean ± SD, min) (range)	37.67 ± 17.40 (20-75)	44.00 ± 14.29 (25-90)	0.400
Healing rate	81%	85%	0.529
Postoperative incontinence			
Clinical	A	A	
WIS	0	0	
Postoperative complications			0.520
Headache	0	0	
Urinary retention	0	0	
Bleeding (minor)	0	1	
Anal fissure	1	1	
Difficulty in defecating	0	0	
Wound healing time (median, wk)	4	4	0.262
Follow up (median, wk) (range)	18 (12-22)	20 (12-24)	
Time to recurrence (median , wk)	10	12	0.354
Recurrence cases *n* (%)			
High-transsphincteric	4 (19)	3 (15)	
Horseshoe-transsphincteric	0 (0)	0 (0)	
Suprasphincteric	0 (0)	0 (0)	
Anterior low-transsphincteric in females	0 (0)	0 (0)	
Re-operation	3	3	

WIS: Wexner incontinence score.

Table 4 Comparative factors of recurrence (mean ± SD)

Factor	Heal (*n* = 34)	Recurrence (*n* = 7)	*P* vaule
Age, yr	41.35 ± 12.00	38.00 ± 11.43	0.502
BMI, kg/m^2	22.0 ± 3.9	30.54 ± 3.54	< 0.001
Timing from diagnosis of fistula-in-ano to operation (median, wk) (range)	16 (4-150)	16 (4-110)	0.985

Table 5 Overall LIFT success rate

Author, year	Success rate	Patient	Follow up period	Incontinence rate
Rojanasakul *et al*[10], 2007	94%	17	4 wk	0
Bleier *et al*[13], 2010	57%	39	NA	NA
Shanwani *et al*[14], 2010	77%	45	9 mo	0
Tan *et al*[15], 2011	78%	93	23 wk	NA
Sileri *et al*[16], 2011	83%	18	4 mo	Same as preoperative
Ooi *et al*[18], 2012	68%	25	22 wk	0
Wallin *et al*[20], 2012	57%	93	19 mo	NA
Abcarian *et al*[21], 2012	74%	40	18 wk	NA
van Onkelen *et al*[36], 2012	82%	22	19.5 mo	0

NA: Not available.

pressive with success rates ranging from 57%-94% with minimal morbidity and little or no impact on continence status[10,13-15].

Some surgeons have used modifications of LIFT by combining it with additional procedures such as transanal advancement flap[36] or bioprosthetic plug[37]. The healing rate improved to 95% in the LIFT with anal fistula plug procedure, but did not improve with the combination of advancement flap.

Our study showed that primary healing was achieved in 17 patients (81%) in the LIFT group and 17 patients (85%) in the LIFT plus group (P = 0.529), with median wound healing time of 4 wk in both groups (P = 0.262). The healing rate following excision of the fistula tract was unchanged from that of the non-excision group, similar to the comparison of healing results in fistulotomy and fistulectomy[38]. Seven patients (4 in the LIFT group and 3 in the LIFT plus group) had treatment failure or suspected recurrence at median time 12 wk (range: 6-16 wk) after surgery. These results showed that the excision of the fistula tract or partial fistulectomy did not improve the rates of success. It should be noted that in this study there were no cases of persistent anal abscess, which may be a common cause of treatment failure, so it should not be assumed that incomplete removal of the fistula tract is the only possible cause of treatment failure (Table 3).

Recurrence of anal fistula is mainly due to infection and technical errors. Infection was one of the reasons for non-healing of internal opening wounds, because it caused the breakdown of the closure wound on the internal sphincter. So, in cases with persistent anal abscess or infected incisional wounds, infection could be a factor for treatment failure. All of our failure cases underwent preoperative endorectal ultrasonography to delineate the association of anal sphincter anatomy with the fistula tract and secondary tract as well as collection or abscess. In our study, there was no incidence of anal abscess, and the failure rate from infection in this study was 2.4% (1 out of 41 cases), resulting from infection of the incision wound.

There were 6 cases (3 in each group) of technical errors in the identification of the fistula tract caused by incorrect ligation of the "true" fistula tract, but these results showed no statistical significance. The error was confirmed by endorectal ultrasonography which demonstrated the same internal opening and fistula tract. The reason for the difficulty in identifying the fistula tract could have been patient obesity, thinness or small size of the fistula tract, or a deep-seated fistula tract. Failure to identify the fistula tract occurred more often in obese patients with BMI of more than 30 (P = 0.001), which suggests that obesity might be a factor for treatment failure[39]. It has been suggested that inserting a draining seton for 8-12 wk[19] preoperatively to eradicate septic foci by adequate drainage and to promote maturation of the fistula tract around the seton, would reduce infection and make it easier to perform LIFT with impressive outcomes (Table 4).

There were minor incidences of morbidity with 1 case of minor bleeding of an external wound which was treated by pressure dressing, and 2 cases of anal fissure which were healed by conservative management. Continence was normal, identical to the preoperative phase with WIS = 0. Most previous reports of the LIFT technique also showed minimal or no impact on continence, and minimal morbidity, even though the healing rates varied.

In recurrence or treatment failure cases, re-operation was performed in 6 of the 7 cases with either LIFT or LIFT plus. All of these patients healed without morbidity or change in continence status. Another possible advantage of the LIFT procedure is that it can be performed in cases of recurrence even when failure occurred with previous use of the LIFT technique[20]. Moreover, in most recurrence cases the fistula type was converted to an intersphincteric fistula type which is easy to handle by simple fistulotomy[15].

The limitations of this study were its small sample size, unequal distribution of fistula type[40] and short follow-up period[41,42].

In conclusion, the LIFT procedure is relative easy to perform, has a high healing rate and appears to be safe with low morbidity and no impact on continence. The excision of fistula tract combined with LIFT does not improve success rates. The results of LIFT and LIFT with partial fistulectomy procedures are similar.

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COMMENTS

Background

The 3 major basic aims of fistula-in-ano management are: (1) control of sepsis; (2) closure of the fistula; and (3) maintenance of continence. Nowadays, operations for fistula-in-ano are classified into 2 groups: first, sphincter-sacrificing procedures such as sphincterotomy and sphincterectomy; second, sphincter-preserving procedures such as anal fistula plug, anal flap, seton and intersphincteric fistula tract (LIFT). There are 2 differences between LIFT and the total sphincter-conservation procedure used: (1) Ligation produces more favorable results than sewing; and (2) Curettage is more practical and less time-consuming than total excision of the fistulous tract.

Research frontiers

This study aimed to compare the effectiveness of clearing fistula tract or granulation tissue using original LIFT and LIFT plus partial fistulectomy.

Innovations and breakthroughs

This study showed no significant difference in healing rates or times between the LIFT and LIFT plus partial fistulectomy, and most importantly, it found that there was no resultant postoperative incontinence either from the LIFT or LIFT plus procedure.

Applications

These results show removal of infected granulation tissue in the fistulous tract and cavity by curettage or partial fistulectomy is equally successful. A second advantage was that there was good postoperative continence status, which may facilitate the management of recurrence or complex cases.

Peer review

This manuscript is impressive in that it studied not only the difference in success rates between the LIFT and LIFT plus partial fistulectomy procedures in the removal of fistula tract, but also the healing rates and postoperative continence status.

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CASE REPORT

Laparoscopic splenectomy for histiocytic sarcoma of the spleen

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Author contributions: Yamamoto S, Tsukamoto T and Kanazawa A contributed equally to this work; Yamamoto S, Tsukamoto T and Kanazawa A were the doctors in charge and performed the operations; Inoue K is a pathologist who was involved in the pathological diagnosis; Shimizu S, Morimura K, Toyokawa T, Xiang Z, Sakurai K, Fukuoka T, Yoshida K and Takii M helped the doctors in charge in managing the ward; and Yamamoto S and Tsukamoto T wrote the paper.

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Abstract

Primary histiocytic sarcoma of the spleen is a rare but potentially lethal condition. It can remain asymptomatic or only mildly symptomatic for a long time. An 81-year-old woman presented with an extremely enlarged spleen. She suffered from progressive anemia and required a red blood cell transfusion once a month. Although computed tomography, ultrasonography, and magnetic resonance imaging were performed for diagnosis, a confirmed diagnosis was not obtained. Her enlarged spleen compressed her stomach, and she suffered from gastritis and a sense of gastric fullness just after meals. She underwent laparoscopic splenectomy for therapeutic and diagnostic purposes. Her postoperative course was uneventful. After surgery, her red blood cell and platelet counts increased markedly. The tumor was diagnosed as splenic histiocytic sarcoma. Post-surgical chemotherapy was not performed, and the patient died of liver failure due to liver metastasis 5 mo after surgery. Laparoscopic splenectomy is minimally invasive and useful for the relief of symptoms related to hematological disorders. However, in cases of an enlarged spleen, optimal views and working space are limited. In such cases, splenic artery ligation can markedly reduce the size of the spleen, thus facilitating the procedure. The case reported herein suggests that laparoscopic splenectomy may be useful for the treatment of splenic malignancy.

Key words: Histiocytic sarcoma; Laparoscopic splenectomy; Malignancy; Splenomegaly; Chemotherapy

Core tip: Surgeons usually avoid choosing laparoscopic surgery for splenic malignancy because an enlarged spleen disrupts optimal views. Some authors reported that initial ligation of the splenic artery led to shrinkage of the spleen; therefore, the operation was easier. We report a case of splenic malignancy that was diagnosed as histiocytic sarcoma and treated by laparoscopic splenectomy with initial ligation of the splenic artery. In this case, because the size of the spleen was reduced after splenic artery ligation, the laparoscopic operation was performed safely. The patient was discharged 12 d after the operation despite her old age.

K, Toyokawa T, Xiang Z, Sakurai K, Fukuoka T, Yoshida K, Takii M, Inoue K. Laparoscopic splenectomy for histiocytic sarcoma of the spleen. *World J Gastrointest Surg* 2013; 5(4): 129-134 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i4/129.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i4.129

INTRODUCTION

Histiocytic sarcoma is a rare, malignant neoplasm that occurs in the lymph nodes, skin, and gastrointestinal tract and that can be defined as a malignant proliferation of cells. In this condition, the affected cells demonstrate morphological and immunophenotypical features similar to those of mature tissue histiocytes[1]. Histiocytic sarcoma of the spleen is an extremely rare and potentially lethal condition that can remain asymptomatic or only mildly symptomatic for a long time. However, its clinicopathological features have not been well characterized[1-3]. Early evaluation and diagnosis before dissemination may improve the prognosis of this disease, but diagnostic imaging has not been sufficiently efficacious. Therefore, early detection remains difficult. If the lesion is confirmed to be confined within the spleen, splenectomy may induce temporary remission of the disease.

Herein, we report a case of splenic histiocytic sarcoma treated by laparoscopic splenectomy. The patient's clinical symptoms were undetectable for approximately 3 mo, but systemic recurrence occurred with a fatal outcome.

CASE REPORT

An 81-year-old woman with a history of hypertension and unstable angina pectoris visited her primary care physician for a periodic examination. She was diagnosed with anemia, which persisted for 1 year, and she was referred to a hematologist, who recommended a full examination. She was diagnosed with idiopathic thrombocytopenic purpura. The patient's anemia progressed gradually, and 2 units of red cell concentrate were administered per week. She was admitted to our hospital, and splenomegaly (> 10 cm in longitudinal diameter) was detected by magnetic resonance imaging (MRI).

On physical examination, the lower end of her spleen was palpable 7 cm below the left costal margin, but no superficial lymphadenopathy was observed. A complete blood count indicated anemia and thrombocytopenia, but her leukocyte count was within the normal range (Table 1).

An abdominal computed tomography scan revealed splenomegaly (9.5 cm in longitudinal diameter; Figure 1A). One year previously, she showed mild splenomegaly (6 cm in longitudinal diameter; Figure 1B). Technetium-99 m colloid scintigraphy revealed a partial defect in her spleen (Figure 2). Because there were no defect lesions in the liver on this scintigram, we diagnosed no liver metastasis.

An abdominal dynamic MRI showed a multilobular splenic tumor, which appeared as an iso-intense solid mass on T1-weighted imaging (Figure 3A) and a high-intensity multi-lobular mass (10.5 cm in diameter) on T2-weighted imaging (Figure 3B). The tumor was enhanced on dynamic MRI from 20 to 120 s after the injection of contrast medium (Figure 4). Based on these findings, the differential diagnoses were malignant lymphoma, metastatic splenic tumor (origin unknown), hemangioma, and hemangiosarcoma, but we could not arrive at a definite diagnosis. Distant metastatic lesions, which are proof of a malignant tumor, were not detected by any imaging modality. Because the patient's anemia and thrombocytope-

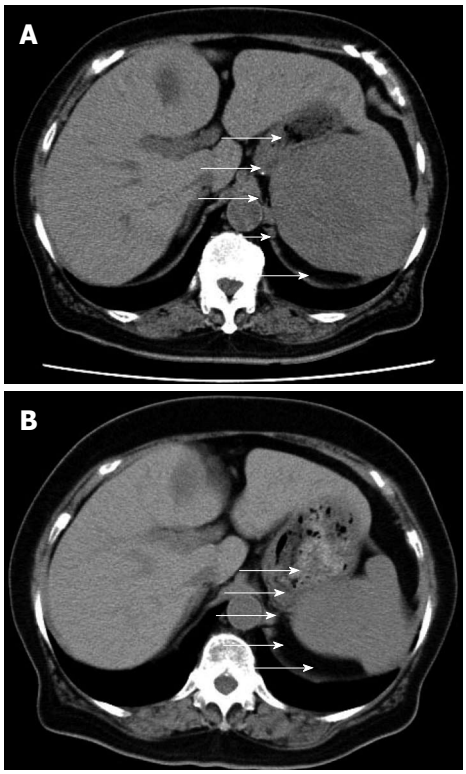

Figure 1 Abdominal computed tomography. A: Just before the operation; B: 1 year before the operation. Arrows show the splenic tumor.

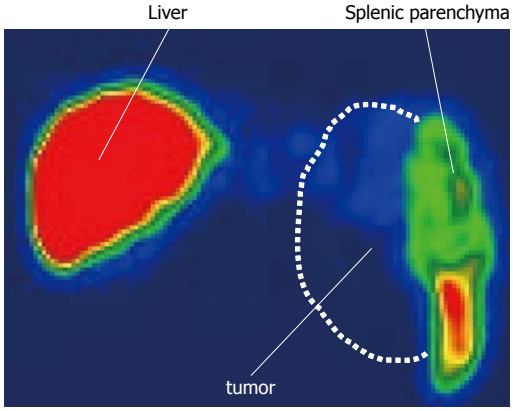

Figure 2 Technetium-99 m colloid scintiscanning. The broken line shows the splenic tumor. The tumor did not uptake technetium-99 m colloid, and the tumor was therefore shown as a defect.

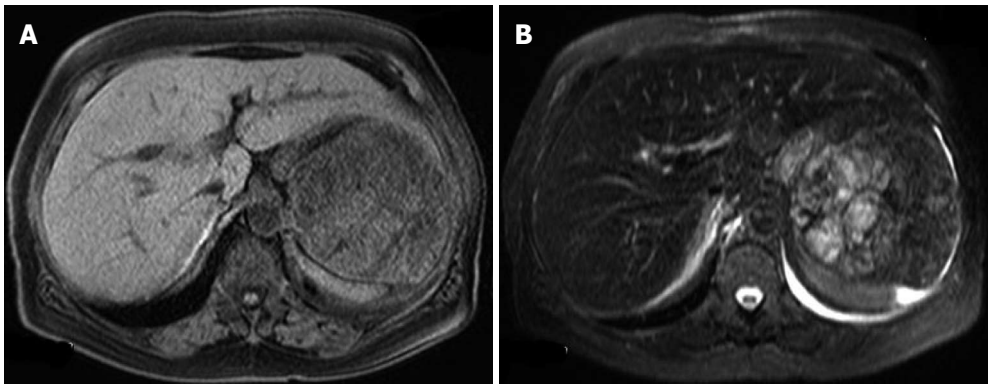

Figure 3 Magnetic resonance imaging just before the operation. A: An iso-intense solid mass on T1-weighted images; B: A high-intensity multi-lobular mass on T2-weighted images.

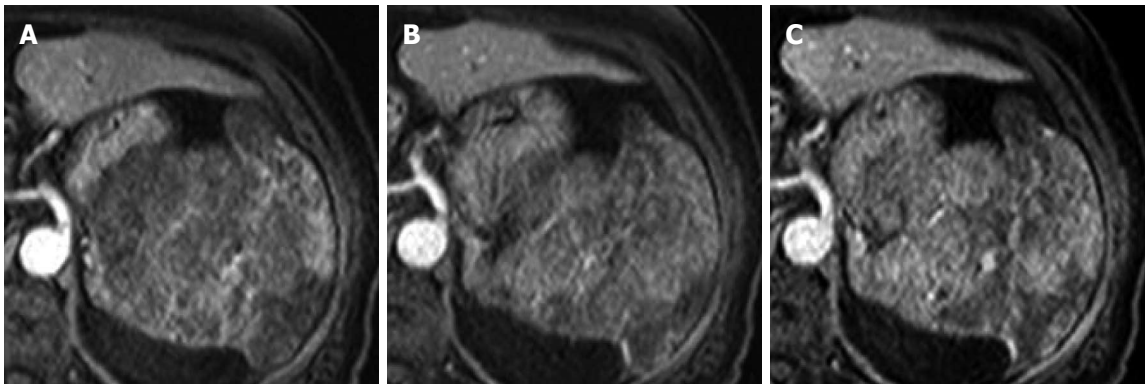

Figure 4 Dynamic magnetic resonance imaging. The tumor was enhanced from 20 to 120 s after the injection of contrast medium. Contrast medium gradually pooled in the tumor. A: 20 s; B: 60 s; C: 120 s.

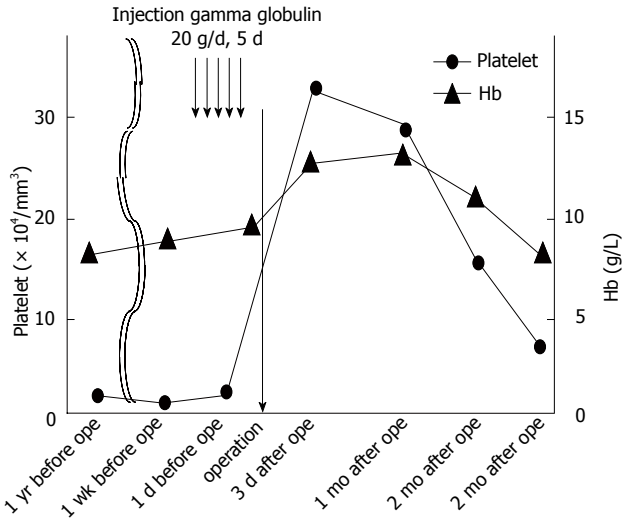

Figure 5 Clinical course of the patient. Transition of the platelet number and hemoglobin value from 1 year before the operation to 3 mo after the operation. The black arrow shows the operation time. The circle shows the platelet number. The triangle shows the hemoglobin value.

nia worsened gradually, red blood cell and platelet transfusions were performed once or twice per week. After admission, gastritis and a sense of gastric fullness, which is a symptom of compression by an enlarged spleen, worsened. We decided to perform splenectomy as an excision biopsy. Laparoscopic splenectomy was selected as the operation procedure.

To prevent the progression of anemia and thrombocytopenia, high-dose gamma globulin was infused (20 g/d for 5 d), but the red blood cell and platelet counts did not increase (Figure 5).

A 12-mm trocar was inserted by the open method at the mid-clavicular line parallel to the umbilicus, and 3 12-mm trocars were inserted around the spleen during the procedure. A laparoscopic view showed that the liver was normal. In addition, no metastatic or disseminated lesions were detected. The spleen occupied nearly the entire left upper and side cavity of the abdomen. After the splenic artery was ligated, the size of the spleen was markedly reduced. The spleen was placed in a polyethylene bag and extracted from the incision through the first port, which was extended to 7 cm. The operation time was 3 h and 58 min, and the blood loss was 236 g.

The weight of the resected spleen was 720 g, and it measured 21 cm × 12 cm × 5 cm. Macroscopically, the spleen showed multiple nodules with different colors from normal splenic tissue (Figure 6).

The microscopic findings were the following. The tumor consisted of cells with a foamy cytoplasm, hemosiderin-containing phagocytic cells, and multilobular megakaryocytes. The MIB-1 labeling index was 8.1% (Figure 7). Immunohistopathological staining was positive for CD68 and lysozyme, partially positive for p53, and negative for CD1a, CD4 and S-100 protein; therefore, the tumor cells

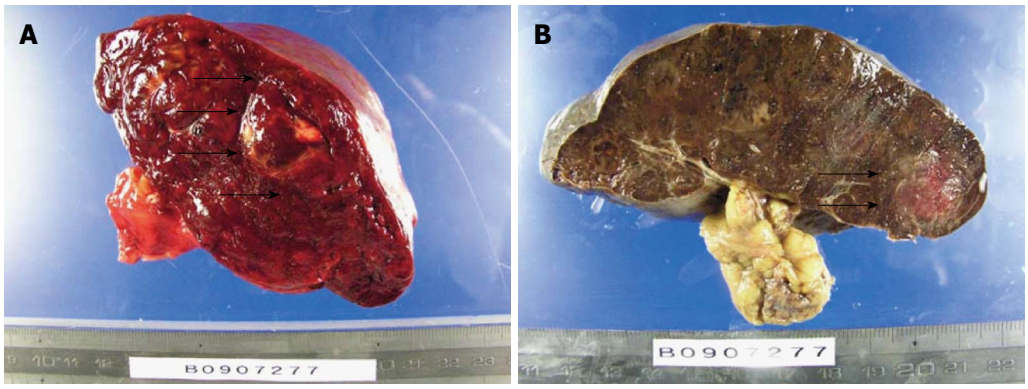

Figure 6 Macroscopic findings of the spleen. A: The raw specimen. Multiple nodules with different colors from normal splenic tissue; B: The specimen after formalin fixation. The arrows show the tumor.

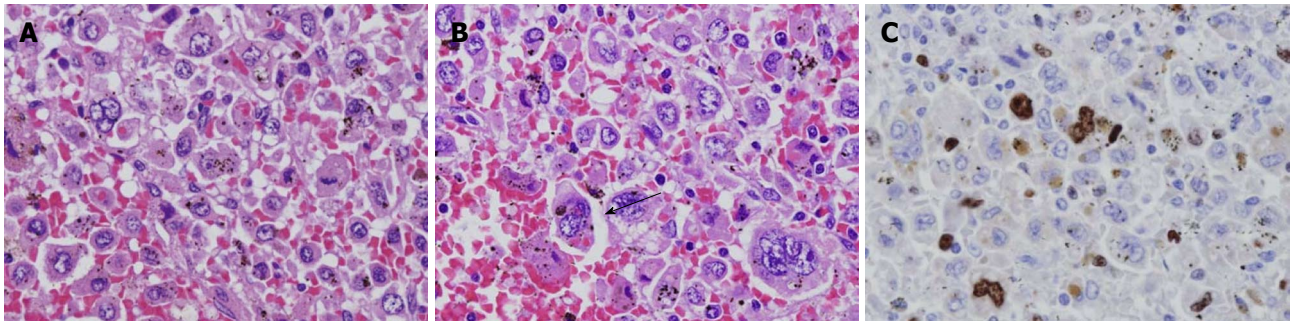

Figure 7 Microscopic findings. A: Giemsa stain. Magnification is × 200; B: Giemsa stain. Magnification is × 400; C: MIB-1 labeling stain. The tumor consisted of cells with a foamy cytoplasm, hemosiderin-containing phagocytic cells (white arrow), and multilobular megakaryocytes. The MIB-1 labeling index was 8.1%.

Table 1 Laboratory data on admission

AST (IU/L)	11
ALT (IU/L)	6
ALP (IU/L)	141
LAP (IU/L)	25
γ-GTP (mg/dL)	10
T-Bil (mg/dL)	1.8
D-Bil (mg/dL)	0.7
Alb (g/dL)	2.3
BUN (mg/dL)	28.3
Cre (mg/dL)	0.8
PT (%)	93.2
AMY (IU/L)	42
HCV-Ab	(-)
HBs-Ag	(-)
WBC/mm^3	6350
RBC/mm^3	291000
Hb (g/dL)	9.2
Ht (%)	27.6
Plt/mm^3	13000

Marked anemia and thrombocytopenia are shown. A dominant elevation in direct bilirubin was observed. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LAP: Leucine aminopeptidase; γ-GTP: γ-glutamyl transpeptidase; T-Bil: Total bilirubin; D-Bil: Direct bilirubin; Alb: Albumin; BUN: Blood urea nitrogen; Cre: Creatinine; PT: Prothrombin time; AMY: Amilaza; HCV-Ab: Hepatitis C virus-antibody; HBs-Ag: Hepatitis B surface antigen; WBC: White blood cell; RBC: Red blood cell; Hb: Haemoglobin; Ht: Haematocrit; Plt: Platelets.

were diagnosed as being of histiocyte origin (Figure 8). From these findings, the tumor was diagnosed as histiocytic sarcoma.

The anemia and thrombocytopenia were improved only 3 d after the operation (Figure 5). The post-operative course was uneventful, and she was discharged 12 d after surgery.

The platelet count decreased gradually 2 mo after surgery, and multiple liver metastases were revealed on magnetic resonance imaging 3 mo after the operation. Her liver functions rapidly deteriorated, and chemotherapy could not be performed. The patient died of liver failure 5 mo after surgery.

DISCUSSION

According to the recent World Health Organization classification of tumors of hematopoietic and lymphoid tissues, histiocytic sarcoma is a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes. Primary histiocytic sarcoma of the spleen is a rare condition, and its clinico-pathological features have not been well described[4]. Clinically, it is generally accepted that most patients with histiocytic sarcoma show a limited response to chemotherapy and a high mortality rate[5].

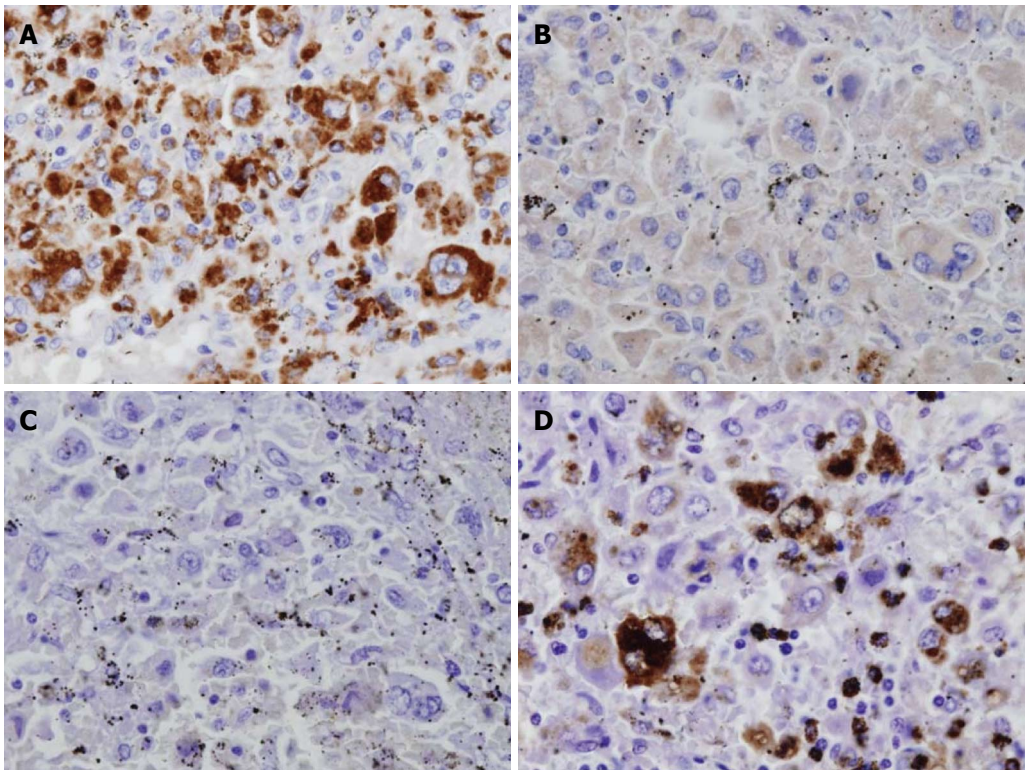

Figure 8 Immunohistopathological staining. A: CD68; B: CD1a; C: S-100 protein; D: lysozyme CD68 stained positive. CD1a and S-100 protein were negative. Lysozyme was partially positive.

Recently, some reports have shown that early diagnosis before dissemination of this disease may improve the prognosis[3]. Hornick *et al*[6] reported that tumor size may be a prognostic factor. Vos *et al*[7] showed that all patients with poor survival in their report had tumors over 3.5 cm in longitudinal diameter. The tumor size may be a strong factor for determining the stage of the disease. In our case, disseminated lesions were not recognized before the operation, but the size of the tumor of the spleen was over 10 cm in longitudinal diameter. Therefore, our patient was considered to be in an advanced stage. Our patient also recurred only 3 mo after the operation and died of the disease 5 mo after surgery.

In our case, we could not confirm the diagnosis preoperatively. Specific hematological markers do not exist for this disease. Recently, Vos *et al*[7] reported CD163, a hemoglobin scavenger receptor, as a new macrophage-related differentiation marker, which is more specific than the conventional histiocyte-related molecules, such as CD68 and lysozyme. However, only histopathological examination can reveal the existence of the disease. Moreover, our patient suffered from abdominal fullness and progressive anemia and thrombocytopenia. These symptoms were thought to be caused by splenomegaly and hypersplenism. Therefore, we decided to perform a splenectomy for both therapy and diagnosis.

Splenic malignancy may be accompanied by severe hematologic disease or a metastatic lesion in many cases. If splenectomy is performed in these cases, additional therapy should be administered as soon as possible after surgery. Laparoscopic splenectomy is less invasive than open splenectomy[8] and more quickly can lead to additional therapy. Some reports have demonstrated not only the feasibility of laparoscopic splenectomy but also its significant benefits over open splenectomy for the treatment of benign hematologic conditions[9-11]. Additionally, in our case of malignancy, anemia and thrombocytopenia were improved, and chemotherapy could be performed.

An enlarged spleen disrupts the optimal operative view. Although hand-assisted laparoscopic[12] splenectomy for a solitary splenic tumor has been reported, the inserted hand also disturbs the optimal view in massive splenomegaly. In our case, we ligated the splenic artery first, expecting a volume reduction of the spleen. In case that the main cause of massive splenomegaly is a space-occupying lesion in the spleen, the spleen size after ligation of the splenic artery may not be equivalent to that of a spleen without space-occupying lesions. However, Trelles *et al*[13] reported that the initial ligation of the splenic artery leads to volume reduction of the spleen in cases of massive splenomegaly. Additionally, in our case, initial splenic artery ligation was effective for inducing a splenic volume reduction.

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FIELD OF VISION

Prognosis and treatment of patients with positive peritoneal cytology in advanced gastric cancer

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Core tip: Gastric cancer staging is still matter of debate as it evolves along with introduction of new diagnostic tools. Use of laparoscopy and washing cytology in gastric cancer staging has identified a particular category of patients with no macroscopic peritoneal disease but with positive peritoneal cytology. Prognosis and management of such patients still remains a controversial issue.

Frattini F, Rausei S, Chiappa C, Rovera F, Boni L, Dionigi G. Prognosis and treatment of patients with positive peritoneal cytology in advanced gastric cancer. *World J Gastrointest Surg* 2013; 5(5): 135-137 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i5/135.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i5.135

Abstract

Positive peritoneal cytology in gastric cancer is classified as M1 disease by the 7th Edition of American Joint Committee on Cancer staging system. With the introduction of laparoscopy and peritoneal washing cytology in the staging of gastric cancer a new category of patients has been identified. These are patients with no macroscopic peritoneal metastases but with peritoneal cytology positive (P0C1). Prognosis and treatment of such patients represent a controversial issue. We evaluate the state of the art of staging system in gastric cancer and discuss standardisation in staging and treatment procedures. There is still a lack of uniformity in the use of laparoscopy with peritoneal cytology in clinical decision making and in the surgical treatment for gastric cancer. Survival of this patient subset remains poor. Multimodal therapies and new therapeutic strategies are required to improve the survival of these patients.

Key words: Advanced gastric cancer; Peritoneal washing cytology; Staging laparoscopy; Reverse transcription-polymerase chain reaction

COMMENTARY ON HOT TOPICS

Gastric cancer is the second most frequent cause of cancer death worldwide[1]. Unfavourable prognosis, mainly in Western countries, is related to the advanced stage of the disease at the diagnosis. The peritoneum is the most common site of metastasis in patients with gastric cancer. Since accurate staging of patients with locally advanced disease is critical for selecting the appropriate treatment strategy, in addition to visible macroscopic peritoneal metastases, only positive peritoneal washing cytology is included in the American Joint Committee on Cancer (AJCC) staging system (7th edition) definition of M1 disease[2]. The standardization of peritoneal cytological examination is essential, and staging laparoscopy is necessary in patient selection for neoadjuvant chemotherapy. The management of patients with positive peritoneal cytology as the only evidence of M1 disease is largely unknown. Though patients with intraperitoneal free cancer cells (IFCC) have traditionally been offered palliative care, prognosis could be improved by a multimodal approach. Both neoadjuvant and adjuvant treatment strategies are

currently being evaluated.

How should we regard patients negative for macro/microscopic peritoneal seeding, but with positive peritoneal cytology: locally advanced disease or metastatic disease? What is the best treatment option for this subset of patients: neoadjuvant therapy or resection and adjuvant therapy?

In their retrospective study Lee *et al*[3] included 1072 patients who underwent surgery for gastric cancer and peritoneal washing cytology: 84% had negative cytology, 16% positive cytology. The patients were stratified into four subgroups: P0C0 (no peritoneal metastases, negative cytology), P0C1 (no peritoneal metastases, positive cytology), P1C0 (peritoneal metastases, negative cytology), P1C1 (peritoneal metastases, positive cytology). Median overall survival was best in the P0C1 subgroup (20 mo) and decreased to 14 and 10 mo respectively for P1C0 and P1C1 subgroups. Patients with P0C1 disease seem to have significantly better survival than those with P1C1 disease. This is probably due to the combination of aggressive surgical resection with lymph node dissection and adjuvant chemotherapy. This is confirmed by the reduction in peritoneal recurrence with associated improvement survival using the aggressive approach reported by Kuramoto *et al*[4].

On the other hand, Mezhir *et al*[5] have essentially abandoned gastrectomy as positive peritoneal cytology even in absence of gross peritoneal disease suggests a poor outcome.

So identifying prognostic factors within P0C1 patients may be crucial for planning the most suitable therapeutic option. Again, the multivariable analysis by Lee *et al*[3] showed that P0C1 group (with N0/2 patients) after resection and adjuvant chemotherapy had a significantly better prognosis.

Lorenzen *et al*[6] demonstrated that gastric cancer patients, whose IFCC status was converted from positive to negative following neoadjuvant therapy, had an improved median survival after surgery, suggesting that surgeons should selectively offer aggressive resection in patients in whom there is a response to induction chemotherapy.

A recent study by Mezhir *et al*[5] has proposed a new approach to patients with M1 disease based solely on IFCC positivity. After chemotherapy for 6-12 mo, if there is no clinical progression, repeat cytology is performed. Patients who remain positive for IFCCs are treated palliatively. Patients who become IFCCs negative have repeat laparoscopy after a further 3-6 mo. If they revert to M1 status, they are treated palliatively. If they remain IFCC-negative and have good performance status, they are considered for gastrectomy. Using this strategy, the authors reported a resection rate of 74% for ICC-positive patients who were converted to negative cytology.

A third option, not included in the analysis, is intraoperative chemotherapy (IPC). Some studies have demonstrated the efficacy of this procedure in patients with advanced peritoneal dissemination and have shown improvement in survival rates and a decrease in the incidence of peritoneal recurrence[7].

Currently there are no level 1 data to support a specific treatment plan. As reported by the review of Matharu *et al*[7] the methodological quality of most studies on intraperitoneal chemotherapy is poor, owing to selection and observer bias. Intraperitoneal chemotherapy can be administered preoperative, intraoperative and postoperative. Yano *et al*[8] treated with neoadjuvant IPC, 25 patients with T3/T4 tumors, no macroscopic carcinomatosis, (in only one case positive peritoneal lavage cytology) and achieved disease T downstaging in 48% of cases.

The use of extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy has been demonstrated, in a randomized controlled trial, to improve the 5-year survival in patients with positive peritoneal cytology and no macroscopic peritoneal carcinomatosis[4]. So, IPC may reduce the frequency of peritoneal recurrence in patients with locally advanced gastric cancer in the absence of macroscopic peritoneal seeding, but is clearly unable to prevent recurrence or disease progression completely. Studies seem to demonstrate that IPC is more effective in preventing peritoneal carcinomatosis than in treating macroscopic carcinomatosis.

The methods for detecting IFCCs represent yet another controversial issue. The sensitivities of conventional cytology, immunoassay, immunohistochemistry (IHC), and reversetranscription polymerase chain reaction (RT-PCR) in predicting peritoneal recurrence are low and vary considerably[8]. Such low sensitivities suggest that a significant number of patients negative for IFCCs are developing recurrent disease. RT-PCR for the detection of a single tumor marker, CEA mRNA, in the peritoneal lavage increases the detection of subclinical peritoneal disease and is more sensitive than conventional cytology. PCR was positive in a significantly greater number of patients with advanced-stage disease or vascular and perineural invasion than in those who were cytology positive. Multiple studies have shown that patients with no visible peritoneal disease at laparoscopy (LAP-) and positive for PCR have a worse survival and earlier recurrence than PCR-patients[9].

A significant challenge when applying such a sensitive technique is to determine the best threshold and the true predictive role of PCR, thus avoiding overinterpretation of the clinical significance of a false-positive PCR[10]. Future studies will also help determine whether analysis of multiple tumor markers rather than a single gene may increase the diagnostic yield and independent predictive value of RT-PCR.

In conclusion, the evaluation of peritoneal cytology in gastric cancer patients is still a grey zone with regards to staging and treatment options. There is lack of uniformity in the utilization of peritoneal cytology in the algorithm of gastric cancer treatment. The optimal management of patients with IFCCs still remains debatable. Therefore, identifying prognostic factors and stratifying patients with IFCCs will be crucial in targeting therapeutic options.

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REVIEW

Management of potentially resectable colorectal cancer liver metastases

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Abstract

Colorectal cancer is a very common malignancy worldwide and development of liver metastases, both synchronous or metachronous, is a common event. Of all patients with metastatic colorectal cancer, up to 77% have a liver-only disease and approximately 10%-20% of patients with colorectal liver metastases are considered resectable at the time of diagnosis. Surgical resection of liver metastases remains the best treatment option and it is associated with a survival plateau and a 20%-25% of long-term survivors. Perioperative chemotherapy for resectable liver metastases may improve resecability of liver metastases and disease free survival, but its impact on overall survival is still unclear and more studies are needed. Moreover, preoperative chemotherapy can increase postoperative complications. Further studies are needed to define the role of adjuvant chemotherapy after a R0 resection of liver metastases and to define the criteria for a better selection of patients candidate to hepatectomy. New strategies such as targeted therapies are emerging with promising results. Optimal management requires a multidisciplinary approach, local and systemic, but it is a still pending question. Colorectal liver metastases represent a major challenge for oncologists and surgeons. In this review will be analyzed available data about assessment and management of the patients with potentially resectable colorectal liver metastases.

Key words: Colorectal cancer; Liver metastases; Perioperative chemotherapy; Surgical resection; Targeted therapies

Core tip: Colorectal cancer is a very common malignancy and its incidence is rapidly increasing worldwide. Of all patients with metastatic colorectal cancer, up to 77% have a liver-only disease and about 10%-20% of them are considered resectable at the time of diagnosis. Surgery actually still represents the best option of treatment, but new strategies such as perioperative chemotherapy and targeted therapies are emerging with promising results. However, optimal management requires a multidisciplinary approach, both local and systemic. This review aims to critically analyze the management of potentially resectable colorectal liver metastases.

Meriggi F, Bertocchi P, Zaniboni A. Management of potentially resectable colorectal cancer liver metastases. *World J Gastrointest Surg* 2013; 5(5): 138-145 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i5/138.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i5.138

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality[1]. The liver is the most common site of CRC metastases and nearly 25% of patients with CRC present with synchronous liver metastases at the time of initial diagnosis and 50%-75% of patients within three years after primary colonic surgery at the time of disease recurrence[2-5]. Though most of

these patients have a poor prognosis, there is a subset of patients with liver metastases, both synchronous or metachronous, that can benefit from radical surgery and possibly even achieve cure[6]. In fact, from 25% to 50% of patients with surgically resected colorectal liver metastases (CLM) today can survive five or more years after surgery[7-11]. Unfortunately, only a small percentage of patients, estimated at 10%-20%, exhibits with initially resectable liver metastases[12] and up to 2/3 of patients with resected CLM will experience a recurrence in the majority cases just in the same organ[13,14]. In the last two decades, we have observed remarkable advances in the treatment of CLM, both from a medical point of view with the advent of new chemotherapeutic and biologic agents, and with the improvement of surgical techniques and a better definition of the resectability criteria. However, up to now, strong scientific evidences about what is the best strategy for the treatment of CLM are still debated. One of the obstacles to be addressed is the difficulty in defining "Who is resectable?". The indications for resection of CLM changed significantly over the years. In the late eighties, Ekberg defined restrictive criteria for resectability: less than four metastases (uni or bilobar), absence of extrahepatic disease, and resection margin of at least 1 cm. Moreover, Steele suggested resection of liver metastases only from colorectal primary, three or less lesions, R0 resections, absence of comorbidities and extrahepatic disease[5,15]. Starting from the nineties, these criteria were gradually extended, in relation to location and size of tumor, number of lesions, and absence of extrahepatic disease[16]. Currently, the number or size of hepatic nodules in the hands of trained surgeons and in high-volume liver departments, are no longer considered an absolute contraindication to hepatectomy if the remnant healthy liver is > 25%-30%[17]. Preoperative liver magnetic resonance imaging and intraoperative ultrasound offer the optimal assessment of the number, size, and proximity of tumors to key vascular and biliary structures. Moreover, recent guidelines from the National Comprehensive Cancer Network (NCCN) (v3.2013) recommend a staging positron emission tomography scan for patients with potentially surgically curable metastatic colorectal cancer. Even the simultaneous presence of potentially resectable extrahepatic disease is no longer an absolute contraindication to surgery of liver metastases, particularly if the extrahepatic disease is surgically resectable lung or ovarian metastases. From 1996 to 2009 were identified at least twelve prognostic scoring-systems, in an attempt to predict survival after resection of CLM as a function of the number of risk factors present in the patient's medical history[18]. One of these scoring-systems was tested by Fong *et al*[3] and assessed five risk factors on approximately 1000 patients: presence of metastatic nodes at the time of the surgery of the primary tumor, disease-free interval < 12 mo, > 1 metastatic lesion; size > 5 cm and a value of Carcinoembrionyc Antigen (CEA) > 200 ng/mL. The 5-year OS ranges from 14% in patients with five risk factors to 60% in those without risk factors[19]. In an attempt to confirm these results, Tomlinson et al have validated the reliability of this "score", recording a 10-year OS of 21% in resected patients with a low score (0-2) and of 10% in those with a high-risk score (3-5)[20]. On the other hand, Nordlinger score included seven risk factors: age ⩾ 60 year, extension into the serosa of the primary cancer, lymphatic spread of the primary cancer, interval less than 2 years from primary tumor to metastases, number of metastases ⩾ 4, largest size of liver metastasis ⩾ 5, definig three risk groups (low, intermediate, high) with different 2-years survival rates[21]. Finally, there are increasing clinical evidences that medical perioperative treatment may improve the outcome of these patients[22,23].

NEOADJUVANT CHEMOTHERAPY

Surgery remains the treatment of choice for cure or prolonged survival if it is possible to obtain a radical resection (R0) and with the preservation of a residual functioning liver of 25%-30% of the original liver volume. The term "neoadjuvant chemotherapy" is reserved for chemotherapy for resectable and potentially resectable liver metastases prior to surgery. The role of neoadjuvant chemotherapy in the management of potentially resectable CLM is still controversial and debated[24]. In fact, not infrequently, in patients with favorable prognostic factors, "upfront" surgery of liver metastases is the preferred strategy. An argument in favor of the use of preoperative chemotherapy is that this may be a good test *in vivo* to evaluate the chemosensitivity of the tumor. Tumor progression while on preoperative treatment is almost always associated with a poor prognosis, even if the metastases will be resected[25]. Perioperative treatment of resectable liver metastases is supported by the phase Ⅲ European Organization for Research and Treatment of Cancer (EORTC) 40983 trial (Table 1). This study randomized 364 patients with 1-4 resectable CLM to 6 cycles of preoperative and 6 cycles of postoperative 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX4) compared with surgery alone. The primary endpoint was progression free survival (PFS). If we consider all of the 364 enrolled patients (182 per arm), the gain in PFS at 3 years was 7.3% in the perioperative chemotherapy arm compared with surgery alone, although this difference was not statistically significant (P = 0.058). If you take into account only the patients who underwent a surgical resection of CLM, then the increase in favor of the perioperative treatment reaches the statistical significance (difference in PFS between the two arms of 9.2%, P = 0.025)[22]. In a recent update of the study after a median follow-up of 8.5 years, the 5-years OS (secondary endpoint) was found of 7 mo longer in the experimental arm (an increase of 3.4%, HR = 0.88; 95%CI: 0.68-1.14, P = 0.339), but also in this case not such to reach a statistical significance. Note that in the experimental arm only 2/3 of resected patients has been able to receive the programmed postoperative

Table 1 European Organization for Research and Treatment of Cancer 40983 Trial

	n	Treatment	HR for progression	3-yr PFS	5-yr PFS	Postoperative OS complications
All pts	364	CHT	0.79	35.4	51.2	-
		Surgery alone	$P = 0.058$	28.1	47.8 ($P = 0.339$)	-
Elegible pts	342	CHT	0.77	36.2	52.4	-
		Surgery alone	$P = 0.041$	28.1	48.3 ($P = 0.303$)	-
Resected pts	329	CHT	0.73	42.4		25%
		Surgery alone	$P = 0.025$	33.2		16%

Reproduced from reference Nordlinger *et al*[22] and Sorbye *et al*[23]. pts: Patients; CHT: Chemotherapy; HR: Hazard ratio; PFS: Progression free survival; OS: Overall survival.

chemotherapy and that the post-surgery morbidity was more significant (25% *vs* 16%, $P = 0.04$), although reversible, in patients treated with preoperative chemotherapy. Operative mortality was 1% in both treatments group[23]. It remains unresolved the question whether the benefit in PFS observed in this study is mainly due to the perioperative treatment in toto or primarily to adjuvant post-resection treatment, in favor of which there are several studies that confirm its effectiveness[26-31]. Two other small phase Ⅱ trials support the use of a preoperative treatment with FOLFOX/XELOX (Capecitabine plus Oxaliplatin) and XELOX with bevacizumab[32,33], but before we could say a definitive word on the best approach to the treatment of potentially resectable CLM we still need further dedicated studies, with or without new biological agents. Another aspect to consider in these challenging economic times is cost-effectiveness: according to literature, the use of neo-adjuvant chemotherapy could be convenient because it could possibly avoid hepatic resection in those patients who do not respond to this treatment. Nevertheless this analysis is controversial for synchronous resectable metastases[34,35]. Neoadjuvant chemotherapy can induce damage to the remnant liver and the risk of hepatic toxicity and surgical complications increase with the duration of pre-opertative treatment[36,37]. Steatosis has been associated with both fluoropyrimidines and irinotecan. Vauthey *et al*[38] reported 20% patients receiving irinotecan having steatohepatitis and this was associated with increased 90-d mortality and morbidity after hepatectomy. Hepatic sinusoidal obstruction syndrome can emerge in patients treated with oxaliplatin but does not seem to be strongly associated with increased postoperative mortality[37,39]. A recent retrospective study evaluated histological specimens from 366 resected patients for CLM after preoperative chemotherapy and found that the two independent prognostic factors for OS after hepatectomy were the overall pathologic response > 75% and, surprisingly, fibrosis > 40% and not necrosis as expected[40]. Another problem with preoperative chemotherapy includes the shrinkage of viable disease, known as "vanishing metastases", so it is not visible and therefore not resected at laparotomy. However, in many cases, this clinical complete response does not match with pathologic complete response. According to Adam *et al*[41], the predictive factors for a complete pathologic response are: age ⩽ 60 year, size of metastases ⩽ 3 cm, CEA levels at diagnosis ⩽ 30 ng/mL, and objective response following chemotherapy. Patients who achieved a complete pathologic response after neoadjuvant chemotherapy had high survival rates (76% at 5 year). Patients should be carefully monitored during chemotherapy and receive surgery before metastases disappear. Therefore, response to neoadjuvant therapy must be closely monitored and it is recommended to revaluate disease after no more than 2 mo of treatment[42]. The duration of treatment *in toto* (preoperative and adjuvant) should not exceed 6 mo[43]. In summary, many oncologists feel that perioperative therapy is the best current option of treatment for resectable CLM and the recent European Society for Medical Oncology guidelines define this subset of patients with clearly R0-resectable CLM as "Group 0". The treatment aims of patients placed in "Group 0" is cure and decrease risk of relapse. Hence, the intensity of neoadjuvant treatment will be "nothing" (upfront surgery) or "moderate" (FOLFOX)[44].

ADJUVANT THERAPY AFTER RESECTION OF LIVER METASTASES

Nearly 70% of patients relapse after an hepatic resection for CLM and most of them just in the liver and within the first two years after surgery[13,14,45]. In an attempt to improve the outcome of these patients was thus adopted the rationale of adjuvant therapy. Two randomized phase Ⅲ studies and a subsequent meta-analysis of data extracted by them, have evaluated the role of the combination of bolus fluorouracil and leucovorin (5-FU/LV) for 6 mo after R0 surgery of CLM *vs* surgery alone[26-28]. The results of these studies, although showing a trend in favor of adjuvant chemotherapy both in PFS and OS, do not provide a strong evidence in favor of postoperative treatment, probably due to their limited statistical power and the use of a chemotherapy regimen that actually does not represent the best combination to be administered in patients considered as metastatic patients. There are two additional meta-analyses that support the use of an adjuvant fluoropyrimidine-based treatment[29,30]. In the study of Ychou *et al*[31], the regimen FOLFIRI, as expected, has

Table 2 Phase Ⅲ trials of adjuvant chemotherapy after resection of colorectal liver metastases

Ref	*n*	CHT	Median PFS (mo)	Median OS (mo)
Langer *et al*[26]	129	5-FU/LV	No difference	No difference
Portier *et al*[27]	173	5-FU/LV	24.4 *vs* 16.6 (P = 0.028)	62.1 *vs* 46.4 (P = 0.13)
Mitry *et al*[28]	278	5-FU/LV	27.9 *vs* 18.8 (P = 0.059)	61.1 *vs* 46.9 (P = 0.125)
Ychou *et al*[31]	306	FOLFIRI *vs* 5-FU/LV	24.7 *vs* 21.6 (P = 0.44)	No difference

CHT: Chemotherapy; PFS: Progression free survival; OS: Overall survival; 5-FU/LV: 5-fluorouracil/Leucovorin; FOLFIRI: 5-FU/LV/Irinotecan.

failed to show advantage in disease free survival (DFS) compared to 5-FU/LV (Table 2). It was argued, as in the classical adjuvant therapy after surgery of the primary tumor, that an oxaliplatin-based regimen[46] may be more effective, but there are no definitive data and studies with the FOLFOX or XELOX regimens with or without biologic agents, are currently ongoing. Several interesting experiences, but difficult to reproduce on a large scale especially for technical difficulties and specific toxicities (*i.e.,* sclerosing cholangitis), were obtained with the administration of a derivate of fluorouracil (floxuridine, FUDR) plus high-dose dexamethasone in the hepatic artery (HAI), using the rationale of the prevalent arterial vascularization of liver metastases and of lower risk of systemic toxicities despite higher doses of chemotherapy[47-53].

In conclusion, it is common practice to administer a postoperative chemotherapy in patients with resected CLM due to the high-relapse rate expectations and the positive impact on PFS, but unfortunately definitive data in favor of adjuvant therapy after R0 resection of CLM are still lacking. Nevertheless, actually the preferred regimen to be administered in these patients are empirically an oxaliplatin-based regimen.

Hence, it will be crucial to identify subsets of patients at increased risk of relapse and candidate to receive adjuvant treatment.

TARGETED THERAPIES

More recently, the introduction of new biological drugs in the available arsenal of the oncologist has improved the results obtained in the treatment of metastatic colorectal cancer. In particular, anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab in patients with *K-RAS* wild-type[54-60] and anti-vascular endothelial growth factor (VEGF) antibody bevacizumab[61-64] have shown a synergistic action when associated to classical chemotherapy regimens with two or three drugs, thus increasing significantly the PFS, the overall response rate and hence also the rate of hepatic resection for CLM if compared with chemotherapy alone, especially when used as "conversion" treatment for unresectable liver metastases. Whether these results provide a real OS advantage, it still remains unclear. Unfortunately, data about targeted therapies in the perioperative or neoadjuvant setting of resectable CLM are lacking. Gruenberger *et al*[32] reported their experience of a phase Ⅱ study with oxaliplatin, capecitabine and bevacizumab in 56 curable CLM patients. This regimen showed a high response rate (73%) with R0 hepatic resections in 52 out of 56 patients and 5 complete pathologic responses. Actually, phase Ⅲ studies with anti-EGFR antibody cetuximab and with anti-VEGF antibody bevacizumab are ongoing to better define the role of these biological agents in the treatment of potentially resectable CLM.

CONCLUSION

CLM are a common problem, but many patients are able to undergo R0 liver resection, and a significant proportion of those patients may achieve cure or at least obtain prolonged DFS[65]. A multidisciplinary team approach is important for coordinating care of patients with CLM. Surgery is the treatment of choice for resectable CLM and requires that an adequate liver remnant remains after surgery. Perioperative chemotherapy with FOLFOX regimen for six mo according to the results of the EORTC 40983 randomized trial improves the outcome of these patients and it is actually recommended for most patients[66-69]. When it an upfront surgery of CLM is performed, then adjuvant chemotherapy with an oxaliplatin-based regimen is a reasonable option. Based on our experience we suggest a close follow up schedule for patients who underwent CLM resection. The role of targeted therapies in neoadjuvant setting of potentially resectable CLM remains to be defined and needs further studies. Finally, where a local approach to CLM is indicated and surgery is contraindicated, the radiofrequency ablation of liver metastases is often considered a good alternative, although generally less effective than surgery in terms of relapse rate and OS[70-76].

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MINIREVIEWS

Operative terminology and post-operative management approaches applied to hepatic surgery: Trainee perspectives

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Abstract

Outcomes in hepatic resectional surgery (HRS) have improved as a result of advances in the understanding of hepatic anatomy, improved surgical techniques, and enhanced peri-operative management. Patients are generally cared for in specialist higher-level ward settings with multidisciplinary input during the initial post-operative period, however, greater acceptance and understanding of HRS has meant that care is transferred, usually after 24-48 h, to a standard ward environment. Surgical trainees will be presented with such patients either electively as part of a hepatobiliary firm or whilst covering the service on-call, and it is therefore important to acknowledge the key points in managing HRS patients. Understanding the applied anatomy of the liver is the key to determining the extent of resection to be undertaken. Increasingly, enhanced patient pathways exist in the post-operative setting requiring focus on the delivery of high quality analgesia, careful fluid balance, nutrition and thromboprophlaxis. Complications can occur including liver, renal and respiratory failure, hemorrhage, and sepsis, all of which require prompt recognition and management. We provide an overview of the relevant terminology applied to hepatic surgery, an approach to the post-operative management, and an aid to developing an awareness of complications so as to facilitate better confidence in this complex subgroup of general surgical patients.

Key words: Hepatic surgery; Terminology postoperative management; Complications; Training

Core tip: Applied anatomy as used in hepatic surgery is different to the traditional morphological teaching. Applied hepatic anatomy is complex but trainees require an understanding of the basic principles to allow an appreciation of the operations performed. Complications require a low threshold of suspicion as they often have important consequences in relation to patient outcome. Recognition of such with rapid alerting of senior staff can facilitate timely and effective management. To date, no universal protocol exists for management of the post-operative period and varies from centre to centre. We provide a practical overview of the terminology, post-operative management, and complications associated with hepatic surgery.

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INTRODUCTION

The structural design and unique innate property of the liver to regenerate functioning parenchyma after tissue loss forms an important basis of hepatic resection sur-

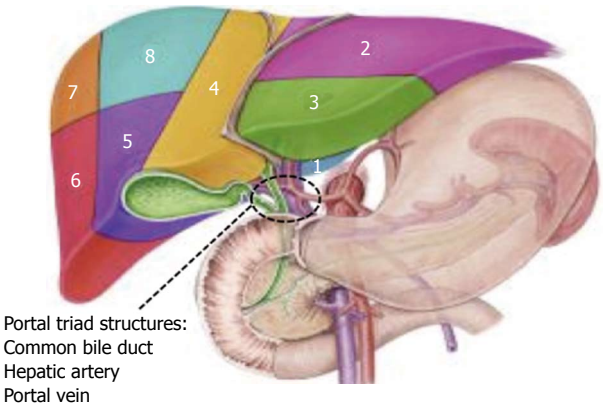

Figure 1 Couinaud classification of hepatic segmental anatomy. The liver is made up of 8 segments: Segment 1 is the caudate lobe and is closely related in position to the inferior vena cava posteriorly; Segments 1-4 make up the left hemi-liver; Segments 5-8 make up the right hemi-liver. Couinaud divided the liver into functional left and right hemi-livers, and the plane between the two runs in Cantlie's line. This line runs from the middle of the gallbladder fossa anteriorly to the IVC posteriorly.

gery (HRS). Early experience was associated with significant mortality and morbidity but these are now reported at 1%-4% and 15%-35% respectively in high volume centres[1-5].

Outcomes have improved as a result of advances in the understanding of hepatic anatomy, improved surgical techniques, and enhanced peri-operative management. Patients are generally cared for in specialist higher-level ward settings with multidisciplinary input during the initial post-operative period but greater acceptance and understanding of HRS has meant that care is transferred, usually after 24-48 h to a standard ward environment. The surgical trainee will be presented with such patients either electively as part of a hepatobiliary firm or whilst on-call, and it is therefore important to understand the key points in managing HRS patients.

Herein we provide an overview of the relevant terminology of hepatic surgery, an approach to the post-operative management, and provide hints to highten awareness of complications so as to facilitate better confidence in this complex subgroup of general surgical patients.

INDICATIONS FOR HRS

In the United Kingdom and Europe the commonest indication for HRS remains colorectal liver metastasis (CRLM). Resection is also performed for other benign and primary malignant hepatobiliary tumours [cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC)], donation for transplantation and trauma[6-8]. Most resections performed for CRLM are on liver with otherwise normal or mildly diseased parenchyma such as post-chemotherapy fatty livers. Less frequently in the United Kingdom, HRS is performed for HCCs arising in cirrhotic patients, and such resections are associated with a higher complication rate[9,10].

LIVER ANATOMY AND SURGICAL TERMINOLOGY

Unlike other general surgical operations where the nature of the procedure is readily grasped, HRS requires some knowledge of hepatic anatomy, and specific nomenclature is applied to such resections[11]. The surgically applied anatomy of the liver is different to the traditional (morphological) teaching in undergraduate medical school. The core principle relates to the Couinaud classification of liver anatomy[12].

In this system the liver is divided into eight functionally independent segments (Figure 1). Each segment has its own vascular inflow, outflow and biliary drainage. In the centre of each segment there is a branch of the portal vein, hepatic artery and bile duct. In the periphery of each segment is the vascular outflow *via* the hepatic veins which link to form the right, middle and left hepatic veins. These in turn drain into the inferior vena cava. Crucially, the segmental portal and hepatic blood supply, together with the biliary drainage are unique, and allow for contiguous segments to be resected without compromising the vascular supply to the adjacent tissue.

In addition, the liver is separated into four sectors by the hepatic veins (Figure 2). Briefly, the right hepatic vein divides the right lobe into anterior and posterior segments; the middle hepatic vein divides the liver into right and left lobes (hemi-livers) and the left hepatic vein divides the left lobe into medial and lateral sectors.

This knowledge forms the basis of the consensus nomenclature outlined in the Brisbane 2000 terminology guidelines for hepatic resections[13]. In Table 1 the operation titles and number of segments are illustrated. While complex, it is more important perhaps for the trainee to be aware as to what constitutes a minor and major hepatic resection, as the extent of resection is associated with mortality and morbidity. A major resection was traditionally defined as $\geqslant$ 3 segments but more recently established as $\geqslant$ 4 segments[14].

DETERMINING THE LIMITS OF SAFE RESECTION

In the case of CRLM, the extent of resection that can be safely performed is now governed by two factors: the ability to resect all malignant tissue, and an adequate predicted volume of hepatic tissue remaining, the so-called functional liver remnant (FLR)[15,16]. As such during the pre-operative work-up it is important that surgeons work as part of a multi-disciplinary team with radiologists, oncologists and gastroenterologists to plan HRS to assess these factors[17].

The primary investigations used in determining the extent of resection are cross-sectional imaging studies with computed tomography (CT) ± magnetic resonance imaging (MRI) and if there is concern regards extra-hepatic disease, positron emission tomography (PET) scans

Table 1 Brisbane consensus nomenclature 2000 for describing hepatic resectional surgery based on liver segmental and sectorial anatomy

Anatomical term	Couinaud segments	Term for HRS	Major or minor resection
Right hemi liver	5, 6, 7, 8	Right hemihepatectomy or right hemihepatectomy	Major
Left hemi liver	2, 3, 4 ($^{+/-}$ 1)	Left hemihepatectomy or left hemihepatectomy	Major
Right anterior section	5, 8	Right anterior sectionectomy	Minor
Right posterior section	6, 7	Right posterior sectionectomy	Minor
Left medial section	4	Left medial sectionectomy or resection segment 4 or segmentectomy 4	Minor
Left lateral section	2, 3	Left lateral sectionectomy or bisegmentectomy 2, 3	Minor
-	4, 5, 6, 7, 8 , ($^{+/-}$ 1)	Right trisectionectomy or extended right hemihepatectomy or extended right hepatectomy	Major
-	2, 3, 4, 5, 8 , ($^{+/-}$ 1)	Left trisectionectomy or extended left hemihepatectomy or extended left hepatectomy	Major

"Non-anatomical" resections are also performed either as the main index procedure or in combination with the above anatomical hepatic resectional surgery. A non-anatomical resection refers to a situation in which there is a small tumour that is excised with a negative margin but leaving a remnant segment – a so-called "chip-shot" or metastectomy.

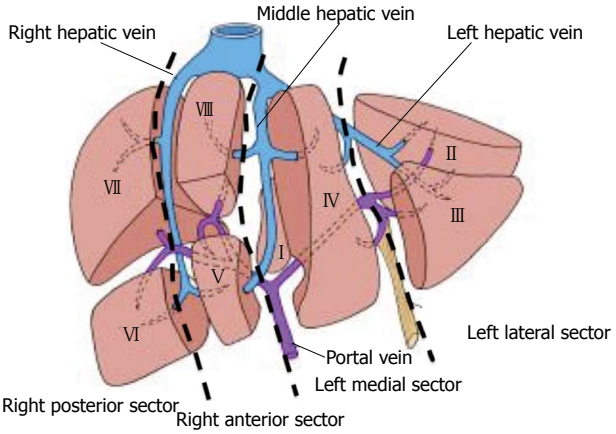

Figure 2 Sectorial anatomy of the liver based on the hepatic veins. The liver is divided into a right and left hemi-liver by the middle hepatic vein (lies in Cantlie's line). The right hemi-liver is divided into anterior and posterior sections by the course of the right hepatic vein; The left hemi-liver is divided into lateral and medial sections by the left hepatic vein.

are useful[18]. If there is concern regards the FLR then portal vein embolization of the diseased portion of the liver can be performed to induce hypertrophy of the remaining parenchyma. For otherwise normal parenchyma the ratio of FLR to total estimated liver volume should be in the order of 25% but 40% may be required in the presence of cirrhosis or other liver disease[19-24].

When proposing operating on cirrhotic livers it is also useful to perform a quantitative assessment of liver function, and in the Far East where HRS is more frequently performed for HCC, indocyanine green clearance (ICG) is carried out in all such patients to confirm the presence of an adequate volume of functioning parenchyma[25-30]. In the setting of CRLM, most patients have traditionally been observed to have normal parenchyma. However the widespread use of chemotherapy and its associated risk of liver injury such as steatohepatitis and sinusoidal obstruction syndrome may increase morbidity and potentially mortality associated with resection[31-33]. As a consequence such parenchyma may no longer be considered "normal" in this subgroup.

Biopsies of CRLM are not performed pre-operatively if a curative resection is planned because of concerns of needle track seeding[34]. In cases of HCC, biopsies are sometimes performed if imaging is inconclusive and may be indicated to assess the surrounding parenchyma[35].

INTRA-OPERATIVE STRATEGIES

There are now a wide range of devices and pharmaceutical agents available to the hepatic surgeon. Their collective aim is to reduce blood loss during surgery as blood loss and the need for blood transfusion are regarded as important prognostic indicators for outcome[36-38]. The most widely used device is the cavitron ultrasonic surgical aspirator (CUSA) that dissects liver tissue utilizing ultrasound.

A number of clamping maneuvers can also be employed to reduced bleeding during the phase in which the liver parenchyma is transected[39,40]. The most commonly performed procedure is the Pringle maneuver in which inflow to the liver is controlled by compressing the hepatic artery and portal vein at the level of the hepatic pedicle. A number of different protocols exist in which the vessels are intermittently clamped and released, usually at 15 min intervals.

APPROACH TO POST-OPERATIVE MANAGEMENT

Many units are now incorporating HRS patients into enhanced recovery programs with early targets for introduction of enteral diet, mobilization, prompt removal of invasive monitoring devices, reduction in the use of opiate analgesia, and judicious use of intravenous fluids[41-43]. These measures mean that most patients will expect to stay less than a week following their surgery. The increasing use of laparoscopic techniques has also contributed to the reduction in hospital stay especially for minor resections[44-46].

ASSESSMENT OF LIVER FUNCTION

Liver enzymes

Perhaps one of the most challenging aspects for the junior trainee in the post-operative period is making sense of liver function tests. A transient early rise in serum hepatic

transaminase levels as a result of hepatocellular damage is common, usually peaking at 24-48 h with the extent of derangement being related to the extent of resection[47]. A persistent rise should alert the surgeon to the presence of ongoing hepatic ischeamia. Such a problem is more likely in those in whom a vascular reconstruction has been performed or if there has been prolonged clamping of the hepatic pedicle. This is an indication for urgent notification of senior staff and a Doppler study is useful in looking at the patency of the hepatic artery and portal veins. Early intervention by means of re-operation or interventional radiological techniques may be appropriate.

An isolated rise in alkaline phosphatase or an elevation of this enzyme in association with gamma-glutamyltransferase may indicate normal hepatic regeneration rather than a pathological process, with levels of the enzyme peaking at around 14 d[48].

A sustained rise in bilirubin coupled with elevation in alkaline phosphatase should prompt a search for a cause of biliary obstruction. This is uncommon after a minor liver resection and is usually seen after a major resection in which a biliary reconstruction has been performed[49-52]. An ultrasound scan is the first line investigation to look for evidence of dilated biliary radicles. Further investigations and management can be arranged depending upon the findings of initial studies.

Synthetic function

Changes in platelet count, prothrombin International normalized ratio (INR) and activated partial thromboplastin times (aPPT), which are markers of coagulation status, may be deranged and reflect the magnitude of resection. Specifically, a post-operative rise in INR between days 1-5 as well as a decrease in platelet count and fibrinogen levels are common and thought to be due to a combination of decreased synthetic function of the remnant liver and a consumptive coagulopathy[53-55]. This is usually self-limiting particularly in the setting of normal liver parenchyma and does not need correction with fresh frozen plasma (FFP) or platelet infusions. While there are no established guidelines for the use of FFP to prevent coagulopathy, some centers do use prophylactic FFP if the INR is > 2, in particular in cirrhotic patients[56]. This can be administered in combination with other products including vitamin K and human recombinant factor VIIa to treat clinically significant coagulopathy.

FLUID AND ELECTROLYTES

Changes in liver function are coupled with fluid and electrolytes imbalances in the post-operative setting. The principles of goal-directed therapy in maintaining adequate fluid balance, haemodynamics and renal function (urine output > 0.5 mL/kg per hour) as outlined in the British Consensus Guidelines on intravenous fluid therapy for adult surgical patients should be followed (www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf). However, there are some important caveats following HRS. In the setting of cirrhosis, colloids or human albumin solutions are preferred rather than crystalloids. In addition, sodium restriction, judicious use of diuretics, and selective paracentesis are additional important measures to be considered. Under normal circumstances liver gluconeogenesis consumes a large proportion of body lactate but in the post HRS setting serum lactate can rise, as it is not efficiently metabolised. There are a number of reports implicating the negative impact of elevated lactate and base excess on outcomes after HRS, and some centers advocate the use of non-lactate containing solutions[57].

Hypo/hyperglycemia, hypocalcaemia and hypophoshataemia particularly after major resection should not be ignored and require correction. Strict control of glucose levels has been shown to improve outcomes using a variety of techniques and most intensive/high dependency care units have dedicated protocols. Phosphate is an important component of efficient cell energy metabolism. A decreased level can affect many systems and functions including respiratory failure, cardiac and neurological dysfunction, and insulin resistance[58]. Replacement can be with phosphate infusions, potassium phosphate solutions and oral and paraenteral replacement. The exact mechanism behind the pathogenesis of hypophosphataemia is likely to be increased renal excretion[59]. Hypocalcaemia should be corrected with calcium gluconate or calcium chloride to optimize coagulation status since calcium is critically important in the coagulation cascade and in liver regeneration[60].

THROMBOPROPHYLAXIS

The prevalence of venous thromboembolism (VTE) after surgery particularly in oncological patients cannot be overemphasised. In HRS there has been reluctance in the past to prescribe pharmacologic thrombo-prophylaxis due to concerns regarding bleeding and so-called 'auto-anticoagulation'. However, VTE can still occur even in the presence of elevated INR and aPPT following HRS[61]. Indeed, evidence now confirms patients are more hypercoagulable and the use of pharmacologic thromboprophylaxis lowers the incidence of symptomatic VTE after major HRS without increasing the rate of blood transfusion[62,63]. The majority of patients undergoing HRS will undergo placement of an epidural catheter and so low molecular weight heparins should be started on the day of surgery unless explicit instructions from the operating team regarding increased risk of bleeding. During the surgery, pneumatic compression devices are employed to reduce the risk of thrombosis and mechanical should be continued with compression stockings post-operatively.

ANALGESIA

It is crucial for the junior doctor reviewing a patient to insure they have adequate analgesia as poor pain control leads to prolonged recovery time, inefficient respiratory effort,

a poor appetite and a general slowing down of recovery. There are many options available that and can be tailored to the patient, the two most commonly used being patient-controlled analgesia with intravenous agents (opioids or paracetamol), and epidural analgesia[64]. Local anaesthetic techniques such as transversus abdominis plane (TAP) blocks and infusion catheters are also useful techniques to spare the use of opioids[65,66]. Patients can then be switched to regular and as required oral analgesics according to the world health organization analgesic ladder[67].

As the liver is an important organ for drug metabolism and detoxification it is important to realise potential risks of each modality in the context of liver parenchyma status, magnitude of resection, and concomitant liver or renal failure. Opiates have traditionally been the main stay of analgesia but can be associated with respiratory depression, excessive sedation, and exacerbation of hepatic encephalopathy[68]. As such patients on opiates require close observation in particular after major resections, HRS carried out in the presence of cirrhosis or renal impairment. Better alternatives to simple morphine in cirrhotics include hydromorphone and fentanyl as they are less affected by renal impairment, and are better secreted by the kidney[69]. Intramuscular routes should be avoided, as bioavailability is variable. Non-steroidal anti-inflammatory agents are generally avoided post hepatectomy due to concerns in relation to coagulation and renal impairment[69].

DRAINS

Unit guidelines will dictate when drains are used and when they should be removed, as there are no published guidelines. In reality, the decision to remove drains is dependent on the reason the drain was inserted, the type of fluid draining and the volume of that fluid. If bile is observed then senior colleagues should be informed as imaging studies may be indicated especially if drainage persists or volume increases. Some have advocated the "3× 3" rule (drain-fluid bilirubin level below 3 mg/dL on day 3 after operation) as criterion for removal of prophylactically placed abdominal drains after hepatic resection[70]. Interestingly, a Cochrane review has shown that routine abdominal drainage for uncomplicated liver resection is not needed and if used a closed drain system is associated with less infectious complication and hospital stay than open systems[71].

NUTRITION

Following major HRS, patients enter a catabolic state and so require early nutritional support to optimise liver regeneration, prevent infections, and promote general recovery. Those undergoing minor resection with normal parenchyma will often only require re-introduction of normal diet the first post-opertaive day. A systematic review of nutrition following HRS confirmed that early nutrition by enteral route is associated with a lower incidence of wound infections and complications as compared to parenteral, and therefore remains the favoured route of nutritional support[72].

In addition to early feeding, data is now emerging to encourage the use of pre- and pro-biotics (known as symbiotic therapy) in an attempt to address gut barrier dysfunction and microbial flora to reduce the gut-mediated systemic inflammatory response syndrome and encourage liver regeneration[73,74]. This therapy is yet to be validated in large randomised controlled trials and not used routinely in current United Kingdom clinical practice.

RECOGNISING POST-OPERATIVE COMPLICATIONS

The mortality rates in the majority of published series are now in the order of 0%-2%, however, with reported morbidity rates of 25% to 45% it is important to be alert to potential complications following HRS in all patients. Risk factors for complications include: age > 65 years; ASA score ⩾ 3; larger extent of resection (multiple tumours, bilobar disease); requirement for blood transfusion; and involved resection margins[75]. Up to 30% can suffer "major" complications; specifically bleeding, liver/kidney/respiratory failure and sepsis and account for the majority of deaths post surgery[75]. In an attempt to allow comparison across series, the Clavien-Dindo classification of post-operative complication is now frequently reported[76].

HEPATIC FAILURE

Around 3%-5% of patients may develop liver failure following their resection and will usually show signs and symptoms from 48-72 h after their surgery[2]. These are usually patients undergoing major resections, or resections carried out in the presence of cirrhosis. The International Study Group of Liver Surgery recently developed a consensus definition for post-hepatectomy liver failure namely 'the impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5[77]. They graded the severity of post-hepatectomy liver failure on the basis to its impact on clinical management: Grade A post-hepatectomy liver failure requires no change of the patient's clinical management. The clinical management of patients with grade B post-hepatectomy liver failure deviates from the regular course but does not require invasive therapy. The need for invasive treatment defines grade C post-hepatectomy liver failure.

In our own practice, the following indices are used in the monitoring of hepatic function and identifying dysfunction: (1) persistent hyperbilirubinemia [serum bilirubin level > 4.1 mg/dL (to convert to micromoles per liter, multiply by 17.104)]; (2) coagulopathy with anINR > 2.5,

Table 2 Abridged version of West Haven criteria

HE grade	Mental state
1	Mild confusion, slowing of ability to do mental tasks, *e.g.*, serial 7's
2	Drowsiness, inappropriate behaviour
3	Somnolent but rousable, marked confusion
4	Coma

Reproduced with permission from reference Ferenci *et al*[79].

despite early attempted correction with clotting factors; (3) abdominal ascites (drainage volumes > 500 mL/d); and (4) encephalopathy with hyperbilirubinemia and exclusion of other acute confusional states[36].

Another practical definition of post-hepatectomy liver failure is indicated by a prothrombin time < 50% and serum bilirubin > 50 mmol/L (the "50-50" criteria) and been shown to predictive factor of mortality when measured at days 3 and 5[78].

Patients with significantly impaired hepatic function may exhibit hepatic encephalopathy (HE). The West Haven criteria (Table 2) grades HE from I to IV according to severity and is widely used[79]. It is based on changes of consciousness, intellectual function, behavior, and is useful in monitoring patient progress. Ammonia levels should be measured if HE is suspected and lactulose and systemic antibiotcs prescribed to alter gut flora and reduce the production and absorption of ammonia[80].

A number of risk factors have been identified for the development of post-hepatectomy liver failure and have been summarised in a recent review[81]. When confronted with a picture of liver failure, it is important to attempt to determine the underlying cause, as some elements are correctable. Causes of liver failure are usually multifactorial and include: bleeding; sepsis; hepatic ischeamia; portal vein thrombosis; venous outflow obstruction; and a poorly functioning liver remnant. There hepatotoxic effects of pre-operative chemotherapy on the parenchyma, and the presence of steatosis may also contribute to insufficiency.

Intensivists, senior surgeons and hepatologists lead the management of this most feared complication. The mainstay of treatment is supportive with blood products administered to support synthetic function, aggressive investigation and treatment of infection, and radiological investigation to ensure patency of major vascular and biliary structures. The use of exogenous antioxidants such as N-acetylcysteine (Parvolex®) has been used by some including our own unit in attempting to reduce the damage by oxygen free radical associated ischaemic reperfusion injury of the liver[82]. However this remains to be accepted as universal practice and currently lacks a strong evidence base[83,84].

BLEEDING AND TRANSFUSION REQUIREMENTS

Intra- and post-operative bleeding, and the requirement for blood transfusion are associated with increased morbidity, mortality and poorer long-term disease-specific outcomes in CRLM and HCC[85,86]. Kooby *et al*[37] in a study of 1351 liver resections noted a variation in operative mortality between 1.2% for no transfusion to 11.1% when more than 2 units of blood were transfused. A recent review by Dixon *et al*[38] highlighted the negative effects of blood loss on outcome in surgical oncology patients, and suggested that the need for transfusion may be an indicator of the quality of surgery performed.

The operating surgeon and anaesthetist incorporate multiple techniques including: low intra-operative central venous pressure; dynamic intra-operative coagulation monitoring; drugs (aprotinin, tranexamic acid); and haemostatic products on the cut surface of the liver to reduce the occurrence of this complication. As a result median blood loss in overall HRS has significantly reduced and reported to be less than 700-800 mL[87]. Indeed, the median transfusion rate in the majority of contemporary series is zero.

Blood loss during surgery should be clearly documented on the operative note. Unit protocols drive the specific haemoglobin criteria for transfusion and should be referred to when assessing the patient in this early stage. During the post-operative phase, patients will have haemoglobin and haematocrit measurements determined regularly. It would be expected that patients would stabilise during the initial 24-48 h and any deterioration following this should trigger referral to senior colleagues and a request for imaging studies. Patients actively haemorrhaging may require re-exploration or radiological embolisation of bleeding vessels.

POST-OPERATIVE SEPSIS

As evidence grows implicating post-operative complications, in particular infection, in poorer disease-free survival, an important aim must be to pro-actively attempt to minimise infections, and when present to identify and implement treatment in an expedient manner[75]. Risk factors known to be associated with infection include: obesity; major resections requiring blood transfusions; presence of co-morbidities (diabetes, chronic obstructive pulmonary disease); and post-operative bile leaks[88]. Standard effective interventions to minimise infections include ensuring adequate chest physiotherapy, early patient mobilisation, prompt removal of indwelling devices, and institution of broad-spectrum antibiotics therapy where indicated.

BILE LEAKS

Bile leakage is an important complication occurring after liver surgery and its reported incidence ranges between 4.8%-7.6% in large series[89-95] and is less common in surgery for CRLM than for HCC or CCA. The International Study Group of Liver Surgery has recently proposed a uniform definition of bile leakage and a grading system according to severity, which is based on drain fluid bilirubin concentration of greater than three times the serum

bilirubin concentration on day 3 after surgery or the need for additional interventions[96]. Management of bile leaks includes treatment of associated infection, defining the location of leak, externalizing the bile with a radiologically placed drain, and the consideration of insertion of biliary stents and/or reconstructive surgery[97].

SUMMARY AND FUTURE DIRECTIONS

No consensus protocol exists for the post-operative management of HRS, as each centre will have different guidelines reflecting preferences of senior staff with regards to the finer points of management. It is important to deliver early nutrition, effective analgesia, and promote good respiratory function. Furthermore close observation in the early post-operative period is required to identify and aggressively manage bleeding, infection and prevent the development of liver failure. The surgical trainee is required to have a basic grounding and have the ability to appreciate exactly what resection has been performed in a patient to allow for meaningful assessment. Such knowledge will provide insight into being able to alert senior staff appropriately and expediently in this challenging dynamic subgroup of patients.

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CASE REPORT

Localized pseudomembranous colitis in the cecum and ascending colon mimicking acute appendicitis

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Abstract

A 61-year-old male was admitted to our hospital due to right lower abdominal pain and watery diarrhea for 3 d. Beginning 3 wk before he arrived in our hospital, he took 3rd-generation cephalosporin (cefixime) for 2 wk due to chronic left ear otitis media. Colonoscopic examination revealed yellowish patches of ulcerations and swelling covered with thick serosanguineous exudate in the cecum and ascending colon. After 7 d of oral metronidazole treatment, his symptoms completely disappeared. We report a case of localized pseudomembranous colitis in the cecum and ascending colon mimicking acute appendicitis associated with cefixime.

Key words: Enterocolitis; Pseudomembranous; Appendicitis; Abdomen; Acute; Diarrhea; Cefixime

Core tip: Pseudomembranous colitis is mostly related to antibiotics, and it presents symptoms of diarrhea, abdominal pain, fever, hypoalbuminemia and hypovolemia. Diarrhea is the most common manifestation, but in geriatric patients, symptoms of pseudomembranous colitis can be different from those of usual cases, and the disease course can be more aggressive. For these reasons, it can be misdiagnosed. Therefore, physicians must consider pseudomembranous colitis in older patients with acute abdominal pain who have been treated with antibiotics. We report a case of an older patient with pseudomembranous colitis that was misdiagnosed as acute appendicitis.

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INTRODUCTION

Patients who are administered antibiotics often experience diarrhea (referred to as antibiotic-associated diarrhea), and when these patients are proven to have inflammation in the colon, it is known as antibiotic-associated colitis. Furthermore, when patients with antibiotic-associated colitis have more inflammation in the colon and show pseudomembrane formation, it is referred to as pseudomembranous colitis.

Here, we present the case of a 61-year-old male patient who was first suspected of having acute appendicitis and had been experiencing right lower abdominal pain, tenesmus, and frequent watery diarrhea for 3 d before visiting the hospital. He also had a history of taking a cephalosporin antibiotic (cefixime) for 2 wk after an outpatient visit to the otolaryngology department to treat otitis media of the left ear 3 wk before visiting us. Based on these findings, we performed hematologic, colonoscopic, and histologic examinations and found pseudomembranous colitis limited to the cecum and the right ascending colon. We also present a literature review.

CASE REPORT

A 61-year-old male had right lower abdominal pain, frequent watery diarrhea. He was underwent antibiotic treat-

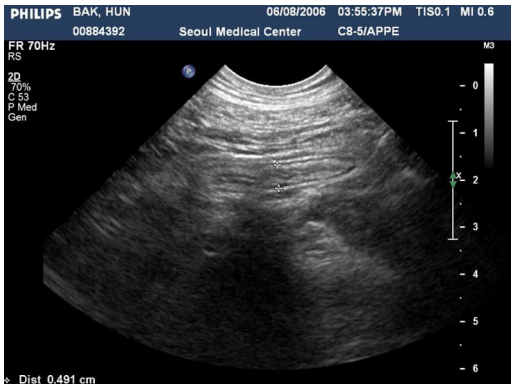

Figure 1 Abdominal ultrasonographic finding. Non-specific colitis in the ascending colon and the cecum and secondary mild inflammation of the appendix.

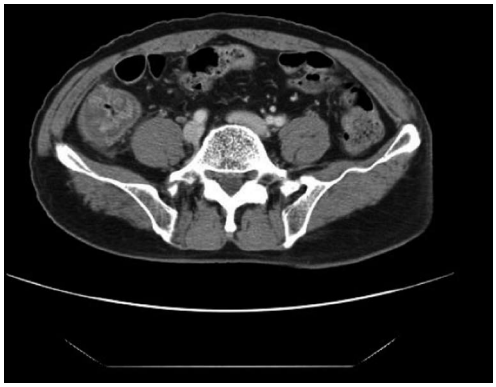

Figure 2 Abdomen computed tomography scan shows circular wall thickening in the cecum and the ascending colon and pericolic infiltration and adjacent lymph nodes.

ment for otitis media in the right ear 3 wk previously and had been taking diabetes medications for 19 years. He had no specific history.

History of present illness

Three weeks before visiting us, he was diagnosed with otitis media in the left ear and had been taking a 3rd-generation cephalosporin antibiotic (cefixime) prescribed by the otolaryngology department at our hospital for 2 wk. He stated that a week before the visit, he began to suffer from discomfort in the right lower abdomen, tenesmus, and intermittent and frequent watery diarrhea several times a day. When he made an outpatient visit to the department of surgery, he reported that he had not been able to tolerate the consistent right lower abdominal pain for the previous 3 d.

Physical findings

When he visited us, his vital signs were blood pressure 110/60 mmHg, pulse rate 80 bpm, respiratory rate 20/min, and body temperature 36 ℃ but without fever or chills. He presented a slightly decreased appetite, and based on the clinical manifestations found through his physical examination, his bowel sounds were normal. Although the right lower abdominal tenderness and rebound tenderness were obvious, our digital exploration did not find any lump.

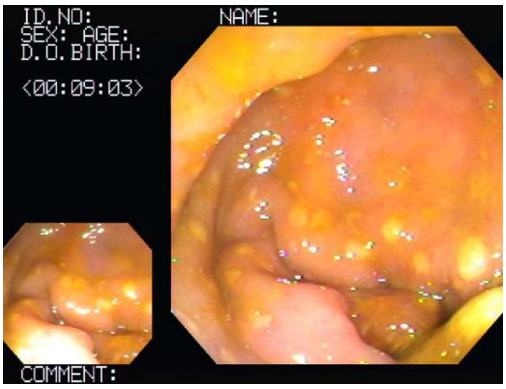

Figure 3 Colonoscopic finding shows multiple elevated yellowish or white pseudomembranes with hyperemic, edematous mucosa in the ascending colon and cecum.

Examination findings

The hematological examination results were peripheral blood white blood cell count 8900/mm^3, hemoglobin 15.3 g/dL, hematocrit 44%, platelet count 123 × 10^3/mm^3, and CRP 15.2 mg/L. Meanwhile, his urinalysis results were normal, except for glucose (+++). His ultrasound results on the day of the visit showed that every layer of the serous membranes of the ascending colon and cecum was hypertrophic, whereas the serous membrane of the appendix was slightly hypertrophic, secondary to inflammatory responses in the colon (Figure 1). The results of an abdominal computed tomography (CT) scan performed the day after the visit showed that the serous membranes of the cecum and ascending colon were generally hypertrophic, and there were inflammatory infiltrates around the colon (Figure 2). A colonoscopy performed on the 4th d also found pseudomembranous colitis limited to the cecum and ascending colon; thus, a biopsy was carried out (Figure 3). The biopsy confirmed that he had typical pseudomembranous colitis with crater-shaped ulcers (Figure 4), and the stool analysis showed that he was positive for *Clostridium difficile* (*C. difficile*) cytotoxin (0.09).

Progress

On the day that the biopsy confirmed pseudomembranous colitis, he began oral treatment with 250 mg of metronidazole 4 times a day. After 3 d, his defecation disorder and right lower abdominal pain mostly disappeared. In addition, when he was discharged, he was able to eat properly. He was orally administered metronidazole for 7 d, and through a colonoscopy performed a month after discharge, we were able to confirm that his intestinal mucosa had returned to normal (Figure 5).

DISCUSSION

Pseudomembranous colitis was first reported in 1893, and it was rare before antibiotics came into widespread

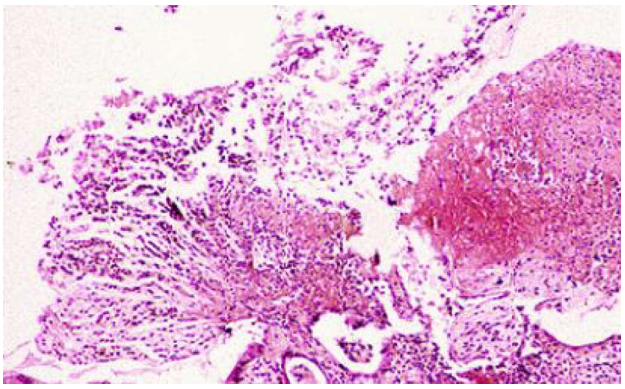

Figure 4 Histological finding shows the typical volcano-like exudate, inflammatory cells, mucofibrinous material and inflammatory colonic mucosa with erosion (HE stain, × 40).

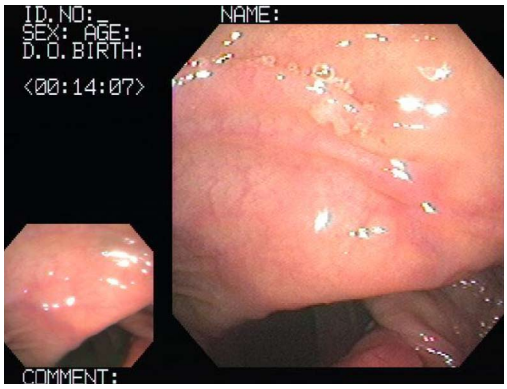

Figure 5 Follow-up colonoscopic finding showing normal mucosa in the ascending colon and the cecum.

use. In the early 1950s, as antibiotics began to be widely used, the incidence of pseudomembranous colitis also began to rise. At the time, people suspected that the main cause of pseudomembranous colitis was *Staphylococcus aureus*, one of the most common nosocomial infections. However, in 1974, a prospective study revealed that approximately 20% of patients who were administered clindamycin experienced antibiotic-associated diarrhea, and half of them suffered from pseudomembranous colitis.

In 1935, Hall and O'Toole claimed that *C. difficile* was a normal part of the flora of infants' intestines. They described it as "the difficult clostridium" because an anaerobic gram-positive bacillus was considered the most difficult bacteria to grow in culture[1]. In an animal study, it was shown that *C. difficile* could secrete powerful toxins, but its clinical significance was discovered in the late 1970s. At that time, for the first time, *C. difficile* and its cytotoxin were found in the feces of almost every patient with pseudomembranous colitis but not in the feces of healthy people; this indicated that the toxins produced by *C. difficile* caused pseudomembranous colitis.

The first case of pseudomembranous colitis that occurred in the cecum and appendix was presented in 1997 by Coyne *et al*[2]. A 76-year-old female patient who was receiving hemodialysis for chronic renal failure experienced pseudomembranous colitis after being administered clindamycin to treat abdominal pain and diarrhea, but pseudomembranous colitis reoccurred a month after using metronidazole, and this led to her death. Based on the colonoscopy performed when she was admitted to the hospital, she was diagnosed with pseudomembranous colitis in her diverticulum, cecum, and appendix across her transverse colon and descending colon.

In approximately 90% of cases, *C. difficile* is found in the rectum and sigmoid colon on colonoscopy. However, in approximately 10% of cases, it occurs in the distal colon; therefore, patients cannot be diagnosed by sigmoidoscopy alone[1]. In 1982, Tedesco *et al*[3] carried out a prospective study on patients diagnosed with pseudomembranous colitis. They stated that 77.3% of the patients were successfully diagnosed through sigmoidoscopy; but in 13.6% of the patients, pseudomembranous colitis occurred between 24 and 60 cm from the anus, and it occurred more than 60 cm from the anus in 9.1% of the patients. Furthermore, in 1999, Lee *et al*[4] studied the clinical characteristics of *C. difficile*-associated diseases and claimed that because less than 10% of patients had lesions in the ascending colon alone without invading the descending colon, sigmoidoscopy was sufficient, and colonoscopy was not needed.

When *C. difficile* occurs in the cecum, it can be observed on a CT scan as an "accordion sign", which is caused by the invasion of the tissues surrounding the cecum and cecal bulb as well as a thickening of the cecal folds. Based on these CT scan results, appendicitis should be distinguished from typhlitis, pseudomembranous colitis, inflammatory diseases, diverticulitis of the cecum, inflammatory bowel diseases, cecal volvulus, pneumatosis intestinalis, ischemia and necrosis, solitary cecal ulcer syndrome, and tumors in the cecum in a patient suffering from right lower abdominal pain[5]. Our patient's CT scan showed the "accordion sign."

C. difficile is an anaerobic gram-positive bacillus that is resistant to antibiotic treatments by forming spores. *C. difficile* is part of the normal flora in the intestine of infants, but this is rarely the case with older children or adults. However, if the normal flora is altered due to antibiotic or antitumor treatments or infections with pathogens, such as *Salmonella* or *Shigella*, *C. difficile* colonization can occur. Therefore, the normal flora in the colon appears to inhibit the growth of *C. difficile*. *C. difficile* secretes powerful exotoxins called toxin A and toxin B, which induce tissue damage to the colon. However, depending on the strain, some exotoxins may be less toxic than others or not toxic at all. Nonetheless, because the level of toxicity is not proportional to the severity of the disease, in general, these toxins are reported as either positive or negative[1].

Almost every antibiotic that shows activity against bacteria can induce antibiotic-associated colitis. The antibiotics that most commonly cause antibiotic-associated colitis are cephalosporin, ampicillin, amoxicillin, and

clindamycin; the ones that cause it less frequently include penicillin, excluding ampicillin, and macrolides (erythromycin, clarithromycin, and azithromycin). In addition, antibiotics that occasionally cause antibiotic-associated colitis include fluoroquinolone, trimethoprim-sulfamethoxazole, metronidazole, tetracycline, and chloramphenicol. It has not yet been clearly established whether sulfonamide, parenteral aminoglycosides, or parenteral vancomycin-as well as other antimicrobial agents against fungi, mycobacteria, parasites, and viruses-can induce antibiotic-associated colitis.

Moreover, *C. difficile*-associated colitis can occur in patients who (1) have had prolonged hospitalization; (2) share a cubicle or ward with a patient suffering from antibiotic-associated colitis; (3) are old; (4) recently had surgery, in particular, gastrointestinal surgery; (5) suffer from intestinal obstruction; or (6) have a malignant tumor[6].

The most distinctive antibiotic-associated colitis induced by *C. difficile* may be pseudomembranous colitis. For example, over 95% of patients diagnosed with pseudomembranous colitis have a positive stool toxin assay. A close examination of their pseudomembrane reveals few normal tissues and raised exudative plaques that have hemorrhagic edematous mucosa with perforated areas. Such plaques can grow and become merged across bowel segments in the final stage of the disease.

The clinical characteristics of antibiotic-associated pseudomembranous colitis vary. One of the most common characteristics is a large amount of watery diarrhea without blood or mucus. Most patients experience severe convulsive abdominal pain and tenderness, fever, and leukocytosis. However, symptoms can vary greatly. On one hand, some patients suffer from diarrhea and show no systemic symptoms. On the other hand, some patients present severe systemic toxicity, high fevers up to 40.0 ℃-40.6 ℃, and peripheral leukocytosis up to 50000/mm^3. The results of stool examinations usually show white blood cells.

If left untreated, the clinical course varies between patients. Some patients experience immediate relief from symptoms after discontinuing the drug, while others continuously produce a large amount of feces up to week 8, which can ultimately lead to hypoalbuminemia or electrolyte imbalance. There also have been some reports of severe patients with toxic megacolon and enterobrosia. The mortality rate of severe patients is approximately 30%, while the symptoms of most patients with mild symptoms improve simply by discontinuing antibiotics. In most patients, symptoms begin to appear 4-10 d after antibiotic administration. However, approximately 25% of patients do not experience any symptoms until they discontinue antibiotics, and a few begin to show symptoms after 4 wk of administration. It has been reported that in some cases, symptoms occur within several hours of antibiotic administration and sometimes even after a single administration of antibiotic as a surgical prophylactic measure[7].

Our aged patient had risk factors for developing pseudomembranous colitis and had a history of taking a 3rd-generation cephalosporin antibiotic (cefixime) for approximately 2 wk. On sigmoidoscopy, we observed several pseudomembranes limited to the cecum and the ascending colon, and the pseudomembranes were proven by biopsy. Moreover, the patient's stool toxin assay was positive (0.09).

Pseudomembranous colitis can be treated by discontinuing the antibiotic that has been used and switching to a conservative treatment alone. In such cases, approximately 30% of patients show improved symptoms in approximately 10 d; however, patients with severe enteritis can also take 250 mg of metronidazole orally 4 times daily for approximately 7-14 d. When oral administration is impossible due to paralytic ileus or megacolon, 500 mg can be administered every 6 h through a jugular vein. Because metronidazole is well absorbed in the upper gastrointestinal tract, the downside of oral administration is that its concentrations can decrease in the feces. However, pseudomembranous colitis can increase the permeability of the colonic mucosa and subsequently allow metronidazole to be delivered to the lumen of the colon. Metronidazole is much more affordable than vancomycin, and due to recent concerns over *Enterococcus*, which is resistant to vancomycin, metronidazole is the primary choice to treat antibiotic-associated colitis[8].

Typically, 125 or 500 mg of vancomycin is administered orally 4 times daily for 7-14 d. The 125 mg dose is cheaper than the 500 mg dose, but they appear to have similar treatment effects. Because vancomycin is rarely absorbed when orally administered, the fecal concentration remains high. However, it is less effective when it is administered through a jugular vein, as the concentration is lower in the lumen of the colon. It can be argued that oral vancomycin is highly effective in treating antibiotic-associated colitis because there is no report of *C. difficile* being resistant to vancomycin. Nevertheless, it is still much more expensive than metronidazole, and considering concerns over vancomycin-resistant enterococci, metronidazole should be the primary choice to treat antibiotic-associated colitis; vancomycin should only be used in cases in which metronidazole cannot be used or in patients who do not respond to metronidazole[9,10].

We administered 250 mg of metronidazole orally to our patient 4 times daily; after 3 d, the right lower abdominal pain, tenesmus, and frequent watery diarrhea disappeared. The reoccurrence rate of pseudomembranous colitis after treatment is reported to be approximately 20%, and possible causes of reoccurrence are reinfections by remaining strains and spore formation[11]. Our patient was administered metronidazole for 7 d total, and based on the result of a sigmoidoscopy performed one month later, we were able to confirm that his intestinal mucosa had returned to normal.

In conclusion, even when right lower abdominal pain is the major clinical manifestation, if the patient has abnormal bowel habits and a recent history of antibiotic administration, even without the presence of fever, chills, or watery diarrhea (which are common clinical characteristics of pseudomembranous colitis), we recommend that

pseudomembranous colitis should be considered in the differential diagnosis of acute appendicitis.

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EDITORIAL

Minimally invasive treatment of cholecysto-choledocal lithiasis: The point of view of the surgical endoscopist

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Abstract

The rate of choledocholithiasis in patients with symptomatic cholelithiasis is estimated to be approximately 10%-33%, depending on the patient's age. Development of Endoscopic Retrograde Cholangiopancreatography and Laparoscopic Surgery and improvement of diagnostic procedures have influenced new approaches to the management of common bile duct stones in association with gallstones. At present available minimally-invasive treatments of cholecysto-choledocal lithiasis include: single-stage laparoscopic treatment, perioperative endoscopic treatment and endoscopic treatment alone. Published data evidence that, associated endoscopic-laparoscopic approach necessitates increased number of procedures per patient while single-stage laparoscopic treatment is associated with a shorter hospital stay. However, current data does not suggest clear superiority of any one approach with regard to success, mortality, morbidity and cost-effectiveness. Considering the variety of therapeutic options available for management, a critical appraisal and decision-making is required. Endoscopic retrograde cholangiopancreatography/EST should be adopted on a selective basis, *i.e.*, in patients with acute obstructive suppurative cholangitis, severe biliary pancreatitis, ampullary stone impaction or severe comorbidity. In a setting where all facilities are available, decision in the selection of the therapeutic option depends on the patients, the number and size of choledocholithiasis stones, the anatomy of the cystic duct and common bile duct, the surgical history of patients and local expertise.

Key words: Cholecysto-choledocal lithiasis; Laparoscopic treatment; Endoscopic treatment; Minimally invasive therapy; Management strategies

Core tip: Development of Endoscopic Retrograde Cholangiopancreatography and Laparoscopic Surgery have influenced new approaches to the management of cholecysto-choledocal lithiasis. At present available minimally-invasive treatments include: single-stage laparoscopic treatment, perioperative endoscopic treatment and endoscopic treatment alone. Current data does not suggest clear superiority of any one approach with regard to success, mortality, morbidity and cost-effectiveness. Considering the variety of therapeutic options available for management, a critical appraisal and decision-making is required. This should preferably be dictate on the patient, the clinical presentation, the timing of diagnosis (established pre-operative diagnosis or incidental intraoperative diagnosis), the surgical pathology and the local expertise.

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INTRODUCTION

The rate of choledocholithiasis (CBDS) in patients with symptomatic cholelithiasis is estimated to be approximately 10%-33%, depending on the patient's age[1-4]. In Western countries CBDS typically originate in the gallbladder and migrate into the common bile duct. Compared to stones in the gallbladder the natural history of secondary CBDS is not well understood. It is unclear whether an asymptomatic choledocholithiasis requires treatment. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy (LC) have suggested that a third of patients with CBDS at the time of cholecystectomy pass their stones spontaneously within 6 wk of surgery[1]. It is not clear what stone size precludes transpapillary migration into the duodenum nor which criteria will predict complications if CBD stones are not treated. On the other hands, complications of ductal stones, including pain, partial or complete biliary obstruction, cholangitis, hepatic abscesses or pancreatitis are well recognized and often serious. Therefore, it is generally recommended to treat CBD stones whenever detected, except in selected patients that have contraindications (*e.g.,* high risk patients, refusal of operative or endoscopic treatment *etc.*), when conservative and expecting modality are accepted[5].

For many years, open cholecystectomy with choledochotomy and/or surgical sphincterotomy and cleaning of the bile duct were the gold standard to treat both pathologies. Development of endoscopic retrograde cholangiopancreatography (ERCP) and laparoscopic surgery and improvement of diagnostic procedures have influenced new approaches to the management of CBDS in association with gallstones.

ERCP has become a widely available and routine procedure, whilst open cholecystectomy has largely been replaced by a laparoscopic approach, which is considered the treatment of choice for gallbladder removal since NIH Consensus on 1993[6]. New imaging techniques such as magnetic resonance cholangiography (MR) and endoscopic ultrasound (EUS) offer the opportunity to accurately visualize the biliary system without instrumentation of the ducts. As a consequence clinicians are now faced with a number of potentially valid options for managing patients with CBDS.

MANAGEMENT STRATEGIES OF CHOLECYSTO-CHOLEDOCAL LITHIASIS

The primary challenge in the management of CBD stones in association with gallstones is to select the best strategy with regard to success, morbidity and cost-effectiveness. At present available minimally-invasive treatments of cholecysto-choledocal lithiasis include: single-stage laparoscopic common bile duct exploration (LCBDE), perioperative endoscopic treatment and endoscopic treatment alone (Table 1).

Laparoscopic common bile duct exploration can be achieved through transcystic approach or by performing choledochotomy. Endoscopic treatment comprises preoperative ERCP with endoscopic sphincterotomy (ES) followed by LC (sequential treatment), intraoperative ERCP with ES (LC + ES, rendezvous technique) as a single stage treatment of CBDS, postoperative ERCP with ES as a two stage treatment of CBDS and ERCP with ES without subsequent gallbladder removal. Each of these options has advantages and disadvantages that have been reported in numerous publications that are summarized in Table 2[7-14].

ANALYSIS OF THE CURRENT LITERATURE

Current data does not suggest clear superiority of any one approach with regard to success, mortality, morbidity and cost-effectiveness. Published data evidence that associated endoscopic-laparoscopic approach necessitates increased number of procedures per patient while LCBDE is associated with a shorter hospital stay[15-17]. Moreover, the long-term sequelae of sphincterotomy can also be avoided with laparoscopic bile duct clearance[18,19].

However there are several issues concerning these results that deserve some considerations. First, coming from experienced laparoscopic centers, the application of these results to the wider surgical community should be made with some caution. Second, when applying the results to clinical practice, it is important to consider the inclusion criteria for each of the studies, since many studies excluded patients from laparoscopic CBD exploration in cases of high-risk patients (American Standards Association status 3-4), acute cholangitis, gallstone pancreatitis or anatomy precluding LCBDE. Finally, most of the trials were limited by their small sample size.

Moreover, it is important also to note that the laparoscopic technique has not been widely accepted by the surgical community. In common practice, from a 2005 survey of English hospitals, it is estimated that only 20% of bile duct explorations are performed laparoscopically[20]. Similarly, a survey of general surgeons practicing in the United States showed that, although 44% of surgeons could perform laparoscopic CBD exploration, only 22% actually did so routinely and that 75% considered the preoperative ERCP as the preferred approach to a patient with choledocholithiasis[21]. The most common reasons for not performing LCBDE were that the procedure was too time consuming (58%), lack of equipment (24%), increased morbidity (1.5%) and lack of skill (1.5%).

DECISION-MAKING IN THE SELECTION OF THE THERAPEUTIC OPTION

Considering the variety of therapeutic options available for management, a critical appraisal and decision-making

Table 1 Management strategies of minimally invasive treatment of cholecysto-choledocal lithiasis

One step surgical treatment	Laparoscopic
Endoscopic + surgical approach	Preoperative ERCP Intraoperative ERCP Postoperative ERCP
Endoscopic treatment alone[1]	Endoscopic stones extraction without subsequent cholecystectomy

[1]Selected patients. ERCP: Endoscopic retrograde cholangiopancreatography.

is required. This should preferably be dictate on the patient, the clinical presentation, the timing of CBD stones diagnosis (established pre-operative diagnosis or incidental intraoperative diagnosis), the surgical pathology and the local expertise.

Patient

An assessment of operative risk needs to be made prior to scheduling intervention. Where this risk is deemed prohibitive, endoscopic therapy should be considered as an alternative since endoscopic treatment is less invasive than surgical approach. For patients aged less than 50-60 years, although the available evidence suggests that ERCP with ES can be safely used for extracting stones, it's important to take in mind late complications of ES including recurrent stone formation and cholangitis[18,19,22-24]. For an individual patient these risks need to be weighed against those of alternative treatment options.

Clinical presentation

Bacterial contamination of bile is a common finding in patients with CBDS and may causes acute cholangitis. Biliary decompression is considered the primary treatment of acute cholangitis due to biliary stones. Immediate decompression could be planned for patients who fail to respond to antibiotic therapy or who have signs of septic shock. Urgent decompression (< 72 h) could be planned for patients who respond to initial therapeutic measures or patients with poor prognostic parameter (elderly patients; associated comorbidities). The most appropriate method of biliary decompression is ES supplemented by stenting and/or stone extraction. Surgical approach in this group is associated with a considerably higher mortality than ERCP and should be avoided[25-29].

Common bile duct stones are a recognized cause of acute pancreatitis. The United Kingdom guidelines for the management of acute pancreatitis advocate urgent therapeutic ERCP in every patient with suspected gallstone etiology and predicted severe pancreatitis or when there is cholangitis, jaundice or a dilated common bile duct[30]. Conversely, the AGA Institute guidelines on acute pancreatitis recommend that early ERCP is not indicated in patients with predicted severe pancreatitis without concomitant cholangitis or high suspicion of a persistent common bile duct stone[31]. Laparoscopic cholecystectomy is recommended as a treatment of choice for biliary

Table 2 Discussion overview of management strategies

Type of procedure	Advantages	Disadvantages
ERCP + ES	Less invasive Procedure of choice in post-cholecystectomy patients, acute cholangitis, gallstone pancreatitis	Equipment Local expertise 2 stage procedure Complications
LCBDE: transcystic	Minimal invasive One stage procedure	Equipment Local expertise Anatomic variations Prolonged OR time
LCBDE: choledochotomy	One stage procedure	Most invasive Necessitate of T-tube Prolonged OR time

ERCP: Endoscopic retrograde cholangiopancreatography; ES: Endoscopic sphincterotomy; LCBDE: Laparoscopic common bile duct exploration; OR: Operative time.

acute pancreatitis. The timing of LC following acute biliary pancreatitis can vary markedly depending on the severity of pancreatitis and the overall health of the patient. In mild disease LC can be safely performed within 7 d, whereas in severe disease, especially in extended pancreatic necrosis, at least three weeks should elapse because of an increased infection risk[32]. Routine preoperative ERCP is considered unnecessary in non-jaundiced patients with mild biliary pancreatitis scheduled to undergoing cholecystectomy since in this group of patients 80% of stones spontaneously pass and it is uncommon to find ductal stones in this group at ERCP[33-37]. Every effort should be made to identify biliary obstruction, including MRCP and EUS when accessible, before resorting to ERCP[38,39]. In the setting of acute pancreatitis, it's important to note that ERCP is generally more difficult to perform because the duodenum and ampulla are edematous[35].

Timing of diagnosis

CBD stones can be diagnosed before the LC (established preoperative diagnosis), during (incidental diagnosis) or after the LC. ERCP with ES is recommended as the primary form of treatment for patients with CBDS post cholecystectomy. This approach is advocated, though it should be noted there are no trials directly comparing endoscopic stone extraction with surgical stone extraction in this setting. Successful endoscopic treatment is possible in the majority of patients and in skilled hands duct clearance can be achieved in over 90%, though in 5%-25% of patients this requires two or more ERCPs[5,40-42]. In patients with preoperative diagnosis or incidental diagnosis, decision may depend on the surgical pathology and local expertise.

Surgical pathology

There are several factors that can affect the choice of the technique including the size and number of CBD stones, the cystic duct size and anatomy, the diameter of the common bile duct, and the past surgical history.

Transcystic stone clearance may be hampered by cys-

tic duct anatomy (tortuous, < 3 mm in diameter), proximal (hepatic duct) stones, strictures and large (> 6 mm) or numerous stones (> 5)[43-45]. Following laparoscopic choledochotomy, closure over a T-tube may be required if the common bile duct is inflamed[46-48]. Extraction of ductal stones *via* an endoscopic biliary sphincterotomy may be difficult or inappropriate for a variety of reasons, including size, shape and number of stones, intrahepatic location, stone impaction, Billroth Ⅱ gastrectomy or Roux-en-y anatomy, recurrent bile duct stones after prior open exploration of the CBD and biliodigestive anastomosis, periampullary diverticula, and Mirizzi syndrome[8,49].

It is important that adequate biliary drainage is ensured in patients with CBD stones that have not been extracted by standard or advanced (such as lithotripsy) endoscopic techniques, eventually by a temporary biliary stent. The use of a biliary stent as sole treatment for CBDS should be restricted to a selected group of patients with limited life expectancy and/or prohibitive surgical risk[50-52].

Local expertise

For successful endoscopic stones extraction, skilled endoscopist, nursing and radiography staff are essential. ERCP training program is mandatory to achieve selective cannulation rates in excess of 80%. It is important that once formal training is completed endoscopists perform an adequate number of biliary sphincterotomies (40-50) per year to maintain their performance. It is recommended that all endoscopists performing ERCP should be able to supplement standard stone extraction techniques with advanced techniques (mechanical lithotripsy, electro-hydraulic lithotripsy and laser lithotripsy) when required[52-57]. There is significant learning curve for laparoscopic bile duct surgery both amongst surgeons and nursing staff[58]. LCBDE requires a flexible choledochoscope together with light source and camera, and disposable instrumentation similar to that required for ERCP (*e.g.*, baskets, balloons, stents). Laparoscopic common bile duct exploration *via* choledochotomy requires advanced laparoscopic skills and longer operative times. As previously reported, closure over a T-tube may be required if the common bile duct is inflamed[46-48].

ENDOSCOPIC SPHINCTEROTOMY WITH STONE EXTRACTION WITHOUT SUBSEQUENT CHOLECYSTECTOMY

Retrospective studies of patients who have undergone endoscopic sphincterotomy for bile duct stones with gallbladders left *in situ* suggest that about 10% of patients develop recurrent biliary problems (mainly acute cholecystitis) over 1 years[59]. The risk of acute cholecystitis after sphincterotomy without a cholecystectomy ranges from 1% to 16%; most of these cases tend to occur soon (within 4-6 wk) after the sphincterotomy in those with gallbladder stones[60-63]. Therefore in patients with CBDS and gallstones ES with stone extraction as sole treatment should be avoided unless there are patient related factors that make cholecystectomy inappropriate. The role of LC in patients with empty gallbladders is less clear. Large scale prospective follow-up of such patients suggests that, following successful ES, there is a low rate of recurrent bile duct stones and a low risk of cholecystitis[60].

CONCLUSION

ERCP/EST should be adopted on a selective basis, *i.e.,* in patients with acute obstructive suppurative cholangitis, severe biliary pancreatitis, ampullary stone impaction or severe comorbidity. In a setting where all facilities are available, decision in the selection of the therapeutic option depends on the patients, the number and size of CBD stones, the anatomy of the cystic duct and common bile duct, the surgical history of patients and local expertise.

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MINIEVIEWS

Current status of surgical treatment for fulminant *clostridium difficile* colitis

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Abstract

Mortality rates attributable to fulminant *Clostridium difficile* (*C. difficile*) colitis remain high and are reported to be 38%-80%. Historically, the threshold for surgical intervention has been judged empirically because level I evidence to guide decision making is lacking. Studies of the surgical management of *C. difficile* infection have been limited by small sample size and the lack of a standard definition of fulminancy. Multiple small and medium-sized series have examined the surgical management of *C. difficile*. However, because of a lack of prospective, randomized studies, it has been difficult to identify the optimal point for surgical intervention in patients with severe fulminant *C. difficile* colitis. Our goal was to analyze the existing body of literature in an attempt to define host constellations, which would predict the development of the more aggressive form of this disease and hence justify an early or earlier surgical intervention. A Pubmed search was conducted using the keywords "fulminant", "clostridium difficile", "surgery", and "colitis". Reviews and meta-analyses proposing indications for surgical consultation or operative management in patients with *C. difficile* colitis were included. After analyzing current literature, we identified a number of parameters that are associated with unfavorable outcomes. The parameters include age greater than 65 years old, peritoneal signs on physical examination, abdominal distension, signs of end-organ failure, hypotension less than 90 mmHg systolic blood pressure, tachycardia greater than 100 bpm, vasopressor requirement, elevated WBC count of greater than at least 16 × 10^9/μL, serum lactate of greater than 2.2 mmol/L, and lastly, radiologic findings suggestive of pancolitis, ascites, megacolon, or colonic perforation. Even though fairly strong evidence exists in contemporary literature, we recommend use of these identified parameters with caution in clinical practice when it comes to the actual decision to treat certain patients more aggressively. The identified risk factors should be used to lower surgeons' threshold for operative treatment early in the course of the disease.

Key words: Fulminant Clostridium difficile; Colitis; Toxic megacolon; Total colectomy; Surgical management

Core tip: Studies of the surgical management of *Clostridium difficile* infection have been limited by small sample size and the lack of a standard definition of fulminancy. Our goal was to analyze the existing body of literature in an attempt to define host constellations which would predict the development of the more aggressive form of this disease and hence justify an early or earlier surgical intervention. We identified a number of parameters that are associated with unfavorable outcomes. The identified risk factors should be used to lower surgeons' threshold for operative treatment early in the course of the disease.

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INTRODUCTION

Clostridium difficile (*C. difficile*), a Gram-positive, spore-forming, anaerobic bacillus has surpassed methicillin-resistant *Staphylococcus aureus* as the most common healthcare-associated infection in the United States and is currently the number one cause of hospital-acquired diarrhea in the country. *Clostridium difficile* infection (CDI) is traditionally associated with risk factors including advanced age, antibiotic use (particularly fluoroquinolones), and acute care hospitalization[1]. National rates of CDI listed as either a primary or secondary diagnosis per ICD-9-CM codes on discharge reporting rose from 5.6/1000 in 2001 to 11.5/1000 in 2010[2]. The rise in incidence of CDI has been largely attributed to a hypervirulent strain of *C. difficile* designated BI/NAP1/027 which exhibits significant fluoroquinolone resistance, increased toxin production, polymorphisms in a toxin production down-regulatory gene, and the presence of a gene encoding an additional binary toxin[3]. While most cases of CDI respond well to oral antibiotic therapy, approximately 3%-10% of patients progress to a fulminant colitis involving concomitant systemic toxicity, organ dysfunction, or the need for vasoactive agents or ventilatory support[4-6]. The number of death certificates with enterocolitis due to *C. difficile* listed as a primary cause of death increased from 793 in 1999 to 7483 in 2008 according to preliminary data from US Vital records[2]. Management of patients with fulminant CDI includes surgical intervention in up to 20% cases and post-operative mortality remains high with various studies citing between 35% and 80%[4]. Traditional surgical management includes subtotal colectomy with margins of resection based on gross colonic appearance in conjunction with end ileostomy. As an alternative to colectomy, a recent study by Neal *et al*[5] has shown diverting loop ileostomy and colonic lavage to be a less morbid and viable option for surgical treatment[6]. Given the increasing incidence of CDI and the underlying imperative to reduce the morbidity and mortality suffered by patients, the aim of this article is to review and summarize information available to date regarding the best practice indications for surgical management of cases of fulminant CDI.

PUBMED SEARCH

A Pubmed search was conducted using the keywords "fulminant", "clostridium difficile", "surgery", and "colitis". Inclusion criteria for our study were restricted to all original articles, reviews and meta-analyses proposing specific indications or guidelines for surgical consultation and operative management in patients with CDI. Of the sixty-three resulting articles dating from 1989 to 2012, four were found to summarize or propose criteria for operative management of fulminant CDI that were relevant to our review.

PATHOGENESIS

CDI can manifest clinically along a wide spectrum spanning from mild diarrhea to fulminant and potentially fatal toxic colitis. It is widely accepted that the primary risk factor for the development of *C. difficile* Associated Disease (CDAD) is recent exposure to broad spectrum antibiotics, particularly ampicillin, amoxicillin, second and third generation cephalosporins, clindamycin, and fluoroquinolones[6-8]. The association of particular antibiotics with predisposition for the development of CDAD is influenced by the drug's dosage, frequency of use, route of administration, and most importantly the individual impact on the typical colonic normal flora[9,10]. It is understood that the disruption of normal colonic flora by antibiotic use inhibits the protective barrier to outside colonization generally provided by these organisms which allows *C. difficile* spores ingested from a contaminated environmental source to germinate and colonize the colon. While the rate of chronic intestinal carriage of *C. difficile* is reported to be low at 0%-3% among asymptomatic adults in the community, the hospital and long-term care facility environments that commonly surround infected individuals as well as the hands and instruments of health-care workers caring for them remain the major source of infection for susceptible individuals *via* environmentally-resistant spore transmission[8]. In contrast to the asymptomatic community carriage rate, the rate of colonization with *C. difficile* was reported to be as high as 20%-40% in hospitalized patients[6].

Colonization with *C. difficile* occurs by the fecal-oral route *via* ingestion of the organism's aforementioned acid-resistant spores. In individuals whose normal colonic flora are depleted by antibiotic use, *C. difficile* is able to vegetate, overgrow, and release its toxins A and B into the colonic lumen from which they are taken up by enterocytes and subsequently become responsible for colonic damage and local inflammation (colitis) *via* cellular cytotoxicity and activation of inflammatory cascades including nuclear factor κB (NF-κB), mitogen-activated protein (MAP) kinases, and COX-2 which lead to release of the proinflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and interleukin-8 (IL-8).

According to the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America Treatment Guidelines updated in 2010, confirmed CDI can be graded according to the following scale: Mild or moderate showing diarrhea, severe with WBC > $15 \times 10^9/\mu L$ or creatinine 1.5 × greater than baseline, and Severe Complicated characterized by ileus, "megacolon", hypotension requiring vasoactive agents, or shock with organ-failure and/or need for ventilatory assistance[6,11]. In those patients developing severe fulminant colitis, the effects of these cytokines are evident at a systemic level as manifested by complications of shock and hypotension. Clearly however, not all patients undergoing antimicrobial therapy develop CDI and from there only a small percentage of patients suffering from CDAD progress to the development of fulminant colitis. It is important then to understand the variables that can be relied upon to predict which patients are at higher risk

Table 1 Major risk factors for the development of *Clostridium difficile* infection and associated disease

Risk factor	Risk	Proposed mechanism	Notes
Age (> 70 yr[10])	CDI and Severe CDAD	Diminished efficacy of immune response with aging[7]	
Medical comorbidities[7]: multiple or those involving major organ systems	CDI and Severe CDAD	Diminished efficacy of immune response	Studies are conflicting with regards to which comorbid illnesses are specifically associated
Broad spectrum antibiotics	CDI	Alteration of normal colonic floral barrier to *C. difficile* colonization	The evidence supporting the association with multiple/prolonged antibiotic use is controversial as this often occurs in patients with recurrent or refractory disease who are already at risk of unfavorable outcomes
Use of 3-4 antibiotics concurrently or prolonged (> 4 wk) use[12]	Severe CDAD		
Suppression of gastric acid production, particularly by proton pump inhibitors[6,7]	CDI	Increased survival of the acid-labile vegetative form of *C. difficile* while passing through the stomach[6,7]	
Immunosuppression[6,13]	CDI and severe CDAD	Disruption of host ability to mount an effective response to both infection and toxemia	

C. difficile: *Clostridium difficile*; CDI: *Clostridium difficile* infection; CDAD: *Clostridium difficile* associated disease.

for developing these consequences of antibiotic use and resultant complications from *C. difficile* infection. These risk factors were summarized in several recent review articles and include the following presented in Table 1.

Other potential risk factors for which conflicting reports exist include steroids, anti-peristaltic medications, and gastrointestinal interventions including the various types of endoscopy (colonoscopy, sigmoidoscopy, esophagogastroduodenoscopy) and enteral feedings including nasogastric tube feedings[6,7]. Common proposed mechanisms for these factors include exposure to *C. difficile* spores *via* the hands and equipment of healthcare providers, alteration of colonic flora by gastrointestinal manipulation and motility changes, and alteration of gastrointestinal mucosa[6,7]. It can be understood then that the ultimate development of CDAD results from a confluence of factors including disruption of normal colonic flora barriers (typically by antibiotic use), combined with exposure to a high-risk contaminated hospital environment and then individually influenced by immune modifying factors including age, major medical comorbidities, and individual immune status.

RESULTS AND DISCUSSION

While the various medical treatment regimens for CDAD are reviewed elsewhere, the focus of this review will be to summarize indications for surgical consultation and management in patients with established severe, complicated CDAD. Current therapeutic guidelines for when to operate in patients with severe, complicated CDAD are poorly established and currently supported by primarily retrospective data. Overall, surgical treatment of patients with severe, complicated CDAD (traditionally with subtotal colectomy and end ileostomy) has been shown to improve morbidity and mortality compared to conservative management of patients (mortality of surgical treatment reported at 34%-80% *vs* mortality in non-surgical care of 50%-70%) with earlier diagnosis and treatment being shown to be beneficial in reducing mortality[4,6,14]. Several recent articles have compiled laboratory, radiologic, and clinical findings associated with the need for surgical consultation and operative management in patients with established severe CDI and their results are summarized in Table 2. These laboratory, radiologic, and clinical parameters represent the highest common factors from our source articles which were themselves drawn from a variety of disparate individual studies. The stated parameters were shown in our source material to demonstrate an association with unfavorable outcomes defined as need for emergent operative intervention and/or *C. difficile*-associated mortality. Table 3 represents these authors' efforts to clearly and centrally summarize the prototypical signs of fulminant *C. difficile* colitis and indications for surgical management common amongst our sources. The diversity present amongst the current body of review and retrospective data regarding the signs of fulminant *C. difficile* colitis as well as indications for surgical management underscores the importance of our efforts to compile a guideline of the highest common factors present amongst patients suffering from this disease in order to guide appropriate treatment.

According to a meta-analysis of outcomes following emergency surgery for *C. difficile* colitis by Bhangu *et al*[17] which encompasses the source material for our included reviews, the most statistically significant ($P < 0.001$) preoperative physiological indicators predictive of post-operative mortality are shock requiring the use of vasopressors, odds ratio (OR) = 3.80, preoperative intubation, OR = 6.31 , acute renal failure, OR = 5.68, and multi-system organ failure, OR = 5.56[16]. Of the signs of fulminant CDAD and indications for surgical management identified in Table 3, age > 75 years, OR = 2.29 and any elevation of white blood cell count above normal limits, OR = 8.01 were found to have a weaker association with post-operative mortality ($P < 0.01$)[16]. Our remaining sum-

Table 2 Previous studies analyzing surgical management of fulminant Clostridium difficile colitis

Article	Indications for surgical consultation and operative management	Notes
Carchman *et al*[6] Review	Indications for Surgical Consultation in Patients with Known or Suspected CDAD	Strength/quality of evidence, B-Ⅲ
	Ileus/significant abdominal distension	
	Admission to intensive care unit	
	Hypotension (+/- vasopressors)	
	Mental status changes	
	WBC counts ⩾ 35 × 10^9 /μL	
	Serum lactate ⩾ 2.2 mmol/L	
	Any evidence of end-organ failure	
	Age ⩾ 80 yr with severe CDAD criteria	
	Immunosuppression with severe CDAD criteria	Strength/quality of evidence, B-Ⅱ
	Indications for Operative Management in Patients with CDAD	
	Diagnosis of *C. difficile* colitis as determined by one of the following:	
	Positive toxin assay result	
	Endoscopic findings (pseudomembranes)	
	CT scan findings (pancolitis +/- ascites)	
	Plus any one of the following criteria:	
	Peritonitis	
	Perforation	
	Worsening abdominal distension/pain	
	Sepsis	
	Intubation	
	Vasopressor requirement	
	Mental status changes	
	Unexplained clinical deterioration	
	Renal failure	
	Lactate level > 5 mmol/L	
	WBC count ⩾ 50 × 10^9/μL	
	Abdominal compartment syndrome	
	Failure to improve with standard therapy within 5 d as determined by resolving symptoms and physical examination, resolving WBC per band count	
Osman *et al*[14] Original article	Summary of the clinical, laboratory, and radiologic features of fulminant *C. difficile* colitis	Severe, complicated CDAD synonymous with fulminant CDAD is considered to be indication for operative management by these authors.
	Clinical:	
	History of diarrhea following antibiotic use	
	Systemic toxicity	
	Pyrexia ⩾ 38 ℃	
	Tachycardia > 100 beats/min	
	Hypotension: BP < 90 mmHg	
	Abdominal signs of Peritonitis	
	Generalized abdominal pain	
	Tenderness	
	Abdominal distension	
	Rebound tenderness	
	Organ failure and requirement for vasopressor therapy	
	Laboratory and Radiologic:	
	Increasing leukocytosis > 16 × 10^9 /L	
	Lactate > 2.2 mmol/L	
	Hypoalbuminemia < 30 g/L	
	Radiologic evidence of toxic megacolon (abdominal X-ray or CT)	
	Free air under the diaphragm	
Butala *et al*[15] Review	Prognosticators for development of fulminant colitis	Strength/quality of evidence, B
	Age > 65 yr	
	Lactate between 2.2-4.9 mmol/L	
	WBC count > 16000/μL-surgery within 30 d	
	History of Inflammatory bowel disease	
	Treatment with intravenous immunoglobulin	
	Colitis associated with signs of organ dysfunction	
Girotra *et al*[16] Original article	Summary of red flags for development of fulminant *Clostridium difficile* colitis	
	Age > 70 yr	
	Presenting symptoms: Triad of abdominal pain, diarrhea, and distension	
	Signs: Tachycardia (heart rate > 100 beats/min), tachypnea (respiratory rate > 20 respirations/min),or hypotension (systolic BP < 90 mmHg)	
	Recent *C. difficile* infection	
	Use of antiperistaltic medications (narcotics or anticholinergics)	
	White blood cell count > 18000/mm^3	
	Radiology studies suggestive of megacolon or perforation	

C. difficile: *Clostridium difficile*; CDI: *Clostridium difficile* infection; CDAD: *Clostridium difficile* associated disease; WBC: White blood cell.

Table 3 Summary of indications for surgical management

Indicator	Carchman *et al*[6]	Bignardi *et al*[9]	Osman *et al*[14]	Butala *et al*[15]
Elevated WBC (count $\times 10^9$)	> 35		> 16	> 16
Serum lactate (mmol/L)	> 2.2 consult > 5 operate		> 2.2	2.2-4.9
Peritoneal signs on physical examination including generalized abdominal pain	Present	Present	Present	
Abdominal distension	Present	Present	Present	
End organ (renal, respiratory) failure/dysfunction	Present		Present	Present
Hypotension (mmHg)	Present	< 90 systolic	< 90 systolic	
Tachycardia (bpm)		> 100	> 100	
Vasopressor requirement	Yes		Yes	
Radiological findings of pancolitis, ascites, megacolon, or perforation	Present		Present	
Age (yr)	> 80	> 70		> 65

WBC: White blood cell.

mary indicators were either not included or unable to be incorporated into this meta-analysis and odds ratios and relative risks were therefore unavailable given the nature of the retrospective review data. It should be reiterated that within the literature, indications for operative management in cases of fulminant CDAD are unsupported by level I evidence and thus the current recommendations including our own summary are supported only by clinical experience.

In terms of treatment options, the Bhangu meta-analysis also found no significant difference in overall mortality following total colectomy and end ileostomy compared to segmental colonic resection, defunctioning stoma, or non-therapeutic laparotomy[16]. While the newer treatment technique of stool transplant is currently being studied to establish its role in management of *C. difficile* infection, studies to date have focused on those patients suffering from recurrent *C. difficile* infection and have not addressed the issue of a role for patients with fulminant CDAD. Further studies in this area are needed. Stool transplant theoretically seeks to re-establish an appropriate balance of colonic microflora in those patients with the classically disturbed bacterial populations found in CDI[18].

CONCLUSION

Mortality rates attributable to fulminant *C. difficile* colitis remain high and are reported to be 38%-80%. Historically, the threshold for surgical intervention has been judged empirically because level I evidence to guide decision making is lacking. Studies of the surgical management of *C. difficile* infection have been limited by small sample size and the lack of a standard definition of fulminancy. Multiple small and medium-sized series have examined the surgical management of CDC. However, because of a lack of prospective randomized studies, it has been difficult to identify the optimal point for surgical intervention in patients with severe fulminant CDC. Therefore, the data gathered from retrospective analyses are valuable in making this decision. It was our goal to analyze the existing body of literature in an attempt to define host constellations which would predict the development of the more aggressive form of this disease and hence justify an early or earlier surgical intervention. Multiple authors have suggested that total colectomy earlier in the course of the disease was associated with improved survival. However the exact timing of the surgical intervention remains one of the main challenges. It is crucial to identify preoperative patients' characteristics that can serve as indications for operative treatment. After analyzing current literature, we identified a number of highest common parameters that are associated with unfavorable outcomes defined as need for emergent operative intervention and/or *C. difficile*-associated mortality. The parameters include age greater than 65 years old, peritoneal signs on physical examination, abdominal distension, signs of end-organ failure, hypotension less than 90 mmHg systolic blood pressure, tachycardia greater than 100 bpm, vasopressor requirement, elevated WBC count of greater than at least $16 \times 10^9/\mu L$, serum lactate of greater than 2.2 mmol/L, and lastly, radiologic findings suggestive of pancolitis, ascites, megacolon, or colonic perforation. Pre-operative intubation, acute renal failure, multi-system organ failure, and shock requiring vasopressors have been shown to be the most statistically significant indicators of post-operative mortality for fulminant CDAD.

Even though fairly strong evidence exists in contemporary literature, we recommend caution with use of these parameters in clinical practice when it comes to the actual decision to treat certain patients more aggressively. The identified risk factors should be used to lower surgeons' threshold for operative treatment early in the course of the disease. Further studies designed in the prospective fashion might be necessary to identify the actual point when irreversible multi-system organ failure occurs during the disease progression in order to reduce potentially preventable fatalities.

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ORIGINAL ARTICLE

Caudal approach to pure laparoscopic posterior sectionectomy under the laparoscopy-specific view

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Abstract

AIM: To study our novel caudal approach laparoscopic posterior-sectionectomy with parenchymal transection prior to mobilization under laparoscopy-specific view.

METHODS: Points of the procedure are: (1) Patients are put in left lateral position and posterior sector is not mobilized; (2) Glissonian pedicle of the sector is encircled and clamped extra-hepatically and divided afterward during the transection; (3) Dissection of inferior vena cava (IVC) anterior wall behind the liver is started from caudal. Simultaneously, liver transection is performed to search right hepatic vein (RHV) from caudal; (4) Liver transection proceeds to the bifurcation of the vessels from caudal to cranial, exposing the surfaces of IVC and RHV. Since the remnant liver sinks down, the cutting surface is well-opend; and (5) After the completion of transection, dissection of the resected liver from retroperitoneum is easily performed using the gravity. This approach was performed for a 63 years old woman with liver metastasis close to RHV.

RESULTS: RHV exposure is required for R0 resection of the lesion. Although the cutting plane is horizontal in supine position and the gravity obstructs the exposure in the small subphrenic space, the use of specific characteristics of laparoscopic hepatectomy, such as the good vision for the dorsal part of the liver and IVC and facilitated dissection using the gravity with the patient positioning, made the complete RHV exposure during the liver transection easy to perform. The operation time was 341 min and operative blood loss was 1356 mL. Her postoperative hospital stay was uneventfull and she is well without any signs of recurrences 14 mo after surgery.

CONCLUSION: The new procedure is feasible and useful for the patients with tumors close to RHV and the need of the exposure of RHV.

Key words: Laparoscopic hepatectomy; Posterior sectionectomy; Caudal approach; Right hepatic vein; Mobilization of the liver; Left lateral position

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INTRODUCTION

In the 1990s and 2000s, when the procedure was first

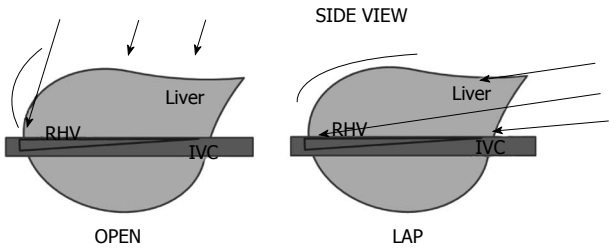

Figure 1 Differences in the view and approach between open and laparoscopic liver surgery. An illustration depicting the differences between the different surgery types. Since the view of operative field is in caudal-to-cranial direction in the laparoscopic procedure (LAP, right), not anterior-to-posterior (dorsal) as in the open procedure (OPEN, left), there is an advantage of good vision for the dorsal part of the liver and inferior vena cava. IVC: Inferior vena cava.

being used, laparoscopic hepatectomy mainly applied to local resections in antero-lateral segments of the liver[1-3]; major hepatectomies were often performed using hand-assisted[4-6] or hybrid[7-10] procedures. However, there are increasing reports for anatomical resections with intrahepatic[11-14] and extrahepatic[15] Glissonian approach and also of the right side liver[16-19]. The laparoscopic Glissonian approach, resection with the control of Glissonian pedicle for the area not dissecting vessels, facilitates anatomical liver resection. However, the boundary plane between the anterior and posterior sectors of the liver, the cutting plane of posterior sectionectomy, is horizontal in supine position. Although the cutting plane should be well opened in the small subphrenic space for successful laparoscopic posterior sectionectomy, gravity obstructs the exposure of the cutting plane in the position of patients. Also, one of the advantages of laparoscopic hepatic surgery is a clear view for the surgeon from caudal and dorsal directions (Figure 1). We have developed a new procedure that facilitates the exposure of the cutting plane in pure laparoscopic posterior sectionectomy. Herein we describe a caudal approach with parenchymal transection prior to mobilization of the liver under the laparoscopy-specific view in the left lateral position.

MATERIALS AND METHODS

A 63-year-old woman was admitted to our hospital for the surgical resection of a 1.5 cm metachronous colorectal liver metastasis in segment six near the right hepatic vein. This procedure was performed for the patient under the permission of the patient with informed consent. The patient was placed in a left lateral position, in which the cutting plane turns to be vertical. The posterior sector was not mobilized and was fixed to the retroperitoneum. The Glissonian pedicle of the posterior sector was encircled and clamped extra-hepatically. A cutting line of the liver surface was defined by ischemic color change. Dissection of inferior vena cava (IVC) anterior wall behind the liver parenchyma was started from caudal. Simultaneously, liver parenchymal transection was performed to search the right hepatic vein (RHV) branch to the main trunk from caudal edge. Liver transection proceeded, exposing the surface of IVC and RHV, to cranial direction.

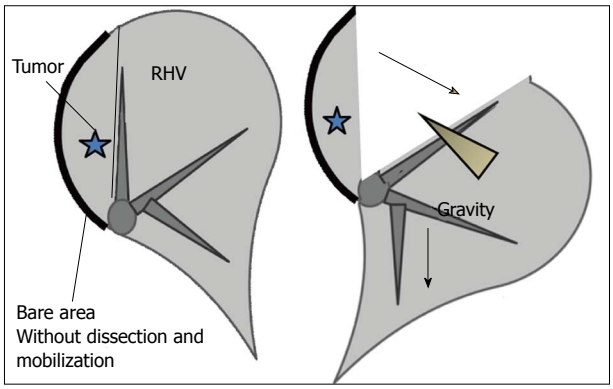

Figure 2 A schematic diagram of the caudal approach of pure laparoscopic posterior sectionectomy without mobilization under laparoscopy-specific view. Since the remnant liver sinks down and the resected liver is fixed to retroperitoneum, the cutting surface is well-opened and the exposure of right hepatic vein (RHV) is facilitated (arrow). Transection of the liver and exposure of the right hepatic vein, dividing its posterior branches one by one, proceed in one direction from caudal to cranial, simultaneously with the dissection of inferior vena cava anterior wall.

The Glissonian pedicle of the posterior sector was divided with a linear stapler during liver transection. Dissection of the IVC anterior wall and transection of the liver with the exposure of RHV simultaneously proceed to the bifurcation of RHV and IVC in one direction from caudal to cranial. Since the remnant liver sinks down and the resected liver was fixed to the retroperitoneum, the cutting surface was well opened and the exposure of RHV facilitated (Figure 2). Liver transection was completed at the point to reach to diaphragm. Dissection of the resected liver from the retroperitoneum was performed and the resected liver was removed. Dissection of the resected liver from the retroperitoneum was easily performed with the use of gravity.

RESULTS

A caudal approach to pure laparoscopic posterior sectionectomy was performed for a 63-year-old woman with a 1.5 cm metachronous colorectal liver metastasis in segment six near the right hepatic vein (Figure 3). She had undergone post-operative adjuvant chemotherapy after open colorectal surgery and her liver had severe fatty change. Although good surgical margins would be achieved with a right hepatectomy, the much smaller liver remnant could cause postoperative liver failure. Therefore, posterior sectionectomy was applied to her lesion. However, since the lesion was close to the RHV, RHV exposure was required for R0 resection of the lesion. Complete RHV exposure was performed during the liver transection, the operation time was 341 min, and operative blood loss was 1356 mL (Figure 4). Her postoperative hospital stay was uneventful and she is well without any signs of recurrences one year and two months after surgery.

DISCUSSION

Most reports of laparoscopic anatomical hepatectomy

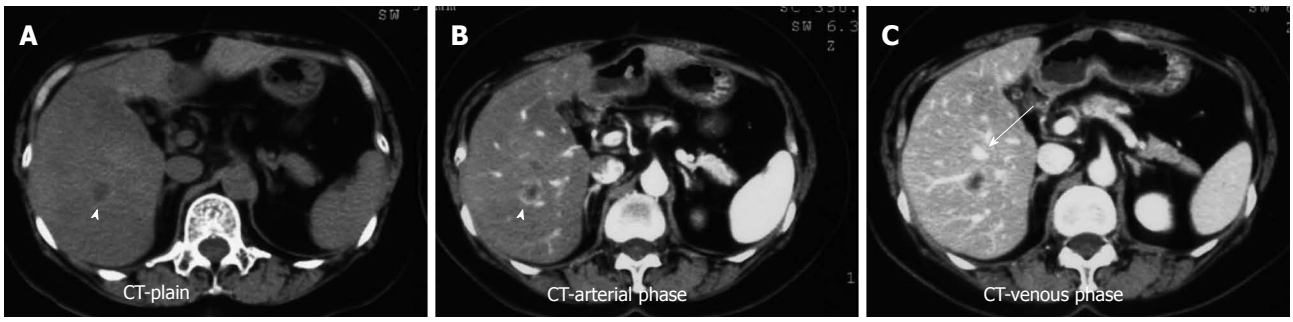

Figure 3 Computed tomography scan findings. A 63-year-old woman with a 1.5 cm metachronous colorectal liver metastasis in the segment 6 close to the right hepatic vein underwent adjuvant chemotherapy after open colorectal surgery and her liver had severe fatty change. Therefore, posterior sectionectomy was applied to her lesion, not right hepatectomy. However, since the lesion is close to the right hepatic vein (RHV), RHV exposure was required for R0 resection.

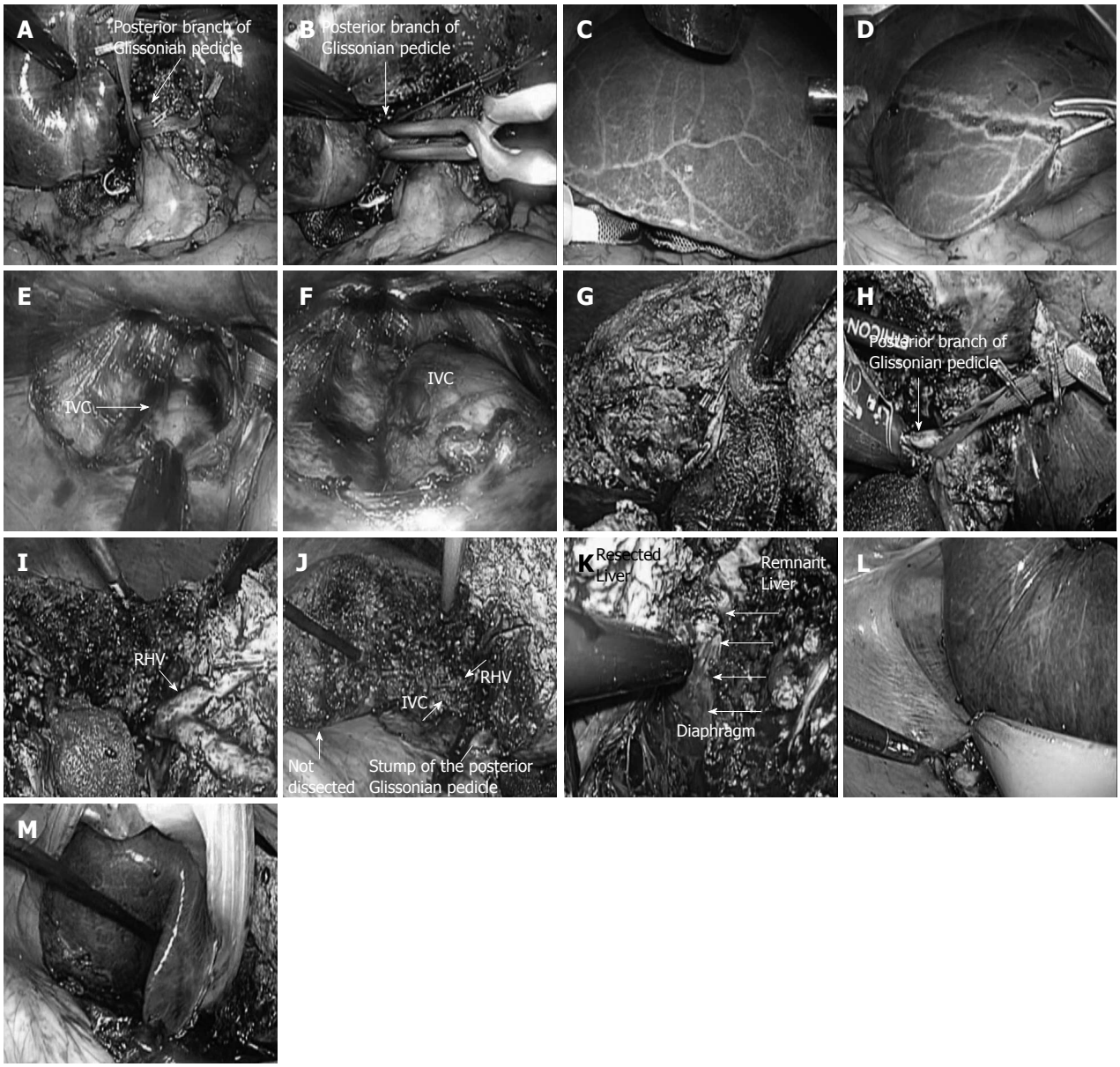

Figure 4 Intraoperative findings of the case. A-D: Part Ⅰ; E-H: Part Ⅱ; I, J: Part Ⅲ; K-M: Part Ⅳ. After cholecystectomy, Glissonian pedicle of the right lobe and posterior sector was encircled (A). The posterior pedicle was clamped (B), allowing the resection line to be visualized as; an ischemic demarcation line (C, D). E, F: The anterior wall of the inferior vena cava was dissected behind the liver; G: Liver parenchyma was transected on the demarcation line, and the peripheral part of the right hepatic vein was exposed, clipped, and divided; H: After the cutting line reached the level of Glissonian, the posterior pedicle was divided with a linear stapler. Transection of the liver and the exposure of the right hepatic vein (RHV) by dividing its posterior branched one-by-one proceeded in one direction from caudal to

cranial, simultaneously with the dissection of the inferior vena cava anterior wall. Since remnants of the liver sunk down and the resected liver was fixed to the retroperitoneum, the cutting surface was well opened and the exposure of the RHV was facilitated. K: Following completion of the liver parenchymal transection; L: Dissection of the resected liver from retroperitoneum was performed; M: The resected liver was removed. Dissection of the resected liver from retroperitoneum was easily performed with the use of gravity. The operation time was 341 min and operative blood loss was 1356 mL. The patient's postoperative hospital stay was uneventful and she was well without any signs of recurrences one year and two months after surgery.

of the right lobe of the liver describe mobilization of the right liver as the first step in the procedure[20-23]. Although Cheng *et al*[24] reported performing a posterior approach to laparoscopic anatomic resection hepatocellular carcinoma at segment seven; they also described the traditional mobilization of the right liver. We had experienced the challenge of exposing the cutting plane in pure laparoscopic posterior sectionectomy due to the direction of cutting plane, especially when exposure of the right hepatic vein was necessary. The cutting plane is horizontal the patient is in a supine position and gravity obstructs the exposure of the cutting plane in the small subphrenic space during laparoscopic surgery.

Here we presented a novel procedure whereby we considered the use of specific characteristics of laparoscopic hepatectomy. These characteristics included a clear view of the dorsal part of the liver and IVC created by a caudal-to-cranial operative field as opposed to the traditional anterior-to-posterior (dorsal) (Figure 1), and facilitated dissection using gravity and unique patient positioning[25]. The operation time of this case was 341 min including the dissection of adhesion after open colorectal surgery and short and mid-term prognosis; an acceptable time for such a procedure. Although, the operative blood loss of 1356 mL is larger than some cases[16,20,21,23,24], the total exposure of right hepatic vein main trunk may have influenced this in part, and this number should be decreased in the future with more experience. In conclusion, this new procedure, "caudal approach pure laparoscopic posterior sectionectomy with parenchymal transaction prior to mobilization of the liver under the laparoscopy-specific view", is feasible and useful for patients with tumors close to the RHV and when exposure of the RHV is necessary.

COMMENTS

Background

From the first report of laparoscopic hepatectomy in 1992, there are increasing experience worldwide and also of anatomical resections. However, the procedures and techniques are far from standardization and there are still tries to innovate the procedure.

Research frontiers

The cutting plane of posterior sectionectomy is horizontal in supine position. Although the cutting plane should be well-opened in the small subphrenic space for the successful laparoscopic posterior sectionectomy, the gravity obstructs the exposure of the cutting plane in the position. On the other hand, one of the advantages of laparoscopic hepatic surgery is a good vision from caudal and dorsal direction.

Innovations and breakthroughs

Here is figured out the novel procedure, caudal approach with parenchymal transection prior to mobilization of the liver under the laparoscopy-specific view in the left lateral position, which facilitates the exposure of cutting plane in laparoscopic posterior sectionectomy.

Applications

This reported new procedure is a feasible and useful innovative procedure for the patients with tumors close to right hepatic vein (RHV) and the need of the exposure of RHV.

Peer review

It is an interesting case report on a technically demanded new method of laparoscopic posterior approach for liver resection with nice operative views.

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BRIEF ARTICLE

Impact of medical and surgical intervention on survival in patients with cholangiocarcinoma

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Abstract

AIM: To examine surgical and medical outcomes for patients with cholangiocarcinoma using a population-based cancer registry.

METHODS: Using the California Cancer Registry's Cancer Surveillance Program, patients with intrahepatic cholangiocarcinoma treated in Los Angeles County from 1988 to 2006 were identified and evaluated for clinical and pathologic factors and therapies received (surgery, radiation, and chemotherapy). The surgical cohort was further categorized into three treatment groups: patients who received adjuvant chemotherapy, adjuvant chemoradiation, or underwent surgery alone (no chemotherapy or radiation administered). Survival was assessed by Kaplan-Meier method; and Cox proportional hazard modeling was used in multivariate analysis.

RESULTS: Of 825 patients, 60.2% received no treatment. Of the remaining 328 patients, 18.5% chemotherapy only, 7.4% chemoradiation, and 13.8% underwent surgery. More male patients underwent surgical resection (P = 0.004). Surgical patients were younger than the patients receiving chemotherapy or chemoradiation (P < 0.001). Of the surgical cohort (n = 114), 60.5% underwent surgery alone while 39.5% underwent surgery plus adjuvant therapy (chemotherapy, n = 20; chemoradiation, n = 21) (P < 0.001). Median survival for all patients in the study was 6.6 mo. Median survival was highest for patients who underwent surgery (23 mo), whereas both chemotherapy (9 mo) and chemoradiation (8 mo) alone were each less effective (P < 0.001). By multivariate analysis, extent of disease, receipt of surgery, and administration of chemotherapy (with/without surgery) were independent predictors of overall survival.

CONCLUSION: This study demonstrates that surgery is a critical treatment modality. Multimodality treatment has yet to be standardized, but play a role in optimal therapy for cholangiocarcinoma.

Key words: Cholangiocarcinoma; Chemotherapy; Surgery; Survival; Therapies

Core tip: Cholangiocarcinoma is an aggressive biliary tract cancer with few treatment options. Surgical resection has been the only available curative-intent treatment in early disease. This study demonstrates that multimodality therapy may provide the best improvement in survival.

M, Singh G, Kim J. Impact of medical and surgical intervention on survival in patients with cholangiocarcinoma. *World J Gastrointest Surg* 2013; 5(6): 178-186 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i6/178.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i6.178

INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary tract that has two major anatomic subtypes: intrahepatic and ductal/perihilar[1]. It is the 2nd most common primary hepatic malignancy worldwide and afflicts nearly 2000-3000 people in the United States annually[2,3]. Partly due to improved diagnostic measures as well as a change in diagnosis coding, the incidence of CCA in the United States has increased by nearly 165% over the past several decades[4-7]. In fact, CCA was often coded as hepatocellular carcinoma until the late 1980s; therefore, the true incidence of cholangiocarcinoma prior to that time remains unknown[8]. Despite improvements in diagnostic techniques, many patients are asymptomatic until the disease has become advanced. Symptomatic patients commonly present with jaundice, but non-specific symptoms (*e.g.*, weight loss, loss of appetite, and abdominal pain) are also frequently reported[9-12].

Surgical resection has long been considered the mainstay of curative treatment for CCA. Unfortunately, most patients with CCA present with advanced unresectable disease. Even when patients are eligible for surgical intervention, overall survival is poor, with 5-year survival rates of 20%-43%[13]. For patients who are eligible for systemic therapy for unresectable disease or adjuvant therapy, the current recommended therapy of gemcitabine and cisplatin provides a very minimal increase in median overall survival (OS) to 11.7 mo[14,15]. The lack of effective therapies has led to the frequent administration of systemic agents in non-standardized regimens[16].

Lack of better standardized therapeutic regimens and prior inconsistencies in coding of CCA have made it difficult to assess multimodality regimens for this disease. The absence of data from prospective randomized trials specifically limited to CCA precludes appropriate clinical practice guidelines[17]. In this investigation, we sought to examine common CCA therapies (*i.e.*, surgical resection, chemotherapy, and radiation therapy) to assess treatment outcomes and to determine which therapeutic regimen(s) have offered improvements in overall survival in a large population based cohort.

MATERIALS AND METHODS

Cancer surveillance program for Los Angeles County

After obtaining City of Hope Institutional Review Board approval, we used the California Cancer Registry's Cancer Surveillance Program (CSP) to identify patients diagnosed with cholangiocarcinoma. CSP for Los Angeles County is a population-based cancer registry that includes data on nearly all cancer diagnoses. The collected data is focused on cancer diagnosis and treatment with the stated CSP aim of improving cancer care in the State of California. This focus on comprehensive data collection for cancer therapy (*i.e.*, chemotherapy, radiotherapy, and curative-intent surgery) distinguishes CSP from other regional and national databases.

CSP reporting for CCA location, staging, and differentiation is based on the International Classification of Diseases for Oncology. After restricting our analysis to liver (C22.0) and intrahepatic bile duct (C22.1) topologies, we selected only cases with histology codes 8160 (bile duct adenocarcinoma) and 8162 (Klatskins tumor). CSP extent of disease was reported as localized, regional [extension only; nodes only; extension and nodes; not otherwise specified (NOS)], distant or unknown. Tumor grade was categorized by CSP as well, moderate, poor, undifferentiated, or unknown. Chemotherapy was classified as negative (none; recommended, not given; or refused) or positive (single agent, multiple agent, or NOS). Radiation data was also classified as negative (none) or positive (beam, implants, isotopes, combination, or NOS). All patients who underwent curative-intent surgical therapy (defined by CSP codes 10, 13, 16, 20-80) were included in the surgery group. Patients who did not have surgery or who underwent non-curative surgery (defined by CSP codes 11, 12, 15, 17 and 90) were included in the non-surgical group.

Statistical analysis

Inclusion criteria consisted of patients diagnosed with CCA from 1988 to 2006 who survived 30 d or longer post-diagnosis that received some form of treatment for their disease. Patients were only included in whom complete survival data was available. Treatment groups were defined as chemotherapy alone, chemoradiation, and surgery. The surgical cohort was then further categorized into three treatment groups: patients who received adjuvant chemotherapy, adjuvant chemoradiation, or underwent surgery alone (no chemotherapy or radiation administered). All quantitative data were expressed as the median and range, unless otherwise indicated. Clinical and pathologic characteristics were compared across the different treatment arms by chi-square analyses.

Cox-proportional hazards modeling was used to evaluate the role of chemoradiation and other variables on overall survival as represented by hazard ratios (HR) with 95% confidence intervals (CI). Variables included in the univariate and multivariate analyses were age, sex, race/ethnicity, socioeconomic status, tumor location, tumor size, T-stage, N-stage, M-stage, tumor grade, American Joint Commission on Cancer 7th edition stage, lymph node number, chemotherapy administration, and radiation administration. Overall survival for the treatment arms was calculated by the Kaplan-Meier method and differences in survival were compared by the log-rank test. Two-sided P-values < 0.05 were considered to be statistically significant. All statistical analyses were completed using SAS software (SAS institute Inc. Cary,

Table 1 Definition of study groups *n* (%)

Total study population	*n* = 825
No treatment	497 (60.2)
Treatment groups	
Chemotherapy	153 (18.5)
Chemoradiation	61 (7.4)
Surgery	114 (13.8)
Surgical subgroups	
Surgery alone	69 (60.5)
Adjuvant radiation	4 (3.5)
Adjuvant chemotherapy	20 (17.5)
Adjuvant chemoradiation	21 (18.4)

The 825 patients included in this study were categorized by type of treatment received. Treatment groups were divided into chemotherapy, chemoradiation, and surgical groups. The surgical group was then subdivided into surgery alone, surgery with adjuvant chemotherapy, and surgery with adjuvant chemoradiation.

NC, United States).

RESULTS

Patient characteristics

There were 825 patients identified with CCA. Of this group, 60.2% (n = 497) did not receive treatment, 18.5% (n = 153) received chemotherapy only, 7.4% (n = 61) received chemoradiation, and 13.8% (n = 114) underwent curative-intent surgery. Of the patients who underwent surgery, 8.4% (n = 69) received surgery only, and 5.5% (n = 45) received surgery plus additional adjuvant treatment (Table 1). Of these, 20 (17.5%) surgical patients received adjuvant chemotherapy, 21 (18.4%) underwent adjuvant chemoradiation, and 4 (3.5%) underwent adjuvant radiation. Given the small sample size of the adjuvant radiation group, this group was excluded from our analysis.

Comparison of treatment arms

Of the three treatment groups (chemotherapy, chemoradiation, and surgical groups), the characteristics that were different between the surgical patients and the non-surgical patients were age, gender, tumor location, and stage (Table 2). Patients in the surgery cohort were more often male, white, and young. Not surprisingly, there were expected differences in extent of disease and type of disease between the groups, with more early stage intrahepatic CCA disease in the surgical cohort. Additionally, over one-half of the chemotherapy group (n = 68; 53.1%) had metastatic disease at presentation, compared to 12.7% (n = 14) of surgical patients.

Comparison of surgical groups

The characteristics found to be significantly different between surgical patients who received surgery alone and those who underwent surgery and additional adjuvant therapy were age, gender, tumor location, and stage (Table 3). Patients in the adjuvant chemoradiation group were male and much younger in age compared to the other groups. Whereas 80.9% of the adjuvant chemoradiation group were < 65 years old, more patients (39.1%) were older than 65 in the surgery alone subset.

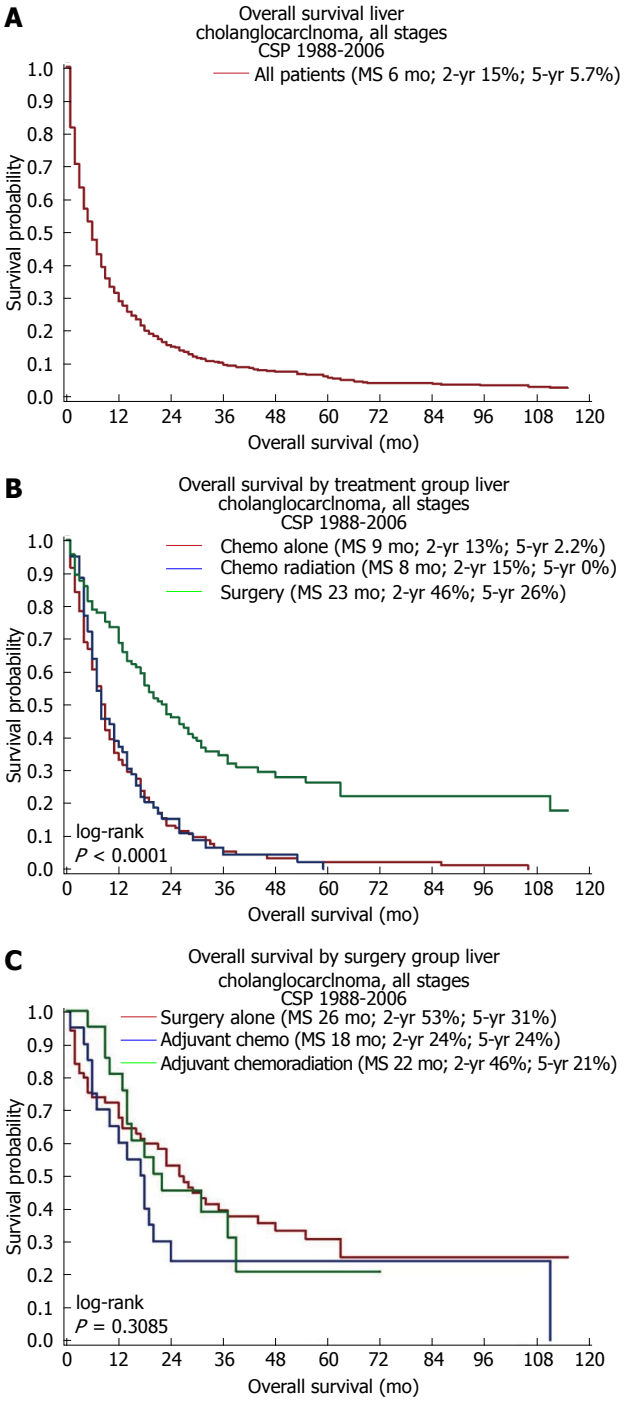

Figure 1 Kaplan-Meier survival of treatment groups. A: Median survival (MS) for all patients in overall cohort was 6 mo; B: MS was highest for surgical patients, with an MS of 23 mo, compared to 9 mo and 8 mo for chemotherapy (chemo) and chemoradiation groups, respectively; C: Surgery alone patients had the highest survival (MS 28 mo), with MS of 18 and 22 mo for the adjuvant chemotherapy and adjuvant chemoradiation groups, respectively. CSP: Cancer Surveillance Program.

Survival according to treatment group

Median survival (MS) for all patients in the overall cohort was 6 mo, with a 5-year survival of 5.7% (Figure 1A).

Table 2 Characteristics of patient and treatment groups *n* (%)

	Chemo only (*n* = 153)	Chemoradiation (*n* = 61)	Surgery (*n* = 114)	*P* value
Age group (yr)				< 0.0001
18-49	29 (19.0)	10 (16.4)	29 (25.4)	
50-64	62 (40.5)	20 (32.8)	44 (38.6)	
65-79	55 (35.9)	31 (50.8)	39 (34.2)	
⩾ 80	7 (4.6)	0 (0.0)	2 (1.8)	
Sex				0.000
Men	57 (37.3)	36 (59.0)	69 (60.5)	
Women	96 (62.7)	25 (41.0)	45 (39.5)	
Race				0.002
Non-hispanic white	74 (48.4)	26 (42.6)	53 (46.5)	
Black	9 (5.9)	7 (11.5)	4 (3.5)	
Hispanic white	37 (24.2)	8 (13.1)	29 (25.4)	
Other	33 (21.6)	20 (32.8)	28 (24.6)	
Socioeconomic status				0.046
Highest	38 (24.8)	18 (29.5)	33 (28.9)	
Middle	96 (62.7)	35 (57.4)	65 (57.0)	
Lowest	19 (12.4)	8 (13.1)	16 (14.0)	
Tumor				0.000
Liver	21 (13.7)	3 (4.9)	22 (19.3)	
Location				
Bile duct	132 (86.3)	58 (95.1)	92 (80.7)	
Grade				0.685
Well differentiated	12 (19.4)	4 (17.4)	19 (21.1)	
Moderately differentiated	20 (32.3)	5 (21.7)	33 (36.7)	
Poorly differentiated	30 (48.4)	14 (60.9)	38 (42.2)	
Tumor size (cm)				0.060
⩽ 5	10 (27.8)	7 (58.3)	34 (50.0)	
> 5	26 (72.2)	5 (41.7)	34 (50.0)	
Summary				0.000
Local	17 (15.3)	9 (21.4)	35 (36.1)	
Stage				
Regional	29 (26.1)	16 (38.1)	36 (37.1)	
T stage				0.001
T1	23 (24.5)	8 (19.5)	37 (37.4)	
T2	2 (2.1)	3 (7.3)	14 (14.1)	
T3	19 (20.2)	10 (24.4)	18 (18.2)	
T4	50 (53.2)	20 (48.8)	30 (30.3)	
N stage				0.211
N0	53 (72.6)	22 (68.8)	71 (79.8)	
N1	20 (27.4)	10 (31.3)	18 (20.2)	
M stage				< 0.0001
M0	60 (46.9)	32 (68.1)	96 (87.3)	
M1	68 (53.1)	15 (31.9)	14 (12.7)	
AJCC7 stage				< 0.0001
Ⅰ	13 (14.4)	2 (6.3)	34 (36.6)	
Ⅱ	1 (1.1)	2 (6.3)	9 (9.7)	
Ⅲ	18 (11.8)	7 (11.5)	23 (20.2)	
Ⅳ	58 (64.4)	21 (65.6)	27 (29.1)	
Chemotherapy	153 (100.0)	61 (100.0)	41 (36.0)	< 0.0001
Radiation	0 (0.0)	61 (100.0)	25 (21.9)	< 0.0001

In general, characteristics that were different between the surgical patients and the non-surgical patients were age, gender, tumor location, and stage. Patients in the surgery cohort were more often male, white, and young. chemo: Chemotherapy; AJCC: American Joint Committee on Cancer.

When comparing outcomes by treatment groups, MS was highest for surgical patients, with an MS of 23 mo (Figure 1B) compared to 9 and 8 mo for chemotherapy and chemoradiation groups, respectively ($P < 0.0001$). When evaluating the surgical subgroups, surgery alone patients had the highest survival (MS 28 mo) (Figure 1C), with MS of 18 and 22 mo for the adjuvant chemotherapy and adjuvant chemoradiation groups, respectively ($P = 0.3085$). Of note, patients who did not receive treatment had an MS of 3.0 mo.

Univariate and multivariate analysis of patient cohort

A Cox regression analysis was performed to identify predictors of survival for CCA (Table 4). On univariate analysis, older age, black race, lower socioeconomic status, undifferentiated tumors, and T4 tumors were significantly associated with poorer survival. Upon multivariate analysis, older age (*i.e.*, above 80 years of age), advanced disease

Table 3 Characteristics of surgical groups *n* (%)

	Surgery alone (*n* = 69)	Adjuvant chemotherapy (*n* = 20)	Adjuvant chemoradiation (*n* = 21)	*P* value
Age group (yr)				< 0.0001
18-49	13 (18.8)	6 (30.0)	10 (47.6)	
50-64	29 (42.0)	6 (30.0)	7 (33.3)	
65-79	25 (36.2)	8 (40.0)	4 (19.0)	
≥ 80	2 (2.9)	0 (0.0)	0 (0.0)	
Sex				0.018
Men	41 (59.4)	13 (65.0)	14 (66.7)	
Women	28 (40.6)	7 (35.0)	7 (33.3)	
Race				0.497
Non-hispanic white	33 (47.8)	11 (55.0)	9 (42.9)	
Black	2 (2.9)	0 (0.0)	2 (9.5)	
Hispanic white	20 (29)	3 (15.0)	5 (23.8)	
Other	14 (20.3)	6 (30.0)	5 (23.8)	
Socioeconomic status				0.603
Highest	18 (26.1)	7 (35.0)	7 (33.3)	
Middle	41 (59.4)	9 (45.0)	12 (57.1)	
Lowest	10 (14.5)	4 (20.0)	2 (9.5)	
Tumor				0.000
Liver	17 (24.6)	3 (15.0)	2 (9.5)	
Location				
Bile duct	52 (75.4)	17 (85.0)	19 (90.5)	
Grade				0.684
Well differentiated	13 (23.6)	3 (20.0)	3 (16.7)	
Moderately differentiated	21 (38.2)	4 (26.7)	6 (33.3)	
Poorly differentiated	21 (38.1)	8 (53.3)	9 (50.0)	
Tumor size (cm)				0.825
≤ 5	24 (54.5)	3 (25.0)	6 (60.0)	
> 5	20 (45.5)	9 (75.0)	4 (40.0)	
Summary				0.016
Local	23 (38.3)	3 (20.0)	7 (38.9)	
Stage				
Regional	24 (40.0)	5 (33.3)	6 (33.3)	
Distant	13 (21.7)	7 (46.7)	5 (27.8)	
T stage				0.071
T1	24 (40.0)	5 (29.4)	7 (36.8)	
T2	9 (15.0)	3 (17.6)	2 (10.5)	
T3	12 (20.0)	3 (17.6)	3 (15.8)	
T4	15 (25.0)	6 (35.3)	7 (36.8)	
N stage				0.396
N0	44 (83.0)	10 (62.5)	14 (82.4)	
N1	9 (17.0)	6 (37.5)	3 (17.6)	
AJCC7 stage				< 0.0001
Ⅰ	22 (40.0)	5 (29.4)	6 (33.3)	
Ⅱ	7 (12.7)	1 (5.9)	1 (5.6)	
Ⅲ	13 (23.6)	3 (17.7)	5 (27.8)	
Ⅳ	13 (23.7)	8 (47.0)	6 (33.4)	

Characteristics found to be significantly different between surgical patients were age, gender, tumor location, and stage. Patients in the adjuvant chemoradiation group were male and much younger in age compared to the other groups. AJCC: American Joint Committee on Cancer.

stage, poorly differentiated or undifferentiated tumors, and lymph node involvement were independent predictors of poorer survival in all treatment groups. Our analysis demonstrated a significant improvement in survival associated with surgical resection (HR = 0.44, 95%CI: 0.34-0.59, $P < 0.0001$) and receipt of chemotherapy (HR = 0.70, 95%CI: 0.59-0.83 $P = 0.001$). In contrast, receipt of radiation therapy was not associated with improved survival.

DISCUSSION

Surgery has been the traditional mainstay of curative-intent therapy for patients with early stage, resectable CCA. Such practice has been largely established on the backbone of single institution reports touting the benefits of surgical resection[10,11,18]. Our current population-based investigation supports this growing body of evidence, also highlighting the superior outcomes when patients with CCA are eligible for and undergo surgical resection. For those surgical patients, favorable prognostic factors include absence of tumor at the resection margins, elevated serum CA19-9 levels, solitary lesion, absence of lymph node involvement, presence of well-differentiated adenocarcinoma, and absence of vascular invasion[19-21]. Nevertheless, the relatively low survival even with appro-

Table 4 Univariate and stepwise analysis for overall survival *n* (%)

		Univariate hazard ratio (95%CI)	Stepwise hazard ratio (95%CI)
Age[1] (yr)			
18-49	107 (13.0)	1.00 (reference)	1.00 (reference)
50-64	230 (27.9)	1.43 (1.11-1.85)	1.64 (1.27-2.13)
65-79	327 (39.6)	1.40 (1.10-1.78)	1.47 (1.15-1.89)
≥ 80	161 (19.5)	2.19 (1.68-2.86)	1.85 (1.40-2.46)
Sex[1]			
Men	390 (47.3)	1.00 (reference)	
Women	435 (52.7)	1.02 (0.88-1.18)	
Race			
Non-hispanic white	373 (45.2)	1.00 (reference)	
Ethnicity[1]			
Black	64 (7.8)	1.50 (1.14-1.97)	
Hispanic white	215 (26.1)	1.04 (0.87-1.24)	
Other	170 (20.6)	1.00 (0.82-1.21)	
Socioeconomic status[1]			
Highest	184 (22.3)	1.00 (reference)	1.00 (reference)
Middle	497 (60.2)	1.25 (1.04-1.49)	1.18 (0.98-1.41)
Lowest	144 (17.5)	1.61 (1.28-2.03)	1.52 (1.20-1.92)
Grade			
Well differentiated	52 (6.3)	1.00 (reference)	
Moderately differentiated	99 (12.0)	1.05 (0.72-1.53)	
Poorly differentiated	135 (16.4)	1.61 (1.13-2.29)	
Undifferentiated	8 (1.0)	2.96 (1.38-6.32)	
Unknown	531 (64.4)	1.71 (1.24-2.35)	
Tumor size (cm)			
≤ 5	95 (11.5)	1.00 (reference)	
> 5	94 (11.4)	1.03 (0.76-1.39)	
T Stage			
T1	150 (18.2)	1.00 (reference)	
T2	28 (3.4)	0.91 (0.57-1.47)	
T3a	64 (7.8)	1.10 (0.80-1.51)	
T3b	13 (1.6)	1.37 (0.72-2.63)	
T4	198 (24)	2.23 (1.76-2.83)	
TX	372 (45.1)	1.85 (1.50-2.29)	
N stage			
N0	278 (33.7)	1.00 (reference)	
N1	77 (9.3)	1.62 (1.24-2.12)	
NX	470 (57)	1.76 (1.50-2.07)	
AJCC7 group[1]			
Ⅰ	93 (11.3)	1.00 (reference)	1.00 (reference)
Ⅱ	15 (1.8)	0.80 (0.41-1.56)	1.07 (0.54-2.09)
Ⅲ	79 (9.6)	1.37 (0.98-1.91)	1.31 (0.93-1.84)
Ⅳ	204 (24.7)	2.81 (2.11-3.72)	2.56 (1.90-3.44)
Unknown	434 (52.6)	2.23 (1.72-2.89)	1.52 (1.16-2.00)
Treatment groups			
Chemo alone	153 (18.5)	1.00 (reference)	
Chemoradiation	61 (7.4)	0.98 (0.72-1.34)	
Surgery	114 (13.8)	0.44 (0.34-0.59)	
None	497 (60.2)	1.50 (1.24-1.81)	
Surgery groups			
Surgery Alone	69 (8.4)	1.00 (reference)	
Adjuvant chemo	20 (2.4)	1.44 (0.82-2.55)	
Adjuvant chemoradiation	21 (2.5)	1.02 (0.56-1.85)	
Adjuvant radiation	4 (0.5)	1.53 (0.55-4.26)	
No surgery	711 (86.2)	3.19 (2.35-4.33)	
Surgery[1]			
No	711 (86.2)	1.00 (reference)	1.00 (reference)
Yes	114 (13.7)	0.34 (0.27-0.43)	0.42 (0.32-0.54)
Chemo[1]			
No	570 (69.1)	1.00 (reference)	1.00 (reference)
Yes	255 (30.9)	0.73 (0.62-0.85)	0.70 (0.59-0.83)
Radiation[1]			
No	707 (85.7)	1.00 (reference)	
Yes	118 (14.3)	0.74 (0.60-0.90)	

[1]Included in step-wise model. On univariate analysis, older age, black race, lower socioeconomic status, undifferentiated tumors, and T4 tumors were significantly associated with poorer survival. Upon stepwise analysis, older age (> 80 year), advanced disease stage, poorly differentiated or undifferentiated

tumors, and lymph node involvement were independent predictors of poorer survival in all treatment groups. There was a significant improvement in survival associated with surgical resection and receipt of chemotherapy. chemo: Chemotherapy; AJCC: American Joint Committee on Cancer.

priate surgical intervention underscores the pressing need for multidisciplinary approach to the management of patients with CCA.

Treatment guidelines suggest that systemic chemotherapy should be the treatment of choice for patients with good performance status who have extensive disease not amenable to surgical resection. In the setting of unresectable or metastatic CCA, the aims of treatment should include prolongation of life but also maintenance of quality of life. Prior studies have reported rates of OS ranging between 5.6 and 14 mo[22-28]. Patients that did not receive treatment in our study had an MS of 3 mo, whereas patients who received chemotherapy or chemoradiation had MS of 8 and 9 mo respectively. The identification of chemotherapy in our study as an independent variable for survival is consistent with prior reports.

There is an inherent limitation with the CSP database, in that the exact chemotherapy regimen and its timing and period of administration are not available for analysis. A phase Ⅲ trial recently demonstrated the benefit of combined gemcitabine and cisplatin over gemcitabine alone with improved OS and progression-free survival[15]. Although the study included all hepatobiliary cancers, including gallbladder and ampullary cancers[15], a benefit to combination chemotherapy was seen in the CCA subgroup. The National Comprehensive Cancer Network (NCCN) now recommends the combination therapy of gemcitabine and cisplatin as the standard treatment for unresectable CCA based on the results of the randomized phase Ⅲ trial ABC-02 and retrospective and pooled data[15, 29-31].

The NCCN also provides guidelines, albeit non-specific, on the use of adjuvant therapies in the management of patients with resectable CCA disease. Depending on the completeness of surgical resection, adjuvant therapies in clinical trial settings or case-by-case individualized therapies are recommended[31]. The lack of definitive recommendations for adjuvant treatment in patients with curatively resected cholangiocarcinoma is based on the absence of level 1 evidence for such conditions. In a recent systematic review and meta-analysis of adjuvant chemotherapy, radiation, or chemoradiation in 6712 patients with resected biliary tract cancer, a significant benefit in OS was observed in favor of any adjuvant treatment in CCA patients with either lymph node positivity or with positive resection margins[32]. In our study, we did not see any positive impact to chemotherapy or chemoradiation in patients with resected cholangiocarcinoma. The reasons for the lack of adjuvant treatment benefits may be related to a true lack of efficacy in adjuvant therapies for patients with CCA. This patient population is typically underpowered to identify a benefit; or patient selection bias may exist wherein patients with favorable T1-T2N0 tumors are selected for surgery only groups.

Radiation therapy must also be considered in the multimodal management of patients with CCA. Although prior small cohort studies have shown disappointing results for radiation alone, chemoradiation therapies in select patients should continue to be investigated in future trials. Nevertheless, the addition of radiation to chemotherapy regimens did not improve survival in our study. Nonsurgical patients had similar MS after receiving either chemotherapy alone (9 mo) or chemoradiation (8 mo). This is consistent with a prospective study by Pitt *et al*[33], who reported that radiation did not provide a survival advantage in patients with perihilar CCA.

In other published retrospective and population-based studies, adjuvant treatment with chemoradiation using fluoropyrimidine-based chemotherapy showed possible improvement in local control and potential improvement in short-term survival in patients with CCA without long-term benefit[34-36]. For intrahepatic CCA, retrospective and population reviews have suggested that adjuvant chemoradiation may provide a slight survival benefit in R1 resections[31]. However, based on the paucity of data, current guidelines can only recommend that chemoradiation be used in unresectable patients without metastatic disease[31].

Novel approaches not examined in our study should also be considered in patients with CCA. Advancements in radiation treatments have led to novel approaches to deliver radiation to patients with CCA including radioembolization with Yttrium-90 microspheres[37,38]. Single-institution data appear promising for patients with liver predominant disease[37]. However, the definitive role of radioembolization should be evaluated in randomized studies prior to its inclusion as a standard measure. We could not fully evaluate the role of radioembolization in our study since this treatment was not integrated to any extent in patients with CCA prior to 2006.

Our study is one of the few that shed light on how multimodal therapy impacts patients with intrahepatic CCA also highlighting the inherent complexity in treating CCA. Our results verify that surgical resection remains the most important variable associated with improved survival for patients with resectable intrahepatic CCA, but our results also indicate that further work is necessary to identify more effective systemic/targeted and regional therapies.

COMMENTS

Background

Cholangiocarcinoma is an aggressive cancer of the bile ducts and liver. Unfortunately, most patients are asymptomatic and only present when symptoms suggestive of advance disease, such as jaundice, presents. Surgery remains the best curative-intent treatment, but is only possible in patients with early stage disease. There are few studies evaluating multimodality treatment: surgery, chemotherapy, and radiation.

Research frontiers

Multimodality therapies are now being investigated for the treatment of cholan-

giocarcinoma, such as radioembolization of the liver; yet these therapies are not standard of care.

Innovations and breakthroughs

The mainstay of treatment is chemotherapy with gemcitabine and cisplatin. Some studies are have evaluated other chemotherapy, including fluoropyramidine-based regimens, with similar results. In single-center trials, radioembolization with Yttrium-90 has been shown to be a safe.

Applications

This study indicates that surgery provides the best survival benefits for patients with cholangiocarcinoma and should continue to be a critical component in the multimodality treatment.

Terminology

Cholangiocarcinoma: an adenocarcinoma of the bile duct system. This may include the bile duct outside of the liver (perihilar) or the smaller bile ducts within the liver (intrahepatic). Adjuvant chemotherapy: chemotherapy given after surgical resection.

Peer review

The authors investigated surgical and medical outcomes for patients with cholangiocarcinoma using a population-based cancer registry. They demonstrated that surgical resection is a critically important modality of treatment for this disease.

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BRIEF ARTICLE

Open versus laparoscopic right hemicolectomy in the elderly population

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Abstract

AIM: To compare short term outcomes of elective laparoscopic and open right hemicolectomy (RH) in an elderly population.

METHODS: All patients over the age of 70 undergoing elective RH at Ninewells Hospital and Perth Royal Infirmary between January 2006 and May 2011 were included in our analysis. Operative details, hospital length of stay, morbidity and mortality was collected by way of proforma from a dedicated prospective database. An extracorporeal anastomosis was performed routinely in the laparoscopic group. The primary endpoints for analysis were morbidity and mortality. Our secondary endpoints were operative duration, length of hospital stay and discharge destination.

RESULTS: Two hundred and six patients were included in our analysis. One hundred and twenty-five patients underwent an open resection and 81 patients had a laparoscopic resection. The mean operating time was significantly longer in the laparoscopic group (139 ± 36 min *vs* 197 ± 53 min, $P = 0.001$). The mean length of hospital stay was similar in both groups (11.2 ± 7.8 d *vs* 9.6 ± 10.7 d, $P = 0.28$). The incidence of post-operative morbidities was 27% in the open group and 38% in the laparoscopic group ($P = 0.12$). Overall in-hospital mortality was 0.8% in open procedures *vs* 1% in laparoscopic.

CONCLUSION: Laparoscopic RH was associated with a significantly longer operative time compared to open RH. In our study, laparoscopic RH was not associated with reduced post-operative morbidity or significantly shorter length of hospital stay.

Key words: Right hemicolectomy; Elderly; Laparoscopy; Open

Core tip: This is the first study to assess open versus laparoscopic right hemicolectomy in the elderly population. Our results, whilst comparable to the published literature, do not show any benefits in terms of operative or short-term outcomes in laparoscopic surgery over open surgery in this particular group of patients.

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INTRODUCTION

An ageing population and a longer life expectancy has led to an increased number of elderly patients present-

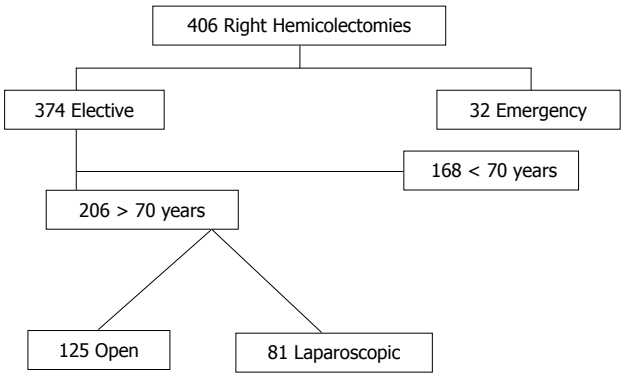

Figure 1 Patients presenting to NHS Tayside for elective right hemicolectomy.

ing with colorectal cancer requiring surgical management. Since the successful introduction of laparoscopic colectomy by Verdeja *et al*[1], laparoscopic surgery for the treatment of colorectal cancer has been widely adapted. Laparoscopic colorectal surgery has been shown in many studies to be associated with superior perioperative outcomes when compared to open colorectal surgery with reported advantages including less analgesic requirements, earlier return of bowel function, as well as shorter hospital stay[2,3].

Laparoscopic colectomy in the elderly has also been shown to be safe[4-12], however it is unknown whether elderly patients gain the same benefits from laparoscopic colectomy that younger patients have been shown to receive. Concern regarding laparoscopic colectomy in the elderly population relates to the age-associated increase in co-morbidities, the significantly longer operative times, and the physiologic effects that prolonged time under anaesthesia and CO_2 pneumoperitoneum have upon the multiple co-morbid conditions of these patients are unknown[13].

In addition, right hemi-colectomy is a very different operation to other colectomies. The operation does not involve the mobilisation of a difficult flexure and can often be completed through a small transverse incision. Studies have suggested that laparotomy *via* transverse skin crease incision can provide benefits in terms of ease of operation, reduced postoperative pain, earlier return of bowel function and more rapid discharge from hospital[14].

The aim of this study was to compare the short-term surgical outcomes of laparoscopically-assisted right hemicolectomy (LRH) and open right hemicolectomy (ORH).

MATERIALS AND METHODS

All patients undergoing a right hemicolectomy in NHS Tayside (Ninewells Hospital and Perth Royal Infirmary) between January 2006 and May 2011 were included in our analysis. Patients were identified from a dedicated prospective database. Data was collected by way of proforma, this included: (1) patient characteristics (admission date, age, gender, presentation); (2) intervention details (type of surgical intervention, details of surgery, length of procedure, grade of surgeon, total length of hospital stay, date of discharge, discharge destination and whether this was different from admission); and (3) complications, outcome and mortality (including peri-operative and in hospital mortality).

Additional information was reported form detailed case-note review as required. The primary endpoints for analysis were morbidity and mortality. Our secondary endpoints were operative duration, length of hospital stay and discharge destination. Data was reported on an intention-to-treat basis.

Operative procedure

Details of the operative procedure have been previously described but are summarised here[15]. All patients were administered prophylactic antibiotics at induction. With LRH a standard four port medial to lateral dissection was performed with high ligation of the ileocolic pedicle. The specimens were either extracted through a right iliac fossa muscle splitting incision or through an extended umbilical incision and an extracorporeal anastomosis performed. An Alexis wound protector (Applied Medical, United States) was used in all cases. An ORH was performed through a transverse muscle cutting incision when possible. A midline incision would be considered if previous laparotomy though a midline incision. A lateral to medial approach with high ligation of the ileocolic pedicle was performed routinely. With both techniques either a side-to-side ileocolic anastomosis or an interrupted end-to-end seromuscular sutured anastomosis was performed at the operating surgeon's discretion.

There has been no consistent definition of the age cut-off for elderly in the literature. However, several studies evaluating the risks of mortality after colorectal surgery have shown an increased mortality rate after surgery in patients aged more than 70 compared to patients aged less than 70[16,17]. We have thus used the age of 70 years as our cut-off, to evaluate the short-term outcomes of laparoscopic colorectal surgery versus open colorectal surgery in our institution.

Statistical analysis

Data were processed using the Statistical Package for Social Sciences, version 18.0 (SPSS, Inc., Chicago, IL, United States, 2010). Qualitative variables were summarised by frequency and percentage, while non-normally distributed quantitative variables were described by the median and range. Student's *t*-test and Fischer's exact test as appropriate. Statistical significance was determined ($P < 0.05$). Data was analysed on an intention to treat basis.

RESULTS

Three hundred and seventy-four patients underwent elective right hemicolectomy during the study period with 206 patients aged 70 years or older (Figure 1). Of these, 106 patients were male. One hundred and twenty-five patients underwent an ORH and 81 patients had a LRH.

Table 1 Demographics and clinical characteristics of patient groups

	Open (n = 125)	Lap (n = 81)
Age, yr (range)	79 (70-93)	78 (70-91)
Sex (M/F)	62/63	44/37
Cancer stage		
1	21	8
2	45	29
3	35	20
4	3	1
Polyp	18	10
Crohn's disease	1	0

Table 2 Operative details and post operative morbidity

	Open (n = 125)	Laparoscopic (n = 81)	P value
Operative time (min)	139 ± 36	197 ± 53	0.001
Length of stay (d)	11.2	9.6	NS
Morbidity	27%	38%	NS
Wound infection	13	11	NS
Pneumonia	8	9	NS
Ileus	5	6	NS
Urinary infection	3	3	NS
Cardiac event	4	3	NS
Anastomotic leak	2	4	NS
Reoperation	2	5	NS
Mortality	1.60%	1.20%	NS

NS: Not significant.

The clinical and demographic data are summarised in Table 1. There were no significant differences between the two groups. The indication for resection was cancer in the majority of cases. Both groups had a similar distribution of early (stages 1 and 2) and advanced tumours (stages 3 and 4; Table 1).

Seven patients required conversion to open surgery. Reasons for conversion include dense adhesions from previous surgery and tumour related factors such as local invasion of surrounding structures or anatomic uncertainty. There was a significant difference in mean operating time with 139 ± 36 min in the open group *vs* 197 ± 53 min in laparoscopic (P = 0.001). The incidence of post-operative morbidities was 27% of open procedures and 38% of laparoscopic procedures (Table 2). Superficial wound infection requiring antibiotics occurred in 10% of ORH and 13% of LRH. The primary site of infection in the laparoscopic group was the extraction site. All incidences resolved with antibiotics. One patient had a deep wound dehiscence in the open group. The incidence of pneumonia and ileus were similar in both groups. Two patients required reoperation in the open group for anastomotic leak related collections. Five patients in the laparoscopic group required re-operation involving laparotomy. One patient required a laparotomy for ischaemic small bowel and four required a laparotomy for anastomotic leak. Overall in-hospital mortality was 1.6% in open procedures *vs* 1.2% in laparoscopic.

The mean length of hospital stay was 11.2 ± 7.8 d in open and 9.6 ± 10.7 d in laparoscopic (P = 0.28). Five percent of patients in the open group required transfer to further inpatient facility for further rehabilitation compared to 2% although this failed to reach statistical significance. Long term oncological outcome was not evaluated in this study.

DISCUSSION

The number of elderly patients presenting with colorectal cancer has paralleled the increased life expectancy in the last decades. This has led to a large, and constantly rising, number of elderly patients with colorectal cancer referred for surgical treatment. Studies have shown that colorectal surgery in elderly patients is generally well tolerated although pre-morbid cardiopulmonary conditions do predispose to higher morbidity and mortality rates as compared to younger patients[5].

Laparoscopic colorectal resection is fast becoming the gold standard of treatment for both malignant and benign colorectal lesions, with improved short-term and comparable long-term outcomes when compared to the open method[2,3,18]. The benefits of laparoscopy have been attributed to less post-operative pain, better pulmonary function and reduced stress response[19-21]. These outcomes are particularly important in elderly patients who are at higher risk of post-operative morbidity and mortality. However, there are concerns regarding the safety of laparoscopic colorectal surgery in elderly patients, mainly related to longer operative time as well as physiological stresses associated with carbon dioxide pneumoperitoneum and steep Trendelenburg required for the main duration of surgery. Hypercapnia, reduce venous return and increase peak airway pressure and decrease pulmonary compliance may all potentially increase the risk of cardiorespiratory complications[22].

Several studies have described laparoscopic colectomy as safe and feasible in the elderly population with reduced morbidity and reduced length of hospital stay when compared to open surgery[5-11] . This is the first study to specifically assess right hemicolectomy in the elderly population. In our series, there was no significant difference in length of hospital stay or morbidity. This conclusion is not drawn from a laparoscopic series which is inferior to other studies as our results are comparable with the published literature[8-11,23]. In addition we have previously published on the benefits of laparoscopic colectomy for cancer in a standard population[15].

The incidence of laparotomy for complications was higher in the laparoscopic group, 6% *vs* 1% in the open group, however this did not achieve statistical significance possibly relating to the small numbers in this study. We believe that elderly patients undergoing right hemicolectomy do not obtain the same benefits of laparoscopic surgery and that this relates to the very different access required and technical aspects of a right hemicolectomy compared to a left sided resection.

Previous studies comparing methods of right hemicolectomy in a standard population have in fact found no significant difference in post-operative outcomes between laparoscopic resection and open colectomy when performed through a transverse incision[14,24]. Laparoscopy and transverse laparotomy may have various advantages on short- and long-term outcome compared to a midline laparotomy. Patients may experience less postoperative pain, have a better pulmonary function, less wound dehiscence, and significantly less incisional hernias. In addition, two meta-analyses[25,26] have suggested a transverse approach is superior to the midline incision, because of its better anatomical and physiological principles and therefore less prone to develop short- or long-term abdominal wall complications. The duration of hospital stay has often been used as a crude marker of recovery however, in the elderly population there are many factors which prevent satisfactory early discharge and a considerable number of patients require periods of further rehabilitation or additional support at home to enable safe discharge. In the United Kingdom, these factors are often out with the control of the surgeon and nursing staff and require considerable input from social services. Therefore the accepted cost-benefit ratio of laparoscopic surgery may not apply to the elderly population[27].

Laparoscopic RH in an elderly population is feasible and our results would support the evidence from previous studies. However, we found no evidence to suggest that it is better than open RH and believe that the decision regarding the method of operation should reflect local expertise, patient co-morbidities and consideration of expected tolerance of longer operating times and physiological effects of pneumoperitoneum.

In conclusion, our results suggest that laparoscopic RH in the elderly population is associated with a significantly longer operative time compared to open right hemicolectomy and that in our study, laparoscopic RH is not associated with reduced post-operative morbidity or significantly shorter length of hospital stay.

COMMENTS

Background

Laparoscopic colorectal surgery is associated with superior perioperative outcomes when compared to open surgery. However, in the elderly population these benefits are often overshadowed by co-morbidities and difficulties in achieving rapid discharge. Right hemicolectomies (RH) represent a distinct group of colorectal resections where the benefits of the laparoscopic approach may be reduced.

Research frontiers

Several studies have advocated the use of laparoscopic colectomy in the elderly population. However right hemicolectomy frequently does not involve the mobilisation of a difficult flexure and can be safely achieved through a small transverse incision thus reducing the potential benefits of laparoscopy. Elderly patients often have a reduced physiological reserve due to co-morbidity and exposing them to the additional physiological challenge of pneumoperitoneum may subject them to added risk.

Innovations and breakthroughs

This is the first article to compare open and laparoscopic right hemicolectomy specifically in an elderly population.

Applications

Authors found no evidence to suggest that it is better than open RH and believe that the decision regarding the method of operation should reflect local expertise, patient co-morbidities and consideration of expected tolerance of longer operating times and physiological effects of pneumoperitoneum.

Peer review

This is a comparative study of the short-term results of laparoscopic and open right hemicolectomy in the elderly, which is based on a prospective database. It is indeed the first study to evaluate the two approaches of right hemicolectomy exclusively in the elderly. As such, it represents a novel research and provides sufficient data for scientific conclusions and further investigation. The impact of laparoscopic and open right hemicolectomy in the older population has been unselectively investigated in several studies where older patients were included in patient groups of various ages.

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CASE REPORT

A rare cause of obstructive jaundice and gastric outlet obstruction

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Abstract

Superior mesenteric artery syndrome is a rare cause of upper gastrointestinal obstruction, and is characterized by 3rd duodenal obstruction between the abdominal aorta and the superior mesenteric artery. Classical symptoms are postprandial epigastric pain, nausea, vomiting, and weight loss, or acute upper gastrointestinal obstruction. We herein describe an unusual presentation, with jaundice due to compression of the common bile duct by the gastric obstruction and dilated duodenum.

Key words: Upper gastrointestinal obstruction; Superior mesenteric artery syndrome; Obstructive jaundice

Core tip: Superior mesenteric artery syndrome is a rare cause of upper gastrointestinal obstruction, with sometime unusual presentation, as in the present case, obstructive jaundice. Clinicians need to be aware of this rare situation and its main radiographic sign *i.e.*, extraluminal compression of the duodenum between the superior mesenteric artery and the aorta.

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INTRODUCTION

Superior mesenteric artery syndrome is a rare cause of upper gastrointestinal obstruction, and is characterized by 3rd duodenal obstruction between the abdominal aorta and the superior mesenteric artery. This can be due to loss of intra-abdominal fat by malabsorption, cancer, anorexia nervosa, or spinal surgery decreasing aorto-mesenteric angle and the distance between the superior mesenteric artery (SMA) and aorta. Classical symptoms are postprandial epigastric pain, nausea, vomiting, and weight loss, or acute upper gastrointestinal obstruction. We report an unusual presentation, with jaundice du to compression of the common bile duct by the gastric obstruction and dilated duodenum.

CASE REPORT

A 31-years old man was admitted in a traumatology unit after a fall from the 3rd floor, and was operated for a thoracic spine injury (without spinal cord injury) requiring a T2-T6 osteosynthesis. Three weeks latter, and after a more than 10 kg weight loss, the patients progressively complain of abdominal discomfort, nausea, vomiting and jaundice. Physical examination only revealed abdominal

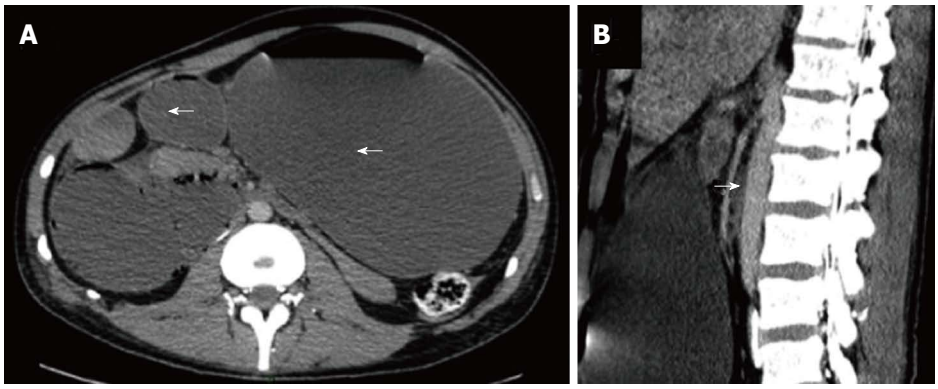

Figure 1 Contrast computed tomography revealing. A: A complete gastric outlet obstruction (white arrow); B: With distension of the stomach, and the duodenum, with a flat bowel after its pass behind the superior mesenteric artery (white arrow).

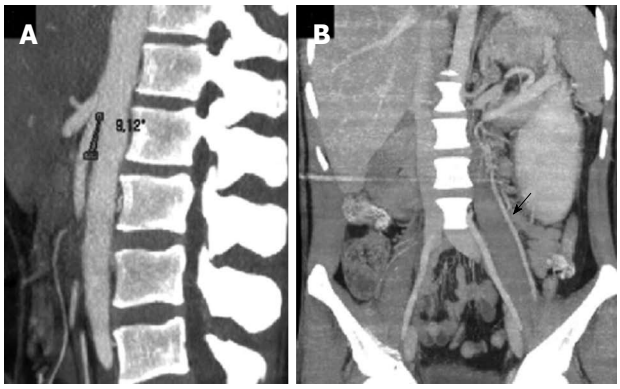

Figure 2 Contrast computed tomography with vascular reconstruction revealing. A: That the aortomesenteric angle was decreased to 9; B: A left renal vein obstruction with left gonadal vein dilatation.

distension without tenderness in an undernourished and jaundiced patient. Blood work was significant for a bilirubin of 168 mmol/L and eleveted liver enzymes Aspartate Aminotransferase (92 UI/L), Alanine Aminotransferase (109 UI/L), and Gama Glutanyltransferase (288 UI/L). The remainder of his laboratory works was within normal limits. Contrast computed tomography (CT) was performed, revealing a complete gastric outlet obstruction (Figure 1), and elucidated the clinical situation.

DISCUSSION

On the basis of clinical presentation and CT scan imaging SMA syndrome was suspected. CT scan reveled distension of the stomach, and the duodenum, with a flat bowel after its pass behind the SMA (Figure 1A). When compared to initial imaging, aortomesenteric angle was decreased to 9° (Figure 1A and 2A), because of the rapid and intense weight loss following surgery, associated with a decreased in retroperitoneal fat thickness. Additionally, because of the chronic gastric outlet obstruction, there either a direct compression of the common bile duct by the distended stomach and duodenum or an increased intraduodenal pressure, responsible for the obstructive jaundice, as proven by the rapid bilirubin and liver function test decreased after nasogastric tube decompression. The mechanism of this upper gastointestinal (GI) obstruction is an extraluminal compression of the duodenum between the SMA and the aorta. This was associated with a left renal vein obstruction with left gonadal vein dilatation (Figure 2B). After nasogastric tube decompression, obstructive jaundice and abdominal discomfort rapidly disappeared. Because of failure of parenteral nutrition and enteral feeding, possibly due to an important catabolism following extensive spine surgery, and anorexia in relation to a depressive syndrome, a Roux-en-Y gastrojejunostomy associated with duodenojejunal flexure lowering (Strong's procedure) was performed, allowing oral feeding and weight gain within the next weeks.

SMA syndrome is a rare cause of upper gastrointestinal, first described in 1842 by Von Rokitanski, and characterized by 3rd duodenal obstruction between the abdominal aorta and the SMA[1]. This can be due to loss of intra-abdominal fat by malabsorption, cancer, anorexia nervosa, or spinal surgery[2,3] decreasing aortomesenteric angle and the distance between the SMA and aorta. Classical symptoms are postprandial epigastric pain, nausea, vomiting, and weight loss, or acute upper GI obstruction[4]. Biliary symptoms such as in this case have been rarely reported[5].

CT angiography with 3-D reconstruction and oral contrast provides the diagnosis. Diagnostic criteria include: aortomesenteric angle < 20°, aortomesenteric distance < 8 mm, gastric and duodenal dilatation above the third duodenum[6]. Left renal vein compression by SMA and its consequences such as varicocele, hematuria or orthostatic proteinuria, can also been seen so-called nutcracker syndrome[7].

Initial conservative treatment, with nasogastric decompression, electrolytic resuscitation and nutritional support, is successful in more than half of patients and seems to be efficient only in patients with short story of SMA syndrome and mild duodenal stenosis[8]. Two surgical options are indicated after medical treatment failure: obstruction bypass such as duodenojejunostomy and gastrojejunostomy or Treitz's ligament lowering (the Strong's procedure) to decompress the duodenum[9]. Clinicians need to be aware of this rare situation and its main radiographic sign, *i.e.*, extraluminal compression of the duodenum between the SMA and the aorta, in order to promptly adapt their therapeutic strategy.

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CASE REPORT

A bizarre foreign body in the appendix: A case report

Nicola Antonacci, Marcello Labombarda, Claudio Ricci, Salvatore Buscemi, Riccardo Casadei, Francesco Minni

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Author contributions: Antonacci N, Labombarda M and Ricci C designed the report; Antonacci N and Buscemi S performed surgical operations; Minni F and Casadei R was attending doctor for the patient; Labombarda M organized the report and Antonacci N wrote paper.

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Abstract

Foreign bodies are rare causes of appendicitis and, in most cases, ingested foreign bodies pass through the alimentary tract asymptomatically. However, ingested foreign bodies may sometimes remain silent within the appendix for many years without an inflammatory response. Despite the fact that cases of foreign-body-induced appendicitis have been documented, sharp and pointed objects are more likely to cause perforations and abscesses, and present more rapidly after ingestion. Various materials, such as needles and drill bits, as well as organic matter, such as seeds, have been implicated as causes of acute appendicitis. Clinical presentation can vary from hours to years. Blunt foreign bodies are more likely to remain dormant for longer periods and cause appendicitis through obstruction of the appendiceal lumen. We herein describe a patient presenting with a foreign body in his appendix which had been swallowed 15 years previously. The contrast between the large size of the foreign body, the long clinical history without symptoms and the total absence of any histological inflammation was notable. We suggest that an elective laparoscopic appendectomy should be offered to such patients as a possible management option.

Key words: Foreign body; Appendectomy; Laparoscopy; Acute appendicitis; Calcified fecaloma; Abdominal pain

Core tip: To our knowledge this is the first case of a marrowbone within an appendix with a delayed presentation which was adequately recognized and treated laparoscopically. Our case showed a unique clinical picture in which a bizarre foreign body remained dormant within the appendix for 15 years. This case could offer a possible diagnostic and therapeutic option for appropriately treating patients with foreign bodies within the appendix.

Antonacci N, Labombarda M, Ricci C, Buscemi S, Casadei R, Minni F. A bizarre foreign body in the appendix: A case report. *World J Gastrointest Surg* 2013; 5(6): 195-198 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i6/195.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i6.195

INTRODUCTION

Foreign body ingestion occurs in more than 100000 patients annually in the United States alone[1]. More than 80% of these occur in the pediatric population with 98% being accidental. The vast majority of objects reaching the stomach pass through the gastrointestinal tract spontaneously with no consequence; therefore, fewer than 1% of these objects require surgical intervention[2]. The primary pathology is due to luminal obstruction while foreign bodies are seldom the cause of appendicitis[2] which presents in the intraluminal exogenous body in only 0.005% of cases[3].

Many foreign bodies in the appendix, such as seeds[4], or steel[5-11] or lead[12,13] objects, dental prosthetic material[14,15], *etc.*,[16] have been described in the literature. Long,

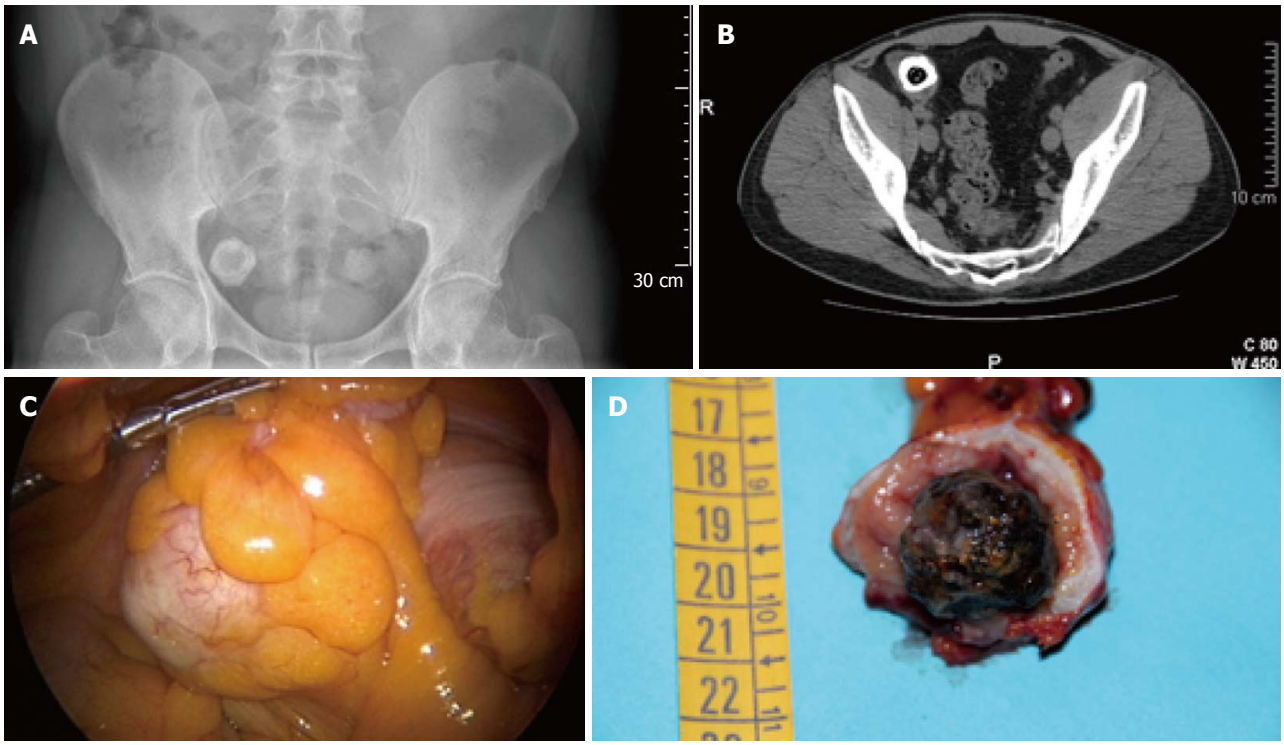

Figure 1 Abdominal pain. A: Lower abdomen X-ray shows a rounded radio-opaque formation in the right iliac fossa; B: Lower abdomen computed tomography showing a roundish-filling defect in right iliac fossa; C: Laparoscopic intraoperative view of the dilated appendix due to the presence of a foreign body; D: The marrow-bone included in a calcified fecaloma.

pointed, thin, sharp and stiff objects are more prone to cause perforation (in the appendix as well as in the duodenum and ileum) and are defined as risky while round and smooth objects have a lower risk of causing perforation. They may however, lead to complications from a secondary obstruction due to a fecal coating and appendiceal lumen obstruction[3]. In fact, it seems that 3% of fecaliths contain foreign bodies[17]. In most cases, foreign bodies generate appendicitis in a few hours, a few days or at most a few months[5,7,8,10,11,18].

However, there are rare cases in which a foreign body leads to appendicitis after many years[6,19,20].

CASE REPORT

A 45-year-old Caucasian man presented to the Emergency Department with mild lower right-side abdominal pain. On examination, clinical findings suggested acute appendicitis with predominant right iliac fossa tenderness but without definite peritonism. His laboratory work-up was normal, and he was afebrile. In abdominal ultrasound scans, the organs examined appeared normal with no signs of acute appendicitis.

Eight months later, the patient was re-evaluated in an outpatient setting. He was interrogated again and reported that he had eaten rice with saffron and marrowbone, a traditional Northern Italian dish, approximately 15 years previously and, while he was swallowing his last mouthful, he accidently ingested a marrowbone. For these reasons, he was hospitalized. His preoperative laboratory work-up was normal. An abdominal X-ray revealed a rounded radio-opaque formation in the right iliac fossa (Figure 1A). Computed tomography revealed the presence of a massive roundish-filling defect of about 2.5 cm × 3.0 cm in the right iliac fossa, identified as diaphyseal-type bone tissue, probably within the proximal portion of the appendix which appeared dilated (12 mm in diameter) (Figure 1B). Exploratory laparoscopy of the abdomen revealed an abnormally dilated appendix due to the presence of a foreign body (Figure 1C). A laparoscopic appendectomy was, therefore, performed. Surprisingly, the specimen removed (Figure 1D) consisted of a marrowbone included in a calcified fecaloma in the lumen of the appendix. There were no postoperative complications and the patient was discharged 2 d after surgery. Histological examination of the specimen revealed a slight muscle hypertrophy of the appendiceal wall due to the chronic decubitus of the foreign body, without signs of inflammation.

DISCUSSION

The presence of foreign bodies in the gastrointestinal tract rarely causes complications and their presence within the appendix is a very rare event. Probably, if the weight of the foreign body is greater than that of the bowel fluid content, its movement is arrested in the cecum during transit where it gravitates towards the lower portion[3]. The appendiceal orifice expands and allows entry into its lumen. Only in a retrocecal appendix is

there almost no possibility of an object entering into the lumen[21] while any other part of the appendix allows free access. Once in the appendix, peristaltic action is insufficient to expel bodies back into the cecum[3]. This is the reason why, in our case, the marrowbone had been stuck in the appendix for years, developing muscular hypertrophy without any signs of inflammation. The formation of a fecal coat probably prevented the development of inflammatory processes, making the patient essentially asymptomatic with occasional mild pain, probably due mainly to mechanical rather than inflammatory insults.

The use of diagnostic laparoscopy for the management of foreign bodies in the gastrointestinal tract as well as in appendix[3,5] has been well described by previous authors[22,23]. Although the advantages of laparoscopic appendectomy have been established for young females of reproductive age and for obese patients[24], in the male population, the technique seems to be at least as safe and effective as the open procedure. For this reason, laparoscopic appendectomy may be useful in the management of foreign bodies in the appendix.

Furthermore, this procedure has also been described in the literature as feasible for foreign bodies in other abdominal locations[25-28].

Rare cases in which a foreign body in the appendix does not generate inflammation have also been described in the literature. In a prospective study involving 62 Eskimo patients[29] having lead shot in the appendix, none had developed clinical evidence of appendicitis, even after 13 years and, in 8 cases where the appendix had been removed, a histologically normal appendix was found. Sian *et al*[13] also reported a case in which 27 lead shot pellets were found in the appendix of a 45-year-old patient who had eaten pigeons in childhood but no inflammation was present. It is therefore possible, although rare, that a foreign body in the appendix even after many years (in our case, 15 years) does not lead to an authentic appendicitis either histologically or clinically.

Foreign bodies in the appendix and in the absence of flogistic reactions are rare. Laparoscopic appendectomy has been shown to be a reliable and safe diagnostic and therapeutic method in elective surgery, even in cases of large foreign bodies.

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CASE REPORT

A black perforated esophagus treated with surgery: Report of a case

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Abstract

A case of a perforated black esophagus treated with minimal invasive surgery is presented. A 68-year-old women underwent a right-sided hemihepatectomy and radio frequency ablation of two metastasis in the left liver lobe. Previous history revealed a hemicolectomy for an obstructive colon carcinoma with post-operative chemotherapy. Postoperatively she developed severe dyspnea due to a perforation of the esophagus with leakage to the pleural space. Video-assisted thoracoscopic surgery (VATS) to adequately drain the perforation was performed. Gastroscopy revealed a perforated black esophagus. The black esophagus, acute esophageal necrosis or Gurvits syndrome is a rare entity with an unknown aetiology which is likely to be multifactorial. The estimated mortality rate is high. To our knowledge, this is the first case published of early VATS used in a case of perforated black esophagus.

Key words: Black esophagus; Acute esophageal necrosis; Video assisted thoracoscopic surgery; Gastrointestinal surgery; Perforated esophagus

Core tip: We describe a clinical case with a review of relevant literature of the rare syndrome black esophagus, also known as acute esophageal necrosis or Gurvits syndrome. It concerns a case of a perforated black esophagus treated with video assisted thoracoscopic surgery (VATS). To our knowledge, this is the first case published of early VATS used in a case of perforated black esophagus.

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INTRODUCTION

The black esophagus, also known as acute esophageal necrosis or Gurvits syndrome, is a rare clinical syndrome with an unknown pathophysiology, though likely to be multifactorial[1]. There are numerous risk factors[2]. Coffee-ground emesis, hematemesis and melena can be presenting symptoms of black esophagus[2,3]. Though the diagnosis is confirmed with gastroscopy where the esophagus is circumferentially black, differential diagnosis consists of malignant melanoma, acanthosis nigricans, pseudomelanosis, melanosis, pseudomembranous esophagitis, infections and ingestion of corrosives[2,4-10]. Mortality and morbidity of the black esophagus is high and therapy includes adequate treatment of underlying illness, systemic fluid resuscitation, intravenous proton pump inhibitors or histamine receptor blocker, total parenteral nutrition and nil-per-os[2]. Surgery is reserved for patients with a perforated esophagus resulting in mediastinitis or abscess formation[1]. We present a case of a black perforated esophagus

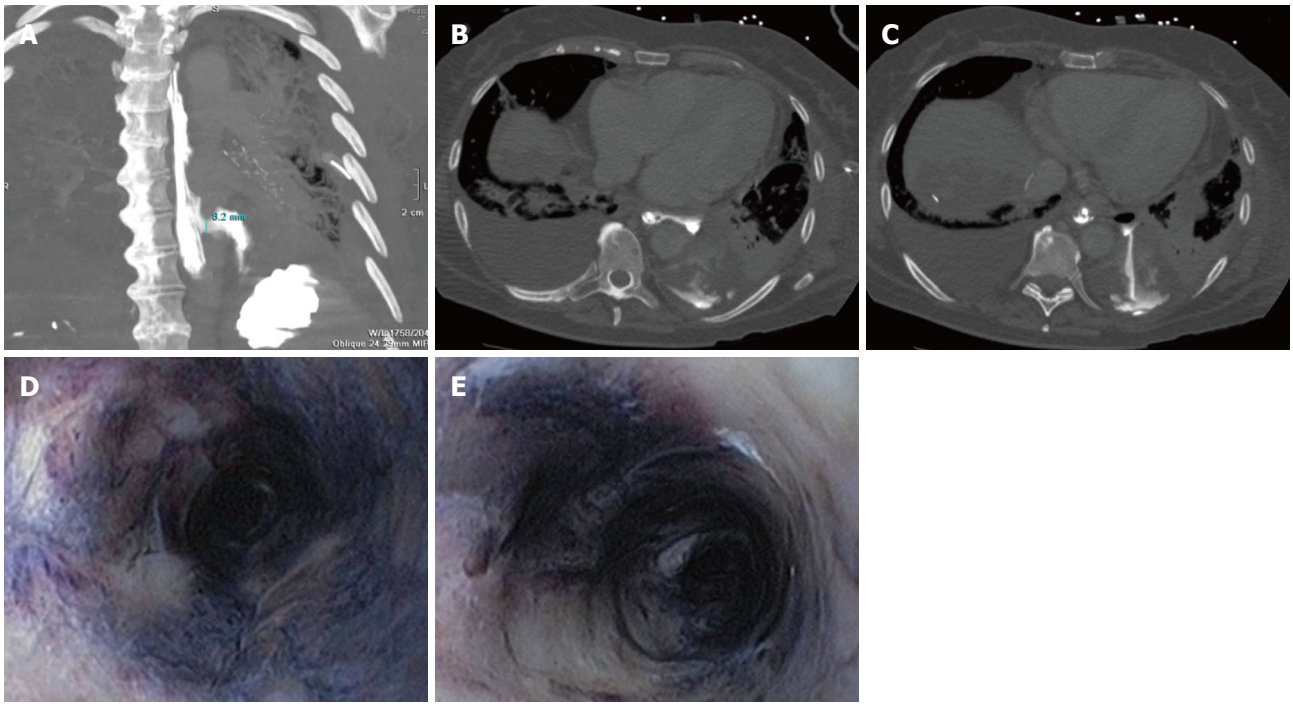

Figure 1 Computed tomography-thorax scan with contrast given via the nasogastric feeding tube. A: A coronal coupe where the esophagus is seen to the left of the vertebral column and the perforation lights up two thirds of the esophagus with leakage of contrast into the pleural space; B and C: Transversal coupes of the thorax with contrast leakage via the esophagus into the pleural space; D and E: A circumferentially black-appearing esophagus at endoscopy.

treated with early video assisted thoracoscopic surgery.

CASE REPORT

A 68 year-old woman was treated 6 mo prior to the current admission for adenocarcinoma of the descending colon. During this admission the patient underwent a left-sided hemicolectomy in an acute setting due to an obstructive ileus. In the post-operative setting the patient received adjuvant chemotherapy (two cycles of capox/bevacuzimab and one cycle of capox) because of liver metastasis. Despite chemotherapy the size, but not the number, of liver metastasis progressed in segments two, three, seven and eight.

It was decided to perform a right hemihepatectomy, and radio frequency ablation of two metastasis in the left liver lobe. In the same setting a cholecystectomy was performed. A nasogastric tube was inserted non-traumatically for post-operative feeding.

On the fourth postoperative day the patient developed severe dyspnea, based on a left sided tension pneumothorax, for which a chest tube was inserted. She was admitted to the ICU for mechanical ventilation due to persisting dyspnea, later complicated with severe sepsis and multi-organ failure, treated with fluid resuscitation, vasopressive medication and haemodialysis.

Subsequent computed tomography (CT-scan) of the chest revealed a pneumomediastinum and leakage of contrast given via the nasogastric feeding tube in the pleural space (Figure 1A-C), with adequate positioning of the nasogastric-tube.

Laboratory investigation of the pleural fluid showed elevated amylase levels (3312 U/L). Suspicion of an esophageal perforation was high, given the elevated pleural-amylase and the result of the CT-scan. This was confirmed with gastroscopy. At 32 cm from the teeth, a perforation was seen. Moreover, the gastroscopy revealed a circumferentially black-appearing esophagus (Figure 1D and E), with an abrupt stop of the abnormal-appearing mucosa at the gastroesophageal junction.

Stenting was considered, but because the friable mucosa and the proven perforation a right-sided video assisted thoracoscopic surgery (VATS) procedure (video assisted thoracoscopy) was performed, in order to adequately drain the pneumomediastinum, placing an intrathoracic flushing-system-drain near the perforation. Of note, perioperatively the esophagus appeared normal from the outside, suggesting that there was no transmural necrosis of the esophagus.

The patient was treated postoperatively with broad-spectrum antibiotics. Serological tests of immunodeficiency-, herpes- and cytomegalovirus were negative.

Twenty three days after initial diagnosis, the esophageal mucosa appeared normal on a repeat gastroscopy and the perforation had healed. The patient was discharged from the ICU in good condition. In the further post-operative course to date , two years post surgey, the patient needs monthly gastroscopy for esophageal dilatation because of strictures.

DISCUSSION

The black esophagus, also known as acute esophageal necrosis or Gurvits syndrome is a rare clinical entity. The exact pathology of the black esophagus is unknown, although it is likely to be multifactorial[1]. The prevalence of black esophagus is estimated between 0.01% and 0.2%[11-13].

There are several etiological theories[1]. One of them is ischemic damage due to hemodynamic compromise and a low-flow state, as can be seen in septic patients. Mucosal damage due to gastric acids, as seen in gastric outlet obstruction, may be a risk factor for black esophagus. Another possible explanation is esophago-gastroparesis and mucosal barrier failure in malnourished and debilitated patients[1].

In the case described above, there could have been more than one cause of the esophageal perforation. The patient was known to have metastatic colon cancer and to be in a sepsis, causing a low-flow state. It is likely, given the clinical course, that the esophageal perforation was caused by ischemia of the esophagus. Histological findings in the literature describe full-thickness necrosis, though mostly necrosis of the mucosa, and submucosa even extending to the muscularis propria is seen, as discussed later[1].

Known risk factors for developing a black esophagus are greater age (average 67 years), male sex (male:female = 4:1), cardiovascular disease, hemodynamic compromise, hypoxemia, hypercoagulable state, gastric outlet obstruction, malnutrition, malignancies, diabetes mellitus, renal insufficiency and trauma[2].

Symptoms of a black esophagus are often upper gastrointestinal bleeding conditions such as coffee-ground emesis, hematemesis and/or melena[2,3]. The distal third of the esophagus is most frequently affected, although it can affect the entire esophagus[2]. The esophagus demonstrates the characteristic diffuse, circumferential black discoloration at endoscopy, with underlying friable hemorrhagic tissue, and a sharp transition to normal-appearing mucosa at the gastroesophageal junction[2]. Biopsy, though recommended, is not required. Histological findings of the black esophagus include necrosis of the mucosa, submucosa even extending to the muscularis propria, absence of viable epithelium and widespread necrotic debris. Common associated findings are leucocytic infiltrates, severe inflammatory changes, deranged muscle fibres and visible vascular thrombi[1]. In the differential diagnosis of black esophagus, factors including malignant melanoma, acanthosis nigricans, pseudomelanosis, melanosis, pseudomembranous esophagitis, infections (candida albicans, herpes simplex viruses-1, cytomegalorvirus and *Lactobacillus acidophilus*) and ingestion of corrosives should be considered[4-10].

Common complications are development of strictures or stenosis of the esophagus, mediastinitis or mediastinal abscesses, perforation or death, with an estimated mortality rate of 32%[2]. Therapy, though not standardized or evidence based, consists of treating the underlying illness, systemic fluid resuscitation, intravenous proton pump inhibitors or histamine receptor blocker, total parenteral nutrition and nil-per-os. Antibiotic therapy is controversial[1]. The use of a nasogastric tube should be resisted , if possible. Surgery is reserved for patients with a perforated esophagus resulting in mediastinitis or abscess formation[1].

To our knowledge, this is the first case published with early use of VATS in the case of a perforated black esophagus.

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CASE REPORT

Intrathoracic major duodenal papilla with transhiatal herniation of the pancreas and duodenum: A case report and review of the literature

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Abstract

Transhiatal herniation of the pancreas is an extremely rare condition. In the published literature we found only eleven cases reported in the period of 1958 to 2011. A coincidental hiatal herniation of the duodenum is described in two cases only. To our knowledge, we report the first case with a hiatal herniation of the complete duodenum and proximal pancreas presenting an intrathoracic major duodenal papilla with consecutive intrahepatic and extrahepatic cholestasis. A 72-year-old Caucasian woman was admitted to our department with a hiatal hernia grade Ⅳ for further evaluation. According to our recommendation of surgical hernia repair soon after the diagnosis of a transhiatal herniation of the proximal pancreas and entire duodenum, we had to respect the declared intention of the patient for a conservative procedure. So we were forced to wait for surgical repair within an emergency situation complicated by a myocardial infarction and reduced general condition. We discuss the therapeutic decision making process and a complete literature review of this rare entity.

Key words: Hiatal hernia; Paraesophageal hernia; Intrathoracic pancreas; Intrathoracic duodenum; Diaphragmatic hernia

Core tip: Hiatal herniation of the pancreas is a rarity. In the world literature we identified 11 cases reported from 1958 to 2011. A 72-year-old Caucasian woman was admitted to the hospital with symptoms of mechanical cholestasis such as mild jaundice, pruritus, diarrhea and fatigue. Our case illustrates the serious sequelae of a hiatal hernia (HH) type Ⅳ that can occur when treated conservatively and therefore we recommend that all HH type Ⅳ should be repaired as soon as possible after the diagnosis. Despite of the fatal outcome we were encouraged to publish this case to improve future decision finding processes in similar cases.

Jäger T, Neureiter D, Nawara C, Dinnewitzer A, Öfner D, Lamadé W. Intrathoracic major duodenal papilla with transhiatal herniation of the pancreas and duodenum: A case report and review of the literature. *World J Gastrointest Surg* 2013; 5(6): 202-206 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i6/202.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i6.202

INTRODUCTION

Hiatal herniation of the pancreas is a rarity. In the world literature we identified 11 cases reported from 1958 to 2011 (Table 1). All reported patients were symptomatic

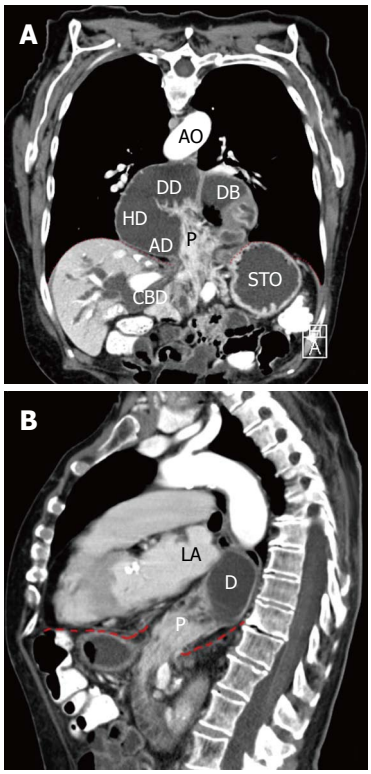

Figure 1 Computed tomographic scan obtained after oral administration of contrast. A: Frontal plane; B: Sagittal plane. The duodenum (D) lies dorsal to the atrial chambers. The descending duodenum is in immediate proximity to the left atrial (LA) chamber. The diaphragm is pointed out as the red dashed line. P: Head of pancreas; CBD: Common bile duct; STO: Stomach; DB: Duodenal bulb; DD: Descending duodenum; HD: Horizontal duodenum; AD: Ascending duodenum; AO: Aorta.

except one case reported by Katz *et al*[1]. Surgical repair of the hernia was performed in all patients except one recently reported case by Rozas *et al*[2].

To the best of our knowledge, we describe the first case of a hiatal hernia (HH) type Ⅳ with herniation of the complete duodenum and proximal pancreas presenting an intrathoracic major duodenal papilla with consecutive intra- and extrahepatic cholestasis.

HH are categorized into four types. Type Ⅰ or sliding HH accounting for 85%-95% is characterized by an intact, circumferential lax phrenoesophageal membrane and widening of the muscular hiatal tunnel[3]. Types Ⅱ, Ⅲ and Ⅳ (5%-15%) are subsumed as paraesophageal hernia (PEH). A type Ⅱ hernia results from a localized defect in the phrenoesophageal membrane while the gastroesophageal junction remains fixed to the preaortic fascia and the median arcuate ligament[3]. A type Ⅲ hernia has aspects of both types Ⅰ and Ⅱ. Typical for a type Ⅳ HH is a large defect in the phrenoesophageal membrane with herniation of other abdominal organs (colon, spleen, pancreas and small intestine).

The uniqueness of our case is characterized by the transhiatal herniation of the duodeno-pancreatic unit (duodenal C, pancreatic head, major and minor duodenal papilla, common bile duct and pancreatic duct) with subsequent mechanical intra- and extrahepatic cholestasis. Cholestasis occurs due to tension and compression of the common bile duct by the diaphragmatic clamp resulting in dilated intra- and extrahepatic bile ducts with temporally elevated liver enzymes and cholestasis parameters. Clinical symptoms can vary from mild obstructive jaundice up to serious organic and systemic damage. A complete literature review and the decision finding process in the treatment of our patient are presented.

CASE REPORT

A 72-year-old Caucasian woman was admitted to the hospital with symptoms of mechanical cholestasis such as mild jaundice, pruritus, diarrhea and fatigue. Several months before, she had already suffered from mild epigastric pain, rated as three out of ten on the numeric rating scale. Her abdominal examination was unremarkable with audible bowel sounds, no epigastric tenderness and no palpable masses. A stool test for occult blood was negative. Laboratory studies revealed a complete blood count within normal limits and normal electrolytes except gamma-glutamyl transpeptidase (G-GT) of 382 U/L [normal adult female range (NAFR): 0-45 U/L, serum glutamic-pyruvic transaminase (GPT) of 96 U/L (NAFR: 0-48 U/L), alkaline phosphotase (AP) of 153 U/L (NAFR: 20-125 U/L) and amylase of 153 U/L (NAFR: < 110 U/L)]. Cholinesterase, bilirubin and lipase were within normal limits on admission.

Her medical history was significant for hypertension, three-vessel coronary artery disease and cholecystolithiasis. In 1995 she underwent definitive resection arthroplasty of the left hip because of an aseptic loosening followed by prosthetic joint infection. Her functional status was limited, with walking restricted to using a cane. In 2004 a total hysterectomy was performed. Neither a pulmonary disease nor a chest trauma was reported. Her current medication included Nifedipine, Amiloride, Hydrochlorothiazide, Acetylsalicylic acid and Simvastatin.

An upper gastrointestinal study (200 mL of soluble contrast) revealed an intrathoracic duodenum with delayed contrast passage. In the following esophagogastroduodenoscopy a prestenotic dilatation of the descending duodenum with no hemorrhage or mucosal damage was found. Microscopic examination of a biopsy specimen from the distal esophagus showed reflux esophagitis grade Ⅰ without any evidence of fungal infection or Barrett's metaplasia. Gastric specimen revealed *Helicobacter pylori* (*H. pylori*) associated gastritis. *H. pylori* eradication therapy was initiated.

Thoracic and abdominal computed tomography (CT) showed a HH type Ⅳ with displacement of the entire duodenum and proximal pancreas through the hiatal orifice into the posterior mediastinum (Figure 1A and B).

An intermittent mechanical intra- and extrahepatic cholestasis was present due to obstruction of the common bile duct caused by the compression of the right diaphragmatic pillar which served as a hypomochlion to the common bile duct (Figure 1A and B).

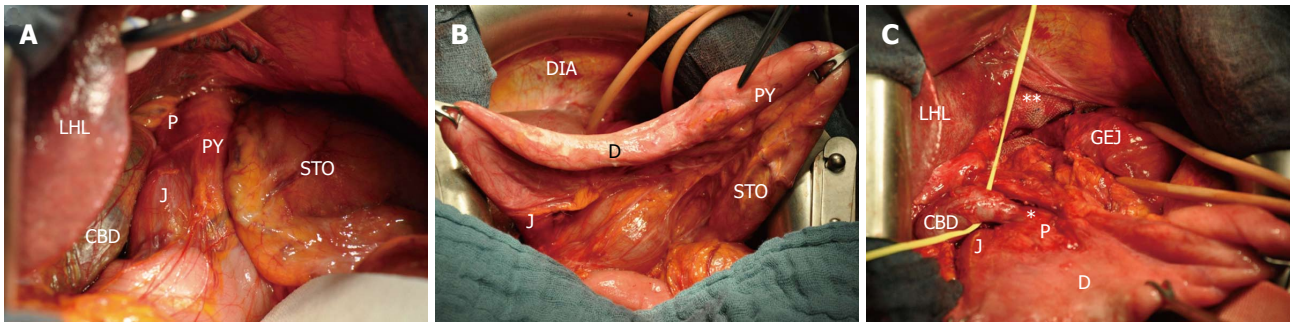

Figure 2 Intraoperative findings. A: After midline laparotomy; B: After reposition of the hiatal content; C: After closure with non-absorbable mesh. Asterisk indicates constriction of the common bile duct; Asterisks indicate closure of the esophageal hiatus with mesh and non-absorbable sutures. STO: Stomach; PY: Pylorus; J: Jejunum; CBD: Enlarged common bile duct; LHL: Left hepatic lobe; P: Pancreas; D: Duodenum; DIA: Diaphragm; GEJ: Gastroesophageal junction.

Table 1 Review of the literature: Transhiatal herniation of the pancreas

Author	Age (yr)	Sex	Herniated part of pancreas	Other herniated organs	Cholest-asis	Pancreat-itis	Sympto-matic	Myocardial Infarction	Surgery
Moore *et al*[9], 1958	67	F	Head	Pylorus, proximal duodenum	-	-	+	-	+
Coral *et al*[5], 1987	56	M	Body-tail	-	-	-	+	-	+
Kafka *et al*[11], 1994	71	F	Head-body	Stomach, duodenum	-	+	+	+	+
Chevallier *et al*[12], 2001	70	M	Body-tail (transient)	-	-	+	+	-	+
Katz *et al*[1], 2002	74	M	Body-tail	-	-	-	-	-	+
Skinner *et al*[17], 2003	52	M	Body	Gastric fundus	-	-	+	-	+
Saxena *et al*[14], 2006	78	F	Complete	-	-	+	+	-	+
Tagaya *et al*[15], 2007	75	F	Body-tail	Jejunum, transverse colon	-	+	+	-	+
Maksoud *et al*[13], 2010	68	M	Complete (transient)	Stomach, transverse colon	-	+	+	-	+
Rozas *et al*[2], 2010	78	F	Head	Stomach	-	+	+	-	-
Coughlin *et al*[16], 2011	61	F	Mid-body	Stomach	-	-	+	-	+

F: Female; M: Male.

The endoscopic retrograde cholangiopancreatography revealed a stenosis about 3 cm proximal to the major duodenal papilla. An endoscopic papillotomy or the insertion of a stent was not necessary at this time because of normal bilirubin levels despite morphologic dilated intrahepatic bile ducts.

Our recommended elective surgical repair of the hernia was refused by the patient due to lack of symptoms. Therefore she was discharged from hospital with periodic aftercare in three month intervals.

The following laboratory tests revealed continuously increasing liver and pancreatic enzymes (GPT: 235 U/L, G-GT: 600 U/L, AP: 241 U/L, lipase: 61 U/L, amylase: 167 U/L). Bilirubin counts were within normal limits. On physical examination she denied any clinical symptoms.

One year later the patient was treated as an inpatient at our facility because of a dislocated distal, left-sided radius multifragment fracture. On the second day of hospitalization, she complained of sudden chest pain without radiation. Additional symptoms were mild dyspnoea, indigestion and nausea. The patient denied palpitations, sweating or anxiety. Our initial concern was that of the presentation of symptoms related to the HH. A cardiac workup based on her clinical symptoms and the history of a three-vessel coronary artery disease revealed a non-ST elevation myocardial infarction (NSTEMI) based on electrocardiogram changes and elevation of CK-MB to 85 [normal level (NL) < 25 U/L], CK of 999 (NL < 170 U/L) and troponin of 1.23 (NL < 0.03 mg/mL).

A percutaneous coronary intervention was performed and a left anterior descending artery stent placed. Thrombocyte aggregation inhibitor therapy was initiated. The distal radius fracture was treated conservatively with a forearm cast for six weeks. The patient had an uneventful recovery and was discharged for rehabilitation care. She still denied any significant abdominal symptoms.

One year after the diagnosis of a HH type Ⅳ and an eventful course, the patient was still opposing an elective surgical repair. Meanwhile G-GT level climaxed 2327 U/L. She still remained symptom-free.

Three months after the NSTEMI, the patient was admitted to the emergency room with a six day history of constant severe epigastric pain, vomiting, weight loss (7 kg/mo) and jaundice. Within our diagnostic investigation a mechanical ileus and again a NSTEMI was diagnosed.

After passing a nasogastric tube with release of 1500 mL of bile stained fluid and infusion therapy to equate water and electrolyte balance the patient was prepared for surgery.

As expected the HH type Ⅳ was identified and found to contain the entire duodenum, pancreatic head and the common bile duct (Figure 2). The esophageal hiatus was

dilated (10 cm in diameter) with no evidence of previous mechanical disruption.

Manual reposition of the herniated content, excision of the thickened hernia sack and a cholecystectomy were performed without complications. The defect was augmented with interrupted non-absorbable sutures and mesh. The enlarged common bile duct was identified and released from adhesions and constrictions (Figure 2C).

After two days of an uneventful postoperative course with monitoring at the intensive care unit, the patient suffered disseminated intravascular coagulopathy with ischemia of the terminal ileum so that a re-laparotomy with right hemicolectomy and an ileotransversostomy became necessary. Extubation was possible after stabilization of the critical hemodynamic condition. Deterioration of general condition occurred shortly after on the intensive care unit with increased demand on catecholamine and the need for re-intubation. On day 20 after repair of the HH the patient developed increasing cardiac complaints with myocardial ischemia and cardiogenic shock, culminating in ventricular fibrillation and death.

DISCUSSION

The mechanisms and sources for diaphragmatic herniation of the pancreas remain unclear. Traumatic or iatrogenic diaphragmatic hernia (DH) are rare entities accounting for less than 1% of all DH[4].

Possible explanations are associated with congenital structural anomalies of the diaphragm or abdominal and thoracic organs like a persistent pneumoenteric defect, a failure of closure of the pleuroperitoneal canal like in Bochdalek's hernia or a traction of a vascular pedicle by other organs as in PEH[1,5]. Congenital diaphragmatic hernia (CDH) occur with a prevalence between 1.7 and 5.7 per 10000 births and are classified in hiatal, posterolateral (Bochdalek), retrosternal (Morgagni) and transverse septum defect hernia[4]. Bochdalek´s hernia is the most common CDH type (95%). The remaining three types occur with an incidence of about 2% each.

Mullin *et al*[6] reviewed 13138 abdominal CT reports for incidental Bochdalek's hernia in adults and identified 22 cases. Only one of the 13138 patients showed dislocation of the pancreas. Further cases of reported herniation of the pancreas as a Bochdalek's hernia are described by Cuschieri *et al*[7] and Oliver *et al*[8]. One case reported by Moore *et al*[9] describes a herniated pancreas through the left-sided ventrolateral part of the diaphragm.

A hiatal herniation of the pancreas is a rarity. Our review of the literature yielded 11 reported cases with herniation of the pancreas or parts of it through the esophageal hiatus (Table 1). To the best of our knowledge we present the first case of a HH type Ⅳ containing the entire duodenum, head of pancreas and an intrathoracic duodenal papilla associated with intra- and extra-hepatic cholestasis.

Possible complications of a HH may result in hemorrhage, incarceration, obstruction, strangulation and perforation. Extrahepatic biliary obstruction as a complication of a HH with intrathoracic gastric volvulus is described by Llaneza *et al*[10]. In only one case the association of a myocardial infarction in patient's history and a pancreatic HH is reported by Kafka *et al*[11]. Another interesting aspect is described by Chevallier *et al*[12] and Maksoud *et al*[13] pointing out that a hiatal herniation of the pancreas may remain reversible. Further cases in the published literature are described in Table 1[14–17]. Whether the patients were symptomatic or not, all described cases (Table 1) underwent surgical repair except one actual case reported by Rozas *et al*[2].

Historically, surgical repair was advocated for the treatment of patients with PEH (types Ⅱ, Ⅲ and Ⅳ HH) regardless of whether they had related symptoms. This approach stem from retrospective reports showing 30%-45% incidence of complications and mortality rates up to 50% among patients left untreated[18,19]. More recently, however, several authors have questioned the need for repair in truly asymptomatic patients[20]. Although our patient was asymptomatic, there were clear-cut signs (compression of the common bile duct) that warranted a surgical repair. Despite our recommendation of surgical hernia repair soon after the diagnosis, we had to respect the declared intention of the patient for a conservative procedure. The uniqueness of this case also supported this dilemma. So we were forced to wait for surgical repair within an emergency situation complicated by a myocardial infarction and reduced general condition.

Our case illustrates the serious sequelae of a HH type Ⅳ that can occur when treated conservatively and therefore we recommend that all HH type Ⅳ should be repaired as soon as possible after the diagnosis. Despite of the fatal outcome we were encouraged to publish this case to improve future decision finding processes in similar cases.

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CASE REPORT

Laparoscopic appendectomy for appendiceal mucocele in an 83 years old woman

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Abstract

Mucocele of the appendix is an uncommon but potentially dangerous pathological entity that presents in a variety of ways. Therefore, optimal surgical therapy is controversial; while some authors adopt a simple appendectomy, others recommend extensive resection, such as right hemicolectomy. We report the case of an 83 years old woman who presented with cystic neoformation in the right iliac fossa that was preoperatively considered an appendiceal mass. We electively performed a laparoscopic resection that histological examination defined as a mucinous cystadenoma. No recurrence was observed in the follow-up period of 9 mo.

Key words: Appendiceal tumor; Laparoscopy; Mucocele; Minimal invasive surgery

Core tip: This report calls the clinician's attention to the fact that patients presenting with chronic lower right quadrant pain may be diagnosed with appendiceal tumors, particularly elderly patients, as was the case in our report. Since the elderly patient population usually has co-morbid conditions, minimal invasive procedures should be considered after preoperative diagnostic procedures to confirm the absence of advanced tumors.

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INTRODUCTION

Appendiceal mucocele is an uncommon pathology of the appendix (0.15%-0.6% of all appendectomies) characterized by the accumulation of mucoid material in the lumen[1,2]. Etiopathogenesis can be inflammatory or neoplastic. Dissemination of neoplastic cells and mucoid material in the abdominal cavity caused by appendiceal perforation clinically results in pseudomyxoma peritonei. Therapy is fundamentally surgical and several options have been reported, ranging from simple appendectomy to right hemicolectomy. We report here a case of an 83 years old woman with one month history of right lower abdominal pain caused by an appendiceal mass that was laparoscopically resected.

CASE REPORT

An 83 years old woman presented with abdominal distension and discomfort in the right lower quadrant of one month duration. In her medical history, she had hypertension for 10 years and rheumatoid arthritis for 2 years. She was taking acetyl salicylic acid and a nonsteroidal anti-inflammatory. She was an active smoker with a 50 pack-

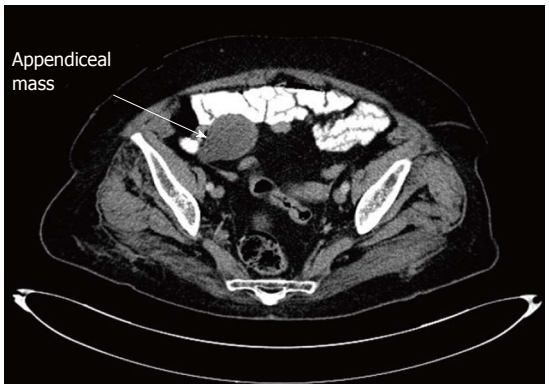

Figure 1 Preoperative contrast enhanced multidetector computed tomography images demonstrated a 4 cm x 3.5 cm x 3 cm, blind ending, tubular, fluid-filled structure (arrow) that appeared to arise from the cecum, consistent with mucocele of the appendix.

year smoking history and was operated on for a perianal fistula 20 years previously. On physical examination, she was afebrile and hemodynamically stable. The abdominal examination was normal except for focal tenderness over McBurney's point without rebound tenderness on palpation and a mass lesion over the right lower quadrant. Ultrasound examination was performed and a cystic mass in the right iliac fossa of about 4 cm in size was reported.

Laboratory analysis was unremarkable. Axial computed tomography (CT) scanning revealed a 4 cm × 3.5 cm × 3 cm, blind ending, tubular, fluid-filled structure that appeared to arise from the cecum, consistent with mucocele of the appendix (Figure 1). Colonoscopy showed evidence of an appendiceal mass covered by cecal mucosa; no other pathology was detected. Intra-operative observation revealed a smooth, cystic tumor of the appendix (Figure 2A). There was no ascites, metastatic peritoneal nodules or ovarian pathology as evidence of malignancy. Laparoscopic excision of the unruptured appendiceal mucocele with the mesoappendix was performed (Figure 2B). We used LigaSure™ for the appendiceal excision but other choices are available, such as simple knotting and cut or stapler use.

Histopathological examination showed low grade epithelial dysplasia, a feature diagnostic of a mucinous cystadenoma, measuring 3.5 cm at its greater diameter. No lymph node involvement was discovered in the appendiceal mesentery. The patient was discharged on postoperative day one and recovered uneventfully. The patient remained well and symptom-free during the follow-up period of 9 mo.

DISCUSSION

Appendiceal mucocele does not have a typical clinical picture. More than two-thirds of patients have their appendiceal mucocele removed on incidental finding[3]. Clinically, it can remain asymptomatic or manifest with acute or chronic abdominal pain which is the most common clinical finding, as was the case in our patient. In an elderly patient, undoubtedly, malignancy should be

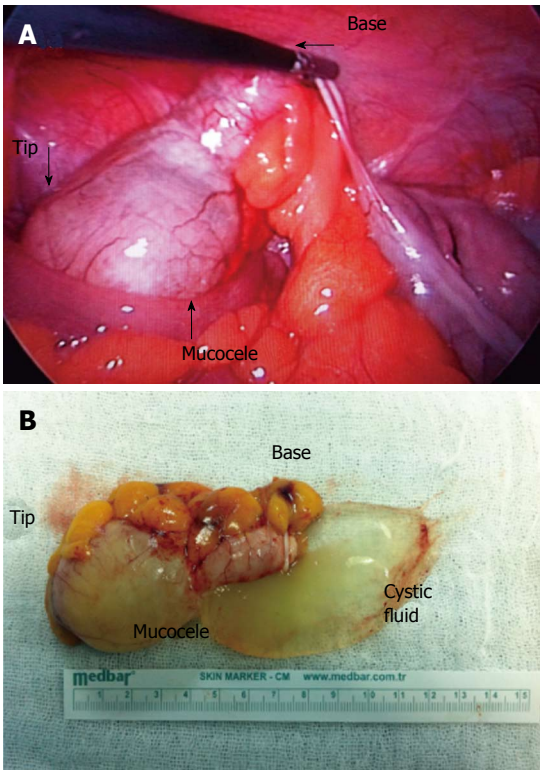

Figure 2 Intra-operative view of smooth cystic tumor of the appendix (A) located at the tip of the appendix (B) after laparoscopic resection (perforated in endobag at the time of extraction).

considered as a differential diagnosis and preoperative diagnostic methods are needed to avoid inappropriate treatment. Also, risk of perforation of the appendix is significantly higher in elderly patients.

Laparoscopic appendectomy is becoming popular because of its advantages, not only for acute appendicitis but also for perforated appendicitis and even suspected malignant lesions. The optimal treatment modality for appendiceal mucocele is still controversial. Surgical management of this entity differs primarily depending on the characteristics of the mass (location and size) and clinical presentation, whereas the approach used (open or minimally invasive techniques) depends partly upon the preference and experience of the surgeon. Although some authors still recommend open procedures for appendiceal masses[4], particularly for those with possible malignancy, laparoscopic techniques have been described to minimize the risk of seeding tumor implants during laparoscopic manipulation[5]. In our case, preoperative imaging studies were not suspicious for malignancy. CT revealed no involvement of the appendiceal base, mesoappendix or local lymph nodes. We ensured isolation of the appendix, wrapping gauze around the appendiceal structures during laparoscopic resection and then putting it into an endobag to avoid any contamination of the abdominal cavity in case of perforation. Fortunately, histopathological examination revealed a low grade appendiceal mucinous neoplasm confined to the appendix and no further therapy was required. In addition to the diagnostic advantages of

laparoscopy, excision of the mesoappendix with the main cystic appendiceal tumor helps assess stage of disease.

In the era of minimally invasive procedures, laparoscopic appendectomy for mucocele should be considered as the primary choice, particularly in elderly patients in the absence of preoperative confirmation of locally advanced malignancy of the appendix. The laparoscopic approach allows diagnostic evaluation and appendectomy to be performed and confers advantages of minimal invasive surgery as well as a short hospital stay and decreased recovery period, particularly in patients with comorbid conditions.

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CASE REPORT

Topical nitrate drip infusion using cystic duct tube for retained bile duct stone: A six patients case series

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Author contributions: Shoji M, Sakuma H and Yoshimitsu Y designed the report; Shoji M, Sakuma H and Yoshimitsu Y were attending doctors for patients; Maeda T, Nakai M and Ueda H organized the report; Shoji M wrote paper.

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Abstract

A retained bile duct stone after operation for cholelithiasis still occurs and causes symptoms such as biliary colic and obstructive jaundice. An endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy (EST), followed by stone extraction, are usually an effective treatment for this condition. However, these procedures are associated with severe complications including pancreatitis, bleeding, and duodenal perforation. Nitrates such as glyceryl trinitrate (GTN) and isosorbide dinitrate (ISDN) are known to relax the sphincter of Oddi. In 6 cases in which a retained stone was detected following cholecystectomy, topical nitrate drip infusion via cystic duct tube (C-tube) was carried out. Retained stones of 2-3 mm diameter and no dilated common bile duct in 3 patients were removed by drip infusion of 50 mg GTN or 10 mg ISDN, which was the regular dose of intravenous injection. Three other cases failed, and EST in 2 cases and endoscopic biliary balloon dilatation in 1 case were performed. One patient developed an adverse event of nausea. Severe complications were not observed. We consider the topical nitrate drip infusion *via* C-tube to be old but safe, easy, and inexpensive procedure for retained bile duct stone following cholecystectomy, inasmuch as removal rate was about 50% in our cases.

Key words: Nitrate; Topical drip infusion; Cystic duct tube; Retained bile duct stone; Cholecystectomy

Core tip: In 6 cases in which a retained stone was detected following cholecystectomy, topical nitrate drip infusion via cystic duct tube (C-tube) was carried out. Retained stones of 2-3 mm diameter with no dilated common bile duct in 3 patients were removed by drip infusion of glyceryl trinitrate or isosorbide dinitrate. Three other cases failed, and endoscopic sphincterotomy in 2 cases and endoscopic biliary balloon dilatation in 1 case were performed. The topical nitrate drip infusion *via* C-tube is old but safe, easy, and inexpensive procedure for retained stone following cholecystectomy, inasmuch as removal rate was about 50% in our cases.

Shoji M, Sakuma H, Yoshimitsu Y, Maeda T, Nakai M, Ueda H. Topical nitrate drip infusion using cystic duct tube for retained bile duct stone: A six patients case series. *World J Gastrointest Surg* 2013; 5(6): 210-215 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i6/210.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i6.210

INTRODUCTION

Common bile duct (CBD) stones are identified in approximately 4%-20% of symptomatic patients who had undergone cholecystectomies[1,2]. When a routine intraoperative cholangiography (IOC) is not performed in patients without symptoms, 0.9% of patients following cholecystectomy will present a retained stone, requiring intervention[3]. This means that most choledocholithiasis

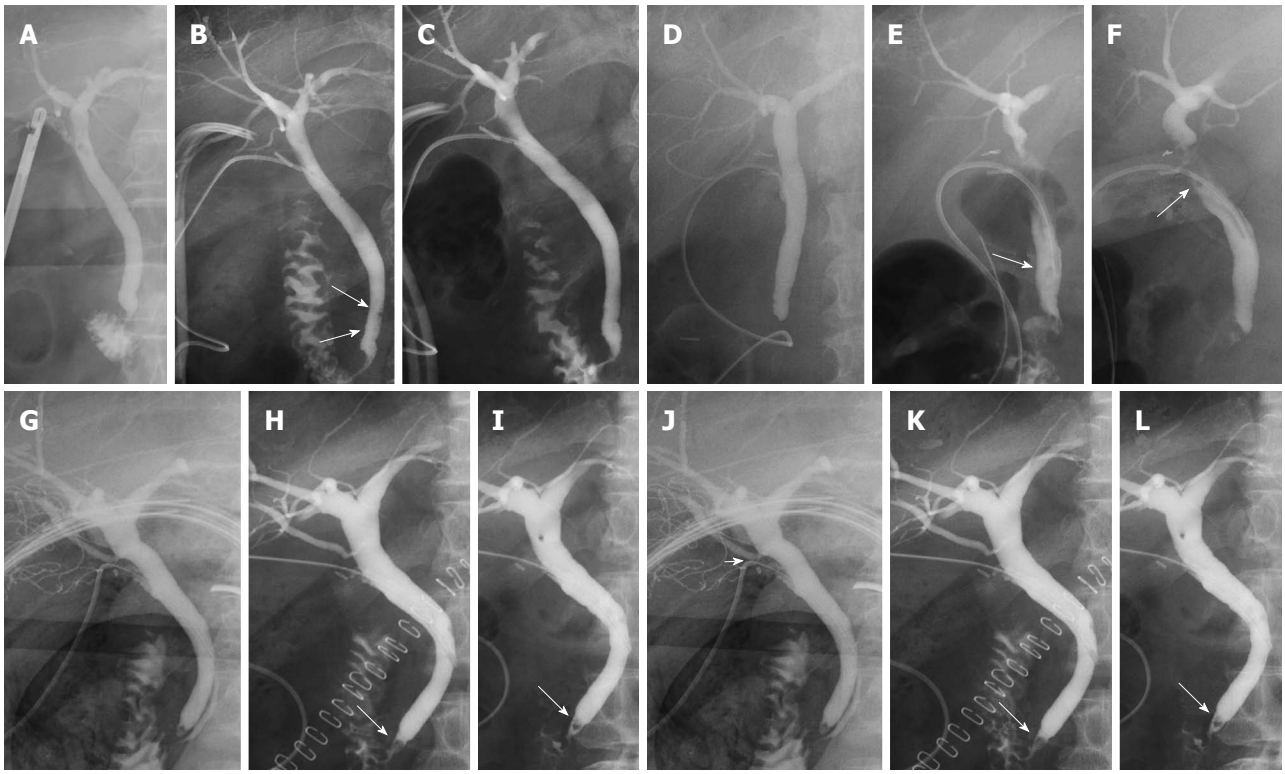

Figure 1 Cholangiography performed in patients. A: Intraoperative cholangiography (IOC) could not identify a filling defect; B: On postoperative day (POD) 7, cholangiography demonstrated a 2 mm-diameter stone (white arrow); C: Topical glyceryl trinitrate (GTN) infusion using cystic duct tube (C-tube) was performed (on the following day the retained stone disappeared) (white arrow); D: IOC could not identify a filling defect; E: On POD 9, cholangiography showed 2 mm-diameter stones at distal common bile duct (CBD) (white arrow); F: GTN was infused three times and the retained stones were removed (white arrow); G: IOC could not show a filling defect, but contrast media did not flow into duodenum; H: Cholangiography showed a 3 mm-diameter floating stone on POD 5 (white arrow); I: Isosorbide dinitrate was infused 6 times, but the stone was not removed (white arrow); J: Since an injury to posterior superior bile duct was suspected by IOC (white arrow head); K: C-tube was placed. On POD 7, cholangiography showed a 6 mm-diameter retained stone at distal CBD without biliary leak (white arrow); L: GTN was infused 4 times, but the stone could not be removed (white arrow).

remain silent or pass spontaneously into the duodenum and some may present with complications including biliary obstruction, acute pancreatitis, and cholangitis in the future. Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilation (EPBD) is a well-established therapeutic procedure for the extraction of a retained stone. However, this is an invasive examination and associated with specific complications such as acute pancreatitis, hemorrhage, and duodenal perforation, or even death. Its morbidity and mortality rates are up to 10.0% and 0.4%, respectively[1]. Moreover, after EST, the function of sphincter of Oddi (SO) is destroyed and the loss of this physiologic barrier between duodenum and biliary tract results in duodenocholedochal reflux and bacterial colonization of the biliary tract. Then, the presense of bacteria in the biliary system causes late complications including recurrence of stones, recurrent ascending cholangitis and even malignancy[4].

It is preferable to select a safer procedure for a retained stone so as to reduce early or late complications. When the existence of a retained stone is suspected, a cystic duct tube (C-tube) is surgically inserted into the cystic duct and the CBD can be drained *via* the cystic duct, and the retained stone can be managed, if necessary, in the postoperative period. It has been reported that topical application of nitrate effectively relaxes SO and should be taken into account for the removal of a retained stone[5]. Therefore, a topical nitrate drip infusion procedure using a cystic duct tube was tested on 6 patients with retained stones after cholecystectomies.

CASE REPORT

We report 6 patients after cholecystectomy with retained stones, who experienced the topical nitrate drip infusion procedure using a C-tube. The main characteristics of each are summarized in Table 1.

Patient 1

A 76-year-old man complained of epigastralgia and jaundice. He had undergone distal partial gastrectomy and Roux-en-Y reconstruction for early gastric cancer 3 years ago. Computed tomography (CT)/magnetic resonance cholangiopancreatography (MRCP) did not show choledocholithiasis. Then, an open cholecystectomy was performed. The brown pigment stones and purulent exudate were seen in the gallbladder. IOC could not identify a filling defect (Figure 1A), but it was probable that a retained stone existed and a C-tube was placed. On postoperative

Table 1 Multiple logistic regression analysis of factors associated with HIV/HBV, HIV/HCV, and HIV/HBV/HCV co-infection

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yr)	76	69	37	75	64	69
Sex	Man	Man	Woman	Woman	Woman	Man
Diagnosis	Acute cholecystitis	Acute cholecystitis	Choledocholithiasis	Choledocholithiasis	Choledocholithiasis	Acute cholecystitis
Preoperative drainage	–	EST	–	–	–	–
Surgical method	Open	Laparoscopic	Laparoscopic	Laparoscopic	Laparoscopic	Open
IOC defect	–	–	+	+	–	–
Stone diameter (mm)	2	2	3	5	3	6
CBD diameter (mm)	6	6	6	8	6	12
Nitrate	GTN 50 mg + NS 200/2 h	GTN 50 mg + NS 500/5 h	ISDN 10 mg + NS 500/3 h	GTN 10 mg + NS 500/3 h	ISDN 5 mg + NS 250/3 h	GTN 50 mg + NS 250/2.5 h
Trial	2	3	2	1	6	4
Stone removal	Yes	Yes	Yes	No	No	No
Complication	–	–	–	Nausea	–	–
2nd procedure	–	–	–	EST	EST	EPBD

GTN: Glyceryl trinitrate; EST: Endoscopic sphincterotomy; ISDN: Isosorbide dinitrate; IOC: Intraoperative cholangiography; CBD: Common bile duct; EPBD: Endoscopic papillary balloon dilation.

day (POD) 7, cholangiography demonstrated a 2 mm-diameter stone (Figure 1B). Infusions of 50 mg of GTN and 200 mL of normal saline were given using a C-tube for 2 h. He had an episode of biliary colic and on the next day the retained stone disappeared (Figure 1C). He was discharged on POD 13.

Patient 2

A 69-year-old man was referred to us complaining of abdominal pain and fever. He had a past history of cerebral hemorrhage and left hemiplegia. Since CT revealed severe acute cholangitis due to cholecystocholedocholithiasis, he needed biliary drainage. EST with stone extraction was performed. After 2 mo, he had recurrent biliary tract symptoms. CT identified recurrent CBD stones. Laparoscopic cholecystectomy was performed. IOC could not identify a filling defect (Figure 1D), but a retained stone was suspected and a C-tube was placed. On POD 9, cholangiography showed 2 mm-diameter stones at distal CBD (Figure 1E). Infusions of 50 mg of GTN and 500 mL of normal saline were given three times and the retained stones were removed on POD 15 (Figure 1F). He needed postoperative rehabilitation and was discharged on POD 31.

Patient 3

A 37-year-old woman presented with abdominal pain. CT scan revealed stones in the gallbladder and distal CBD. For this, laparoscopic cholecystectomy was performed. IOC demonstrated a 3 mm-diameter filling defect. However, since the CBD was not dilated, laparoscopic CBD exploration was not carried out. A C-tube was placed percutaneously. The brown pigment stones were seen in the gallbladder. On POD 4, when cholangiography *via* C-tube identified the retained stone, 10 mg of isosorbide dinitrate and 500 mL of normal saline were topically infused *via* a C-tube. The following day the retained stone was removed and she was discharged on POD 11.

Patient 4

A 75-year-old woman was positive for fecal occult blood test and total colonoscopy detected early sigmoid colon cancer. CT revealed stones in the gallbladder and distal CBD. Laparoscopic cholecystectomy and sigmoidectomy were performed at the same time. IOC demonstrated a 5 mm-diameter filling defect. Diameter of the CBD was 8 mm, and extraction of the stone was not carried out. On POD 5, cholangiography *via* C-tube identified the retained stone, and 10 mg of GTN and 500 mL of normal saline were topically infused. Because she complained of nausea, the treatment was stopped. Nausea disappeared as soon as the drip infusion stopped. On POD 8, EST was performed and the retained stone was extracted. She needed rehabilitation for poor performance status and was discharged on POD 28.

Patient 5

A 64-year-old woman was admitted to our hospital with fever and liver dysfunction. CT/MRCP revealed no evidence of a CBD stone. Laparoscopic cholecystectomy was performed. There were about 200 brown pigment stones in the gallbladder. IOC could not show a filling defect, but contrast media did not flow into the duodenum (Figure 1G). A C-tube was placed, and cholangiography showed a 3 mm-diameter floating stone on POD 5 (Figure 1H). Infusions of 5 mg of ISDN and 250 mL of normal saline were given 6 times, but the stone was not removed (Figure 1I). EST was performed on POD 9. The stone faded away and the C-tube was removed. She was discharged on POD 15.

Patient 6

A 69-year-old man presented with abdominal pain and anorexia. He underwent a carotid endarterectomy and had been treated with an antiplatelet agent. Transabdominal ultrasonography and CT revealed gallstones, pericholecystic fluid, and gallbladder wall thickening. He was diagnosed as acute

cholecystitis, and open cholecystectomy was performed. Since an injury to posterior superior bile duct was suspected by IOC (white arrow head) (Figure 1J), a C-tube was placed. On POD 7, cholangiography showed a 6 mm-diameter retained stone at distal CBD without biliary leak (Figure 1K). Infusions of 50 mg of GTN and 250 mL of normal saline were given 4 times, but the stone could not be removed (Figure 1L). EPBD and extraction of stone with rendezvous technique using a C-tube was performed on POD 11. He was discharged without complication on POD 19.

DISCUSSION

In our cases, the rate of removing retained stones by topical nitrate drip infusion using the C-tube was 50%. In three successful patients, the diameter of retained stone was 2-3 mm and CBD was not dilated. All of them were asymptomatic postoperatively. Infusion trial ranged from 1-3 times. On the other hand, the procedure failed in three patients. The diameter of retained stone was 3-6 mm and CBD had a range of 6-12 mm. Infusion trial ranged from 1-6 times. Topical application of GTN and ISDN was used intravenously at the regular dose and there were no side effects such as hypotension and headache. One patient developed an adverse event of nausea but severe complications were not observed. EST in 2 cases and EPBD in 1 case were performed as second procedures.

Spontaneous stone migration occurred in 21% of patients with choledocholithiasis within one month and 83% of those were asymptomatic. The size of a retained stone (dichotomized at 8 mm) is the only independent factor to predict migration through duodenum[6]. However, Whether migration depends on the relationship between a size of a retained stone and a diameter of CBD has not been reported. Gallstones with a diameter up to 5 mm can migrate in CBD and trigger acute pancreatitis, cholangitis, and hepatic abscess[7]. In patients with retained stones after laparoscopic cholecystectomy, 35% of these passed calculi spontaneously within 6 wk of operation without ERCP, while 65% of these had persistent bile duct stones retrieved by endoscopic intervention[8]. Therefore, it is difficult to manage a retained stone with no dilated CBD after cholecystectomy.

Recently, before surgery, MRCP and endoscopic ultrasound (EUS) have been used to accurately estimate the biliary system without cannulating the ducts. Both MRCP and EUS have sensitivity and specificity of over 90%[1,2]. However, when a retained bile duct stone is less than 4 mm or CBD is dilated more than 10 mm, detection by both ERCP and MRCP may not be possible[9]. Small stones can cause acute biliary pancreatitis. At the time of surgery, IOC is an effective procedure of identifying a retained bile duct stone. Laparoscopic IOC has a sensitivity of 80.0%-92.8%, and specificity of 76.2%-97.0%[1]. There is a time lag between preoperative examinations and the operation, and IOC can reflect bile duct stones in real time. During an operation, when it was suspected in a series of examinations that a patient still had CBD stones, the surgeon needs to select an operative stone extraction (laparoscopic/open or transcystic duct/choledochostomy) or pre/postoperative ERCP. There is no difference in performance for morbidity and mortality when laparoscopic choledochotomy and perioperative ERCP are compared. However, hospital stay is shorter for patients who had undergone laparoscopic choledochotomy[2]. EPBD had less infections over the short and long-term[10] and less stone recurrence over the long term than EST[11]. However, Disario *et al*[12] had reported that EPBD showed an increase of morbidity rates and death for pancreatitis when compared with EST for biliary stone extraction.

For years, the T-tube has been used to decompress the biliary duct and avoid biliary complications in the postoperative period. It also makes postoperative cholangiography possible, and if a retained stone is detected, the stone can be extracted by choledochoscopy *via* the T-tube. However, the T-tube causes complications up to 10% such as bile peritonitis due to T-tube dislocation, which can lead to re-operation and even death, and requires a prolonged hospital stay. Recently, it was reported that primary closure might be effective for T-tube drainage after choledochotomy in preventing postoperative complications[13]. In contrast, the C-tube, which is placed in the CBD *via* the cystic duct has the advantages of easier surgical technique, less complication and shorter hospital stay. It is possible that postoperative direct cholangiography repeatedly performed on various conditions such as contrast media concentration and posture of a patient would show the same results as the T-tube.

The non-operative elimination of a retained stone has long been tried because repeated surgery is undesirable. Staritz *et al*[5,14] first reported that GTN effectively decreased papillary baseline pressure, relaxed SO muscle, and facilitated bile flow into duodenum. GTN had no influence on SO motility. Also, sublingual application of GTN facilitated endoscopic extraction of CBD stones. GTN is a donor of nitric oxide, which is one important element of a non-adrenergic non-cholinergic pathway to the SO[15]. Luman *et al*[16] reported that topical application of 5 or 10 mg of GTN reduced tonic and phasic contractions of SO without side effects. Wehrmann *et al*[17] reported that topical application of 10 mg of GTN or 10 mg of ISDN evoked a profound inhibition of SO motility, and the effect of ISDN was longer than of GTN. Both GTN and ISDN were not accompanied with adverse effects. In two meta-analyses[18,19], prophylactic GTN administered by either sublingual or transdermal route was useful for prevention of post-ERCP pancreatitis. The main adverse events of nitrate were hypotension and headache. However, they were easily managed by conventional treatment. We consider the adverse events are rare because blood concentration of a drug in a topical application is lower than in an intravenous administration.

It is estimated that the incidence of choledocholithiasis is 15%-40% in patients over 60 years old compared

with 8%-15% in those under 60 years old undergoing open cholecystectomy for cholelithiasis[20]. Among patients at high-risk (high age, surgically altered anatomy as in patient 1, and antiplatelet agents treatment as in patient 6), which are increasing in recent years, the non-invasive procedure for retained stone is preferable. Also, in the patients with no dilated CBD who had undergone a choledochotomy postoperative bile duct stricture tends to occur, which is a life-threatening complication requiring expertise on the part of surgeon, radiologist, and gastroenterologist[21]. Representative medical treatments for retained stones are gallstone resolution and extracorporeal shock waves. Presently however, results have not been clear-cut in clinical practice. A recent study suggested that direct peroral cholangioscopy can remove a retained stone without complication[22].

Hence, inasmuch as the topical nitrate drip infusion *via* C-tube is an old procedure, it is safe, easy, and inexpensive for a retained bile duct stone following cholecystectomy. The removal rate is admittedly not so high, about 50% in our cases. In particular, it is effective in cases in which stone diameter is smaller than 6 mm or CBD is not dilated. There are two principal mechanisms by which topical nitrate infusion removes retained stones. First, nitrates relax SO. Topical dose of nitrates can be as effective as an intravenous dose. Secondly, flow of a drip infusion can drain the retained stone after dilatation of SO with nitrates. Main adverse events are recognized such as biliary colic and nausea in patient 4 and pancreatitis can occur from blockage of pancreatic exocrine secretions by retained stones. When infusing a topical nitrate, the patient remains under careful supervision. If not successful, the C-tube is useful for the rendezvous technique and clearance by ERCP with EST or EPBD as in patient 6.

In conclusion, our cases demonstrated the potential effectiveness of topical nitrate drip infusion using a C-tube for a retained stone when stone size is small and CBD is not dilated. An indication for a kind and dose of nitrate, and volume and speed of drip infusion should be taken into consideration. However, this is the small sample size and more studies including randomized control trials are required in the future. These may show there is an advantage of the topical nitrate drip infusion using a C-tube for retained stone before an endoscopic procedure.

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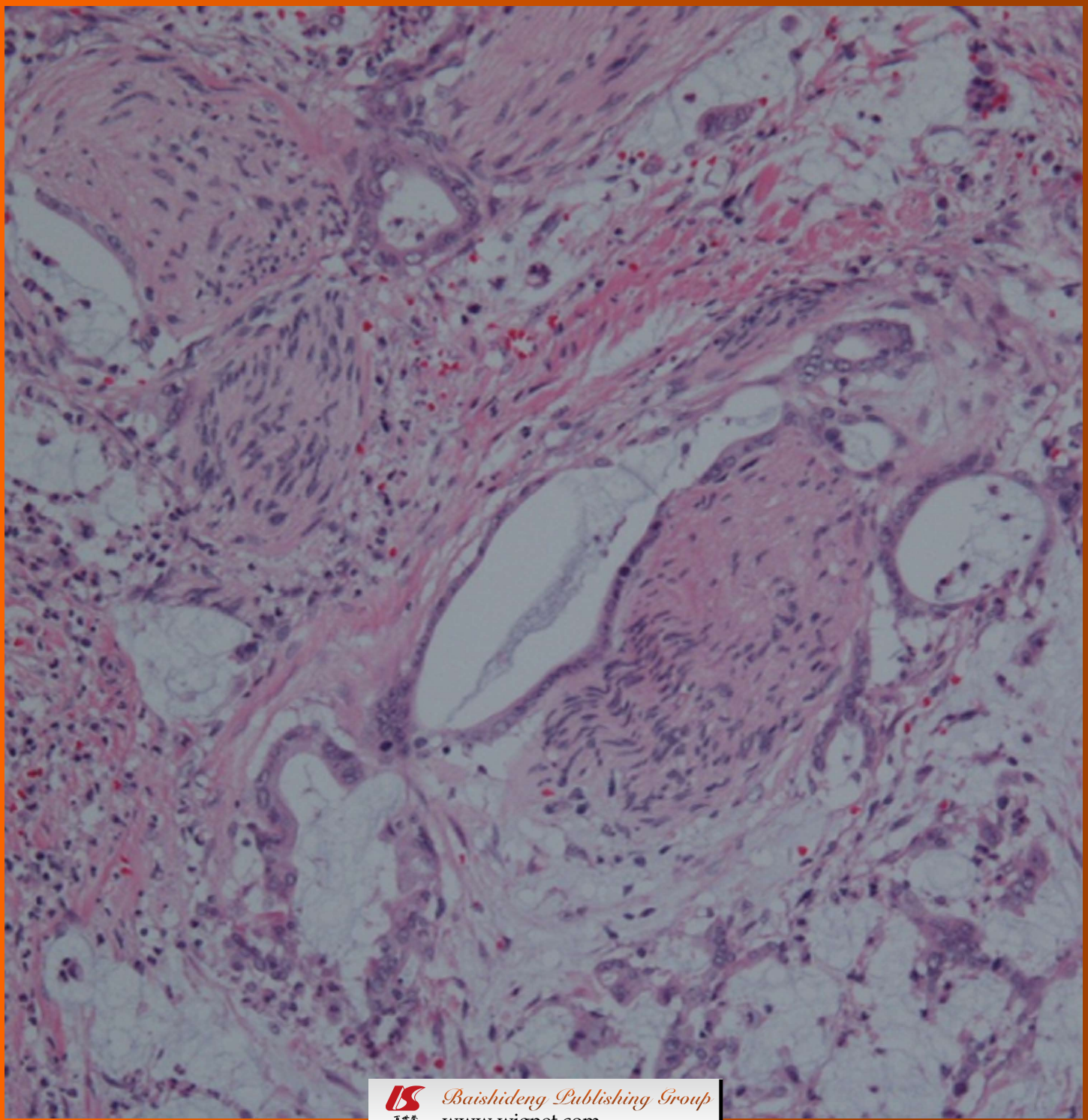

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BRIEF ARTICLE

Emergency laparotomy in octogenarians: A 5-year study of morbidity and mortality

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Abstract

AIM: To determine the morbidity and mortality associated with emergency laparotomy for a clinically acute abdomen in patients aged ⩾ 80 years.

METHODS: In this retrospective audit, octogenarians undergoing emergency laparotomy between 1st January 2005 and 1st January 2010 were identified using the Galaxy Theatre System. Patients undergoing abdominal surgery through groin crease incisions or Lanz or Gridiron incisions were excluded. Also simple appendectomies were excluded. All patients were aged 80 years or more at the time of their surgery. Data were obtained using casenote review with a standardised proforma to determine patient age, American Society of Anesthesiologists (ASA) grade, indications for surgery, early (within 30 d) and late (after 30 d) complications, mortality and length of stay. Data were inserted into a Microsoft Excel spreadsheet and analysed.

RESULTS: One hundred patients were identified from the database (Galaxy) as having undergone emergency laparotomy. Of those, 55 underwent the procedure for intestinal procedures and 37 for secondary peritonitis. There was a 2:1 female predominance; average age 85 and ASA grade 3. Bowel resection was required in 51 out of the 100 patients and 22 (43%) died. Other procedures included appendicectomy, adhesiolysis, repair of AAA graft leak and colostomies for the pathological process resulting in an acute abdomen. Twelve of 100 patients (12%) suffered intra-operative complications, including splenic and bowel-serosal tears. Seventy patients (70%) had postoperative complications including myocardial infarction, wound infection, haematoma and sepsis. Overall mortality was 45/100 patients (45%). The major causes of death were sepsis (19/45 patients, 42%), underlying cancer (13/45 patients, 29%); with others including bowel obstruction (2/45 patients, 4%), myocardial and intestinal ischaemia and dementia.

CONCLUSION: Emergency laparotomy in octogenarians carries a significant morbidity and mortality. In particular, surgery requiring bowel resection has higher mortality than without resection.

Key words: Laparotomy; Perioperative care; Aged; Mortality; Morbidity

Core tip: Aging is associated with an increase in operative and anaesthetic risk during emergency laparotomy. Literature addressing the outcomes following emergency laparotomy in the elderly is limited. The morbidity and mortality rates in this subgroup of patients were explored, and in our study we determined the mortality rate to be 45%.

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INTRODUCTION

An aging United Kingdom population has lead to an increase in the number of emergency general surgical admissions in octogenarians; indeed 8739 patients over the age of 75 required emergency laparotomy in 2010-2011[1]. This has significantly increased from 4486 patients in 2001 reflecting the increased life expectancy of today's population, with the average person living to 80 years compared with 74 years in 1983[2].

Laparotomy is a major intervention. Given that it is a considerable surgery to undertake it is not surprising that laparotomy is associated with significant morbidity and mortality, especially in the emergency setting, with current literature quoting mortality figures of 10%-55%[3-5].

Elderly patients present a higher risk for abdominal surgery owing to an increase in the number and severity of medical co-morbidities which may add to the complexity of both surgery and anaesthesia. The aging cardiovascular and immune systems predispose elderly patients to increased postoperative infection and cardiovascular events such as stroke, myocardial infarction and venous thromboembolism. Also older patients have a reduced physiological reserve to cope with longstanding hypotension secondary to anaesthesia and blood loss during surgery; and may take considerably longer to recuperate postoperatively although recent studies and scoring systems show that this is very subjective and that many older patients recover well postoperatively and return to function as well as their peers[6,7].

MATERIALS AND METHODS

In this 5 year retrospective study, patients undergoing emergency laparotomy for intestinal conditions or secondary peritonitis between 1st January 2005 and 1st January 2010 were identified using the galaxy theatre management system used at Medway Maritime Hospital NHS trust (Galaxy Theatre System, Sanderson Ltd, 1-2 Venture Way, Aston Science Park, Birmingham, United Kingdom). Patients included in the study were those who were aged 80 years or over at the time of their operation. Laparoscopy alone without subsequent conversion to laparotomy and procedures involving inguinal incision for hernia repair were excluded from the study, as were other procedures such as simple appendicectomy if performed by Lanz incision. Medical records for the remaining relevant patients were sought and reviewed individually using the pro-forma shown in Figure 1. The American Society of Anesthesiologists (ASA) grade was determined from the anaesthetic pre-operative assessment chart and is shown in Table 1. Data was inserted into a spreadsheet and analysed using Microsoft Excel software.

RESULTS

Overall, 100 patients underwent emergency laparotomy for abdominal pathology between 1st January 2005 and 1st January 2010. Eight additional patients were excluded from the study as these patients underwent laparoscopy, and local approaches for hernia repair rather than a midline laparotomy incision.

Patients

Data was collected from 100 patients who underwent emergency laparotomy between 1st January 2005 and 1st January 2010, all of whom were 80 years or over at the time of surgery. Overall, the mean age was 85 years (range 80-96 years); 2:1 female predominance and mean ASA grade of 3.08 (range 1-5).

Indications for surgery

The indications for surgery and their corresponding patient numbers are shown in Table 2. Thirty seven of 100 patients underwent laparotomy for secondary peritonitis; of which 14/37 had lower gastrointestinal (GI) perforation including perforated diverticulitis and perforated appendicitis; 16/37 had upper GI perforation including perforated gastric and duodenal ulcers; and the remaining 7/37 had perforation of unknown or undocumented site. Twenty of 37 patients died, of which 10/37 had a upper GI perforation, and 9/20 had lower GI perforation. There was no statistically significant difference in mortality by the site of perforation.

Laparotomy to relieve colonic obstruction secondary to malignancy or adhesions was performed in 40/100 patients. The mortality in this group of patients was 17/40 patients (42.5%)

The mortality by indication for surgery is shown in Figure 2.

Procedures

Bowel resection was required in 51/100, patients with the main indication being malignancy, or ischaemia of the bowel secondary to adhesions. Of the 51 patients requiring bowel resection, 23/51 died (mortality 45%). Thirty one of 51 patients required bowel resection secondary to obstruction, with a mortality of 13/31 (42%). Seventeen of 51 patients required bowel resection from the complications of GI perforation and secondary peritonitis. Of these patients, 14/17 had lower GI perforation (*i.e.,* perforated diverticulitis) and 2/17 had upper GI perforation. No patients undergoing laparotomy for peptic ulcer perforation required resection. Nine of 17 patients with secondary peritonitis died, giving a mortality of 53%.

Mortality

The overall mortality for emergency laparotomy in octogenarians in this study is 44/100 (44%). There is a 2:1 female predominance. Sepsis represented the most frequent cause of death (19/45 patients, 42%), closely followed by death due to the underlying disease process, chiefly colonic cancer (12/45 patients, 27%). Other causes were myocardial infarction (2/45 patients, 4%), cerebrovascular disease (2/45 patients, 4%), death due to medical co-morbidities such as exacerbation of chronic

Name:
Age:
PAS:
Diagnosis:_____

Date of operation:_____

Operation:_____

ASA:_____

Pre-op complications:_____

Intra-op complications_____

Post-op complications_____

Date of admission_____

Date of discharge_____

Date of death_____

Cause of death____

Figure 1 Proforma for data collection.

Table 1 American Society of Anesthesiologist's pre-operative risk classification

ASA grade	Description
I	Normal healthy patient
II	Mild systemic disease – no functional limitation
III	Severe systemic disease – definite functional limitation
IV	Severe systemic disease which is a constant threat to life
V	Moribund patient who is unlikely to survive > 24 h with or without surgery

Reproduced from[8]. ASA: American Society of Anesthesiologist.

airways disease (4/45 patients, 8%). Two of 44 (4%) patients died due to ischaemic bowel postoperatively and 2/44 patients (4%) had an unknown cause of death. One further patient was deemed to have died of inanimation and dementia. Pictorial representation of mortality by cause of death is shown in Figure 3.

Sepsis represented 42% of the mortality. There were 2 sources of infection in these patients: 8/19 (42%) patients had abdominal sepsis and 8/19 (42%) had respiratory sepsis. The remaining 3/19 (16%) had sepsis of unknown origin.

The survival curve shown in Figure 4 shows that procedure associated mortality occurs early, with 50% of deaths occurring within 2 wk of surgery. The majority of patients who leave hospital following laparotomy survive more than 30 d. Twelve of 44 (27%) patients died following discharge from hospital, all of these deaths were unrelated to the operation but to the underlying illness or to unrelated acute problems which occurred more than 1 year later.

Twelve of 100 patients (12%) suffered intra-operative complications, including splenic and bowel-serosal tears, and abandonment for futility. Seventy patients (70%) had postoperative complications including myocardial infarction (4/70, 5%), wound infection (6/70, 7.5%) and sepsis (32/70, 46%) which was largely of respiratory origin. Multi-organ failure occurred in 2 patients (2.5%). Other complications include cardiovascular problems including atrial fibrillation (AF) and congestive cardiac failure (8/70, 10%). The other causes of morbidity making up the remaining 39% included cardiovascular accident (CVA), scrotal oedema, stoma problems, rectal bleeding and acute renal failure.

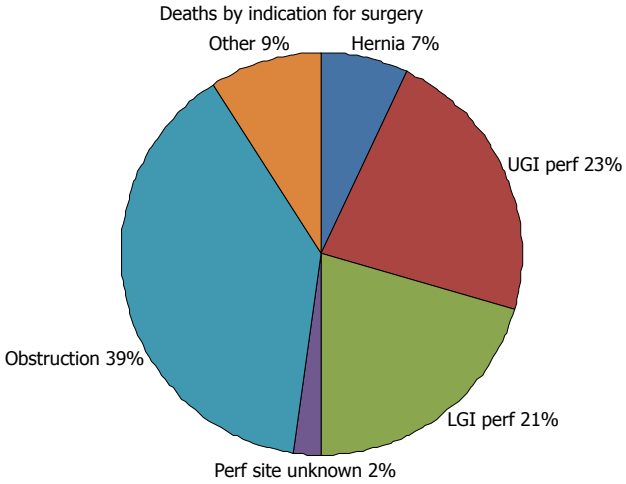

Figure 2 Absolute mortality by indication for surgery (excel chart). UGI: Upper gastrointestinal; LGI: Lower gastrointestinal tract.

Cost analysis

On average emergency laparotomy costs £10000 per patient, giving a total surgical cost for our cohort of £100000. Added to this the average length of stay was 27 d (range 1-192 d). Our patients on average spent 3 d in critical care. The cost of a critical care stay for 3 d is £4200 and the cost per day for an national health service (NHS) bed is £400. So the average cost of an emergency laparotomy per patient assuming 27 d stay with 3 d critical care admission is £23800. This gives a total cost for our cohort of £238000. Forty four percent of these patients died (*i.e.*, a loss of £104720) which limits the cost effectiveness of this procedure and highlights the importance of patient selection in terms of cost effectiveness and productivity.

DISCUSSION

A change in United Kingdom demographics has lead to an increasingly elderly population and prompted increased demand for acute surgical care in octogenarians[9]. The catchment population of Medway Maritime hospital is generally of low socioeconomic status[10], and patients tend to present to hospital late with extensive surgical disease and multiple medical and social co-morbidities. Given their poor physiological reserve for extensive surgery and anaesthesia, the decision to treat these patients operatively must be undertaken with extreme care and consideration; and must take into account the patient'

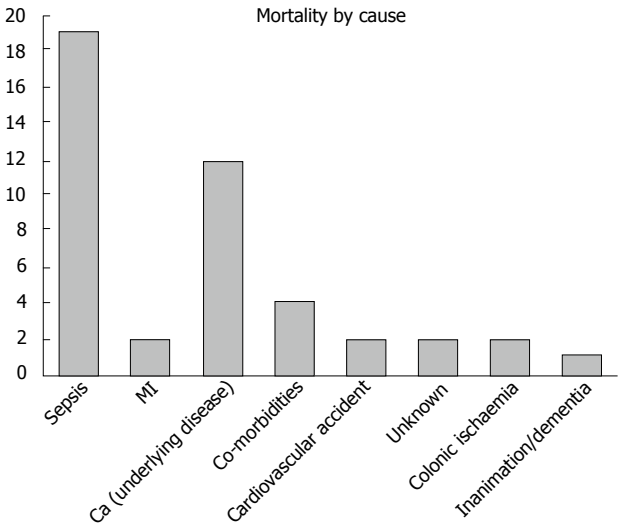

Figure 3 Bar chart depicting mortality by cause of death (excel chart).

s future quantity and quality of life and the health beliefs of patients and their relatives. Additionally in today' s age of austerity surgeons are also urged increasingly to consider cost implications of emergency surgery in patients with a potentially limited prognosis[11]. Thus the indications for surgery in this age group are often limited. Trends in management of elderly patients are inconsistent; previously there was a tendency towards conservative or palliative management of these patients, however with newer techniques and increased patient expectations these opinions are shifting towards increasingly operative intervention[12].

Studies have shown that the number of octogenarians requiring admission to acute surgical wards and ICU beds has been increasing. Reiss *et al* showed 7.5% of general surgical admissions in their series were aged 80 years or over, and more recently a 5 year study in Bath showed that 8.8% of admissions to intensive care unit (ICU) in 5 years were in elderly patients and a Turkish study done in 2002 showed 19% of cases in their series to be aged over 80 years[9,12,13].

Mortality rates in octogenarians have been documented as between 10% and 55%, with an increased risk in emergency as opposed to the elective setting[3]. We show a mortality rate for emergency laparotomy only of 44% which is in keeping with previous studies. There is limited literature documenting morbidity data in the group of patients in our study. We show a morbidity rate of 70% within 30 d of operation. Mortality and morbidity are often inextricably linked and therefore may lead to increased numbers seen. 25/44 patients who died had morbidity postoperatively, however 12 of these had complications completely unrelated to their abdominal pathology such as hypertensive episodes, exacerbations of chronic obstructive pulmonary disease (COPD) and angina.

Surgical treatment of secondary peritonitis; which can be defined as the localized equivalent of the systemic inflammatory response within the peritoneal cavity secondary to contamination from another process for example bacteria from colonic perforation or chemical from pancreatic enzyme leakage, is documented to have a significant morbidity and mortality studies show there is a direct link between the age of the patient and the risk of severe sepsis[13-16]. We show that mortality is 53% in secondary peritonitis, which is not significantly higher than in obstructive indications for laparotomy. There is no significant difference in mortality if the location of the perforation is in the upper or lower GI tract.

Table 2 Indications for surgery

Indication for surgery	Number of patients
Hernia	12
Secondary peritonitis	37
Colonic obstruction	40
Leaking colonic anastomosis	1
Aorto-bifemoral graft removal	1
Intra-abdominal bleeding	1
Bowel ischaemia	5
Pseudo-obstruction	1
Colo-vesical fistula	1
Abdominal aortic aneurysm repair	1

Postoperative mortality in our study can be seen to occur most commonly within the first 2 wk and during the initial surgical admission. Death later following discharge is from unrelated causes such as acute MI or dementia, and therefore the immediate postoperative care of these patients is of high importance, as most patients who are discharged from hospital recuperate and there is a relatively low mortality following successful discharge.

A high preoperative ASA grade (3-5) of patients, suggesting significant medical co-morbidity preoperatively, was unsurprisingly seen to be associated with increased operative complications and a higher risk of perioperative death. Tan *et al*[17] demonstrated a similar conclusion in trauma patients from the Auckland registry, by showing that key comorbidites taken from the APACHE 2 score which include cirrhosis, severe heart failure (NYHA IV), severe COPD, dialysis patients and the immunosuppressed have an increased mortality regardless of age. In our cohort these patients are represented by those with ASA 5 (life threatening illness) and all of these patients died, regardless of their age. However survival and mortality rates were of a similar proportion of those of ASA grades 3 and 4, which still represent severe comorbidity, and the mean ages of those who survived and died were equal. This suggests comorbidity rather than age is important in predicting mortality and is in agreement with the findings in the aforementioned study.

The high incidence of sepsis postoperatively may demonstrate that elderly patients are at increased risk of infection due to an aging immune system, reduced physiological reserve, and high incidence of polypharmacy. Sepsis in our patients had either a urinary or respiratory source; which may reflect poor respiratory function postoperatively from an aging respiratory tract, poor analgesia and the increased use of catheters and urinary incontinence in this age group. It may also suggest poor

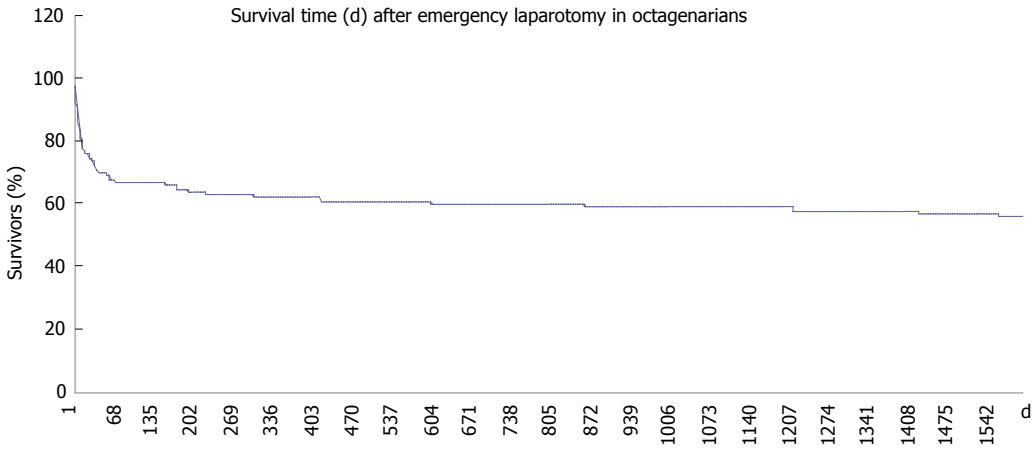

Figure 4 Survival post emergency laparotomy.

hydration and nutrition in these frail patients, although this should be correlated with the admission and post-operative malnutrition universal screening tool scores, a tool developed by the British Association of Parenteral and Enteral Nutrition in order to assess patients nutritional status[18]. An objective study to determine quantitatively the effect of malnutrition on octagenarians undergoing emergency abdominal surgery may be an area for further study development.

Given the high risk nature of this group of patients, a multidisciplinary approach to care may be most appropriate in order to optimize patient care. This may involve elderly care physician input, dieticians, physiotherapists and occupational therapists alongside the general surgical team. This would allow optimisation of co-morbid conditions, optimize postoperative functioning and nutrition and allow prompt and safe discharge to an appropriate environment. This arrangement has already been established in orthopaedics in the care of elderly patients with femoral neck fractures and is well documented by the national hip fracture database[19]. These orthopaedic patients are essentially in a similar position to the patients in our study; they are elderly patients with acute surgical problems.

In a conclusion, emergency laparotomy is a procedure which is well recognized to carry significant intra- and postoperative risk; and one which is not undertaken lightly by surgeons. The decision to operate in octogenarian patients is difficult and requires careful consideration of the patient's pre-morbid condition and counselling of both patients and relatives; thus highlighting the importance of patient selection[20]. It has been shown that the seniority of both the anaesthetist and operating surgeon influences mortality, hence elderly patients should receive consultant led anaesthetic and surgical care on an appropriate emergency list at a reasonable time of day[3]. Guidelines for the care of the elderly postoperative patient following extensive surgery are currently not routinely used and may be of significant use to medical and nursing staff untrained in elderly care, and therefore we recommend that these be put in place.

COMMENTS

Background

Ageing is associated with increases in operative and anaesthetic risk during emergency laparotomy. Literature concerning the outcomes following emergency laparotomy in the elderly is limited.

Research frontiers

Many scoring systems exist to aid the surgeon and anaesthetist in determining preoperative risk, such as the American Society of Anesthesiologists (ASA) score, POSSUM and APACHE scores but these are of limited use in older patients or in the emergency setting. The decision to manage operatively or conservatively is very important and poses many difficult ethical and moral problems. Future quality and quantity of life in patients, whether undergoing surgery or not, is subjective and unpredictable therefore preoperative counselling of patients and relatives is highly important

Innovations and breakthroughs

Emergency laparotomy is a topic of major concern to both surgeons and managers alike. The high complication risk may lead to longer hospital stays and prove a costly procedure for trusts. Current literature concerning patients over 80 years old and the outcomes following their surgery is lacking and therefore we undertook this project in order to fully evaluate this potentially dangerous subgroup of patients, and add to the current literature to guide clinical decision making.

Applications

Current literature is lacking for octogenarian patients, therefore this study was undertaken in order to guide healthcare professionals in the decision making process and management of elderly patients with acute abdominal surgical problems.

Peer Review

The topic was reviewed as being clinically relevant, and was comparative with previous literature as described in trauma patients.

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CASE REPORT

An 81-year-old gentleman with symptomatic Bochdalek hernia

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Abstract

An 81-year-old gentleman with congenital polycystic kidney disease presented to his primary care physician with dysphagia, gastroesophageal reflux refractory to medical management, and 11.25 kg weight loss in a 6 mo-period. A barium swallow misdiagnosed a paraesophageal hernia for a Bochdalek hernia. Herein, we highlight how a Bochdalek hernia may be disregarded in the differential diagnosis and how providers can resort to a more common diagnosis, a paraesophageal hernia, which is more frequently encountered in old age and whose radiologic appearance might mimic a Bochdalek hernia.

Key words: Polycystic kidney disease; Paraesophageal hernia; Bochdalek hernia; Diaphragmatic hernia; Diaphragmatic hernia repair

Core tip: Bochdalek hernias are seldom encountered in elderly patients. Hence, our goal is to briefly shed light on this less common hernia of the diaphragm and highlight its diagnosis and current treatment options, which are very different from that of a paraesophageal hernia, a common misdiagnosis.

Rajput MZ, Fisichella PM. An 81-year-old gentleman with symptomatic Bochdalek hernia. *World J Gastrointest Surg* 2013; 5(7): 222-223 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i7/222.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i7.222

INTRODUCTION

Congenital diaphragmatic defect, a hernia of Bochdalek, is a rare defect resulting from the failure of the posterolateral diaphragmatic folds to fuse *in utero*[1]. While often devastating in neonates who present with life-threatening respiratory distress, these hernias may occasionally remain asymptomatic, and the defect will not be recognized until later in life. Typical symptoms of a Bochdalek hernia include abdominal pain, dyspnea, gastroesophageal reflux, nausea, and vomiting[1,2]. On physical exam, patients may exhibit diminished breath sounds and presence of bowel sounds in the chest[3]. However, many patients remain asymptomatic, and the diagnosis is made only incidentally through routine imaging for other reasons. Moreover, polycystic kidney disease may be considered as indicator of a soft tissue disease with enhanced risk for hernias. The incidence of late-onset Bochdalek hernias has not been clearly determined, although reported rates range from 0.17% to as high as 12.7%[4,5]. Symptomatic patients are typically males with left-sided defects[3].

Frontal and lateral radiographs of the chest may demonstrate loops of bowel with air fluid levels in the chest with concomitant elevation of the hemidiaphragm; however, it may be difficult to appreciate the presence of a hernia on plain films, especially with coexisting thoracic pathology, such as atelectasis, consolidation, or an anterior mediastinal mass[6]. Moreover, chest radiographs may reveal no abnormalities despite the presence of the defect, particularly if the herniation is intermittent and the patient is asymptomatic. As a result, chest computed tomography (CT) scan is considered the test of choice to confirm the diagnosis[7]. A barium swallow can also be an

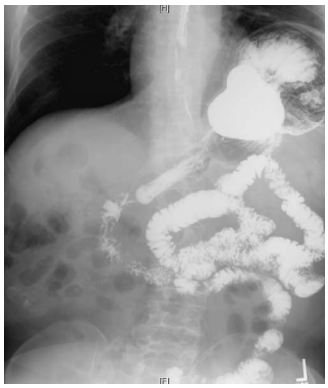

Figure 1 Barium swallow showing a left sided Bochdalek hernia with herniated gastric fundus.

adequate diagnostic test, as in the case herein presented, which was initially incorrectly diagnosed in another hospital as a paraesophageal hernia.

CASE REPORT

An 81-year-old gentleman with congenital polycystic kidney disease presented to his primary care physician with dysphagia, gastroesophageal reflux refractory to medical management, and 11.25 kg weight loss in a 6 mo-period. After an upper endoscopy ruled out any organic abnormalities, he underwent a barium swallow, which is shown in Figure 1. Subsequently the patient was referred to our center for treatment of a paraesophageal hernia, although the barium swallow clearly demonstrates a Bochdalek hernia. As Bochdalek hernia is seldom encountered in patients in their 80s, the health care providers disregarded this eventuality in his differential diagnosis and resorted to a more common diagnosis, a paraesophageal hernia, which is more frequently encountered in old age and whose radiologic appearance might mimic a Bochdalek hernia. Hence, our letter has the goal to briefly shed light on this less common hernia of the diaphragm and highlight its diagnosis and current treatment options, which are very different from that of a paraesophageal hernia.

DISCUSSION

Although there are no well-established indications for surgery, given the risk of incarceration and strangulation, repair of the hernia is advised regardless of symptomatology[3]. Traditionally, surgery has been performed either via laparotomy, particularly in the emergency setting, or thoracotomy, which is often the approach of choice in chronic hernias due to the dense adhesions of the herniated stomach in the chest[1]. Minimally-invasive techniques, particularly thoracoscopy, may also be utilized; thoracoscopy provides the surgeon excellent visualization of the herniated viscera and eases the difficulty in lysing adhesions to the thoracic cavity[1,7,8]. Interrupted, nonabsorbable sutures are typically used in the repair with mesh placement in larger defects[1,3]. Both open and minimally invasive approaches have yielded excellent results with no reported reoccurrences found among the literature[3]. Our patient underwent a left thoracotomy with lysis of dense adhesions along the fundus of the stomach and reduction of the herniated viscus back into the abdomen. The diaphragmatic defect was repaired with an oval-shaped Gore-Tex, DualMesh patch. The patient was discharged home on post-operative day 5 with complete resolution of his symptoms and no recurrence on follow-up imaging. At one year, he is doing well.

In summary, although rare, a hernia of Bochdalek may need to be considered in the differential diagnosis for patients in the old age who have foregut symptoms. A careful and unbiased interpretation of radiologic tests is essential to recognize the disease and perform the correct operation.

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CASE REPORT

Reconstruction of the hepatic artery with the middle colic artery is feasible in distal pancreatectomy with celiac axis resection: A case report

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Abstract

Despite the advance of diagnostic modalities, carcinoma in the body and tail of the pancreas are commonly presented at a late stage. With unresectable lesions, long-term survival is extremely rare, and surgery remains the only curative option for pancreatic cancer. An aggressive approach by applying extended distal pancreatectomy with the resection of the celiac axis may increase the resectability and analgesic effect but great care must be taken with the arterial blood supply to the liver and stomach. Sometimes, accidental injury to the pancreatoduodenal artery compromises collateral blood flow and leads to fatal complications. Therefore, knowledge of any alternative restoration of the compromised collateral flow before surgery is essential. The present case report shows a patient with a pancreatic body cancer in whom the splenic, celiac, and common hepatic arteries were involved with the tumor, which extended almost to the root of the gastroduodenal artery. We modified the procedure by reanastomosis between the proper hepatic artery and middle colic artery without vascular graft. The postoperative course was uneventful, and the patient was discharged on postoperative day 19. The patient was immediately free of epigastric and back pain.

Key words: Pancreatic body-tail cancer; Celiac artery resection; Arterial reconstruction

Core tip: The present case report shows a patient with a pancreatic body cancer in whom the splenic, celiac, and common hepatic arteries were involved with the tumor, which extended almost to the root of the gastroduodenal artery. We modified the procedure by reanastomosis between the proper hepatic artery and middle colic artery without vascular graft.

Suzuki H, Hosouchi Y, Sasaki S, Araki K, Kubo N, Watanabe A, Kuwano H. Reconstruction of the hepatic artery with the middle colic artery is feasible in distal pancreatectomy with celiac axis resection: A case report. *World J Gastrointest Surg* 2013; 5(7): 224-228 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i7/224.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i7.224

INTRODUCTION

Carcinoma of the body of the pancreas is often discovered at an advanced stage by reason of lack of symptoms. Because the only long-term survivors of cancer of the pancreatic body have been those who have undergone resection, complete surgical resection is the only treatment that may lead to a prolonged survival[1]. However, the

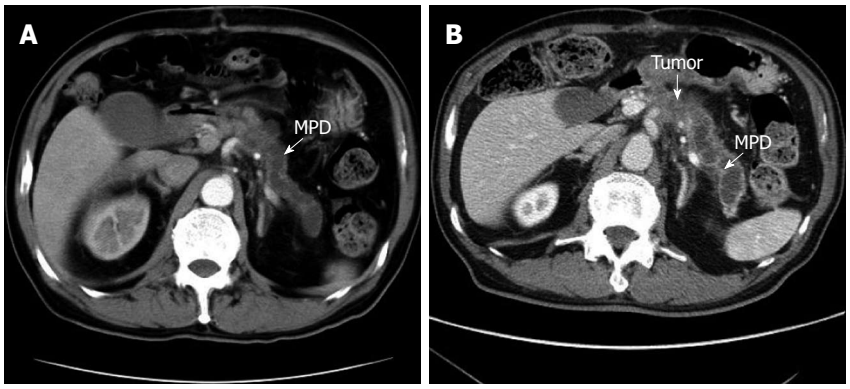

Figure 1 Computed tomography scan demonstrating the dilatation of the main pancreatic duct (A) and a tumor of the pancreatic body which invaded the celiac artery after the abdominal aortic aneurysm operation (B). MPD: Main pancreatic duct.

resection rate is low, and chances for resection are often lost to distant metastasis, regional invasion into adjacent organs, or the involvement of major vessels. Tumor involvement of the common hepatic artery (CHA) and/or celiac axis (CA) is a primary reason for this. Several high-volume pancreatic centers have reported that advanced pancreatic body/tail carcinoma can be safely treated by left-sided pancreatectomy with en bloc resection of infiltrated major vascular structures[2]. These methods were supported by the reported prognosis of the patients, which seems to be similar to that in patients without resection of major vascular structures[3].

Hirano *et al*[4] reported that, in patients who underwent distal pancreatectomy with en bloc celiac axis resection (DP-CAR), the surgical margins were histologically clear in 95% of patients and the postoperative mortality rate was 0%, despite a high morbidity rate (48%). The estimated overall 1- and 5-year survival rates were 72% and 17%, respectively, and the median survival was 21 mo. Moreover, radical distal pancreatectomy with en bloc resection of the celiac artery, celiac plexus, and celiac ganglions is reported to provide patients with locally advanced cancer of the pancreatic body with complete and enduring pain relief[5]. Therefore, radical surgery is justifiable in patients with advanced cancer of the pancreatic body, even when it has invaded adjacent major vessels, such as the celiac artery and/or the portal vein. When performing DP-CAR surgery, it is essential to preserve the arterial blood supply to the stomach and liver. The arterial blood supply during this procedure is maintained by the collateral pathways *via* the pancreatoduodenal arcades from the superior mesenteric artery to the gastroduodenal and hepatic arteries, which develop immediately after ligation of the celiac artery[6]. However, there are some cases in which the gastroduodenal artery arises from the area close to the CA. In such a situation, it would be difficult to preserve the gastroduodenal artery during DP-CAR surgery. In addition, the effort to preserve the gastroduodenal artery during surgery introduces risk of injury. In this case, we performed DP-CAR with reconstruction of the common hepatic artery by use of the middle colic artery in the patient with gastroduodenal artery (GDA) arising from the area close to the CA. We here report a technique used for reconstruction that was feasible in the case of shutoff of the arterial blood supply to the liver in DP-CAR.

CASE REPORT

A 78-year-old male was referred to the emergency ward of the Gunma Prefectural Cardiovascular Center with acute onset abdominal pain. A computed tomography (CT) scan of the thorax and abdomen confirmed an infrarenal abdominal aortic aneurysm (AAA) and evidence of a contained acute rupture to the left retroperitoneum. Therefore, emergency surgery for AAA was performed. A follow-up CT revealed dilatation of the main pancreatic duct from the body to the tail. However, a tumor at the body of the pancreas was not identified (Figure 1A). Four months after the operation, the patient had severe epigastric and back pain, and his serum level of carbohydrate antigen 19-9 (CA19-9) was elevated to 652 U/mL. Therefore, he was referred to the Department of General Surgical Science, Graduate School of Medicine, Gunma University 6 mo after the AAA surgery. Dilatation of the main pancreatic duct was evident in CT, and the tumor, identified at the body of the pancreas, had invaded the CA and CHA (Figure 1B). Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a stricture of the main pancreatic duct in the body of the pancreas (Figure 2). Abdominal angiography showed that the CA and splenic artery (SA) were involved with a tumor of the pancreatic body (Figure 3). These findings were consistent with a diagnosis of locally advanced cancer of the body of the pancreas that invaded the CA and SA. Preoperative evaluation of angiography showed that the GDA arose near the CA (Figure 3).

The patient then underwent a DP-CAR. An extended Kocher maneuver was performed. Because of the previous surgery, there was severe adhesion at the retroperitoneum. The origin of the superior mesenteric artery (SMA) and CA was palpated and confirmed to be uninvolved. The greater sac was then entered adjacent to the colon, and the splenocolic ligament was divided, allowing the inferior border of the body and the tail of the pancreas to be incised. The tumor originated from the body of the pancreas, and the celiac and common hepatic arteries were involved. Following the common hepatic artery, it was found to be densely encased by a tumor extending almost to the root of GDA. The GDA was exposed and

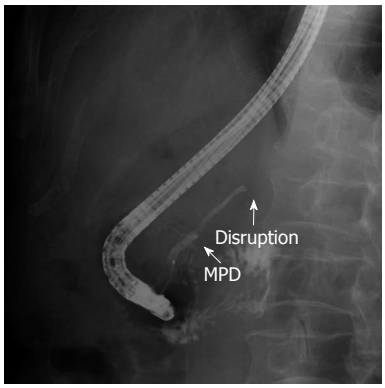

Figure 2 Endoscopic retrograde cholangiopancreatography showing a stricture of the main pancreatic duct in the body of the pancreas. MPD: Main pancreatic duct.

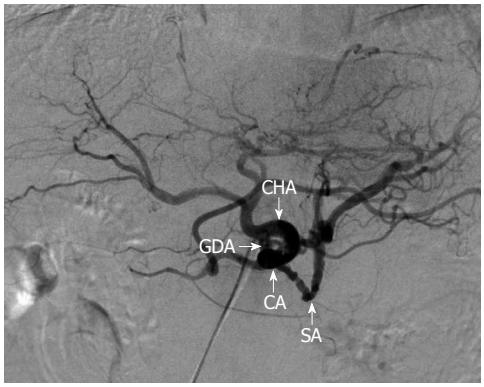

Figure 3 Abdominal angiography showing splenic and celiac arteries involved with a solid tumor in the pancreatic body and the gastroduodenal artery arising from the area close to the celiac. SA: Splenic CA: Celiac axis; CHA: Common hepatic artery; GDA: Gastroduodenal artery.

encircled with a proximal vessel loop. By dissecting the right celiac ganglion and celiac nerve plexus, the origin of the CA was exposed. The body and the tail of the pancreas were freed from the posterior abdomen in this inflamed adhesion retroperitoneal plane. The dissection was continued from the hilum of the spleen to the superior mesenteric vein. The spleen was released from its attachment to the diaphragm, allowing it to be lifted and retracted medially. A portion of Gerota's fascia was lifted with the specimen to expose the left kidney and renal vessels. Gerota's fascia was then excised in continuity. The inferior mesenteric vein was ligated inferiorly. At that time, we completely excised the GDA, which was involved with the tumor under the pancreas. Despite the presence of tumor involvement at the GDA, curative pancreatic resection with arterial resection was considered to be possible. Therefore, the GDA was ligated and divided proximal to the artery. After cutting the proper hepatic artery at the root of the GDA, the stump of the proper hepatic artery (PHA) and the middle colic artery (MCA) were anastomosed using an end-to-end technique with 7-0 prolene interrupted sutures and surgical loupes at × 2.5 magnification (Figure 4). The pulsation of the

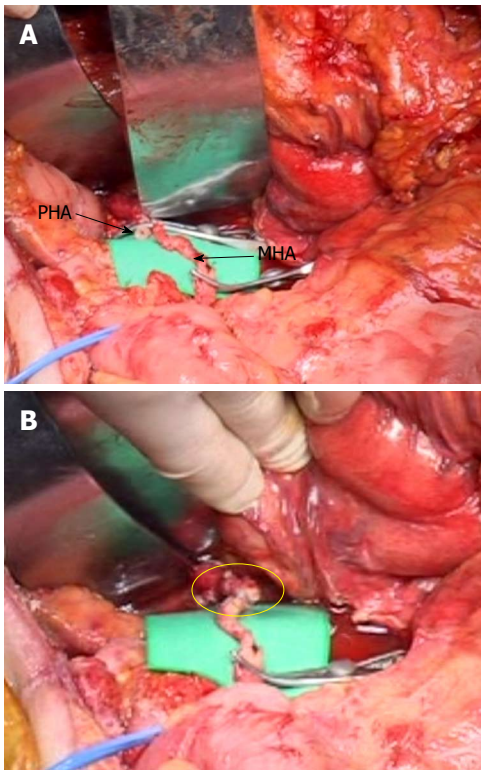

Figure 4 Operative photograph showing that reconstruction was completed. End-to-end anastomosis was performed between the proper hepatic artery (PHA) and the middle colic artery (MCA) (yellow circle). A: Before anastomosis; B: After anastomosis.

PHA recovered after completion of the anastomosis and was also identified by Doppler ultrasonography. The neck of the pancreas was transected over the right side of the portal vein (PV). The left side of the SMA was dissected with the surrounding lymph node. Care was taken to preserve the inferior pancreaticoduodenal artery (IPDA) arising from the SMA or the first jejunal artery. The left gastric artery was then divided, and, thereafter, the short gastric vessels along the greater curvature were ligated. Finally, the celiac trunk was divided at its origin with a transfixing suture, and the specimen was removed.

Histopathological examination of surgical specimens revealed mucinous carcinoma of the pancreas. There was prominent formation of mucinous nodules and a mucinous carcinoma including a large quantity of mucus (Figure 5). The peak aspartate/alanine aminotransferase (AST/ALT) was 1844/1265 U/L on the first postoperative day and gradually returned to a normal level over two weeks. The postoperative course was uneventful, and the patient was discharged on postoperative day 19. Postoperative 3D-CT angiography revealed that patency was maintained in the anastomosis between the GDA and the MCA (Figure 6). The patient was free from epigastric and back pain immediately and doing well after the operation. Five months after the operation, metastatic lesions were noted in the hilar of the liver by CT scan but without local recurrence. The patient was diagnosed with cholangitis and died of hepatic failure about 6 mo after the surgery.

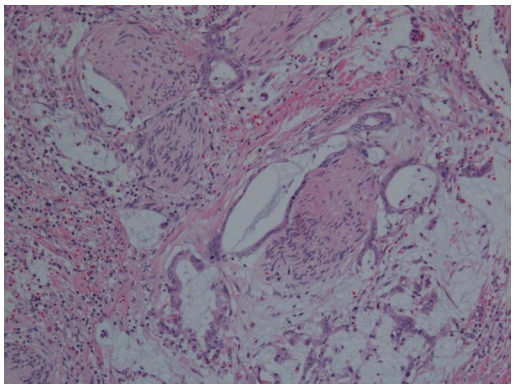

Figure 5 In the pathological findings, there was a prominent formation of mucinous nodules and mucinous carcinoma including large quantities of mucus. Final histolopathological diagnosis of the resected specimen shows mucinous carcinoma (with an intraductal papillary-mucinous tumor, Hematoxylin eosin staining, ×100).

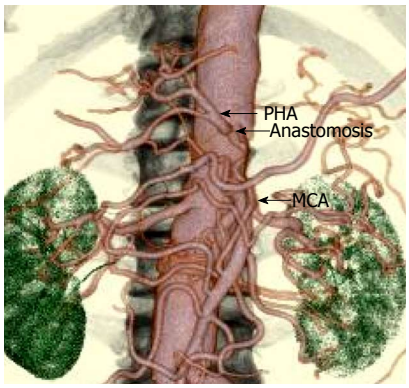

Figure 6 Postoperative evaluation of the proper hepatic artery by 3D-computer tomography angiography. The arrows indicate the anastomosis between the proper hepatic artery (PHA) and the middle colic artery (MCA).

DISCUSSION

Adenocarcinoma of the body and tail of the pancreas often presents in the advanced stage and is considered unresectable in the majority of patients. The traditional determinants of unresectability with such cancers are the presence of hepatic metastases, peritoneal dissemination of the tumor, and local invasion of major vascular structures, even in the absence of distant disease. With unresectable lesions, long-term survival is extremely rare. Surgery is the only curative option for pancreatic cancer[1]. Improved operative techniques have led to improved results and long-term survival outcomes for patients with pancreatic cancer following surgery[7]. Through cumulated experience in the operative and perioperative management of patients undergoing pancreatic surgery, the criteria for resectability have gradually expanded.

Hirano *et al*[4] reported that they performed DP-CAR on 37 patients to treat locally advanced cancer of the pancreatic body involving the common hepatic artery and/or celiac axis. The estimated 1- and 5-year survival rates were 72% and 17%, respectively, and the median survival was 21 mo. Moreover, radical distal pancreatectomy with en bloc resection of the celiac artery, celiac plexus, and celiac ganglions is reported to provide patients with locally advanced cancer of the pancreatic body with complete and enduring pain relief[5]. Since the perineural and neural invasion of the nerve plexus is one reason for the high recurrence rate of pancreatic cancer, dissection of the surrounding neural plexus is necessary in curative surgery. Concomitant resection of the celiac artery with a distal pancreatectomy facilitates lymph node and neural plexus dissection around the celiac artery.

Great care was taken to maintain the arterial blood supply to the liver and stomach during the surgery before the transection of the CA. It is essential to protect the blood flow from the SMA *via* the pancreaticoduodenal arcades to the GDA. Arterial blood flow through the GDA can nourish the liver and stomach *via* the PHA, right gastric artery, and right gastroepiploic arteries (GEA). However, vascular anomalies in the peripancreatic region, including the hepatic artery and SMA as well as the CA, have been reported elsewhere[8]. Because collateral circulation is significantly important in DP-CAR, a careful preoperative work-up is necessary. Even with vascular anomalies, it is justifiable to perform extended surgery with arterial resection for pancreatic cancer, given that surgery is the only curative option. Sometimes the dorsal pancreatic artery, which arises from the SMA, leads to the GDA. At times, an SMA dorsal artery plays an important role in the collateral circulation in patients with celiac axis stenosis[9]. In such cases, considerable attention must be paid when dissecting around the GDA. However, definitive assessment or recognition of the risk of ischemia of the liver and the stomach can only be made intraoperatively. In our case, the GDA was intact in the preoperative examination but arose from the area close to the CA and was involved with a tumor under the pancreas. In that situation, it is difficult to preserve the GDA for curative surgery. We decided to anastomose the PHA with the MCA during the curative operation. A specimen of the pancreas revealed that microscopic curative resection was possible. In addition, there were no serious complications following surgery. Therefore we believe that the techniques used for this reconstruction, which was a feasible and safe procedure, required shutoff of the arterial blood supply to the liver in DP-CAR.

DP-CAR surgery may facilitate resection in patients with tumors that are classified as T4 and require total clearance of the pancreatic and celiac lymph nodes[2-4]. The clinical benefit of extended pancreatic resections must, however, be balanced with the risk of the procedure. Therefore, knowledge of the reconstruction artery during DP-CAR surgery is essential. Konishi *et al*[10] reported that they reconstructed the hepatic artery using a graft of the splenic artery from the resected specimen because of weak pulsation of the proper hepatic artery after occlusion of the celiac axis. No complications related to hepatic ischemia were observed. Kondo *et al*[11] reported that, in compromised collateral flow *via* the pancreatoduo-

denal arcades, the MCA and GEA bypass is one of the procedures of choice to reestablish collateral flow.

Immediately after the AAA operation, dilatation of the main pancreatic duct from the body to the tail of the pancreas is the most likely indicator of a main duct type intraductal papillary mucinous tumor (IPMN). However, in this case the tumor grew rapidly after the AAA operation. The final pathological diagnosis showed mucinous carcinoma. Mucinous carcinoma of the pancreas is a rare type of tumor that is sometimes difficult to diagnose. Sakamoto *et al*[12] reported that endoscopic ultrasonography (EUS) and contrast-enhanced harmonic EUS are useful for the correct diagnosis of small pancreatic tumors, including synchronous and metachronous occurrence of IPMN and ductal adenocarcinoma. If EUS is performed at the earliest possible time, an accurate differential diagnosis between main pancreatic duct type IPMN and mucinous carcinoma can be made.

In the case reported here, the results remain unsatisfactory, although the patient is doing well and the resection resulted in the elimination of epigastric and back pain immediately after surgery. To improve the possibility of survival, a search for effective systemic chemotherapeutic agents and their testing in trials with neoadjuvant and/or adjuvant therapy with radiotherapy is essential to complement the oncologic benefit achieved after a complete surgical resection.

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CASE REPORT

Hepatic paraganglioma and multifocal gastrointestinal stromal tumor in a female: Incomplete Carney triad

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Core tip: The Carney triad (CT) describes the coexistence of multiple neoplasms including gastrointestinal stromal tumors (GISTs), extra-adrenal paraganglioma and pulmonary chondroma. We report a case of an incomplete CT. CT is a very rare syndrome but Carney et al thoroughly documented its clinical manifestations. The presence of pulmonary chondroma and paraganglioma should be verified, especially in young women with multifocal GISTs to rule out CT.

Hong SW, Lee WY, Lee HK. Hepatic paraganglioma and multifocal gastrointestinal stromal tumor in a female: Incomplete Carney triad. *World J Gastrointest Surg* 2013; 5(7): 229-232 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i7/229.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i7.229

Abstract

The Carney triad (CT) describes the coexistence of multiple neoplasms including gastrointestinal stromal tumors (GISTs), extra-adrenal paraganglioma and pulmonary chondroma. At least two neoplastic tumors are required for diagnosis. In most cases, however, CT is incomplete. We report a case of an incomplete CT in a 34-year-old woman with a multifocal GIST and non-functional paraganglioma of the liver. Preoperative evaluation with a gastrofiberscope and abdominal computed tomography revealed multiple gastric tumors resembling GISTs and a single liver lesion which was assumed to have metastasized from the gastric tumors. The patient underwent total gastrectomy and partial hepatectomy. Histologic findings confirmed multiple gastric GISTs and paraganglioma of the liver. We report a case of a patient with incomplete expression of CT.

Key words: Carney triad; Gastrointestinal stromal tumor; Paraganglioma

INTRODUCTION

The Carney triad (CT) initially described the triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma, and pulmonary chondroma[1]. Later, gastric leiomyosarcoma was replaced with gastric gastrointestinal stromal tumors (GISTs) and several cases of paragangliomas were known to be non-functioning[2]. GISTs in childhood or adolescence can occur as sporadic diseases unrelated to a syndrome, and can present as either a familial disorder [Carney-Stratakis syndrome (CSS)] or part of non-hereditary CT[3]. The differential diagnosis of CT from sporadic gastric GISTs is crucial because CT differ considerably from sporadic gastric GISTs in clinical both course and prognosis[2]. Here, we report a CT case with multiple gastric GISTs and paraganglioma of the liver.

CASE REPORT

An otherwise healthy 34-year-old woman visited our hospital after being diagnosed with gastric tumors *via* gastro-

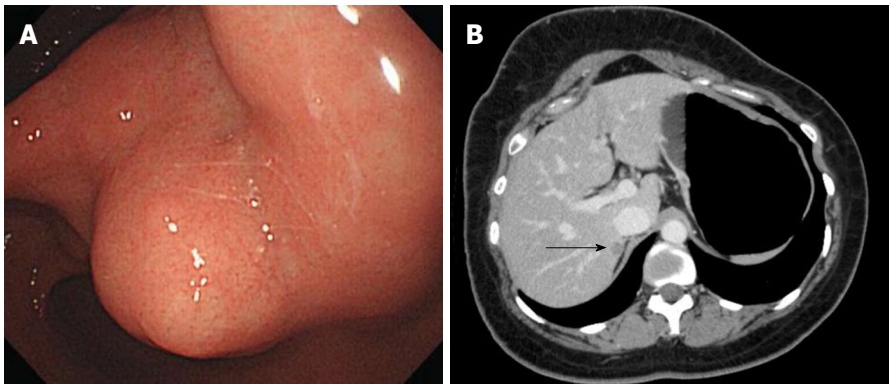

Figure 1 Esophagogastroduodenoscopy. A: Gastroendoscopy revealed an antral submucosal tumor without ulceration and hemorrhage; B: Computed tomography revealed a hypoattenuating nodule in segment VII of the liver, with peripheral weak enhancement in the portal phase (arrow).

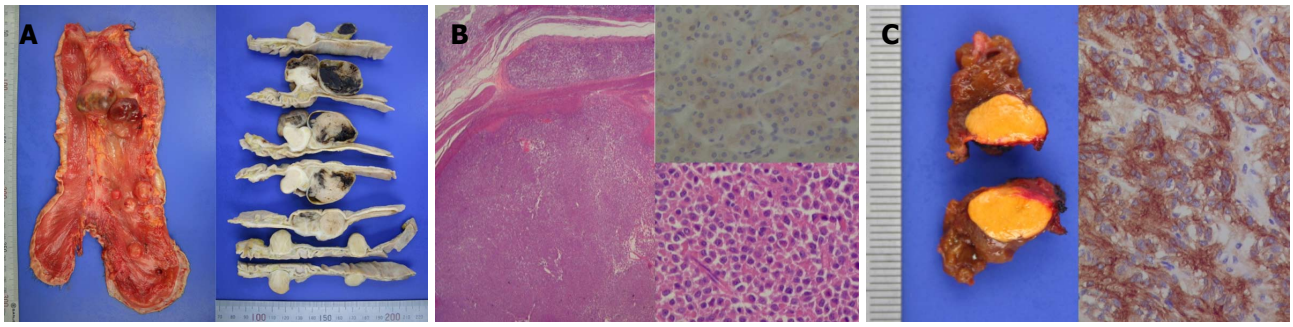

Figure 2 The patient underwent total gastrectomy, regional lymphadenectomy, and partial hepatectomy of segment Ⅶ. A: Macroscopically, gastric tumors were located in the submucosal layer, were round to oval and, relatively well demarcated, and exhibited multiple nodules (n = 8); B: Gastric tumor demonstrated cellular epithelioid gastrointestinal stromal tumors with discohesive pattern of growth (HE, × 40) and mild nuclear atypia (hematoxylin and eosin, × 200) (lower right), exhibiting diffuse cytoplasmic membranous immunoreactivity for CD117 (immunohistochemical stain, × 200) (upper right); C: Hepatic partial resection revealed an oval, well circimscribed, orange yellow, soft, solid tumor, 12 mm × 7 mm (left) and microscopically, synaptophysin-positive, hepatic tumor cells were arranged in nests (so called 'zellballen') (right), surrounded by S100 protein-positive, sustentacular cells (immunohistochemical stain, × 400).

fiberscopic screening at a community hospital. She had no specific symptoms or signs related to gastric tumors. She had no specific past medical history involing hypertesion. There was no abnormality of her past or familial history related to endocrine disease or gastrointestinal malignancies. An initial physical examination showed no significant abnormalities. Laboratory findings were also unremarkable. Tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9, were within normal limits.

Esophagogastroduodenoscopy revealed a multifocal gastric tumor, suspicious for a GIST, in the whole stomach. The tumors were multiple small exophytic polypoid lesions in the whole stomach from fundus to antrum. The largest tumor was approximately 4 cm, was located in the antrum and was not ulcerated (Figure 1A). Abdominal computed tomography revealed pathologic lesions in the proximal antrum, enlarged perigastric lymph nodes, and a lesion in segment Ⅶ of the liver. This hepatic lesion was assumed to have metastasized from the gastric tumors (Figure 1B). Chest radiography revealed no evidence of lung metastasis. Positron emission tomography revealed hyper-dense areas in the antrum and perigastric lymph nodes in areas other than the liver.

The patient underwent total gastrectomy, regional lymphadenectomy, and partial hepatectomy of segment Ⅶ. Based on macroscopic examination, the sporadic gastric stromal tumorlets were multifocal subserosal exophytic polypoid nodules (n = 8). The tumors ranged from 7 mm × 5 mm to 40 mm × 35 mm (Figure 2A). The largest tumor was located at the lesser curvature of the antrum. The gastric mucosa was grossly unremarkable, without ulceration or tumefaction. All eight tumors were diffusely immunoreactive with CD 117 (KIT) and CD34 antibodies, confirming the diagnosis of GISTs (Figure 2B). The average mitotic count was 6/50 high power fields suggesting an intermediate risk of malignancy (prognostic group 2C). The resection margins and lymph nodes were free of neoplasia. The hepatic tumor was 12 mm × 7 mm in diameter, with a bright orange yellowish color and a relatively well-defined timorous nodule. Microscopically, the tumor cells were arranged in small nests (so called "zellballen", which are distinctive cell balls), set in a vascularly rich stroma. Immunohistochemical stains disclosed synaptophysin-positive tumor cell nests surrounded by S100 protein-positive sustentacular cells (Figure 2C). These findings were consistent with benign primary paraganglioma. A 24 h urine study assaying for metanephrine, epinephrine, and norepinephrine was performed 10 d after the operation and revealed no abnormalities.

The postoperative course was uneventful, and the patient was discharged from the hospital in good condition. No adjuvant chemotherapy was administered, and no evi-

dence of recurrence was detected at the 1-year follow-up.

DISCUSSION

Multifocal hyperplasia of the interstitial cells of Cajal is a precursor of hereditary GIST in patients with germline mutations of c-KIT or alpha platelet-derived growth factor receptor (PDGFRA), but precursor lesions of sporadic GISTs have not yet been defined[4]. Carney *et al*[1] first described the association of gastric epithelioid leiomyosarcoma with pulmonary chondroma and functioning extra-adrenal paraganglioma of unknown origin, which today is known as CT. CT is defined by the coexistence of the following three tumors: extra-adrenal paraganglioma: only functioning extra-adrenal paragangliomas were initially included and non-functioning extra-adrenal paragangliomas were added later; gastric GISTs, previously known as gastric epithelioid leiomyosarcoma; and pulmonary chondroma (hamartoma)[2]. For the diagnosis of CT, at least two of the these major components are necessary. Recently, CSS was reported. This syndrome is a dyad of paraganglioma and gastric stromal sarcoma. CSS is inheritable in an autosomal dominant pattern, affects both males and females, and does not present pulmonary chondroma[5]. We considered our case as CT because the patient had no family history of related tumors.

CT predominately affects females (over 80% of cases) in their 2nd and 3rd decades and often presents with unpredictable outcomes[6]. The first tumor identified is usually a gastric GIST. The most common initial clinical manifestation is a GIST with bleeding. Associated symptoms and signs are anemia, hematemesis, and melena. Gastric GISTs in CT are usually multifocal and, antrumal based. These tumors are wild-type for common mutations in the receptor tyrosine kinase gene KIT and for the homologous oncogene PDGFRA in contrast to most sporadic GISTs in adults[7,8]. Gastric GISTs in CT frequently metastasize to regional lymph nodes, thus contrasting with common GISTs. The reason for this high rate of lymph node metastasis is not known[9]. Surgical resection is the only curative therapy for gastric GISTs with CT. Although partial resection is initially performed, further resection or total gastrectomy is required when multiple tumors reside in the entire stomach or recur after tumor resection.

In our case, the preoperative detection of perigastric lymph nodes suggested metastasis. However, a pathologic assessment did not reveal metastasis. According to clinical practice guidelines for GISTs in Japan, for the treatment of a GIST that has already metastasized to other organs but is considered to be resectable, surgery is the preferred treatment modality[10]. In this case, percutaneous biopsy of the liver lesion had a substantial risk of tumor cell spillage through the needle track. Moreover the tumor was located immediately adjacent to the inferior vene cava, so percutaneous biopsy was considered to be difficult and risky for this patient. Therefore, we performed a total gastrectomy and resection of the liver tumor simultaneously, without preoperative pathologic confirmation of the liver lesion.

Other CT neoplasms are usually found when the lesion is evaluated for gastric GISTs. These neoplasms are often misinterpreted as metastatic GISTs and are treated as such. Our patient was preoperatively diagnosed with a multifocal gastric GIST with hepatic metastasis. The incidence of hepatic metastasis from gastric GISTs in CT was reported to be 17.7%[2]. Postoperative histologic findings were consistent with primary hepatic paraganglioma and we confirmed the diagnosis of CT.

The most common combination is the association of GISTs with pulmonary chondroma (75%)[6]. Combinations of GIST and paraganglioma as observed in our case, account for 44% of CT cases[6].

Frequent sites of paraganglioma in CT are the aortopulmonary body, sympathetic chain, retroperitoneum, and carotid body. Only two cases of hepatic paraganglioma similar to our case were reported among 79 patients with CT in Carney's series[2]. Paragangliomas are rare neuroendocrine tumors arising from neural-crest-derived chromaffin cells. Although paragangliomas may present anywhere along the sympathetic paraganglia chains from the neck to the pelvis, most reside intra-abdominally, in the superior para-aortic area[11].

Mortality from the triad depends on gastrointestinal hemorrhage, metastatic disease and hypertensive phenomena. Symptoms and signs of catecholamine excess were observed in 13 (35%) of 37 paraganglioma patients with CT[2]. In our case, we could not confirm whether the hepatic paraganglioma was functioning because the preoperative diagnosis of the liver lesion was metastasis and because initial blood and urine chemistry evaluation for catecholamine could not be performed. Considering the lack of symptoms or signs, the paraganglioma was assumed to be non-functioning. When CT is suspected in patients with multiple gastric GISTs, a radiologic and chemical work-up should be undertaken to rule out paraganglioma.

Although most CD117-expressing GISTs are aggressive, these tumors respond to imatinib. Tumors in younger patients with CT are less aggressive and less responsive to imatinib but still metastasize[12]. Most deaths of CT patients are due to malignant GISTs but several cases are due to paraganglioma (3/77, 3.8%)[13]. At the onset of the syndrome, all three types of tumors are detected in very few cases (1%). The mean interval between the detection of the first and second tumors has been reported to be 8.4 years[2]. Eventually, early surgery can reduce both short and long-term mortality from bleeding and metastasis, respectively.

In conclusion, CT is a very rare syndrome, but Carney and colleagues thoroughly documented its clinical manifestations. The presence of pulmonary chondroma and paraganglioma should be verified, especially in young women with multifocal GISTs, to rule out CT. A careful long-term follow-up is required to detect metachronous tumors.

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BRIEF ARTICLE

Fulminant *Clostridium difficile* infection: An association with prior appendectomy?

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Author contributions: Clanton J, Daley T and Subichin M were responsible for the original concept and design of the study; Clanton J and Drolshagen K were responsible for data collection; Daley T and Subichin M performed the statistical analysis, with interpretation of the data performed by Clanton J, Subichin M, Drolshagen K and Firstenberg MS; Clanton J did the primary writing of the manuscript with substantial contributions and revisions from Subichin M, Daley T, Drolshagen K and Firstenberg MS; all authors approved the final version.
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Abstract

AIM: To examine if fulminant *Clostridium difficile* infections (CDI) resulting in colectomy was associated with a prior appendectomy and whether any association affected the severity of the disease.

METHODS: A retrospective chart review was performed on patients who underwent colectomy for CDI between 2001 and 2011. The appendectomy rate was calculated based on the absence of an appendix on the surgical pathology report. This was compared to an established lifetime risk of appendectomy in the general population. A chart review was performed for mortality and traditional markers of CDI disease severity. Fisher's exact test was used to calculate the likelihood of association between prior appendectomy, mortality, and clinical markers of severity of infection.

RESULTS: Fifty-five specimens were identified with pseudomembranous colitis consistent with CDI. All patients had a clinical history consistent with CDI and 45 of 55 (81.8%) specimens also had microbiological confirmation of CDI. Appendectomy was observed in 24 of 55 specimens (0.436, 99%CI: 0.280-0.606). This was compared to the lifetime incidence of appendectomy of 17.6%. The rate of appendectomy in our sample was significantly higher than would be expected in the general population (43.6% *vs* 17.6%, $P < 0.01$). Disease severity did not differ based on presence or absence of an appendix and no association was detected between prior appendectomy and mortality (OR = 0.588, 95%CI: 0.174-1.970).

CONCLUSION: The rate of appendectomy in the patients whose CDI led to colectomy, was significantly higher than the calculated lifetime risk, suggesting an association of appendectomy and severe CDI resulting in colectomy. Larger prospective studies are needed to assess any potential causal relationships affecting fulminant CDI.

Key words: Appendectomy; Fulminant colitis; *Clostridium difficile*

Core tip: We demonstrated a significant relationship between fulminant *Clostridium difficile* infections and previous appendectomy. Early surgical management of at risk patients might improve outcomes and further studies can hopefully explore the role of appendectomy on chronic colonic colonization and future infection risks.

Clanton J, Subichin M, Drolshagen K, Daley T, Firstenberg MS.

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INTRODUCTION

The appendix has long been considered a vestigial organ. However, comparative analysis of primate anatomy shows that the appendix may have developed independently among different species and has been maintained over time[1]. The exact nature of any function or clinical implications of removal of the appendix is still relatively unknown.

Examination of biofilms in the colons of deceased organ donors demonstrates that the appendix has the highest density of microbes and this density progressively decreases in the bowel distally toward the rectum[2]. For this reason it is thought that the appendix may serve as a "safe house" for flora of the gut. Specifically, in infections of the large bowel, the appendix may potentially serve to re-inoculate the colon with normal flora as a defense mechanism against infection.

A similar mechanism may be seen in exposure and recovery from *Clostridium difficile* infection (CDI). The normal flora of the bowel is altered secondary to antibiotics allowing an opportunity for *Clostridium difficile* to overgrow in the colon[3,4]. Therefore, CDI represents a disruption in colonic flora without resolution. Fulminant CDI represents a refractory disruption of the colonic microbiology and physiology and can require surgical intervention.

CDI is clinically important as an increasing phenomenon in the US and other industrialized nations[5,6]. Infection is associated with increased hospital length of stay, total charges, and mortality rate among hospitalized patients[7,8]. The clinical presentation of infected patients is highly variable, ranging from mild diarrhea to fulminant colitis[9]. Clinical severity scores have been created in order to determine severity with mixed results[10]. Additionally, nosocomial spread of CDI can also occur, but is often asymptomatic[11].

CDI involving the appendix is exceedingly rare[12,13]. Additionally, the presence of an appendix has been preliminarily demonstrated to be inversely associated with CDI recurrence[14]. However, additional studies have shown no consequence or even a harm from an intact appendix when concerning development or relapse of CDI[15,16]. It is our belief that an intact appendix may allow for quicker recovery of colonic flora after antibiotic administration and potentially "protect against" the more severe disease. Based on these recent findings, our intent was to assess our own experience for a potential association between prior appendectomy and CDI requiring colectomy.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, a review of the Department of Pathology's database of pathological colon resection specimens was performed. A search of all the surgical pathology specimens from January 1, 2000 to January 1, 2012 at Summa Akron City Hospital in Akron, Ohio was conducted using SoftPath v 4.3. All pathological specimens of colectomies during the time period that demonstrated pseudomembranes were initially included. Seventy-three cases were suitable for chart review based on examination of final diagnosis and gross description. The pathology reports of the selected cases were reviewed for the presence or absence of an appendix, ischemia, and perforation.

A total of 73 specimens were initially identified with the presence of pseudomembranes. All of the specimens were colectomy specimens that included the cecum (total, subtotal, or partial colectomy). The choice as well as timing of surgery was made by the surgeon based on each patient's individual clinical picture. The pathology reports were reviewed and the presence or absence of an appendix in each specimen was recorded. Seven cases were excluded because they did not specifically mention either the presence or absence of an appendix in the specimen.

A retrospective chart review of the included cases was performed in order to identify and record patient characteristics and traditional markers of severity of infection. Patient characteristics included age and sex only. Severity markers included white blood cell count, lactic acid level, tachycardia (defined as heart rate greater than 100), hypotension (systolic blood pressure less than 80) fever (maximum temperature > 101.5 $^{\circ}$F), abdominal pain, diarrhea, or the need for vasopressor support. Thirty-day mortality was also recorded for each patient by electronic chart review.

The charts were then reviewed for a microbiological confirmation of the diagnosis of CDI. The early confirmatory test of choice was a stool enzyme immuno-assay (EIA) for *Clostridium difficile* toxin A and B. Late in the study period, in 2011, the test at the study hospital was changed to a more sensitive molecular polymerase chain reaction test.

After the chart review, four cases were excluded because the diagnosis was confirmed to be something other than CDI. Seven additional cases were excluded because they had a negative microbiological test for CDI, all by EIA testing. Ten cases were retained in the sample population because although clinical history was consistent with CDI, due to patient's rapidly progressive course no testing of CDI was performed before surgery. A clinical history of CDI included both the presence of diarrhea or abdominal pain and a recent history (within the last 30 d) of antibiotic use. Fifty-five cases with pseudomembranes present on pathology plus a clinical history of CDI were included in the initial analysis. Of these 55, 45 patients had preoperative microbiologic confirmation of CDI.

As a cohort, the study sample was compared to the appendectomy rate in the general population. This rate was obtained using the National Hospital Discharge Survey (NHDS). This dataset is maintained by the Centers for Disease Control and Prevention (CDC) for the evalu-

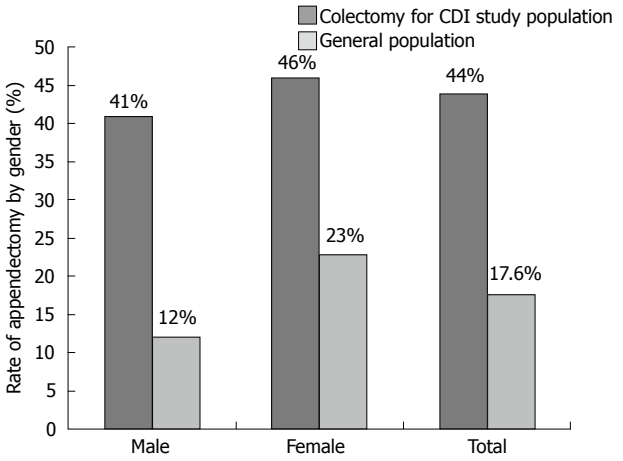

Figure 1 Rate of appendectomy by gender. CDI: *Clostridium difficile* infection.

ation of national trends of disease processes and procedures. Greater than 200000 charts from hundreds of hospitals are reviewed to generate a nationally representative sample of hospital discharges. The NHDS is the longest continuously running survey of hospital utilization, collecting data since 1965. The rate of appendectomy as published in the Journal of Epidemiology in 1990 was initially used[17]. Current NHDS data from 2007-2010 was reviewed to determine any changes in the rate of appendectomy in the population over time.

For analysis, 95% and 99% confidence intervals for the proportion of appendectomy in the sample population were calculated using a modified Wald method. This was then compared to the calculated lifetime risk of appendectomy from the NHDS data, both as a group and divided individually by gender. Fisher's exact test and Student's *t*-test were also used to determine whether there were independent associations between history of appendectomy and all markers of severity including thirty-day mortality. Fisher's exact test was used for discrete variables while a Student's *t*-test was used for continuous variables.

RESULTS

Fifty-five pathological specimens were identified with pseudomembranous colitis consistent with CDI. All patients had a clinical history consistent with CDI and 82% (45/55) had microbiological confirmation of CDI. In the sample population, 44% (24/55) of patients had a surgically absent appendix noted on pathology (95%CI: 0.314-0.567, 99%CI: 0.280-0.606). There were 27 male specimens and 28 female specimens. Divided by gender, 41% of the observed male specimens had a documented prior appendectomy (95%CI: 0.245-0.593, 99%CI: 0.206-0.645), while 46% of the female specimens had a documented prior appendectomy (95%CI: 0.295-0.642, 99%CI: 0.253-0.690) (Figure 1).

All patients had undergone total or subtotal colectomies except for two patients who had partial right colectomies performed. The description of pseudomembranes ranged from focal and patchy to extensive and diffuse. Ischemia was present in 51% (28/55) of specimens. Perforation was noted in only one pathology specimen, with a prior appendectomy.

The lifetime risk of appendectomy from the NHDS is 17.6% overall (12.0% for males and 23.1% for females)[17]. A standard deviation was determined to be 0.003625583% due to the large sample size of the data.

The 95% and 99% confidence intervals of appendectomy rate for the CDI colectomy group were compared to the confidence interval for the rate in the general population. There was a statistically significant difference in the rate of appendectomy between the sample group and the overall population ($P < 0.01$). This finding was consistent when the sample group was divided by gender ($P < 0.01$).

A separate analysis was performed excluding all patients who did not have a confirmatory microbiological test for CDI (leaving 45 total patients). Evaluating only the patients with pseudomembranes on pathology, a clinical history of CDI, and a positive microbiological test for CDI yielded similar results. Forty-nine percent (22/45 cases) had a prior appendectomy (95%CI: 0.350-0.630, 99%CI: 0.311-0.670). Using the above method, this also yielded a statistically significant difference ($P < 0.01$).

There was a mortality rate of 49% (27/55) in our sample population. There was no association between mortality and prior appendectomy (OR = 0.588, 95%CI: 0.174-1.970). Presence of ischemia had no correlation with prior appendectomy (OR = 0.666, $P = 0.7245$). Furthermore, there were no statistically significant associations for any markers of clinical severity and appendectomy (Table 1).

DISCUSSION

Our study demonstrated a significant difference in the rate of appendectomy in patients with fulminant CDI resulting in colectomy compared to the general population. The national incidence of appendectomy was far less than our sample's appendectomy rate associated with fulminant CDI. This remained true when our sample group was examined by gender as well. While a statistically significant association between incidence of appendectomy and CDI was seen, appendectomy did not appear to influence either mortality or severity of CDI.

Recent evidence has suggested an association between CDI and appendectomy[14,15]. However, these studies have been limited by participant accuracy and recall bias when conducted by personal interviews. They may also be confounded by low response rates. A strength of this study is the accurate and precise determination of prior appendectomy based on pathologic specimens. To maximize accuracy, only pathology specimens in which the appendix was noted as present or absent were used to determine the rate of previous appendectomy in our study population. In addition, there was also a strict definition of CDI in this

Table 1 Characteristics of and severity of illness within the *Clostridium difficile* infection colectomy group

	Appendix absent (n = 24)	Appendix present (n =31)	P-value
Age (yr), mean ± SD, (range)	78.4 ± 6.6 (60-96)	72.3 ± 13.9 (36-90)	0.051
Sex (male)	46.00%	52.00%	0.788
Mortality	42.00%	55.00%	0.418
Vasopressor use	37.50%	42.00%	0.787
WBC (thou/cm^2) (pre-op)	34.70%	37.70%	0.647
Lactate (mmol/L) (72 h max)	2.6	3.3	0.192
Diarrhea	58%	65%	0.781
Abdominal pain	83%	68%	0.226

CDI: *Clostridium difficile* infection; WBC: White blood cells.

study, which included both a clinical history of CDI and histopathologic confirmation of pseudomembranes on a pathology report. Although the majority of the patients (45/55) had microbiological confirmation, a sub analysis was performed using even stricter criteria - clinical history, pseudomembranes, and microbiological confirmation - which demonstrated similarly significant results.

Although the pathology specimens were initially examined for pseudomembranous colitis, it alone cannot be considered pathognomonic for CDI. *Clostridium difficile* toxin B has been isolated from > 95% of cases of pseudomembranous colitis colons themselves[18]. However, pseudomembranous colitis is merely a descriptive diagnosis that can still be easily confused with other forms of infectious or ischemic colitis and ultimately relies upon concurrent clinical and/or microbiological confirmation of CDI, as per our inclusion criteria[19].

Given the nature of our sample population, the ability to have a reliable control group is very limited. Our strict use of pathologic specimens makes a control group especially difficult. We considered different methods such as including a random sample of colectomy specimens as a cohort. However, a random sample of colectomy specimens would be a poor representation of the general population and may have confounding factors given the specific indications for colectomy. Therefore, we desired to compare the rate of appendectomy in the study population of patients requiring colectomy for fulminant CDI to the appendectomy rate found in the general public. With this small sample size, strikingly different rates of appendectomy led to significant results in our cohort.

The rate of appendectomy in the general population was obtained using the NHDS. The use of this data for analysis of national trends and comparative groups has been well substantiated in the literature[20-23]. This data provided an appropriate control group comparable to other commonly reviewed large sources of national disease and procedure incidence[24].

We initially reviewed the published data on appendectomy rates from 1990 as well as current NHDS data available considering widespread use of CT scanning and laparoscopy that may have affected the appendectomy rate over time. A decrease in the national number of appendectomies per year was noted from 1990 to 2010, despite an increasing population[25]. Our analysis used the originally published lifetime appendectomy rate of 17.6% from 1990. Had we used only current data, our results comparing appendectomy rate would be even far more significant.

The possibility that the appendix may play a role in *Clostridium difficile* infection has important clinical implications; primarily as a CDI risk stratification tool. Patients already at an increased risk for developing CDI (*i.e.*, excessive antibiotic exposure, previous history of CDI, *etc.*) are often monitored closely for signs and symptoms of CDI. If patients can be better categorized into a "high risk" group based on a history of appendectomy, this may result in overall better patient care. However, this may need to be substantiated with a larger number of patients. The patients in our sample had a mortality rate consistent with other published studies[26]. Patients were chosen for operative intervention primarily based on age, associated comorbidities, vasopressor requirements, and ominous laboratory or radiographic findings, consistent with current clinical practice guidelines[27]. In the future, the initial detection of appropriate risk factors can allow for early intervention in CDI, which may positively impact outcome.

Once a commonplace practice, this data may add a new wrinkle to the indifferent performance of the incidental appendectomy during another unrelated surgical procedure[28]. In fact, according to data from the CDC there were still an estimated 30000 to 44000 incidental appendectomies performed each year from 2007 to 2010[25]. If the appendix is seen as a protective organ, an argument could be made for reducing or eliminating incidental appendectomies altogether. Taken a step further, there may be another reason for preservation of the appendix after appendicitis, as is already being practiced in some parts of Europe[29].

There are several limitations to this study. Differences in severity or mortality may be observed with a larger sample size or when non-surgical CDI patients are also included as part of the study population, *i.e.*, those who may be severely ill but do not require colectomy. The data collected was only from a single center. The patients who undergo colectomy represent a small minority of those diagnosed with CDI. The decision for surgical intervention was made individually by the surgeon based on each patient's clinical picture. Potential risk factors previously linked to CDI as well as previous treatment prior to colectomy were also not individually addressed in this study, as there was not appropriate power to detect any individual effects. A distinction between initial versus recurrent CDI was not able to be collected due to the study design, although if the appendix has an effect on incidence, it would likely similarly affect relapse in the same way. Additionally, age at appendectomy and potential analysis was impossible to determine due to study design. Also,

though there is a known variability in the incidence of appendicitis and appendectomy among gender, there was an approximately even gender distribution in our groups of patients with and without an appendix.

In conclusion, there was a statistically significant association between prior appendectomy and fulminant CDI resulting in colectomy compared to the general population. This association was present among those patients with simply a clinical history of CDI and with microbiological confirmatory testing. In the study population, mortality and traditional markers of severity were not associated with prior appendectomy. Our preliminary data supports that appendectomy may place patients at risk for developing fulminant CDI. However, larger prospective studies are needed to elucidate causal relationships. Future prospective studies could include patients with varying degrees of illness.

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COMMENTS

Background

The appendix has long been considered a vestigial organ. However, comparative analysis of primate anatomy shows that the appendix may have developed independently among different species and has been maintained over time. The exact nature of any function or clinical implications of removal of the appendix is still relatively unknown.

Research frontiers

A retrospective chart review was performed on patients who underwent colectomy for *Clostridium difficile* infections (CDI) between 2001 and 2011. The appendectomy rate was calculated based on the absence of an appendix on the surgical pathology report. This was compared to an established lifetime risk of appendectomy in the general population. A chart review was performed for mortality and traditional markers of CDI disease severity. Fisher's exact test was used to calculate the likelihood of association between prior appendectomy, mortality, and clinical markers of severity of infection.

Innovations and breakthroughs

Fifty-five specimens were identified with pseudomembranous colitis consistent with CDI. All patients had a clinical history consistent with CDI and 45 of 55 specimens also had microbiological confirmation of CDI. Appendectomy was observed in 24 of 55 specimens. This was compared to the lifetime incidence of appendectomy of 17.6%. The rate of appendectomy in our sample was significantly higher than would be expected in the general population. Disease severity did not differ based on presence or absence of an appendix and no association was detected between prior appendectomy and mortality.

Applications

The authors found that the rate of appendectomy in the patients whose CDI led to colectomy, was significantly higher than the calculated lifetime risk, suggesting an association of appendectomy and severe CDI resulting in colectomy. Larger prospective studies are needed to assess any potential causal relationships affecting fulminant CDI.

Peer review

This is a well written and unique designed paper in a subject which is of interest to all.

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BRIEF ARTICLE

Small bowel carcinoid: Location isn't everything!

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Abstract

AIM: To investigate the prognostic significance of the primary site of disease for small bowel carcinoid (SBC) using a population-based analysis.

METHODS: The Surveillance, Epidemiology and End Results (SEER) database was queried for histologically confirmed SBC between the years 1988 and 2009. Overall survival (OS) and disease-specific survival (DSS) were analyzed using the Kaplan-Meier method and compared using Log rank testing. Log rank and multivariate Cox regression analyses were used to identify predictors of survival using age, year of diagnosis, race, gender, tumor histology/size/location, tumor-node-metastasis stage, number of lymph nodes (LNs) examined and percent of LNs with metastases.

RESULTS: Of the 3763 patients, 51.2% were male with a mean age of 62.13 years. Median follow-up was 50 mo. The 10-year OS and DSS for duodenal primaries were significantly better when compared to jejunal and ileal primaries (P = 0.02 and < 0.0001, respectively). On multivariate Cox regression analysis, after adjusting for multiple factors, primary site location was not a significant predictor of survival (P = 0.752 for OS and P = 0.966 DSS) while age, number of primaries, number of LNs examined, T-stage and M-stage were independent predictors of survival.

CONCLUSION: This 21-year, population-based study of SBC challenges the concept that location of the primary lesion alone is a significant predictor of survival.

Key words: Small bowel carcinoid; Primary tumor location; Survival; Prognosis; National Comprehensive Cancer network guidelines

Core tip: Duodenal carcinoids have a significantly better overall survival than jejunal and ileal carcinoids; however, location of small bowel carcinoid is not an independent predictor of survival.

Hari DM, Goff SL, Reich HJ, Leung AM, Sim MS, Lee JH, Wolin E, Amersi F. Small bowel carcinoid: Location isn't everything! *World J Gastrointest Surg* 2013; 5(8): 239-244 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i8/239.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i8.239

Table 1 American Joint Committee on Cancer staging for small bowel carcinoid

Stage	TNM	Size or depth of invasion	Lymph node status	Distant metastases
0	TisN0M0	Carcinoma in-situ; tumor size < 0.5 mm	None	None
I	T1N0M0	Invasion into the lamina propria or submucosa; tumor size 1 cm or less	None	None
ⅡA	T2N0M0	Invasion into the lamina propria and/or submucosa and tumor size > 1 cm	None	None
		Invasion into the muscularis propria	None	None
ⅡB	T3N0M0	Invasion into the submucosa	None	None
ⅢA	T4N0M0	Invasion into the serosa/visceral peritoneum or into nearby organ or structures	None	None
ⅢB	T1-4N1M0	Any	Positive regional lymph nodes	None
Ⅳ	T1-4N0-1M1	Any	Any	Yes

Source: Ref[9,35], with permission.

INTRODUCTION

Primary malignancy of the small bowel remains a rare entity, with fewer than 8810 new cases expected in 2013[1]. However, this represents a steadily rising incidence with a 66% increase over 2003 estimates[2]. The number of estimated deaths from small bowel malignancy has remained virtually unchanged over the same time period (1110 in 2003 *vs* 1170 in 2013). The explanation for this phenomenon is multifactorial but centers around a changing histologic profile.

Historically, adenocarcinoma was the predominant histology of small bowel tumors, followed closely by carcinoid tumors. However, in a recent twenty-year analysis (1985-2005), small bowel carcinoids (SBC) surpassed adenocarcinoma in incidence by the year 2000, and by 2005, SBC represented 44.3% of all resected small bowel tumors. Patients undergoing resection for carcinoid histology had better observed five year survival rates (62.6%) than those with adenocarcinoma (32.5%)[3].

SBC are a heterogeneous group of tumors and remain a conundrum when discussing prognosis with patients. Prior investigators have developed survival tables based on the location of the primary lesion, portending a better prognosis for lesions of the duodenum *vs* those of jejunal or ileal origin[4]. More recently, a proposed clinical nomogram for small bowel carcinoid does not include location as an independent prognostic factor, relying heavily on histopathologic features, such as percentage of Ki67(+) staining[5].

Location and tumor pathology have each been identified as possible predictors of clinical outcomes for SBC[2,6-8]. Currently, tumor-node-metastasis (TNM) staging for SBC mainly depends on extent of tumor size and depth, with node positive disease representing Stage IIIB disease (Table 1)[9]. Herein, we analyze a 21-year database of histologically proven SBC to identify independent factors contributing to survival.

MATERIALS AND METHODS

The National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) registry is a government-run database that collects population-based data from 14 regional and three additional cancer registries, which together represent approximately 28% of the United States population. Data in the SEER database contain no patient-specific identifiers and is publicly available; therefore, this study is exempt from institutional board review approval requirements.

Using the NCI's SEERStat software version 7.1.0, we identified patients with new cases of pathologically confirmed malignant SBC from 1988 to 2009[10]. Quality assurance studies are mandated each year to ensure a 98% case ascertainment. We excluded patients if the location of primary site was unknown or the patients had anatomically-overlapping small bowel lesions. Patients were also excluded if the number of lymph nodes (LNs) examined was unknown. We assessed age, sex, race, tumor location, tumor size, year of diagnosis, geographic region, number of primary tumors, extent of surgical resection, number of LNs examined (LNE), LN positivity, cause of death, and survival in mo. Categories for extent of surgery were defined as follows: local excision (endoscopic excision or surgical enucleation), resection (surgical excision of a segment of bowel ± mesentery), and debulking (resection of primary lesion and other known sites of disease). Data regarding neo-adjuvant or adjuvant chemotherapy or endocrine therapy are not included in the SEER database.

Statistical analysis

Summary statistics and Kaplan-Meier survival curves were generated using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, United States). We determined *P*-values by a Log-rank test. We performed Cox's proportional hazard regression analysis incorporating variables with $P < 0.1$ (is this correct) on the log rank test and built a final model utilizing a stepwise, forward and backward, selection method.

RESULTS

The SEER database contained 6996 adult (> 18 years old) patients with malignant SBC between 1988 and 2009. Of this group, 3763 patients with known tumors of the duodenum (n = 872), jejunum (n = 324) and ileum (n = 2567) that had adequate data on lymph node assessment were included in this study. Patient demographics and

Table 2 Patient demographics based primary tumor site (*n* = 3763)

	Duodenum (*n* = 872)	Jejunum (*n* = 324)	Ileum (*n* = 2567)	Total (*n* = 3763)
Age				
≤ 40	4%	7%	5%	5%
41-50	13%	11%	14%	14%
51-60	24%	25%	28%	27%
61-70	28%	28%	26%	27%
> 70	31%	29%	26%	28%
Gender				
Female	46%	43%	51%	49%
Male	54%	57%	49%	51%
Race				
White	68%	82%	88%	83%
Black	23%	16%	9%	13%
Asian/other	9%	2%	2%	4%
Geographic region				
East	39%	33%	34%	35%
Northern plains	15%	14%	16%	15%
Pacific coast	40%	44%	43%	42%
Southwest	7%	9%	7%	7%
Year of diagnosis				
1988-1992	4%	10%	8%	7%
1993-1997	7%	10%	13%	11%
1998-2003	30%	32%	30%	30%
2004-2009	58%	48%	50%	52%
Number of primaries				
1	88%	91%	88%	88%
2+	12%	9%	12%	12%
Extent of surgery				
Local excision	62%	4%	39%	17%
Resection	35%	89%	88%	76%
Debulking	3%	7%	9%	7%
Number of lymph nodes examined				
0	81%	35%	20%	36%
1-6	13%	34%	29%	26%
7-12	4%	19%	23%	18%
13+	3%	11%	28%	20%
Tumor size (cm)				
0.1-1.0	42%	20%	20%	25%
1.1-2.0	15%	41%	35%	31%
2.1+	9%	24%	31%	25%
Unknown	34%	14%	14%	18%
T-stage				
T1	60%	8%	12%	23%
T2	10%	12%	14%	13%
T3	3%	42%	39%	31%
T4	5%	32%	29%	24%
TNOS	21%	6%	6%	10%
N-stage				
N0	12%	13%	16%	15%
N1	7%	52%	64%	49%
Unknown	81%	35%	20%	36%
M-stage				
M0	97%	75%	74%	79%
M1	3%	25%	26%	21%
TNM-stage				
I	6%	1%	4%	4%
II A	2%	1%	3%	2%
II B	1%	5%	4%	3%
III A	1%	2%	2%	1%
III B	5%	37%	45%	35%
IV	3%	25%	26%	21%
Unknown	83%	30%	16%	33%

tumor characteristics of this subset are listed in Tables 2 respectively.

The majority of patients were older than 50 years of age for all primary tumor sites (mean age 62.13 ± 13.06 years), Caucasian, diagnosed after 1998 and had only one primary malignancy (Table 2). While 62.2% of duodenal tumors were treated with local endoscopic excision, 89% of patients with jejunal tumors and 88% of patients with ileal tumors underwent surgical resection. Given that a majority of patients with duodenal tumors underwent local excision, 81% of duodenal resection specimens did not have any assessment of regional LN (LNE = 0) while the majority of those that underwent surgical resection for jejunal and ileal tumors had at least 1 LNE (65% and 80%, respectively).

Patients with duodenal primaries had smaller tumors compared to those with jejunal and ileal tumors as well as lower T-stage. Due to lack of LNE, the N-stage of 81% patients with duodenal tumors was unknown compared to 35% and 20% of those with jejunal and ileal tumors. Patients with jejunal and ileal tumors presented with more advanced primary tumors (T3: 42% and 39%; T4: 32% and 29%, respectively).

We assessed the outcomes based on primary tumor site using Kaplan-Meier OS and DSS. Kaplan-Meier OS estimates. Median follow-up was 50 mo. Based on primary tumor site, patients with duodenal tumors had a significantly higher 10-year OS compared to jejunal and ileal tumors (63.9% *vs* 53.4% and 50.4%, respectively, $P = 0.02$, Figure 1A). Similarly, patients with duodenal tumors had a superior 10-year DSS compared to jejunal tumors and ileal tumors (91.7% *vs* 74.6% and 67.8%, respectively, $P < 0.001$, Figure 1B).

We investigated the impact of the primary site when combined with other known clinical and pathological determinants of SBC-specific mortality and performed a multivariable regression analysis using a Cox proportional hazards model (Table 3). In this model, primary tumor site was not an independent predictor of DSS; in addition gender, race, extent of surgery and N-stage were not independent predictors of DSS (all $P > 0.05$). However, age, number of primaries, number of LNE, T-stage and M-stage were independent predictors of DSS. Patients older than 50 years of age did worse compared to younger patients. Patients with more than one primary malignancy did better compared to those with only one malignancy. Patients with at least one LNE did better than those with zero LNE. Patients with more advanced T-stage and those with metastatic disease also fared worse than with lower T-stage and no evidence of metastatic disease.

DISCUSSION

In the past 40 years there has been a 300%-500% increase in the incidence of neuroendocrine tumors (NET)[4,7,11,12]. SBC now represents almost 75% of all gastrointestinal NET and SBC has surpassed adenocarcinoma as the

Table 3 Multivariable regression analysis based on 10-year disease-specific survival

Parameters	Reference	Comparison	HR	[1]*P* vaule
Primary site	Duodenum	Jejunum	1.020 (0.616-1.690)	0.752
		Ileum	0.956 (0.612-1.493)	0.966
Age	≤ 40	41-50	1.628 (0.775-3.420)	0.198
		51-60	2.491 (1.254-4.949)	0.009
		61-70	3.643 (1.849-7.178)	< 0.001
		> 70	6.777 (3.456-13.292)	< 0.001
Gender	Male	Female	1.028 (0.855-1.237)	0.767
Race	Caucasian	Black	1.320 (0.968-1.799)	0.079
		Asian/other	1.243 (0.671-2.305)	0.489
Number of primaries	1	2+	0.401 (0.284-0.564)	< 0.001
Extent of surgery	Resection	Local excision	0.721 (0.404-1.287)	0.269
		Debulking	1.067 (0.809-1.407)	0.647
Number of lymph nodes examined	13+	0	1.621 (1.063-2.445)	0.025
		1-6	1.673 (1.245-2.248)	< 0.001
		7-12	1.525 (1.114-2.087)	0.008
T-stage	T1	T2	1.741 (0.939-3.227)	0.079
		T3	3.205 (1.895-5.422)	< 0.001
		T4	4.793 (2.809-8.178)	< 0.001
		TNOS	1.486 (0.787-2.807)	0.222
N-stage	N0	N1	1.856 (1.010-3.411)	0.438
		Unknown	1.527 (08.10-2.880)	--
M-stage	M0	M1	2.744 (2.175-3.461)	< 0.001

[1]Log-rank test.

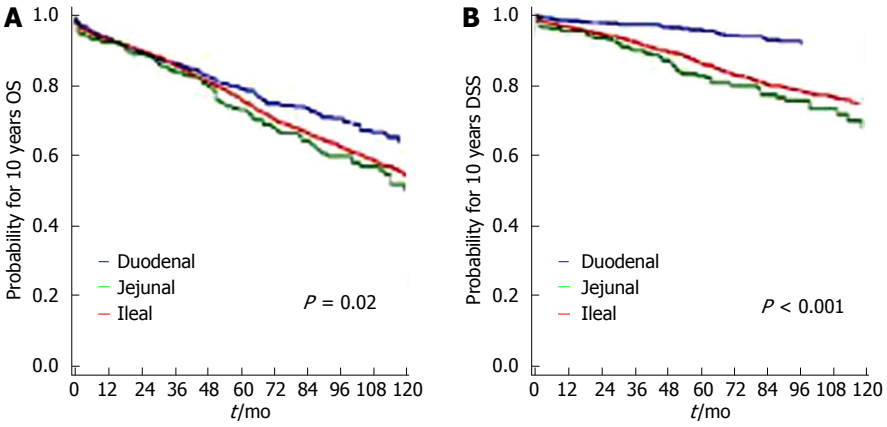

Figure 1 Kaplan-Meier estimate. A: Kaplan-Meier estimates of overall survival (OS) according to primary site of small bowel carcinoid (SBC); B: Kaplan-Meier estimates of disease-specific survival (DSS) according to primary site of SBC.

most common SB malignancy[4,13-15]. For many years, there was inadequate data regarding predictive prognostic variables. As a result, the management of GI carcinoids has been an evolving process. For localized GI carcinoids, it was evident that survival varied significantly based on location of the primary tumor with observed 5-year survival rates favoring carcinoids of the appendix, colon and rectum (85%-90%) relative to those of the stomach (73%), cecum (68%) and small bowel (67%)[16]. As a result, individualized TNM staging systems for GI NET have been established based on the site of the primary tumor[9].

Several studies have reported the observation that duodenal SBC tumors portend a superior survival when compared to SBC tumors of the jejunum and ileum[17-19]. Similarly, we have observed a superior 10-year DSS for duodenal SBC compared to jejunal and ileal SBC. However, this was only statistically significant on univariate analysis and following multivariable regression analysis, primary tumor site was not an independent predictor of survival.

Given the complexity of surgical decision making, it was not surprising that the extent of surgical resection was not an independent predictor of survival, as operative planning is often influenced by a myriad of factors including, but not limited to, radiologic determination of the presence or absence of metastatic disease, assessment of impending obstruction, and potential complications of a proposed procedure. Currently, the National Comprehensive Cancer network (NCCN) guidelines are lacking specific recommendations regarding surgical management; as an example, options for loco-regional

management of a duodenal SBC range from endoscopic excision to pancreaticoduodenectomy.

Perhaps more intriguing is the combination of findings that N-stage was not an independent predictor of survival, yet the number of LNE was a significant predictor. This addresses diagnostic and prognostic challenges not unique to SBC. Patients without adequate lymph node sampling are likely to be under-staged, however the responsibility for this rests not only with the operating surgeon, but with the examining pathologist as well[20,21]. Unlike other histologies, there are no specific recommendations regarding the extent of LN examination required for adequate pathologic staging. Consequently, as demonstrated in our study, a significant portion of patients with SBC lack complete pathologic staging. The association of LNE with increased disease-specific survival could be a surrogate for any number of systems-based variables in a population study such as this; perhaps patients with greater LNE were cared for in a specialized cancer center.

As expected, we also observed that evidence of metastatic disease is an independent predictor of survival. Currently, cytoreductive surgery with R0 resection has prolonged survival for SBC, but it has not been studied in a controlled fashion, and may be affected by selection bias and underlying tumor biology[22]. To date, for patients with unresectable or metastatic disease, options for adjuvant therapy are limited and that have not been proven to be efficacious for SBC. Somatostatin analogues and targeted therapies such as mTOR inhibitors and tyrosine-kinase inhibitors have been shown to increase time to progression of disease, but no studies have demonstrated a statistically significant DSS benefit in a metastatic setting[23,24].

In this study, we confirmed that patients with early stage disease do better regardless of primary tumor site. Therefore, early detection and treatment could significantly impact outcomes for SBC. In recent years, there have been substantial advances in our ability to detect and clinically stage SBC[25-29]. Computed tomography and magnetic resonance enteroclysis, capsule endoscopy and octreotide scanning have been shown to have greater than a 90% sensitivity rating for detection and localization of SBCs[30-34].

This study, like many population-based studies, has its limitations. Although this is a large sample size, a majority of the patients had ileal primaries compared to duodenal. Due to the treatment and current NCCN guidelines for SBC, patients with duodenal tumors usually do not have LNs examined and as result, lack complete TNM-staging. While the NCCN guidelines propose resection and regional lymphadenectomy for jejunal and ileal tumors, more than a quarter of those patients did not have adequate surgical and pathologic staging in the database. The SEER database lacks indications and specific surgical technique performed as well as patient co-morbidities and peri-operative mortality that may play a role in surgical decision making. Recurrence is a common occurrence with SBC and this information is not discernible in the SEER database. Similarly, synchronous *vs* metachronous metastasis are also not specified[35,36].

In the largest study to date evaluating the impact of primary site in SBC, we revealed that primary site is not an independent predictor of SBC-specific survival. We also observed that more than 25% of patients with jejunal and ileal SBC are not receiving the standard of care surgical treatment with a regional lymphadenectomy as per the NCCN guidelines. Further studies are needed to assess the extent of surgical resection and adequate LAD for all stages of jejunal and ileal SBC.

COMMENTS

Background

Primary malignancy of the small bowel remains a rare entity, with fewer than 8810 new cases expected in 2013. However, this represents a steadily rising incidence with a 66% increase over 2003 estimates. The number of estimated deaths from small bowel malignancy has remained virtually unchanged over the same time period (1110 in 2003 *vs* 1170 in 2013).

Research frontiers

Several studies have reported the observation that duodenal small bowel carcinoid (SBC) tumors portend a superior survival when compared to SBC tumors of the jejunum and ileum. Similarly, we have observed a superior 10-year disease specific survival for duodenal SBC compared to jejunal and ileal SBC. However, this was only statistically significant on univariate analysis and following multivariable regression analysis, primary tumor site was not an independent predictor of survival.

Innovations and breakthroughs

In the largest study to date evaluating the impact of primary site in SBC, the authors revealed that primary site is not an independent predictor of SBC-specific survival. Authors also observed that more than 25% of patients with jejunal and ileal SBC are not receiving the standard of care surgical treatment with a regional lymphadenectomy as per the National Comprehensive Cancer network guidelines.

Peer review

The manuscript is a retrospective analysis of small bowel carcinoids obtained from the Surveillance, Epidemiology and End Results database. The paper is clear and easy to follow, its methods clearly stated and the results extremely clear. The discussion is perfectly in line with the results obtained from the statistical analysis, and the authors also very clearly express and motivates the limits of their retrospective results.

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BRIEF ARTICLE

Comparison between open and laparoscopic reversal of Hartmann's procedure for diverticulitis

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Abstract

AIM: To compare the open and laparoscopic Hartmann's reversal in patients first treated for complicated diverticulitis.

METHODS: Forty-six consecutive patients with diverticular disease were included in this retrospective, single-center study of a prospectively maintained colorectal surgery database. All patients underwent conventional Hartmann's procedures for acute complicated diverticulitis. Other indications for Hartmann's procedures were excluded. Patients underwent open (OHR) or laparoscopic Hartmann's reversal (LHR) between 2000 and 2010, and received the same pre- and post-operative protocols of cares. Operative variables, length of stay, short- (at 1 mo) and long-term (at 1 and 3 years) post-operative complications, and surgery-related costs were compared between groups.

RESULTS: The OHR group consisted of 18 patients (13 males, mean age ± SD, 61.4 ± 12.8 years), and the LHR group comprised 28 patients (16 males, mean age 54.9 ± 14.4 years). The mean operative time and the estimated blood loss were higher in the OHR group (235.8 ± 43.6 min *vs* 171.1 ± 27.4 min; and 301.1 ± 54.6 mL *vs* 225 ± 38.6 mL respectively, $P = 0.001$). Bowel function returned in an average of 4.3 ± 1.7 d in the OHR group, and 3 ± 1.3 d in the LHR group ($P = 0.01$). The length of hospital stay was significantly longer in the OHR group (11.2 ± 5.3 d *vs* 6.7 ± 1.9 d, $P < 0.001$). The 1 mo complication rate was 33.3% in the OHR (6 wound infections) and 3.6% in the LHR group (1 hemorrhage) ($P = 0.004$). At 12 mo, the complication rate remained significantly higher in the OHR group (27.8% *vs* 10.7%, $P = 0.03$). The anastomotic leak and mortality rates were nil. At 3 years, no patient required re-intervention for surgical complications. The OHR procedure had significantly higher costs (+56%) compared to the LHR procedure, when combining the surgery-related costs and the length of hospital stay.

CONCLUSION: LHR appears to be a safe and feasible procedure that is associated with reduced hospitality stays, complication rates, and costs compared to OHR.

Key words: Hartmann's procedure; Hartmann's reversal; Diverticular disease; Laparoscopy; Healthcare-related costs; Colorectal surgery

Core tip: The present study examined the intra-operative and post-operative clinical outcomes of open *vs* laparoscopic Hartmann's reversal in patients first treat-

ed for diverticulitis, one of the most common gastrointestinal diseases. By selecting a homogeneous sample of patients, we are able to describe the advantages of laparoscopy in this specific population. The laparoscopic reversal of Hartmann's procedure appeared to be safe and feasible, with advantages in reduced hospitality stays, complication rates, and heath-related costs compared to the open approach.

de'Angelis N, Brunetti F, Memeo R, Batista da Costa J, Schneck AS, Carra MC, Azoulay D. Comparison between open and laparoscopic reversal of Hartmann's procedure for diverticulitis. *World J Gastrointest Surg* 2013; 5(8): 245-251 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i8/245.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i8.245

INTRODUCTION

Diverticular disease is common in developed countries. The prevalence is largely age-dependent; it is uncommon (approximately 5%) in patients younger than 40 years and drastically increases to 65% in patients aged 65 years and up to 80% in those aged 80 years and older[1-3]. Differences are observed among countries, with a higher prevalence in the United States than in Europe and a low prevalence in African nations[4,5].

Diverticular disease occurs as a result of herniation of the mucosa and submucosa through the muscular layer of the colonic wall. Diverticulosis refers to the presence of one or more diverticula, and the disease has a clinical spectrum from asymptomatic to symptomatic disease with potentially lethal complications. Particularly, diverticulitis, which can affect 20%-30% of individuals with diverticulosis, is one of the most common causes of hospitalization related to gastrointestinal disease[6]. Approximately 15% of patients who have had at least 1 episode of complicated diverticulitis could benefit from surgical management[7].

Currently, in cases of complicated diverticulitis associated with perforation and subsequent purulent or fecal abdominal contamination (*i.e.*, Hinchey classification Ⅲ or Ⅳ), 2-stage surgical management is widely performed[8]. This approach comprises a segmental resection of the involved colon and a diverting proximal stoma (Hartmann's Procedure, HP)[9], and, subsequently, a colostomy reversal and restoration of bowel continuity in a second operation[6,10]. HP, as the first step of such 2-stage interventions, is the most commonly performed surgery in the emergency setting for perforated sigmoid diverticulitis[9].

HP was described for the first time in 1921[11] for the resection of left-sided colonic carcinoma. The omission of a primary intestinal anastomosis was intended to reduce the morbidity and mortality related to anastomotic dehiscence. It remains unclear whether Hartmann originally intended the colostomy to be reversible. Currently, reestablishing continuity after HP (*i.e.*, Hartmann's reversal, HR) is usually performed after 3-6 mo, to allow a complete resolution of the pelvic inflammation. HR remains a technically challenging operation that can be performed in only 1/3 of cases[7,12]. HR is associated with a serious risk of surgical morbidity (up to 60% of cases), including a high rate of anastomotic leakage (up to 16%), and a considerable mortality risk (range, 4% to 10%)[7,12-14].

The published results on HR are difficult to interpret because they are based on heterogeneous pathologies (*e.g.*, diverticulitis, sigmoid volvulus, and carcinomas) among different patient groups. Moreover, with the introduction of the circular stapling devices and the development of modern laparoscopic techniques, the restorative procedure has achieved important improvements in patient outcomes, with shorter hospital stays and reduced anastomotic leakage. Since the first use of laparoscopy for HR in 1993[15], the few studies that have examined the role of laparoscopy in performing HR have been primarily small case series, multicenter studies, or retrospective analyses of heterogeneous samples of patients[16-21].

The present study aimed to examine the intra-operative and post-operative clinical outcomes of laparoscopic HR (LHR) compared to open HR (OHR) in patients first treated for complicated diverticulitis.

MATERIALS AND METHODS

Study sample

This is a retrospective, single-center study on a prospectively maintained colorectal surgery database. Data on patients with complicated diverticulitis who underwent conventional HP in the General Surgery Unit of the Henri-Mondor Hospital, Créteil, France, were identified and retrieved after obtaining approval from the Henri-Mondor Hospital Institutional Review Board. The OHR procedures were performed between January 2000 and January 2005, whereas the LHR procedures were performed between January 2005 and January 2010. This temporal disparity occurred because of the hospital unit tended to perform, from 2005 on, HR surgeries using a laparoscopic approach. In total, the study sample includes 46 consecutive patients who underwent OHR (n = 18) or LHR (n = 28) between 2000 and 2010. All patients underwent HP for diverticulitis, as confirmed by histopathological examinations of the surgical specimens. Only Hinchey scores Ⅲ and Ⅳ were included in the analysis. Other indications for HP (*e.g.*, carcinoma, trauma, and ischemia) were excluded from this analysis.

Surgical procedures

In the pre-operative assessment, both groups underwent an anatomical evaluation (*e.g.*, barium enema or endoscopy) of the remaining proximal colon and rectal stump. All patients underwent bowel preparation (including enemata to empty the rectal stump) approximately 24 h before surgery. They all received perioperative broad-spectrum

Table 1 Patients' characteristics

	OHR (n = 18)	LHR (n = 28)	P value
Age (yr)	61.4 ± 12.8	54.9 ± 15.4	0.1
Male/female ratio	5/13	12/16	0.3
Body masse index (kg/m^2)	24.8 ± 2.9	24.1 ± 3.1	0.4
ASA score			0.06
Ⅰ	4 (22.2)	16 (57.1)	
Ⅱ	12 (66.7)	10 (35.7)	
Ⅲ	2 (11.1)	2 (7.1)	
Comorbidity	10 (55.6)	10 (35.7)	0.2
Diabetes	2 (11.1)	3 (10.7)	
Cardiovascular disease	9 (50)	9 (32.1)	
Pulmonary disease	4 (22.2)	2 (7.1)	
Hinchey Score at HP			0.5
Ⅲ	14 (77.7)	20 (71.4)	
Ⅳ	4 (22.3)	8 (28.6)	
Episodes of acute diverticulitis before HP			0.2
None	13 (72.2)	16 (57.1)	
One	5 (27.8)	8 (28.6)	
Two or more	0 (0)	4 (14.3)	
Mean time from HP to reversal (d)	143.7 ± 64.8	129.1 ± 62.8	0.4

Data are presented as means ± SD or n (%). OHR: Open Hartmann's reversal procedure; LHR: Laparoscopic Hartmann's reversal procedure; ASA: American Society of Anesthesiology; HP: Hartmann's procedure.

parenteral antibiotics and subcutaneous low-molecular-weight heparin.

After inducing general anesthesia, the OHR was performed through an abdominal midline vertical incision. The dissection of the peritoneal attachments and rectal stump was achieved using monopolar and/or bipolar electrosurgery devices. Colorectal anastomosis was performed mechanically without stoma protection. In the LHR surgeries, the patients were placed in a modified lithotomy position with the lower limbs slightly flexed on stirrups. A 3-5 trocars technique was used, depending on the level of operative difficulty encountered. The first surgical step was always the excision of the colostomy and the mobilization of the bowel out of the abdomen. Then, the stapler anvil was introduced into the proximal colon by purse string suturing, as previously described[22]. The bowel was returned to the abdominal cavity after having dissected any existing adhesions. Adhesiolysis was achieved with the Harmonic Scalpel (Ultracision®, Ethicon Endo-Surgery, Johnson and Johnson, United States). Colorectal anastomosis was performed mechanically without stoma diversion. In both surgical procedures, the rectal mobilization was systematically performed to ensure the feasibility of the end-to-end anastomosis and to avoid bladder injury. In all cases, the colostomy wall defect was closed using 3 layers of interrupted non-absorbable sutures.

The OHR procedures were performed by 2 experienced general surgeons, 1 (Brunetti F) of whom performed all LHR surgeries.

Surgical outcomes

The OHR and the LHR groups were compared for demographic, operative, and post-operative variables. The main outcomes were the short-term (*i.e.*, 30 d) and long-term (*i.e.*, at 1 year and 3 years) complication rates (including mortality and morbidity). Additionally, the mean invoiced costs per OHR and LHR patient (including surgical materials and hospitality stay) for the French Public Health System (Assistance Publique Hopitaux de Paris) were calculated.

Statistical analysis

Statistical analysis was performed with SPSS (IBM, SPSS Statistics, Version 20 for Macintosh, Chicago, Illinois, United States). The groups were compared using the Chi-squared or Fisher's Exact Test for the categorical variables and the *T*-test for the continuous variables. The following variables were analyzed: age, gender, presence and type of comorbidity, ASA score, Hinchey score, number of episodes of diverticulitis before HP, time between HP and its reversal, extent of colon mobilization, operation time, estimated blood loss, time to flatus, time to resumption of diet, hospital stay, and complication rates. A P value < 0.05 was considered significant.

RESULTS

The demographic characteristics of the OHR and LHR patients are shown in Table 1. The two groups showed no differences in terms of the mean age, gender distribution, body mass index, ASA scores, presence of comorbidities, Hinchey scores, number of episodes of diverticulitis before HP, and d between HP and its reversal. Averaged between both groups, the HR was performed 134.8 ± 63.3 d after the primary resection.

In both groups, all anastomoses were mechanical supra-peritoneal end-to-end anastomoses without stoma diversion. In the majority of the cases, a splenic flexure mobilization was performed to ensure a free-tension anastomosis. The n° 29 stapler was most frequently used in both procedures. No conversion to open surgery occurred in the LHR group. The mean operative time and the amount of estimated blood loss were significantly superior in the OHR compared to the LHR group (Table 2).

Concerning the post-operative variables, the LHR group showed a significantly lower time to flatus, time to resumption to regular diet, and hospital stay (Table 3). The short-term complication rate (1 mo) was also lower in the LHR group compared to the OHR group. No anastomotic leaks occurred. All observed complications were medically managed, except for 1 case of hemorrhage of the inferior epigastric vessel, which required hemostatic laparoscopic surgery, at postoperative day 1 in the LHR group. Regardless of the surgical procedure, the early post-operative complication rate was 15.2%, including mainly wound infections and one case of hemorrhage. Patients with and without complications had similar demographic and operative characteristics. The only variable that was significantly associated with post-

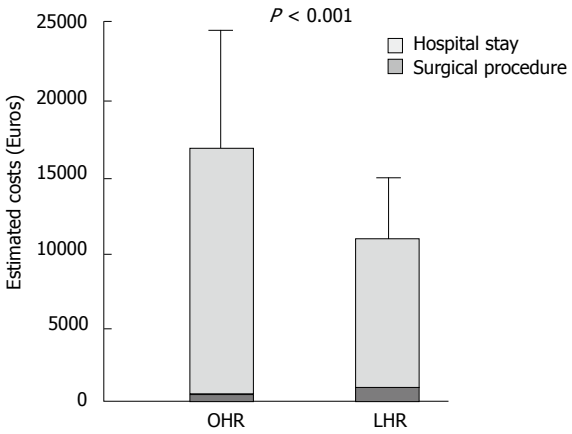

Figure 1 Estimated average costs for open Hartmann's reversal and laparoscopic Hartmann's reversal, including surgical procedure and length of hospital stay. The average costs are estimated in Euros. OHR: Open Hartmann's reversal; LHR: Laparoscopic Hartmann's reversal.

operative complications was the length of hospital stay ($P < 0.001$).

At 12 mo, the complication rate remained significantly higher in the OHR group (Table 3), including midline incisional hernias and incisional hernia of the previous colostomy, which were electively surgically managed. The overall mortality rate was nil. At 3 years, no patient required re-intervention for surgical complications.

The OHR procedure had significantly higher costs (average +56%) compared to the LHR procedure, when combining the surgery-related costs and the length of hospital stay (Figure 1).

Table 2 Operative variables

	OHR (n = 18)	LHR (n = 28)	P value
Extent of mobilization			0.5
Splenic flexure	16 (88.9)	27 (96.4)	
Transverse	2 (11.1)	1 (3.6)	
Stapled end-to-end anastomosis N° (mm)			0.07
N° 28	0 (0)	2 (7.1)	
N° 29	18 (100)	21 (75)	
N° 31	0 (0)	5 (17.9)	
Operation time (min)	235.8 ± 43.6	171.1 ± 27.4	0.001
Estimated blood loss (mL)	301.1 ± 54.6	225 ± 38.6	0.001

Data are presented as means ± SD or n (%). OHR: Open Hartmann's reversal procedure; LHR: Laparoscopic Hartmann's reversal procedure.

Table 3 Post-operative variables

	OHR (n = 18)	LHR (n = 28)	P value
Time to Flatus (d)	4.3 ± 1.7	3 ± 1.3	0.006
Time to Resumption to regular diet (d)	5.5 ± 1.7	3.9 ± 1.2	0.001
Length of hospital stay (d)	11.2 ± 5.1	6.7 ± 1.9	<0.001
1 mo complication rate	6 (33.3)	1 (3.6)	0.004
Wound infection	6 (33.3)	0	
Hemorrhage	0	1 (3.6)	
12 mo complication rate	5 (27.8)	3 (10.7)	0.03
Midline incisional hernia	4 (22.2)	0	
Incisional hernia of the previous colostomy	1 (5.6)	3 (10.7)	

Data are presented as means ± SD or n (%). OHR: Open Hartmann's reversal procedure; LHR: Laparoscopic Hartmann's reversal procedure.

DISCUSSION

The present study described the clinical outcomes of two surgical approaches (*i.e.*, open *vs* laparoscopic) to perform HR in a homogeneous sample of patients first treated for complicated diverticulitis (Hinchey scores Ⅲ or Ⅳ). In accordance with the previous literature, our study demonstrated that LHR is safe and feasible, with reduced operative time and more rapid post-operative recovery.

HP, originally described for distal colon cancer complicated with bowel obstruction, has evolved over the years, finding its current main indication in benign pathologies, such as diverticulitis[11,23]. This finding may be particularly true in developed regions, such as North American and Europe, in which the introduction of widespread screening programs for colorectal cancers and advanced endoscopic techniques, such as the placement of endoluminal stents, has relegated the HP primarily to emergency interventions for inflammatory diseases or iatrogenic perforations[24-26]. However, HP remains a rarely performed procedure because of its infrequent indication and the availability of other treatment options, such as antibiotic therapies, laparoscopic lavage, and drainage, or primary resection with immediate anastomosis[17,27,28]. Moreover, HR is not possible in all patients, with reversal rates ranging between 21% and 85% of patients[12,19,25].

For this reason, the current literature on HP and HR is characterized by studies of samples that include all possible indications, thus grouping together patients with diverticulitis, inflammatory bowel diseases, cancers, or trauma. However, this grouping may bias the interpretation of results and influence the risk of underestimating or overestimating the clinical outcomes of HR, with either the open or laparoscopic approach, in relation to specific pathologies.

A recent review showed that LHR offers several advantages over OHR, including more rapid post-operative recovery, less post-operative pain, earlier restoration of bowel function, more rapid return to normal diet, and reduced morbidity[23]. However, the reduced surgical invasivity and the clinical advantages of the laparoscopic approach does not seem to have increased the number of patients candidate to undergo HR, which might have been expected.

In contrast with previous studies[17-21,29], we analyzed a homogeneous sample of consecutive patients diagnosed with diverticulitis who underwent surgery in the same hospital unit with the same laparoscopic technique, to report the data related to a specific subset of patients representing those most often seen in clinical practice.

In our study, the majority of patients (58.7%) with diverticular disease underwent HP at the first episode of

acute diverticulitis, in accordance with the disease evolution, which can present with perforation at the first attack[8]. On average, the OHR and LHR were performed 4.5 mo from the HP, which is less than the 7.5 mo reported in other published studies[23]. Moreover, in contrast with other reports[17], the time interval between HP and its reversal did not influence the overall morbidity or complication rates in either the OHR or the LHR group in our study. The reduced time interval between HP and its reversal was justified by the overall optimal status of the patients (*e.g.*, nutritional status), which is also related to the underlying benign pathology and is supported by the low incidence of impossible adhesiolysis (*i.e.*, no conversion was needed), although all patients were classified with a Hinchey score Ⅲ or Ⅳ.

The operative time was significantly lower when the HR was performed laparoscopically, as was expected[17,23]. In the literature, many different laparoscopic procedures are described[19,25,30]. The technique used in the present study, starting with the mobilization of the stoma and the primary preparation of the afferent loop before the placement of the trocars, may contribute to the time saving[22]. Although the ideal laparoscopic technique and the advantages of one over the others is still a matter of debate, it remains an important risk factor for post-operative morbidity[31,32]. In our study, we had no mortality and no anastomotic leaks, in contrast with previous literature[7,13,14,22]. In all interventions, whether OHR or LHR, a tension-free anastomosis was systematically obtained, frequently by the complete mobilization of the splenic flexure, and this process may have favored the anastomotic healing, although there is controversial literature on this topic[19,21,32].

The LHR was associated with a shorter recovery time and a lower incidence of post-operative complications. In particular, the LHR, characterized by minimal invasiveness and surgical trauma, was associated with a reduced time to flatus and resumption of normal diet, which surely contributed to the shortened hospital stays. However, note that we had no intra-operative complications in either group and no conversions from the laparoscopic to the open technique. This finding may be related to the experience of the surgeon operating in a high volume surgical center, which may play an important role regarding this technically challenging intervention[33]. The early complications observed were abdominal wound infections in the OHR group and one case of hemorrhage in the LHR group, with an overall complication rate of 15.2%. The delayed post-operative complications (at 1 year) included midline incisional hernias and incisional hernia of the previous colostomy, for an overall incidence of 17.4%. No further surgical complications were observed within 3 years of follow-up. The complication rates in our studies are within the ranges reported in other recent case series[16,17,22].

In addition to the clear clinical advantages of LHR for the patients, a more rapid recovery time has a great influence on the overall costs of the surgery and hospitalization. Indeed, LHR may have a higher intra-operative cost for surgical materials; however, this cost is overbalanced by lower expenses in the post-operative period because of reduced hospital stays and incidences of complications. This aspect cannot be underestimated because it influences healthcare system policy makers. Moreover, as the population ages, diverticular disease appears to be increasing, thereby representing a significant risk to health with subsequent indications for healthcare expenditures in the elderly population. In the French healthcare system, the major determinant of cost is the length of hospital stay, which is estimated at 1500 euros/d per patient in our department. Thus, although the differences among healthcare systems across European countries and the lack of updated data preclude a precise estimate of diverticulitis-related healthcare costs, a considerable financial burden is expected[2].

The main limitations of this study are the non-randomized study design and the small sample size. However, a single-center randomized controlled trial with an adequate sample size comparing OHR *vs* LHR appears to be unfeasible because this procedure represents less than 1% of laparoscopically performed colorectal surgeries in a high volume surgical center[17]. This limitation may be counterbalanced by the fact that in the present single center study, we compared OHR to LHR in a homogenous patient sample, with the same indication for HP (*i.e.*, complicated diverticulitis).

In conclusion, in accordance with the previous literature, LHR appears to be a safe and feasible procedure for patients first treated for complicated diverticulitis and offers the advantages of reduced length of hospital stays, lower complication rates, and reduced costs compared to OHR. Although the available evidence supporting the superiority of LHR is mainly based on non-randomized small studies, the laparoscopic approach may now be considered the gold standard technique for HR in high volume colorectal surgical centers.

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COMMENTS

Background

In cases of diverticulitis Hinchey classification Ⅲ or Ⅳ, the Hartmann's procedure is the most frequently performed. The reversal of Hartmann's procedure is associated with high risks of surgical morbidity and mortality, and only a third of the patients can beneficiate of it.

Research frontiers

Laparoscopic Hartmann's reversal is investigated as the surgical technique to achieve better surgical and clinical outcomes.

Innovations and breakthroughs

Most of the previously published studies have examined the laparoscopic Hartmann's reversal in heterogeneous sample of patients operated for various indications. This may bias the interpretation of the clinical results in relation to

the specific pathology. The study assessed the advantages of laparoscopy over open approach in patients with diverticular disease only.

Applications

The results of the study provide relevant evidence for the application of laparoscopy for Hartmann's reversal, in order to have lower morbidity, shorter hospital stay, and reduced costs for the Healthcare System.

Terminology

The Hartmann's procedure is the surgical resection of the rectosigmoid colon with closure of the rectal stump and formation of an end colostomy. The Hartmann's reversal is the restoration of bowel continuity by the closure of the colostomy.

Peer review

This retrospective cohort study compares the open to laparoscopic reversal of Hartmann's procedure in a homogenous population with complicated diverticulitis. It is the first to isolate diverticulitis as indication. The results are very interesting and in accordance with previous results, underlining the minimal invasiveness of laparoscopic surgery and the same (or better) security profile.

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CASE REPORT

Successful bowel surgery at hemoglobin 2 g/dL without blood transfusion

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Abstract

We were unable to find reports in the published medical literature of any cases of bowel surgery being successfully performed at such a low hemoglobin level, without blood transfusion or blood products pre or post-surgery, with the patient's uncomplicated recovery. This study is about such a case. A patient presenting with severe gastrointestinal bleeding was diagnosed with enteric fever and multiple ileal ulcers. He had an extremely low hemoglobin level (2 g/dL) and mild renal and hepatic impairment. He was immediately admitted for right hemicolectomy under general anesthesia though he refused transfusion of blood or blood products prior to, during, or after surgery on religious grounds (Jehovah's Witnesses). After the surgery and having survived these potentially life-threatening circumstances, he left the hospital without major complications. In such circumstances, lives may be saved by prompt clinical decision-making, collaboration and swift surgical intervention coupled with the immediate consultation and input of the patient and family.

Key words: Gastrointestinal bleed; Low hemoglobin level; Jehovah's witnesses; Multiple terminal ileal ulceration; Enterotomy; Right hemicolectomy.

Core tip: It is unheard of in the medical history to take up a patient with hemoglobin of 2 g/dL for anesthesia and major bowel surgery, without transfusing blood or blood products prior to, during or after surgery; and saving the life without complications. We would like to report regarding such a patient who was treated at our hospital.

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INTRODUCTION

Few, if any case studies in the published medical literature

Table 1 Blood reports of the patient at admission along with normal values

Tests	Value at admission	Normal values
Hemoglobin (g/dL)	4 to 2 (in 12 h)	13.5-17.5
Serum creatinine (μmol/L)	353.6	68-118
Prothrombin time/INR (s)	1.3	0.9-1.2
Serum bilirubin (μmol/L)	114.57	2-17
SGOT (U/L)	218	5-40
SGPT (U/L)	132	5-30
Widal test	Salmonella typhi: "O" titre 1/640 Salmonella typhi: "H" titre 1/640 Salmonella paratyphi: "AH" titre 1/80 Salmonella paratyphi: "BH" titre 1/40	

Originated from ref.[1-3] with permission. SGPT: Serum glutamic pyruvic transaminase; INR: International normalized ratio; SGOT: Serum glutamic oxaloacetic transaminase.

report on the successful, uncomplicated surgical outcome of a patient with hemoglobin of 2 g/dL for anesthesia and major bowel surgery, without blood transfusion or blood products pre or post-surgery. Thus, we would like to report our recent experience treating such a patient at our hospital.

CASE REPORT

A 39-year-old male patient was admitted to Sunrise Hospital, Cochin, Kerala, India; after being referred from a nearby hospital [from where he left against medical advice] with a history of severe lower gastrointestinal bleeding. The diagnosis was enteric fever with bleeding from the gastrointestinal tract. Salmonella typhi "O" and "H" titre was 1/640, which was confirmed by tube agglutination test (stained febrile antigen set, Manufacturer- Span diagnostics ltd, Sachin, Surat, Gujarat, India). His hemoglobin was extremely low (4 g%) at admission. On examination, he was very pale and icteric, with a pulse rate of 120/beats per minute and blood pressure of 110/70 mmHg and mild distension of the abdomen was present. Table 1 shows the blood investigations of the patient at admission. An immediately performed colonoscopy showed multiple terminal ileal ulcerations with diffuse active bleeding that was not amenable to either colonoscopic or radiological intervention at that stage. Hence, immediate surgical intervention was planned.

It was decided as absolutely necessary to transfuse blood and blood products to correct the hemoglobin level, which had dropped to 2 g/dL within 12 h of admission. We discussed with the patient's relatives the urgent need for blood transfusion, before proceeding with surgery to arrest the ongoing bleeding. However, the patient, his wife and other relatives were firm in their decision not to receive blood or blood products, due to their religious beliefs. Giving erythropoietin alone at that time was not an option in this patient with active bleeding. Thus, we were faced with the option of not performing the surgery at all, but at the almost certain cost of the patient's life. Wanting to give the patient the chance to survive, it was decided to offer the patient surgery, despite his clinical condition and the treatment constraints mentioned above that make for an extremely risky surgery. The patient was prepared for laparotomy with a high-risk consent that also listed the distinct possibility of death during surgery and the continued unwillingness to receive blood or blood products.

The patient was given general anesthesia, during which minimal intravenous fluids were administered to maintain the blood pressure at 100/60 mmHg, as over-hydration could lead to a further drop of in hemoglobin levels. The bowel was found to be thickened at the ileocecal region. Enterotomy was performed and linear ulcers with bleeding base were observed at the terminal ileum. Limited right hemicolectomy was performed, excising the distal 21 cm of ileum including the ulcer, cecum, appendix and a portion of ascending colon. The entire bowel was edematous,and the blood that oozed during resection appeared thin and watery. To reduce the duration of surgery, reconstruction was attempted by side-to-side ileocolic stapler anastomosis, but staplers did not hold due to bowel wall edema. Revision of anastomosis with hand-sewn, end-to-end, ileocolic two-layer suturing was performed with 3-0 Vicryl (polyglycolic acid)-continuous all coat and 3-0 silk, intermittent seromuscular.

Postoperatively, the patient was kept in the intensive care unit for 10 d with nasal oxygen to enrich the available hemoglobin with oxygen. He had features of renal and hepatic impairment, which gradually improved (Table 2). Improvement in hemoglobin level is presented in Figure 1. Total parenteral nutrition and albumin infusion were initiated. He was given intravenous ferric carboxymaltose and recombinant erythropoietin. Small doses of frusemide were given intravenously for the benefit of hemoconcentration.

The patient was put on oral fluids on the fifth day of surgery, which was gradually switched over to soft diet by the seventh day. A high protein, high calorie diet was given together with oral iron supplementation. Gradually, his hemoglobin level improved, as shown in Table 2. The biopsy report showed linear ulcers in the distal ileum, with the largest measuring 1.5 cm. Microscopy showed a mucosal ulcer infiltrated by histiocytes, lymphocytes, plasma cells and occasional neutrophils consistent with typhoid ulcer ileum. No granulomas were present.

DISCUSSION

We were unable to find reports in the published medical literature of any similar cases of bowel surgery being successfully performed at such a low hemoglobin level with the patient's uncomplicated recovery. Various reports of surgeries performed without blood transfusion in severely anemic patients (hemoglobin level less than 5 g/dL)

Table 2 Hematological and biochemical improvement during the course of treatment

Parameters	Day 0	Day 1	Day 3	Day 5	Day 8	Day 14	Day 17	Day 21	Day 29	3 mo	[1]Normal values
Hemoglobin (g/dL)	2	3	2.8	4.1	4.8	5	5.6	6.5	8.2	13	13.5-17.5
Albumin (g/L)	28	30	34	38	36						35-55
Creatinine (μmol/L)	353.6	203.3	256.4	150.3	141.4	115				97.2	68-118
Bilirubin (μmol/L)	114.6	25.6		17.1	15.4						2-17

[1]Originated from ref.[1-3] with permission.

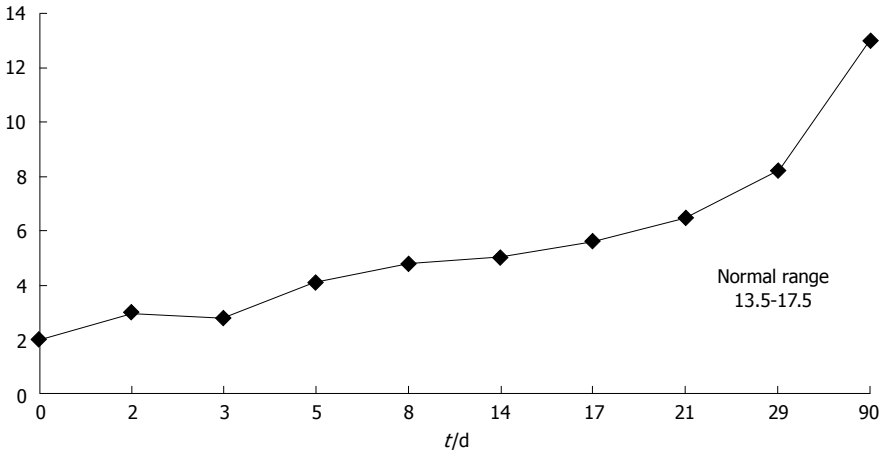

Figure 1 Improvement of hemoglobin during the course of treatment.

showed mortality of approximately 50%[4], which further increased to 91% in the 2 to 3 g/dL group[5].

Hemoglobin is the major oxygen-carrying protein in blood. Low hemoglobin level is generally defined as less than 13.5 g/dL for men and less than 12 g/dL for women. Unless it is very severe, anemia, perse, does not cause any problems with anesthesia or surgery. Severe anemia can precipitate cardiac arrest due to (1) increased cardiac output; (2) vasodilatation associated with anesthesia; and (3) hemodilution during resuscitation of hemorrhagic shock using saline. The degree of hemodilution is directly associated with acid base imbalance and is proportional to the level of compromise of metabolic recovery, which in turn is projected on to mortality[6]. In addition, tissue hypoxia due to reduced oxygen-carrying capacity of the blood leads to end-organ damage and systemic immune response syndrome. There also is a risk of surgical site infection, delayed wound healing and bowel leak at the site of the anastomosis.

Jehovah's Witnesses are a Christian denomination with non trinitarian beliefs distinct from mainstream Christianity and have a worldwide membership of over 7.78 million people. Their beliefs are based on interpretations of the Bible and they prefer to use their own translation. They refuse blood transfusions, which they consider to be a violation of God's law based on their interpretation of Acts 15:28, 29. Since 1961, the willing acceptance of blood transfusion by an unrepentant member has been grounds for expulsion from the religion. Watch Tower Society literature directs Witnesses to refuse blood transfusions, even in "a life-or-death situation"[7]. They refuse transfusions of whole blood or of any of its four primary components - red cells, white cells, platelets and plasma (serum)[7,8].

It is always a dilemma for the surgeon to decide whether to urgently operate on a bleeding patient with hemorrhagic shock without blood transfusion. We believe that life-saving interventions should not be delayed for patients with active bleeding, even though blood transfusion may be refused. Atabek and colleagues have reported a case of active bleeding in a Jehovah's Witness patient, where early surgery led to rescue of the patient[9]. Initial conservative treatment with delayed surgery led to a 75% mortality rate, compared with a 20% mortality rate in patients who underwent emergency surgical intervention within 24 h of admission to the hospital[10,11].

Our patient was at high-risk for cardiac arrest due to oxygen depletion, but eventually survived without complications. Anastomotic site healing was also potentially in jeopardy, but he recovered without leak.

In conclusion, even in the rarest of situations, such as the one described, a successful attempt to save the patient's life can be made, even though the general condition of the patient is clinically unstable. Prompt decision-making and effective communication among the treating doctors and with the patient and his relatives were important factors that helped the patient's positive outcome. Had the clinical team refused to perform surgery on this patient, or even delayed the operation because of his extremely low hemoglobin, death would likely have been assured.

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CASE REPORT

Colonic tumour precipitating caecal volvulus within a diaphragmatic hernia

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Abstract

An 85-year-old woman presented with sudden onset of generalised abdominal pain and absolute constipation for 4 d. On examination she had a distended abdomen. Plain abdominal radiograph revealed a gas filled viscous within the left upper quadrant. Subsequent computed tomography suggested caecal volvulus herniated through a left diaphragmatic hernia. The patient underwent reduction of the internal hernia, right hemicolectomy and mesh repair of the diaphragmatic hernia. Postoperative recovery was uneventful. Histology revealed a Dukes' A colonic cancer within the caecum. Herniation of caecal volvulus through a diaphragmatic hernia is a very rare condition and may have been precipitated by the colonic tumour.

Key words: Colonic cancer; Caecal volvulus; Bowel obstruction; Diaphragmatic hernia; Bowel ischaemia

Core tip: In patients presenting with acute bowel obstruction rare causes such as caecal volvulus must be included in the differential diagnosis. Herniation of caecal volvulus through a diaphragmatic hernia is a very rare condition and may have been precipitated by the colonic tumour.

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INTRODUCTION

Internal hernias through a diaphragmatic hernia are extremely rare, accounting for only < 1% of all hernias. Diaphragmatic herniae are generally thought to be congenital but other aetiological factors such as trauma have been suggested[1]. The true incidence of diaphragmatic hernia is not known[2]. Furthermore symptoms and/or herniation through such hernias are very rare[1].

Intestinal obstruction due to internal herniation of the caecum in the form of caecal volvulus has not been reported in the literature previously. Caecal volvulus is defined as the axial rotation of the caecum accompanied by a twisting of the mesentery and of its vessels[3]. The classical clinical presentation is that of symptoms of an intestinal obstruction[4]. We report a case of caecal volvulus herniated through a left diaphragmatic hernia that may have been precipitated by a colonic tumour. Prompt surgical intervention following radiological imaging ensured the patient had an excellent post-operative outcome.

CASE REPORT

An 85-year-old female was admitted with a 4-d history

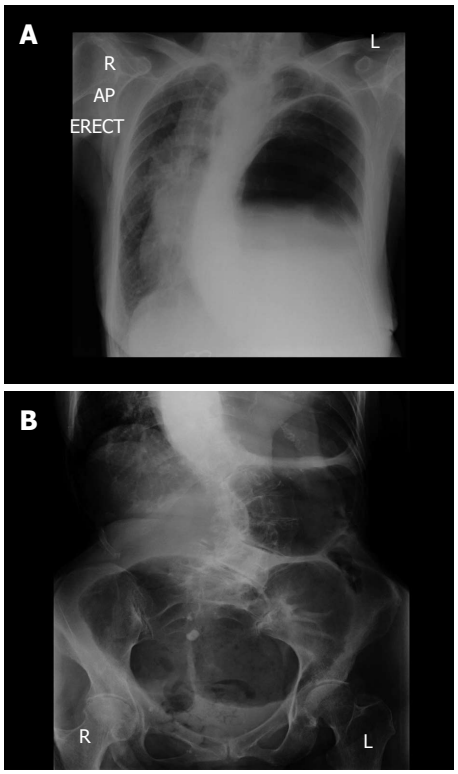

Figure 1 Plain radiographic images of the patient upon emergency admission. A: Erect chest radiograph upon admission demonstrated that the patient had a collapsed left lung and elevated left hemidiaphragm with a large viscous identified under the left hemidiaphragm; B: Plain abdominal radiograph on admission revealed a gas filled viscous within the left upper quadrant consistent with caecal volvulus.

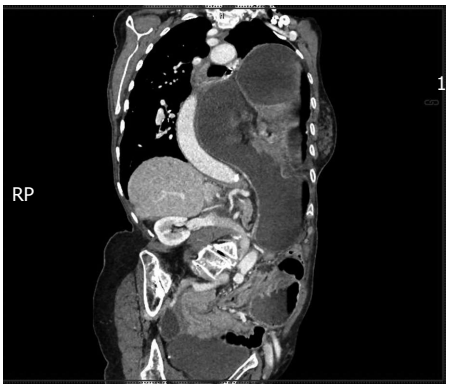

Figure 2 Computed tomography findings on admission. A sagittal computed tomography scan with intravenous contrast clearly demonstrated that the caecum had herniated thorough a diaphragmatic hernia and was the cause of the intestinal obstruction.

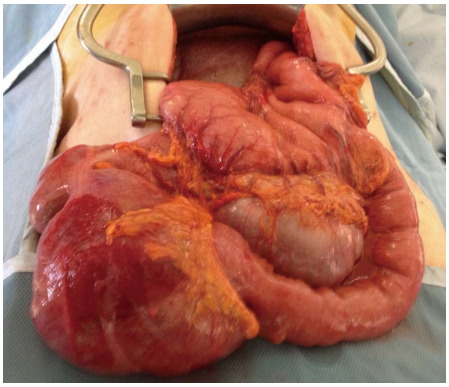

Figure 3 Operative findings at laparotomy. Following reduction of the caecal bascule from the diaphragmatic hernia the caecum demonstrated multiple serosal defects that necessitated right hemicolectomy.

of sudden onset abdominal pain associated with absolute constipation. She had no relevant past medical history and had had no previous abdominal surgery. On examination she had tender but soft abdomen with no signs of peritoneal irritation. The abdomen was markedly distended. There was also hyperactive bowel sound on auscultation. Digital rectal examination demonstrated soft stool in rectum.

Full blood count, urea and electrolytes, liver function tests, and C-reactive protein were all within normal limits. Erect chest radiograph revealed a collapsed left lung and elevation of the left hemidiaphragm with a large viscous identified under the left hemidiaphragm in keeping with volvulus of the large bowel (Figure 1A). Plain abdominal radiograph revealed a gas filled viscous identified within the left upper quadrant in keeping with volvulus of the caecum (Figure 1B). A computed tomography scan with intravenous contrast was performed subsequently which demonstrated that the caecum had herniated through the diaphragmatic hernia and was causing intestinal obstruction (Figure 2). There were no features suggestive of malignancy.

The patient received initial management with intravenous fluid, nasogastric tube drainage, and anti-emetic and analgesic medications. After fluid resuscitation, the patient underwent an emergent laparotomy. A mobile caecum and ascending colon with a long, unfixed mesentery was herniated through the diaphragmatic hernia. The caecum was twisted 270° inside the hernial sac and had developed tears in the outer serous membrane of the bowel termed serosal tears. Furthermore the caecum around the serosal tears appeared congested and ischaemic (Figure 3). A right hemicolectomy with a stapled ileo-transverse colonic anastomosis was performed. The diaphragmatic hernia was repaired with a mesh to prevent further herniation. Specifically the hernia sac was excised and the edges of the hernial defect were freshened. A composite mesh was used for the hernial repair. The polypropylene surface of the mesh was sutured into contact with the diaphragm and the polyglactin surface was left exposed to the peritoneal cavity. Histological analysis of the resected bowel revealed a sessile polyp in the ascending colon measuring 38 mm × 32 mm that was 22 mm from the proximal resection margin. This polyp was a well to moderately differentiated adenocarcinoma arising in a tubulovillous adenoma (pT_2, pN_0, pM_x; Dukes' A). Histology confirmed the adenoma was infiltrating the muscularis mucosae with the cells displaying an irregular tubular structure. There was no evidence of lymphovascular invasion. The patient's postoperative recovery was uneventful and she was discharged after 13 wk.

DISCUSSION

Diaphragmatic hernias resulting from the developmental failure of posterolateral diaphragmatic foramina to fuse properly and was originally described by Salaçin *et al*[5]. Diaphragmatic hernias typically vary in size, are predominantly left sided, can present at any age and are usually found incidentally[5-7]. Approximately 100 cases of Bochdalek's hernias in asymptomatic adults have been reported in the literature. The true prevalence of Bochdalek's hernia remains unknown, with estimates ranging from 1 in 2000-7000[5,6]. Putative causes for late-presenting diaphragmatic hernias include congenital herniation, trauma, physical exertion, pregnancy, sneezing or coughing[5]. The size of the hernia seen on cross-sectional imaging does not necessarily correspond to the size of the diaphragmatic defect, which may be substantially larger[8].

Left-sided diaphragmatic hernias may contain fat, retroperitoneal structures, or intraperitoneal contents, although the latter two conditions are rare[8]. Colon-containing diaphragmatic hernias are exceedingly rare and do usually occur through left-sided defects[9]. The reported case is the first to report a caecal volvulus within a diaphragmatic hernia. Caecal volvulus occurs as a result of axial rotation of the caecum about its mesentery. The ischaemia and serosal tears observed in the reported patient are likely due to venous congestion of the caecum due to the twisted mesentery[10]. Other authors have also reported that intestinal volvulus causes intestinal ischaemia[11]. Previous reports in the literature suggest that tumours may precipitate volvulus[12,13]. The putative mechanism suggests that high peristaltic bowel centred on the tumour cause a loop of bowel to descend inferiorly. This displaces empty small bowel loops upwards, initiating rotation of the mesentery and causing volvulus[13].

Martin *et al*[14] described the first open repair of a diaphragmatic hernia. Although laparoscopic repair of a diaphragmatic hernia has been described this approach is probably best reserved for the elective setting[15]. In our case after the standard right hemicolectomy was performed for the caecal volvulus the diaphragmatic hernia required repair. Consensus on whether synthetic mesh or primary closure produce the safest and most durable repair for diaphragmatic hernia has yet to be agreed[16]. The placement of synthetic mesh repair in close proximity to the esophagus runs the risk of erosion[17]. Synthetic mesh was chosen for the large diaphragmatic defect as in our case. Ethicon Vypro mesh was used for its dual surface properties. It has a fascial side, which induces tissue ingrowth and thus results in better tissue fixation. On the other hand, on its peritoneal side it has a low-porosity smooth visceral surface that minimizes visceral adhesion.

In summary, precise radiological evaluation and prompt surgical repair results in good outcome in patients presenting with bowel obstruction secondary to a diaphragmatic hernia.

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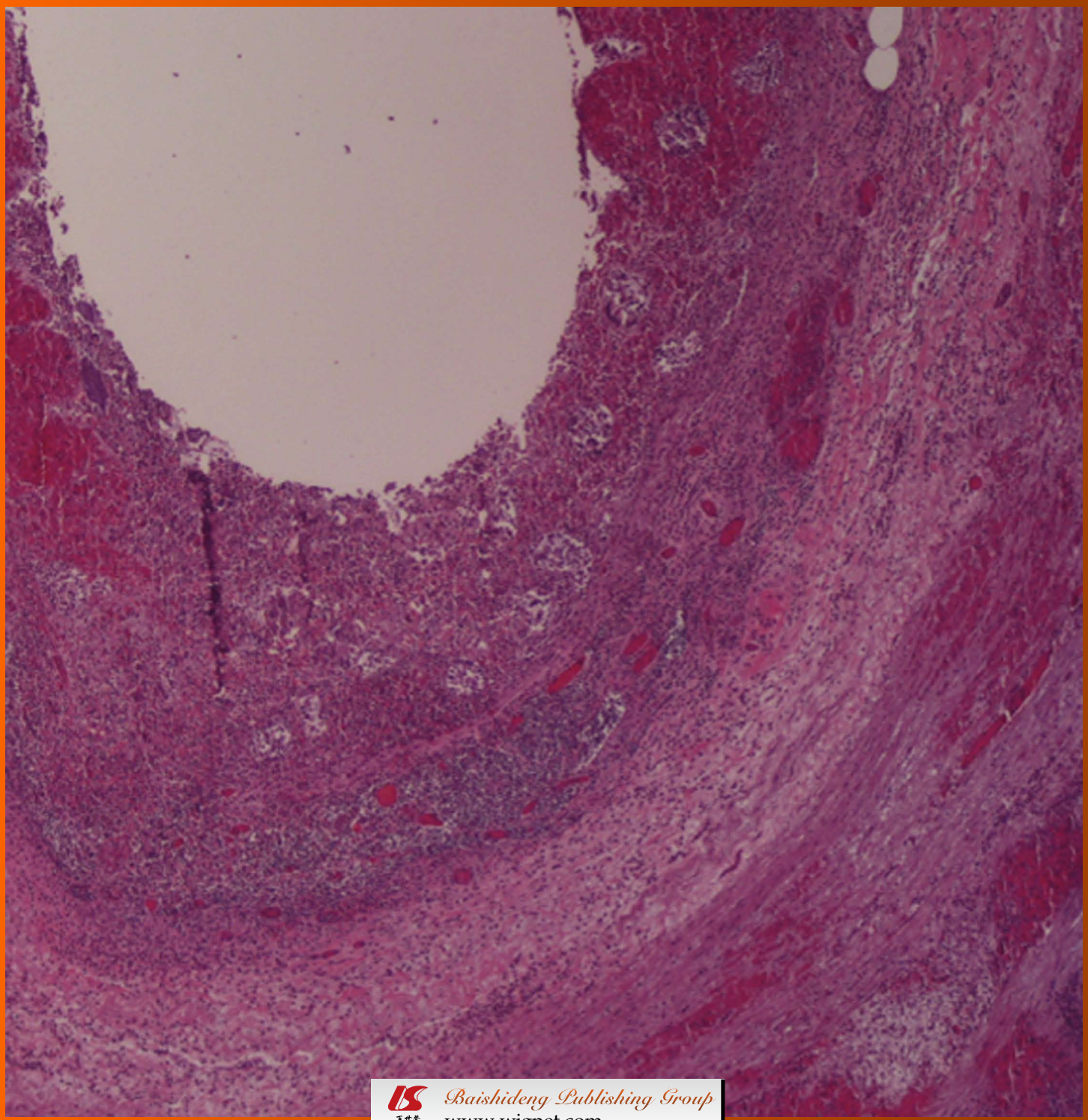

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CASE REPORT

Post-colonoscopy appendicitis: A case report and systematic review

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Abstract

Colonoscopy is a widely used diagnostic and therapeutic modality with a relatively low morbidity. However, given the large volume of procedures performed, awareness of the infrequent complications is essential. Perforation is an established complication of colonoscopy, and can range from 0.2%-3% depending on the series, population and modality of colonoscopy. Acute appendicitis after colonoscopy is an extremely rare event, and a cause-effect relationship between the colonoscopy and the appendicitis is not well documented. In addition, awareness of this condition can aid in prompt diagnosis. Relatively mild symptoms and exclusion of bowel perforation by contrast studies do not exclude appendicitis from the differential diagnosis for post-colonoscopy pain. In addition to the difficult diagnosis inherent to postcolonoscopy appendicitis, treatment strategies have varied greatly. This paper reviews these approaches. We also expand upon prior articles by giving guidance for the role of nonoperative management in these patients. This case and review of the literature will help to create awareness about this complication, and guide optimal treatment of pericolonoscopy appendicitis.

Key words: Colonoscopy complications; Appendicitis

Core tip: The manuscript highlights a recent interesting case from our institution demonstrating appendicitis after colonoscopy, which was managed surgically. This paper reviews the relevant literature including all related previously published cases, and makes recommendations about defining the syndrome of post-colonoscopy appendicitis and how it should be managed.

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INTRODUCTION

Colonoscopy is a widely used diagnostic and therapeutic procedure. Thousands of colonoscopies are performed yearly in the United States alone. Although the risk and complications are low, the high volume of cases makes awareness of these rare complications imperative. Bleeding and perforation are by far the most common complications of colonoscopies; these complications can range from 0.2%-3% depending on the series, population and modality of colonoscopy[1]. Acute appendicitis after colonoscopy is an extremely rare event, and a cause-effect relationship between the colonoscopy and the appendicitis is not well documented. In addition, awareness of this condition can aid in prompt diagnosis. Some degree of mild cramping or gas pain can be normal following colonoscopy, but providers and patients must remain vigilant for unusual symptoms that signal complications of this procedure. Relatively mild symptoms and exclusion of bowel perforation by contrast studies do not exclude appendicitis from the differential diagnosis for post-colonoscopy pain. This case and review of the literature

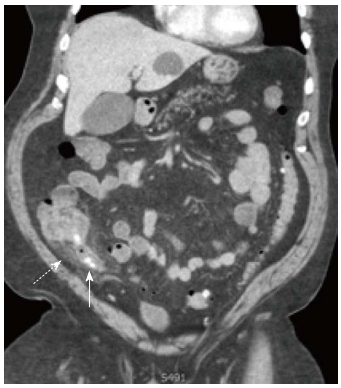

Figure 1 Coronal image of acute appendicitis following colonoscopy. Solid arrow: Appendicolith; Dashed arrow: Appendix.

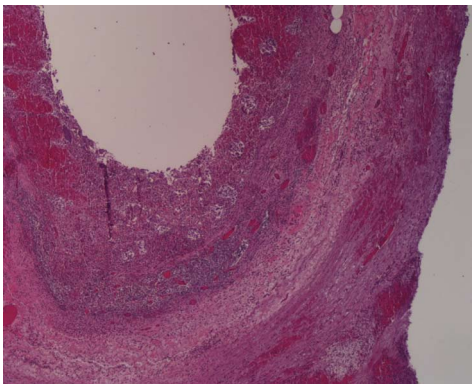

Figure 2 Histology slide of acute appendicitis.

will help to create awareness about this complication, and guide optimal treatment of pericolonoscopy appendicitis.

CASE REPORT

A 67-year-old male was scheduled for colonoscopy for colorectal screening. Colonoscopy and bowel prep were uneventful. Previous to the colonoscopy this patient was asymptomatic. The patient had an unremarkable bowel preparation and denied any abdominal pain, nausea, vomiting or anorexia before the procedure. He underwent colonoscopy without complication. The endoscope was advanced to the cecum and the appendix orifice was visualized. No abnormality was found during the colonoscopy. Twenty-four hours after the endoscopic procedure, the patient developed right lower quadrant pain and nausea. Physical examination demonstrated localized rebound tenderness at McBurney's point. Computer tomography (CT) scan of the abdomen and pelvis demonstrated a thickened appendix with surrounding fat stranding and an appendicolith (Figure 1). The patient underwent open appendectomy on the day of presentation and convalesced rapidly without further complications. The pathology report was consistent with early acute appendicitis without sign of perforation (Figure 2). The patient recovered from surgery without any other complication.

The search strategy employed for identifying articles for this review involved using PubMed. Specifically, to identify the articles of interest we used terms ("Colonoscopy" AND "appendicitis" AND "complication") to produce 14 results, 9 of which were germane to our study. The terms ("postcolonoscopy" "appendicitis") were then used, producing 6 total results and only 2 additional references. We used references from these papers to identify additional papers, identifying 21 articles describing cases of postcolonoscopy appendicitis. Additional articles were used for supporting structure to the topic review. PRISMA guidelines were followed.

Inclusion criteria for the review include literature describing cases of appendicitis with a temporal relationship to colonoscopy, and only papers written entirely in English were included. Of the twenty original papers identified using the original search terms above, only 5 were excluded as they involved topics outside of the scope of this review.

Data was extracted independently. Patient characteristics such as age, gender, treatment, and time to presentation were extracted and summarized in Table 1.

DISCUSSION

Colonoscopy is a widely used diagnostic and therapeutic procedure. It is relatively safe but is not exempt from risk. Mechanical complications following diagnostic colonoscopy are rare, and bowel perforation in particular has an extremely low incidence (0.3%)[1,2]. Some of these complications can be serious and can lead to surgical intervention. Although exceedingly rare, 27 cases of pericolonoscopy acute appendicitis have been reported.

While it seems possible that the development of appendicitis after colonoscopy could be a coincidence, Occam's razor might suggest a more causal relationship. The pathophysiology of this condition is not completely understood. Several possible mechanisms have been proposed based on the endoscopic findings and timing of presentation. These include barotrauma from overinsufflation[2], compression of stool into the appendix leading to obstruction and/or inflammation[3], direct trauma by inadvertent intubation of the appendiceal lumen[4] and exacerbation of pre-existing preclinical disease[5]. In addition, a case of acute appendicitis has been recently reported twelve hours after virtual colonoscopy, in which carbon dioxide is used to insufflate the colon prior to high resolution CT scanning[6]. Diagnosis of this complication has ranged from immediate presentation[7,8] to ten days following colonoscopy[9]. When diagnosed during colonoscopy, the trademark findings include erythema and edema around the appendiceal orifice[7]; late diagnosis can contribute to peritonitis and death[9].

Taken together, these reports can be classified as pericolonoscopy acute appendicitis. This is indeed a heterogenous group. Clearly occasional patients have visible appendicitis at the time of colonoscopy[7], and some

Table 1 Case reports of pericolonoscopy appendicitis

Author	Age	Gender	Time to diagnosis	Treatment	Perforation?	Postcolonoscopy?[1]
April *et al*[18]	52	M	8 h	Appendectomy	Nonperforated	Postcolonoscopy
Bachir *et al*[14]	28	M	2 d	Appendectomy	Nonperforated	Postcolonoscopy
Moorman *et al*[19]	71	F	Next morning	NS	Perforated	Postcolonoscopy
Moorman *et al*[19]	47	M	27 h	Laparotomy, appendectomy	Perforated	Postcolonoscopy
Moorman *et al*[19]	84	M	4 h	Laparotomy, appendectomy	Acute appendicitis	Postcolonoscopy
Pellish *et al*[17]	50	M	Immediate	Laparoscopic appendectomy	nonperforated	Postcolonoscopy
Volchok *et al*[30]	60	M	16 h	Appendectomy	Nonperforated	Postcolonoscopy
Johnston *et al*[20]	55	M	16 h	Appendectomy	Perforated	Postcolonoscopy
Chae *et al*[21]	48	F	4 d	Appendectomy	No perforation	Postcolonoscopy
Izzedine *et al*[22]	61	M	1 d	Antibiotics->appendectomy	Perforation	Postcolonoscopy
Petro *et al*[7]	53	M	Immediate	Open appendectomy	No perforation	Precolonoscopy
Rosen *et al*[23]	24	M	48 h	Laparotomy, appendectomy	NS	Postcolonoscopy
Rosen *et al*[23]	55	M	Several hours	Antibiotics only	NS	Postcolonoscopy
Srivastava *et al*[9]	65	M	10 d	Laparotomy, appendectomy	Appendiceal abscess	Postcolonoscopy
Takagi *et al*[24]	56	M	72 h	Laparotomy, appendectomy	Phlegmonous appendix	Postcolonoscopy
Lipton *et al*[25]	69	M	96 h	Laparotomy, Appendectomy	Gangrenous appendix	Postcolonoscopy
Hirata *et al*[26]	69	M	12 h	Laparotomy, appendectomy	Acute appendicitis	Postcolonoscopy
Vender *et al*[4]	44	F	Several hours	Laparotomy, appendectomy	NS	Postcolonoscopy
Vender *et al*[4]	55	M	48 h	Antibiotics	NS	Postcolonoscopy
Vender *et al*[4]	57	F	Immediate	Laparotomy, appendectomy	Acute appendicitis	Postcolonoscopy
Brandt *et al*[27]	65	F	48 h	Laparotomy, appendectomy	NS	Postcolonoscopy
Houghton *et al*[28]	35	M	8 h	Laparotomy, appendectomy	Acute appendicitis	Postcolonoscopy
Musielak *et al*[29]	33	M	6 h	Laparosopic appendectomy	Acute Appendicitis	Postcolonoscopy
Musielak *et al*[29]	45	F	4 h	Laparosopic appendectomy	Perforated	Postcolonoscopy
Penkov *et al*[10]	50	F	7 d	Laparoscopic appendectomy	appendicitis	Postcolonoscopy
Horimatsu *et al*[31]	68	M	1 d	Antibiotics	NS	Postcolonoscopy with EMR
Kothari *et al*[11]	27	F	Immediate	Laparoscopic appendectomy	Purulent erosive appendicitis	Precolonoscopy

[1]Postcolonoscopy appendicitis defined above in text. M/F: Male/female; NS: Not specified; EMR: Endoscopic mucosal resection.

other patients might also have been beginning to develop appendicitis at the time of colonoscopy without obvious mucosal findings at the orifice and with only subtle or variant symptoms when presenting for their procedure. This also raises the question of when pericolonoscopy appendicitis could be a coincidence as opposed to a complication. Penkov raises this question, and stresses the importance of prompt imaging to facilitate treatment[10].

Given the mechanisms proposed above, we suggest trying to distinguish appendicitis diagnosed at colonoscopy or appendicitis that might have begun before colonoscopy from "true" postcolonoscopy appendicitis. Appendicitis diagnosed during colonoscopy likely stems from a process beginning prior to the colonoscopy with attenuated or atypical signs, as in the case described by Kothari *et al*[11] with a lower Gastrointestinal (GI) bleed. In contrast, the mechanisms hypothesized to cause postcolonoscopy appendicitis should result in either immediate symptoms or symptoms beginning after a short delay if proceeding via the classical mechanism of intraluminal obstruction and distension. Thus, we propose to define post colonoscopy appendicitis as appendicitis diagnosed by standard criteria with symptoms that begin after the procedure but within 72 h following the colonoscopy, and in the absence of any endoscopic evidence of appendicitis or cecal inflammation at the time of the initial procedure. These criteria should help limit the potential for mere coincidence.

Based on cases reported in the literature, acute appendicitis after colonoscopy appears to be much more common in males. In this series we observe 8 women out of 26 cases. Although men have appendicitis more commonly than women (1.4:1)[12], the apparent predilection of postcolonoscopy appendicitis for men may also reflect increased rates of colonoscopy for men in certain populations such as United States Medicare beneficiaries[13]. The age of patients with this complication cluster from 50-70 in line with recommendations for screening colonoscopy, with notable younger exceptions among patients with gastrointestinal bleeding or ulcerative colitis[11,14]. It is possible that more than one mechanism can be implicated, especially when a patient may have an anatomical or immune predisposition to develop the inflammatory process, triggered by the preparation and or the procedure itself. Since our patient had no underlying disease and exhibited a typical presentation of appendicitis with symptoms beginning one day after colonoscopy, we believe that his appendicitis was most likely triggered by pneumatic pressure impacting the fecalith into the the appendiceal lumen, consistent with the demonstration of multiple appendicoliths on his preoperative imaging and confirmed on his pathology report. The pathophysiology of postcolonoscopy appendicitis may offer an interesting model to study appendicitis at large, as it provides a more precise onset for the time of intraluminal obstruction than the spontaneous inception of obstruction in typical appendicitis.

Table 1 summarizes demographic data, timing of

presentation and treatment in previous reports of acute appendicitis following colonoscopy[9-31]. Appendectomy was the preferred treatment with few exceptions. Delay in diagnosis might preclude early appendectomy and can increase complications. Srivastava *et al*[9] report on a patient diagnosed with appendiceal abscess at 10 d following colonoscopy. A contrast study excluded leak at the polypectomy site on day 5 following colonoscopy in an afebrile patient with a normal white count. This delay in diagnosis and treatment ultimately resulted in multiorgan system failure and death. Although rare, it is likely that failure to consider appendicitis is the largest barrier to prompt diagnosis.

The majority of these cases were addressed by open appendectomy, which is an acceptable but notable alternative to the laparoscopic approach. It is possible that providers chose laparotomy due to concerns about colonoscopic bowel perforation. Recognizing appendicitis as a potential complication of colonoscopy might have permitted an initial laparoscopic approach.

Recent randomized trial evidence suggests that antibiotics alone can be used to treat uncomplicated appendicitis[15]. Uncomplicated diverticulitis should also be treated without surgery[16]. In addition, there is also the criteria for conservative management of selected colonoscopic perforations[1]. Taken together, these lines of evidence raise the question of whether there may be a role for conservative management of post-colonoscopy appendicitis in select patients in whom the bowel preparation was adequate and in whom there is no evidence of perforation, no history of immunocompromise, and adequate mental status for observation. Patients with peritonitis should be excluded from nonoperative therapy as the value of this conservative approach is tested in this population. A nonoperative approach would be especially attractive in managing a complication of a screening procedure.

With this case report, we intend to emphasize and create awareness that acute appendicitis is a rare but real complication of colonoscopy. We stress the importance of recognizing this condition promptly to provide early treatment and avoid further complications. These cases should continue to be documented especially to define the best overall approach in managing this complication.

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CASE REPORT

Giant cystic lymphangioma originating from the lesser curvature of the stomach

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Abstract

Cystic lymphangiomas are rare benign tumors. Most frequently occurring in children and involving the neck or axilla, these tumors are much less common in adults and very rarely involve the abdomen. The known congenital and acquired (traumatic) etiologies result in failure of the lymphatic channels and consequent proliferation of lymphatic spaces. This case report describes a very rare case of a giant mesenteric cystic lymphangioma in an adult male with no clear etiology and successful resolution by standard radical resection. A previously healthy 44-year-old male presented with a 6-wk history of progressive upper abdominal pain, vomiting, anorexia and unintentional weight loss accompanied by rapid abdominal distension. A palpable mass was detected upon physical examination of the distended abdomen and abdominal computed tomography scan showed a giant multilobulated cystic process, measuring 40 cm in diameter. Exploratory laparotomy revealed an enormous cystic mass containing 6 L of serous fluid. The process appeared to originate from the lesser omentum and the lesser curvature of the stomach. Radical resection of the tumor was performed along with a partial gastrectomy to address potential invasion into the adjacent tissues. Histological analysis confirmed the diagnosis of a multicystic lymphangioma. The postoperative recovery was uneventful and the patient was discharged after 6 d. At 3-mo follow-up, the patient was in good health with no signs of recurrence.

Key words: Multicystic lymphangioma; Mesentery; Cystic process; Abdominal pain; Abdominal distension

Core tip: A 44-year-old man presented with abdominal distension and unexplained weight loss. Computed tomography scan of the abdomen showed an enormous multilobulated cystic process. Subsequent exploratory laparotomy revealed a cystic mass containing 6 L serous fluid, originating from the lesser curvature of the stomach. Pathological examination of the resected specimen obtained by radical partial gastrectomy indicated multicystic lymphangioma, a rare benign tumor caused by congenital or traumatic defects of lymphatic channels. Although these large tumors can cause mass effect symptoms and result in serious complications, this case had an uneventful recovery and no complaints at 3-mo follow-up.

van Oudheusden TR, Nienhuijs SW, Demeyere TBJ, Luyer MDP, de Hingh IHJT. Giant cystic lymphangioma originating from the lesser curvature of the stomach. *World J Gastrointest Surg* 2013; 5(10): 264-267 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i10/264.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i10.264

INTRODUCTION

Cystic lymphangiomas are rare, slow-growing, benign

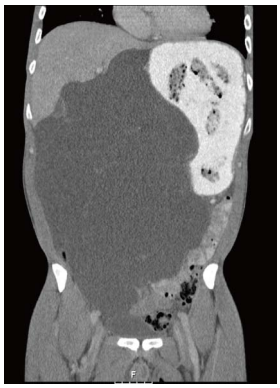

Figure 1 Abdominal computed tomography-scan revealing an enormous cystic process.

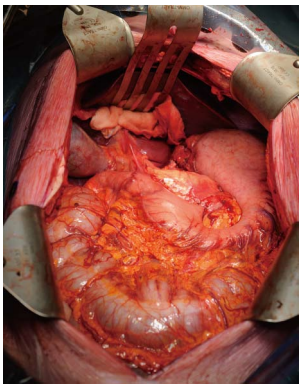

Figure 3 Status after radical resection with partial gastrectomy.

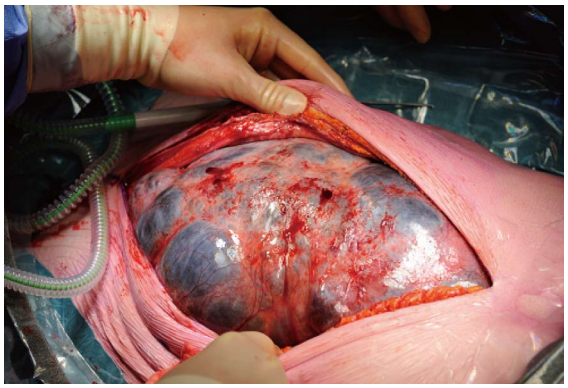

Figure 2 First view after midline incision.

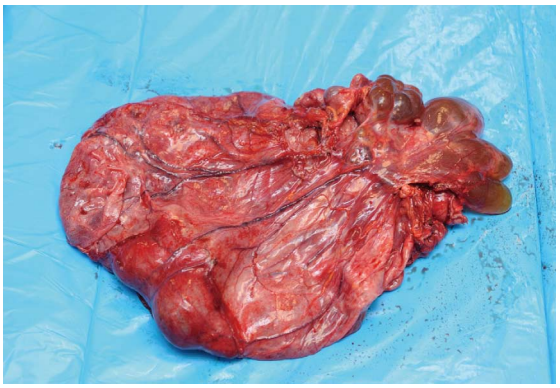

Figure 4 Resected cystic process with near complete fluid drainage.

tumors, originating from lymphatic channels[1]. Most frequently, these tumors are diagnosed in children (up to 90% manifest before the age of three[2-4]) and are generally localized to the neck or axilla (95% of cases); localization to the abdominal cavity is more common among the rare adult cases[5,6]. Regardless of age, clinical presentation is diverse, varying from complaints of mild nausea to acute abdominal pain, with mass effect accounting for the transition to a symptomatic state[7]. Diagnosis in asymptomatic cases has been made as a coincident finding during laparotomies to address other issues[8].

Here, we describe the case of a giant mesenteric cystic lymphangioma (GMCL) occurring in a middle-aged adult male, which was successfully treated with partial gastrectomy. At > 44 cm, this GMCL is the largest reported to date in the publicly available literature.

CASE REPORT

A 44-year-old man presented to a local clinic with a roughly 6-wk history of progressive upper abdominal pain, vomiting, and anorexia. The patient also reported unintentional weight loss of at least 4 kg that was accompanied by a progressive distension of the abdomen. Upon referral to our center for further analysis, computed tomography (CT) was performed to evaluate the palpable abdominal mass detected by routine physical examination. The CT-scan showed a giant multilobulated cystic process, measuring at least 40 cm in diameter (Figure 1), with unclear origin. The differential diagnosis at that time contained cystic lymphangioma, duplication cyst, pancreatic cyst, gastro-intestinal stromal tumor and multicystic mesothelioma.

During this initial examination period, the patient could not tolerate any food and required continuous analgesic drug treatment to control severe abdominal pain. An exploratory laparotomy was performed and revealed an enormous lobulated mass at the midline incision (Figure 2). Near complete drainage of the mass (total of 6 L serous fluid) was required to gain access to the abdominal cavity. The tumor was then observed to originate from the lesser omentum and lesser curvature of the stomach. The left gastric artery and vein were found to be completely enveloped by the tumor, and were therefore dissected. Radical resection of the tumor along the minor curvature of the gastric antrum was carried out with a tristapler (Figure 3).

The resected mass process, with some remaining fluid, measured 19 cm × 17 cm × 4 cm (Figure 4). Pathological analysis confirmed the diagnosis of multicystic lymphangioma attached to the serosal side of the stomach, and indicated no signs of malignancy. Diagnosis was based on dilated cystic structures (Figure 5), delineated with endothelial lining as proven by CD31-staining (Figure 6). Absence of red blood cells and presence of lymphoid tissue confirmed the diagnosis of lymphangioma. Postoperative recovery was uneventful and the patient was discharged 6 d later with complete relief of all prior

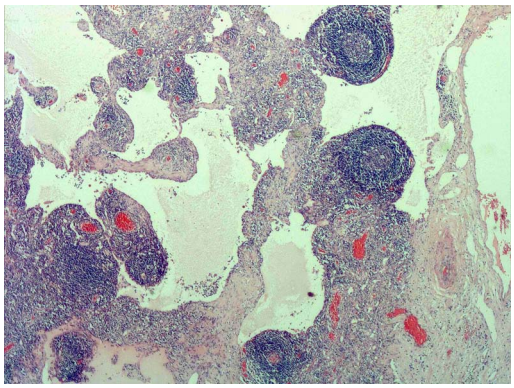

Figure 5 Microscopic view of specimen, depicting various lymphatic spaces (hematoxylin-eosin stain, x 100).

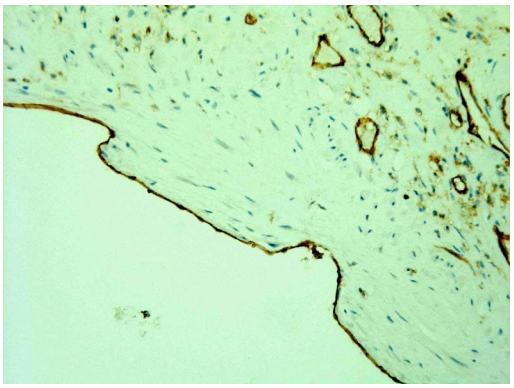

Figure 6 Endothelial lining of cysts (CD31 immunostain, x 400).

symptoms. At 3-mo follow-up, the patient appeared in good health and had no complaints.

DISCUSSION

The precise etiology of cystic lymphangiomas remains to be fully elucidated, but involves acquired or congenital failure of lymphatic channels. While the latter may zmore childhood manifestations, the former is more likely associated with the adult manifestations, possibly related to inflammatory conditions or physical trauma such as created by surgical or radiation therapies[3,9]. These two etiologies are not mutually exclusive, and it is possible that a congenital impairment in communication between mesenchymal slits and the venous system may put a patient at greater risk of drainage blocking in response to trauma[10]. However, in the current adult case described herein, no precipitating cause could be identified.

Mesenteric lymphangiomas are histologically distinct from mesenteric cysts. While mesenteric cysts originate from mesothelial tissue[11], lymphangiomas are composed of alternating lymphoid tissue, lymphatic space, and foam cells. Thus, the histological analysis of the resected mass from our patient provided a clear result for this differential diagnosis.

The presenting symptoms of the current case were in line with the characteristic mass effect symptomology of cystic lymphangiomas, including nausea, weight loss and abdominal distension[12]. However, as the mass size reaches a critical threshold, and depending on its spatial orientation, more severe and life-threatening complications may occur, such as partial bowel obstruction, torsion, volvulus, perforation or rupture, and hemoperitoneum. In some cases, nerves are entrapped in the large mass, resulting in additional pain[13-15]. Therefore, immediate treatment is recommended upon diagnosis.

The treatment of choice is surgical resection, usually carried out by laparoscopy which has good safety and efficacy profiles[1,4,15]. The particularly enormous size of the cystic lymphangioma in our case further justified use of the laparotomy approach, since no free space was present in the abdomen. In addition, a radical resection (involving tissues of the related organ of origin) was performed to help reduce the risk of recurrence since these tumors, although benign, tend to invade adjacent structures[11].

In conclusion, this case report describes a rare adult case of cystic mesenteric lymphangioma. Despite being the largest tumor of its type reported to date, the standard surgical treatment of radical resection including a partial gastrectomy was able to rapidly and successfully resolve the condition. Cystic mesenteric lymphangioma should be considered as differential diagnosis when patients present with a multilobulated cystic tumor in the abdomen. Radical resection remains a sufficiently safe and effective treatment option for this type of benign tumor.

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CASE REPORT

Laparoscopic-assisted catheter insertion for continuous ambulatory peritoneal dialysis: A case report of simple technique for optimal placement

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Abstract

A 40-year-old male underwent tube placement surgery for continuous ambulatory peritoneal dialysis (CAPD). A 2-cm skin incision was made, and the peritoneum was reflected enough to perform secure fixation. A swan-necked, double-felted silicone CAPD catheter was inserted, and the felt cuff was sutured to the peritoneum to avoid postoperative leakage. An adequate gradient for tube fixation to the abdominal wall was confirmed. The CAPD tube was passed through a subcutaneous tunnel. Aeroperitoneum was induced to confirm that there was no air leakage from the sites of CAPD insertion. Two trocars were placed, and we confirmed that the CAPD tube led to the rectovesical pouch. Tip position was reliably observed laparoscopically. Optimal patency of the CAPD tube was confirmed during surgery. Placement of CAPD catheters by laparoscopic-assisted surgery has clear advantages in simplicity, safety, flexibility, and certainty. Laparoscopic technique should be considered the first choice for CAPD tube insertion.

Key words: Continuous ambulatory peritoneal dialysis; Dialysis catheter; Tube insertion; Surgical technique

Core tip: Continuous ambulatory peritoneal dialysis (CAPD) is currently considered the preferred choice for dialytic treatment, based on improved quality of life and patient survival. The open surgical technique for tube placement is easy, though a painful large incision is needed and unexpected tube dislocation may occur. Minimally invasive technique and optimal tube position should be guaranteed in the placement of CAPD catheters. We suggested that placement of CAPD catheters by laparoscopic-assisted surgery has clear advantages in simplicity, safety, flexibility, and certainty. Here, we present our surgical procedures and discuss key techniques and pitfalls with literature review.

Hori T, Nakauchi M, Nagao K, Oike F, Tanaka T, Gunji D, Okada N. Laparoscopic-assisted catheter insertion for continuous ambulatory peritoneal dialysis: A case report of simple technique for optimal placement. *World J Gastrointest Surg* 2013; 5(10): 268-271 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i10/268.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i10.268

INTRODUCTION

Peritoneal dialysis (PD) is considered the first choice for dialytic treatment because it offers improved quality of life and patient survival compared with hemodialysis. PD, including continuous ambulatory peritoneal dialysis

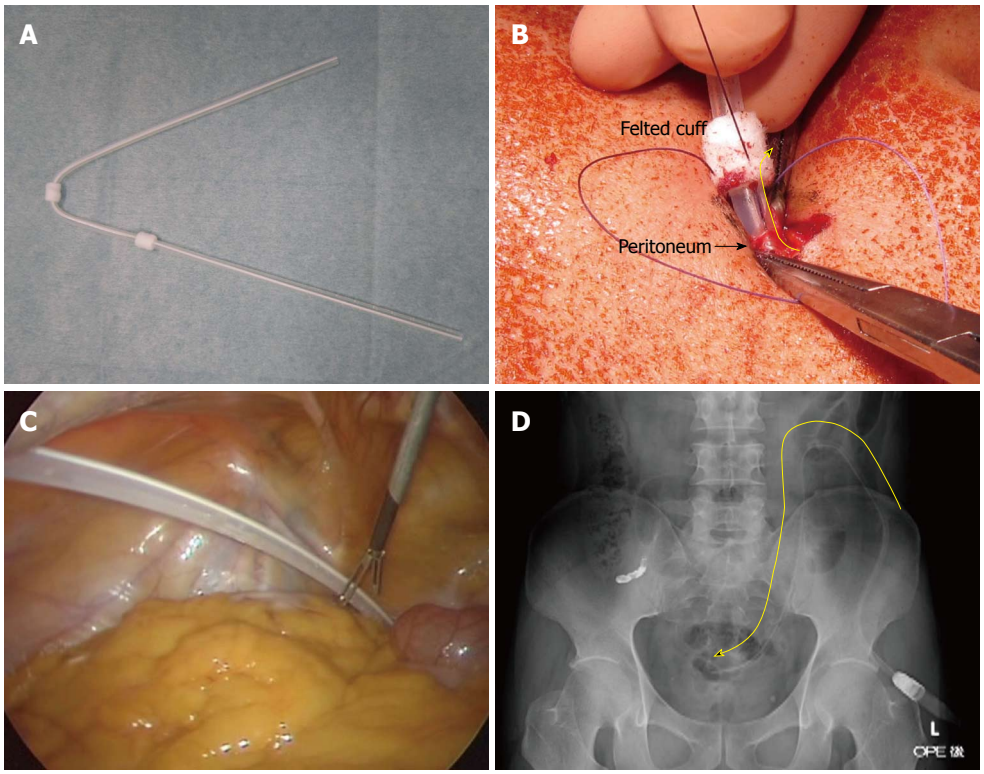

Figure 1 Actual material and surgical procedures. A: Double-felted swan-neck silicone catheter; B: Tube fixation to peritoneum. Peritoneum was reflected enough to make a secure fixation. A tight running suture was placed between the peritoneum and the felt cuff (yellow arrow); C: Laparoscopic view for tube placement. The catheter has been adequately directed by the fixation to the abdominal wall. The laparoscopic view confirmed that the catheter led to the rectovesical pouch; D: Intraoperative radiograph. Optimal and reasonable curve of catheter without any distortions was confirmed (yellow arrow).

(CAPD), is widely used in the treatment of end-stage renal failure[1-3]. The most frequent complications of PD are peritonitis[4-6], infection of the catheter exit site[7-9], mechanical complications[2,10,11], and dialysate leakage[12-14].

CAPD catheter insertion by the open method is easy, though a painful large incision is needed and unexpected tube dislocation may occur. With open surgery, minimally invasive technique and optimal tube position should be assured. Recent surgical innovations and technological improvements have been made, mainly in laparoscopic and laparoscopic-assisted surgery and advanced devices[2,10,11,13,15-19]. We present a case of laparoscopic-assisted catheter placement for CAPD induction in detail, and discuss key techniques and pitfalls for this minimally-invasive surgery.

CASE REPORT

A 40-year-old male suffered from renal failure due to immunoglobulin a nephropathy, and CAPD was introduced using a swan-necked, double-felted silicone catheter (JB-5; JMS Co. Ltd., Osaka, Japan; Figure 1A). Site marking was performed before surgery. After induction of general anesthesia, a urethral catheter was inserted to avoid bladder injury during surgery. A 2-cm skin incision was made, and the peritoneum was opened at the most caudal point to insert the CAPD tube (Figure 2). The abdominal wall was lifted with Kocher's forceps, and a 5-mm trocar for a camera was placed opposite the site of subcutaneous tube fixation after confirmation of intra-peritoneal adhesion (Figure 2). The peritoneum was reflected enough to perform secure fixation. The CAPD tube was inserted, and the felt cuff was sutured to the peritoneum with a tight running pattern to avoid postoperative leakage, using absorbable, atraumatic suture material (Figure 1B). The CAPD tube passed under the fascia, and the fascia was tightly closed from the caudal end with interrupted sutures. Hence the CAPD tube passed through the fascia at the most cranial aspect (Figure 2). An adequate gradient for tube fixation to the abdominal wall for a well-orientated catheter was confirmed. Subcutaneous tunneling was performed to accommodate the shape of the swan neck. The CAPD tube was passed through this tunnel, and the second felt was placed subcutaneously (Figure 2). Buried absorbable sutures were used for skin closure.

Aeroperitoneum was induced to confirm that there was no air leakage from the sites of CAPD insertion. A 5-mm laparoscope was inserted. No adhesions or ascites were observed. A 3-mm trocar was placed in the lower abdominal wall near the pubic bone as a working port, without bladder injury. The catheter had already been directed by the fixation to the abdominal wall. The CAPD tube was grasped with 3-mm laparoscopic forceps (Figure 1C). We confirmed by laparoscopy that the CAPD tube led to the rectovesical pouch (Figure 1C), and no stylet was required for tube placement. Tip position was

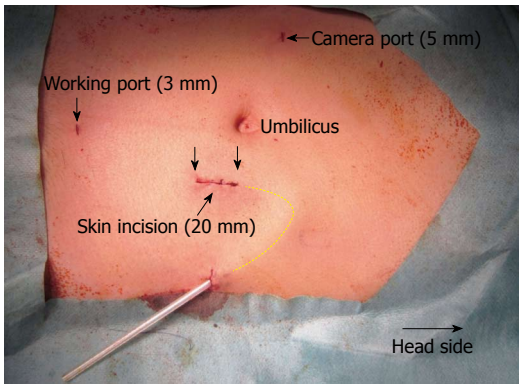

Figure 2 Findings after surgery. A 2-cm skin incision was made. Peritoneum was opened at the most caudal point to allow catheter insertion (red arrow). The catheter passed under the fascia, and then the fascia was tightly closed with interrupted sutures from the caudal side. Hence, the catheter passed through the fascia at the most cranial aspect (blue arrow). Note that the intentional discrepancy between the preperitoneal fixation points at the peritoneum (red arrow) and fascia (blue arrow) allowed proper orientation of the catheter through the abdominal wall. Two trocars (5 and 3 mm) were placed. Subcutaneous tunneling was performed, and the catheter was passed through the tunnel (yellow dotted line).

reliably observed laparoscopically. Enough carbon dioxide gas was removed from the trocar wound to prevent iatrogenic eosinophilic peritonitis, and the stab wounds for trocar placement were closed with buried absorbable sutures. The CAPD tube had a radiodense line, and intraoperative radiographs revealed optimal and reasonable curve of the CAPD tube (Figure 1D). Intentional discrepancy between the preperitoneal fixation points in the peritoneum and fascia as described above resulted in an adequate curve without any distortions (Figure 1D). Optimal patency of the CAPD tube should be confirmed during surgery. Normal saline (100 mL) was injected through the CAPD tube, and then a total of 79 mL was retrieved (79% retrieval rate). Total operative time for all procedures was 45 min.

The patient received a second-generation cephem antibiotic intravenously until postoperative day 3, and the postoperative course was uneventful. CAPD was introduced during the early postoperative period without obstruction, leakage, or infection.

DISCUSSION

PD including CAPD is currently considered the preferred choice for dialytic treatment, based on improved quality of life and patient survival. The open surgical technique for tube placement is easy, though a painful large incision is needed and unexpected tube dislocation may occur. Minimally invasive technique and optimal tube position should be guaranteed in the placement of CAPD catheters, and many physicians have established excellent laparoscopic techniques and advanced devices[2,10,11,13,15-19]. Patients in renal failure may have concurrent peritonitis, and peritonitis can also occur after CAPD induction[20-22]. In patients with mild ascites, sampling for culture or neutrophil counts is very easy with laparoscopy. Even though CAPD tubes are specially-designed devices, an artificial catheter is a foreign body. We suggest that bacteriological and microbiological assessments should be routinely performed during laparoscopic surgery if mild ascites is present.

Complications of CAPD include peritonitis, infection of the catheter exit site, mechanical obstruction, and dialysate leakage[2,4-14]. Many surgeons have previously demonstrated that laparoscopic surgery reduced these complications[2,10,11,15,17,23]. Omental wrap or plugging is one cause of mechanical obstruction[24,25]. Fibroadhesion and sclerosing peritonitis also decrease tube efficiency[26,27]. These mechanical obstructions require omentopexy, omentectomy, and other additional surgeries[22,23]. So-called "abdominal cocoon syndrome" can result in death and requires removal or reinsertion of the catheter[26,27]. Laparoscopic surgery has the advantage of flexible catheter placement according to intra-abdominal findings to prevent these complications[16].

Laparoscopic surgery results in less pain, shortened convalescence, improved cosmesis, and absence of wound complications[15,19,28]. A simple question arises: Is pure laparoscopic surgery better than laparoscopically-assisted surgery? Pure laparoscopic surgery has been documented to be an ideal technique for the placement of CAPD catheters[10,19]. Reports suggest that pure laparoscopic surgery has the advantage of preventing major complications in CAPD[10,19]. We agree that laparoscopic surgery offers many advantages in CAPD tube placement, but suggest that pure laparoscopic surgery requires more advanced techniques and involves technical difficulties because of the tangential view and access, especially in securely fixing the catheter to the peritoneum. We agree that pure laparoscopic surgery is ideal, but only in the hands of experienced surgeons. Laparoscopic surgery using single and two-port methods have been reported[17,18]. We employed two ports because it allowed greater flexibility for intraoperative procedures and required only a negligible second stab wound for a 3-mm port.

It has been reported that a pure laparoscopic intraperitoneal approach has the advantage of ensuring adequate insertion, which prevents mechanical obstruction and allows secure fixation to the peritoneum, preventing intractable leakage[10]. However, we found a 2-cm incision to be large enough for an optimal lead and secure catheter fixation. Mechanical obstruction[2,10,11] and dialysate leakage[12-14] are still the most serious complications in CAPD, and reasonable tube placement with secure fixation to the peritoneum are extremely important during surgery. We performed laparoscopic-assisted surgery with a minimally open method to create an adequate preperitoneal tube curve with secure fixation to the peritoneum. An adequate gradient for tube fixation to the abdominal wall can be made even with a 2-cm incision.

Image studies are important in CAPD tube placement[12,29]. Intraoperative radiographs revealed that our intentional discrepancy between the peritoneal and fascial

fixation points worked well to create an optimal tube curve without any distortions and with a secure tip position.

Placement of CAPD catheters by laparoscopic-assisted surgery has clear advantages for simplicity, safety, flexibility, and certainty. Laparoscopic technique should be considered the first choice for CAPD tube insertion. In conclusion, laparoscopic approach is a very useful tool in the induction of PD programs.

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CASE REPORT

Hematogenous umbilical metastasis from colon cancer treated by palliative single-incision laparoscopic surgery

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Author contributions: Hori T and Okada N perform this surgery; Nakauchi M provided the opinion of SILS in this case; Yoshioka A, Hiramoto S and Kikuchi-Mizota A evaluated the meaning of protein assays; Kyogoku T performed histopathological assessments; Oike F, Tanaka T and Gunji D helped to discuss this surgery; Sugimoto H, Tanaka J, Morikami Y, Shigemoto K, Nakatsuji M and Okae S performed preoperative studies including endoscopic investigations, and provided informative opinions; Ota T and Kaneko M made detailed radiological studies; Hori T wrote this paper.
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Abstract

Sister Mary Joseph's nodule (SMJN) is a rare umbilical nodule that develops secondary to metastatic cancer. Primary malignancies are located in the abdomen or pelvis. Patients with SMJN have a poor prognosis. An 83-year-old woman presented to our hospital with a 1-month history of a rapidly enlarging umbilical mass. Endoscopic findings revealed advanced transverse colon cancer. computer tomography and fluorodeoxyglucose-positron emission tomography revealed tumors of the transverse colon, umbilicus, right inguinal lymph nodes, and left lung. The feeding arteries and drainage veins for the SMJN were the inferior epigastric vessels. Imaging findings of the left lung tumor allowed for identification of the primary lung cancer, and a diagnosis of advanced transverse colon cancer with SMJN and primary lung cancer was made. The patient underwent local resection of the SMNJ and subsequent single-site laparoscopic surgery involving right hemicolectomy and paracolic lymph node dissection. Intra-abdominal dissemination to the mesocolon was confirmed during surgery. Histopathologically, the transverse colon cancer was confirmed to be moderately differentiated tubular adenocarcinoma. We suspect that SMJN may occur via a hematogenous pathway. Although chemotherapy for colon cancer and thoracoscopic surgery for the primary lung cancer were scheduled, the patient and her family desired home hospice. Seven months after surgery, she died of rapidly growing lung cancer.

Key words: Umbilicus; Sister Mary Joseph; Single-incision laparoscopic surgery; Palliative operation; Hematogenous metastasis

Core tip: Cutaneous metastasis localized to the umbilicus is termed "Sister Mary Joseph's nodule" (SMJN). SMJN is a rare nodule that originates from tumors in the abdomen or pelvis, and patients with SMJN show a poor prognosis. Previous reports of SMJN described direct disseminative or lymphogenous pathways. To our knowledge, SMJN via the hematogenous pathway

is very rare. We herein report a case of advanced colon cancer with SMJN via a hematogenous metastatic pathway treated by palliative single-incision laparoscopic surgery.

Hori T, Okada N, Nakauchi M, Hiramoto S, Kikuchi-Mizota A, Kyogoku M, Oike F, Sugimoto H, Tanaka J, Morikami Y, Shigemoto K, Ota T, Kaneko M, Nakatsuji M, Okae S, Tanaka T, Gunji D, Yoshioka A. Hematogenous umbilical metastasis from colon cancer treated by palliative single-incision laparoscopic surgery. *World J Gastrointest Surg* 2013; 5(10): 272-277 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i10/272.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i10.272

INTRODUCTION

Cutaneous metastasis localized to the umbilicus is termed "Sister Mary Joseph's nodule" (SMJN). Sister Mary Joseph Dempsey (born Julia Dempsey; 1856-1939) was the surgical assistant of William J Mayo at St. Mary's Hospital in Rochester, Minnesota from 1890 to 1915[1]. She drew Mayo's attention to the phenomenon, and he published an article about it in 1928[2]. The condition was then termed "pants button umbilicus". This palpable nodule is currently considered to result from metastasis of malignant cancers[3-5]. SMJN is a rare nodule of the umbilicus that develops secondary to metastatic cancer[1,6]. Primary malignancies are usually located in the abdomen or pelvis[7-11]. SMJN is associated with a grave prognosis[9,12].

We herein report a case of SMJN originating from colon cancer. We also discuss the usefulness of single-incision laparoscopic surgery (SILS) for palliative surgery and the possibility of a metastatic pathway in our case.

CASE REPORT

An 83-year-old woman presented to our hospital with a 1-month history of a rapidly enlarging umbilical mass with a necrotic odor. Physical examination revealed a 5.0 cm × 4.5-cm hard, ulcerated umbilical nodule (Figure 1A). She also had two swollen right inguinal lymph nodes. Needle biopsy of the umbilical tumor revealed tubular adenocarcinoma. Endoscopy and contrast radiography of the gastroduodenal and colorectum revealed advanced transverse colon cancer with a very narrowed lumen and oozing of blood (Figure 1B). Dynamic enhanced computer tomography showed tumors of the transverse colon, umbilicus, right inguinal lymph nodes, and left lung (Figures 2). Feeding arteries and drainage veins for the umbilical tumor were the inferior epigastric vessels (Figure 3A), and no vessels had developed along the round ligament of the liver. Fluorodeoxyglucose-positron emission tomography showed uptake at these same points (Figure 3B). Blood examination showed anemia and increased levels of carcinoembryonic antigen, carbohydrate antigen 19-9, and cytokeratin 19 fragment, although other tumor markers were within their normal ranges. Imaging of the left tumor indicated primary lung cancer, and a diagnosis of advanced transverse colon cancer with SMJN and primary lung cancer was made.

Ten days after the first medical examination, the patient underwent local resection of the umbilical tumor (Figure 4A) and subsequent single-site laparoscopic surgery involving right hemicolectomy with paracolic lymph node dissection (Figure 4B), by using a single access port (EZ Access: Hakko Medical Co. Ltd., Chikuma, Nagano, Japan) and trocar (EZ trocar, Hakko Medical Co. Ltd.). Indocyanine green (ICG) was injected into the paraumbilical portion beforehand. The umbilicus and caulescent tumor were resected *en bloc* with establishment of surgical margins and ligation of vessels and urachal tract. The round ligament of the liver and the urachus were also ligated. ICG injection revealed the drainage lymph nodes in the abdomen (Figure 4C), and these drainage lymph nodes were dissected. Intra-abdominal dissemination to the mesocolon was confirmed during surgery. After making skin flap, peritoneum was sutured with a running pattern. The fascia was tightly closed with interrupted sutures by using absorbable material. Buried absorbable sutures were used for skin closure. The operative time was 1 h 57 min, and the blood loss volume was 30 mL.

Histopathologically, the transverse colon cancer was confirmed to be moderately differentiated tubular adenocarcinoma. Marked invasion into vessels was observed in the primary colon cancer, and multiple obvious arteriovenous shunts were present (Figure 5A). Immunohistological staining for CK7, CK20, TTF1, and CDX2 in the umbilical tumor were performed to identify the primary tumor. The positive CK 20/CDX2 and negative CK7/TTF1 status indicated that the umbilical tumor was consistent with a moderately differentiated adenocarcinoma of colonic origin, not lung origin. The peritoneum of the umbilicus showed normal findings (Figure 5B). Although the lymph nodes of the mesocolon near the primary colon cancer were positive for metastasis, the drainage lymph nodes from the SMJN, which were detected by ICG, were all negative.

The postoperative course was uneventful. Although chemotherapy for the colon cancer and thoracoscopic surgery for the primary lung cancer were scheduled, the patient and her family desired home hospice. Seven months after surgery, she died of rapidly growing lung cancer.

Normal colon, primary colon tumor, and SMJN specimens underwent analysis by western blotting, gelatin zymography, and real-time PCR. The following results were obtained: (1) Cell cycle: cyclin D1, cyclin-dependent kinase 2, epidermal growth factor receptor, Akt, mitogen-activated protein kinase, and p53; (2) Apoptotic induction: caspase-3 and terminal deoxynucleotidyl transferase dUTP nick end labeling; (3) Immortalization: telomerase; (4) Neoangiogenesis: vascular endothelial growth factor (VEGF); and (5) Invasion and metastasis: E-cadherin and matrix metalloproteinase-2 and -9. In addition, to evaluate vascular activity, tissue inhibitor of metalloproteinase-1 and thrombomodulin (TM) were evaluated. The actual intensities of each are shown in Figure 6.

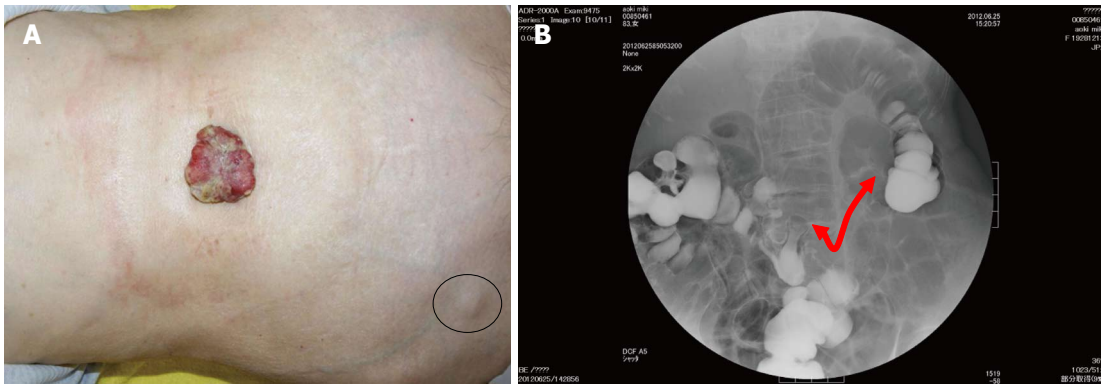

Figure 1 Findings of diagnostic nodule and colonorectal enema. A: A 5.0- × 4.5-cm hard, ulcerated, caulescent tumor was observed in the umbilicus. Two swollen right inguinal lymph nodes were palpable (circle); B: Colonorectal enema showed an apple core sign at the transverse colon near the hepatic flexure, red arrow: the length of narrowed lumen.

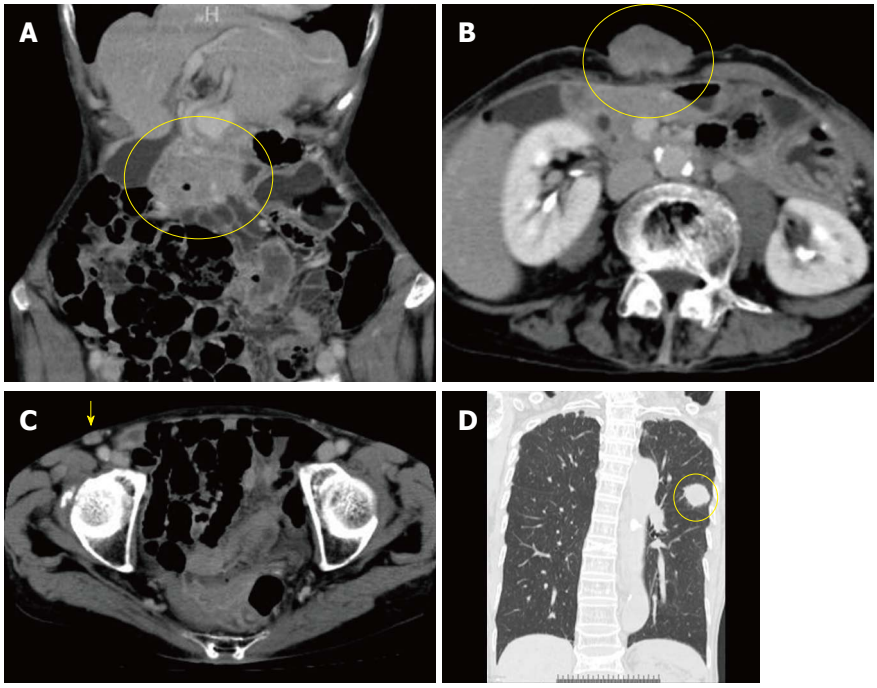

Figure 2 Computer tomography showed tumors of the transverse colon (A, circle), umbilicus (B, circle), right inguinal lymph nodes (C, arrow) and left lung (D, circle). The lung tumor was accompanied by a typical spicula. Vessels along the round ligament of the liver did not develop to and from the umbilical tumor.

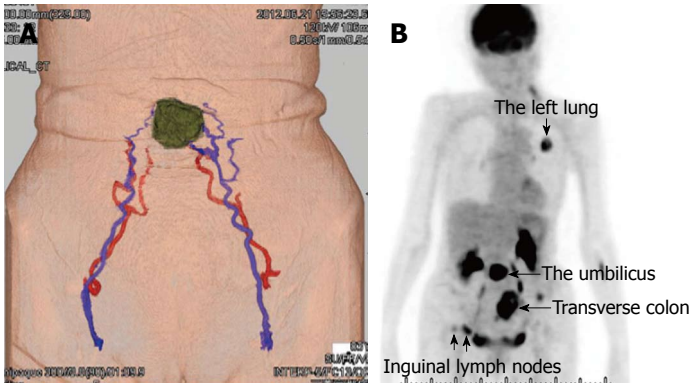

Figure 3 Findings of dynamic computer tomography and fluorodeoxyglucose-positron emission tomography. A: Dynamic computer tomography revealed feeding arteries and drainage veins for the umbilical tumor were the inferior epigastric vessels; B: Fluorodeoxyglucose-positron emission tomography showed uptake in the transverse colon, umbilicus, right inguinal lymph nodes, and left lung (arrows).

DISCUSSION

Although SMJN is a rare first manifestation of colon cancer, current documents report that this nodule usually arises from gastrointestinal and gynecological neoplasms, most commonly from the stomach, colon, pancreas,

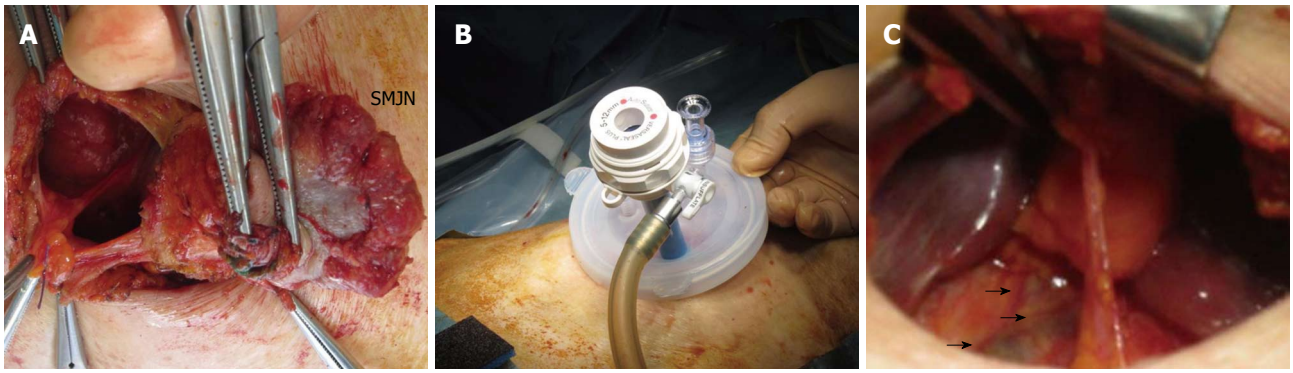

Figure 4 Intraoperative findings and surgical procedures. A: The umbilicus and caulescent tumor were resected *en bloc* with establishment of a surgical margin and ligation of vessels; B: Single-site laparoscopic surgery involving right hemicolectomy with paracolic lymph node dissection was subsequently performed. C: Indocyanine green was injected into the paraumbilical portion beforehand, allowing for detection of the drainage lymph nodes in the abdomen (arrow). SMNJ: Sister Mary Joseph's nodule.

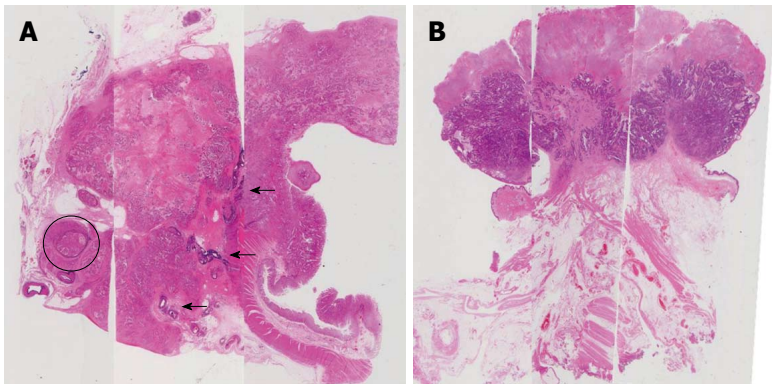

Figure 5 Histopathological findings of the primary colon cancer and Sister Mary Joseph's nodule are shown (hematoxylin and eosin staining). A: In the primary colon cancer, severe invasion and tumor thrombosis were observed in the vessels (circle), and nontortuous arteries and multiple A-V shunts were also present (arrows); B: The umbilical tumor was consistent with a moderately differentiated adenocarcinoma of colonic origin. The peritoneum of the umbilicus revealed normal findings.

and ovary and less frequently from the uterus, cervix, gallbladder, and small intestine[7-11,13]. In addition, diagnostic characteristics and imaging findings have been described[10,14-18]. SMJN is associated with a grave prognosis[9,12]. Our case also had a poor prognosis.

SILS was rapidly accepted as a minimally invasive surgical technique. This approach has been applied to a variety of surgical procedures[19,20]. Although SILS has advantages in terms of superior cosmetics, fewer wound complications, and less pain[20,21], many surgeons currently consider that SILS is associated with a higher procedure failure rate with more blood loss and longer operative times than conventional laparoscopic surgery[19,22-25]. The confined surgical field and limited approach direction in SILS may compromise its safety and certainty[22,24,25]. In our case, the incision for resection of the umbilicus with a safe margin was suitable for SILS, caused less pain, was attractive for palliative surgery. Although we agreed that SILS is associated with some problems in terms of its safety and certainty[22,24,25], we consider that SILS still has an advantage in terms of being a palliative surgery that minimizes wound complications and postoperative pain. In cases of malignancy, we suggested that SILS is still available for palliative surgery, even though SILS accompanies some problems.

Metastasis of SMJN occurs mainly by a direct disseminative pathway[26], and may involve lymphogenous and hematogenous pathways[27-29]. Metastatic lesions can reach the umbilicus *via* spread through lymphatic ducts, the venous network, the arterial network, contiguous extension, or even *via* iatrogenic seeding with laparoscopy[29]. These different pathways may help to explain why such a wide variety of malignant tumors can produce SMJN[30]. The tumor may spread to the umbilicus through the lymph ducts or blood vessels, by contiguous extension, or through embryologic remnants[26-28]. Regarding the metastatic pathway in our case, the histopathological findings denied direct dissemination and revealed less invasion to the lymphogenous tract. However, to our knowledge, SMJN *via* the hematogenous pathway is very rare.

Histopathological findings revealed umbilical tumor without direct disseminations and developed lymphoid ducts. The ICG injection detected drainage lymph nodes from umbilical tumor to intra-abdominal lymph nodes, and these "secondary" lymph nodes were not metastatic. Histopathological and ICG injection showed metastatic lymphatic networks did not develop around umbilical tumor. Histopathological assessments revealed that primary and umbilical tumors showed advanced invasions into vessels with arteriovenous shunts. The imaging findings of the inferior epigastric vessels with inguinal lymphoid metastasis as well as the results of VEGF and TM may support the development of the hematogenous pathway in our case. Metastatic route to umbilicus is so complicate[26-30], and it seems difficult to establish the haematogenic route. We just speculated that our SMJN maybe

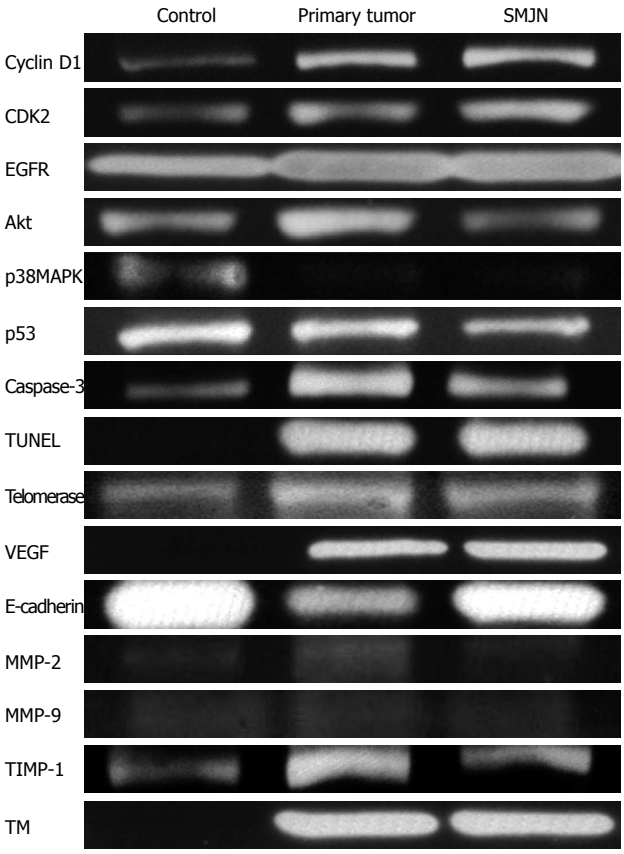

Figure 6 Actual intensities of the normal colon, primary colon tumor, and Sister Mary Joseph's nodule in western blotting gelatin zymography, and real-time polymerase chain reaction (telomerase) are shown. CDK2: Cyclin-dependent kinase 2; EGFR: Epidermal growth factor receptor; MAPK: Mitogen-activated protein kinase; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF: Vascular endothelial growth factor; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase; TM: Thrombomodulin; SMNJ: Sister Mary Joseph's nodule.

mainly occur *via* haematogenic pathway.

The presence of SMJN is often a poor prognostic factor because affected patients have advanced metastatic disease at the time of initial diagnosis[9,12]. The average survival time after the appearance of an SMJN is reportedly 10-11 mo[12]. Our patient actually died approximately 7 mo after surgery.

Sister Mary is gone, and 74 years have passed since she died. Is umbilical metastasis, namely SMJN, necessarily associated with a poor prognosis? Future studies are still needed to elucidate the carcinogenesis of her signature nodule.

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CASE REPORT

Surgically resected gastric metastasis of pulmonary squamous cell carcinoma

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Author contributions: Kim YI performed the operation and follow up of the patient; Kang BC performed the image diagnosis; Sung SH performed the pathological diagnosis; Kim YI designed and wrote the paper.
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Abstract

Gastric metastasis of pulmonary carcinoma has been reported to range from 0.19%-5.1%. An autopsy review of cancer disclosed 1.7%-29.6% of gastric metastases, primarily from breast cancer, lung cancer and melanoma. A 71-year-old man was referred to our department because of persistent cough, sputum and sweating for 20 d. Chest posteroanterior view and chest computed tomography scan demonstrated an irregular tumor mass measuring 5.8 cm with central necrosis at the right lower lung. Bronchoscopic biopsy revealed pulmonary squamous carcinoma. Esophagogastroduodenoscopy revealed a huge bleeding ulcer at the body of the stomach and a biopsy diagnosed a metastatic lesion. We performed a palliative total gastrectomy, splenectomy and distal pancreatectomy. The patient did not receive any adjuvant chemotherapy due to his refusal. He was controlled conservatively and survived for 11 mo after surgery. Surgical resection may provide an option for safe palliative treatment. Although gastric metastasis from lung cancer is associated with dismal outcomes, a longer survival or more favorable outcome has been demonstrated in patients undergoing palliative surgical resection of the metastatic site. Considerable improvements in the understanding of metastatic diseases and therapeutic strategies are needed to improve the clinical outcome.

Key words: Squamous cell carcinoma; Lung cancer; Gastric metastasis

Core tip: The common gastrointestinal metastatic site of lung cancer is the small bowel, with sporadic case reports involving the stomach. Most patients with gastric metastasis are asymptomatic. The survival and standard treatment of gastric metastasis from the lung are not satisfactory. Although gastric metastasis from lung cancer is associated with dismal outcomes, a longer survival or more favorable outcome has been demonstrated in patients undergoing palliative surgical resection of the metastatic site.

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INTRODUCTION

Gastrointestinal tract involvement by lung cancer is considered a late stage of the disease because of diffuse hematogenous tumor spread. It is generally detected in patients with a documented previous history of a primary lung malignancy. In contrast, the finding of lung cancer initially manifesting as gastrointestinal tract involvement is exceedingly rare and has been cited in isolated

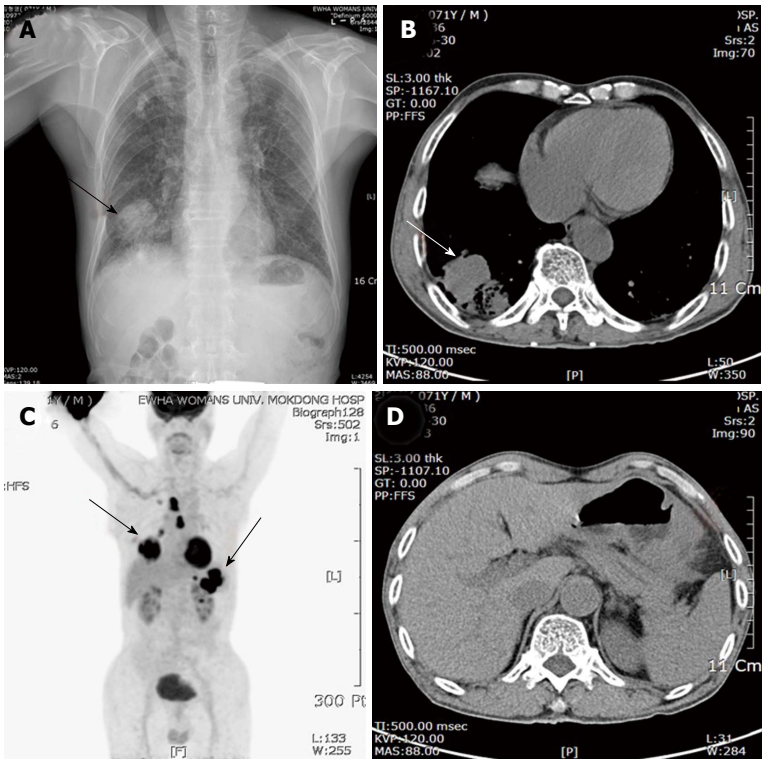

Figure 1 Chest posteroanterior view, computed tomography scan and [^{18}F] fluoro-2-deoxy-*D*-glucose positron emission tomography-computed tomography. A: A solitary mass with solid opacity in the right lower lung (RLL) (arrow); B: Chest computed tomography (CT) scan demonstrated an irregular mass measuring 5.8 cm in size with central necrosis at RLL (arrow); C: [^{18}F] fluoro-2-deoxy-*D*-glucose-positron emission tomography (FDG-PET)/CT showed a FDG-avid mass on the right lower lobe, mediastinum, stomach and splenic hilum; D: Abdominal CT showed an encircling mass at the body of the stomach with multiple enlarged perigastric lymph nodes and splenic hilar invasion.

case reports. Gastric metastasis from lung carcinoma is rare and its incidence has been reported to range from 0.19%-5.1%[1-5]. Metastatic disease involving the stomach is an unusual and difficult clinical problem. An autopsy review of cancer disclosed 1.7%-29.6% of gastric metastases related to breast cancer, lung cancer and melanoma as the most frequent primaries[1,6]. It is rarely found in clinical situations because only a few patients are symptomatic. The common clinical presentations of gastrointestinal metastases are abdominal pain, gastrointestinal bleeding, obstruction and perforation associated with small bowel metastasis[7].

The survival and standard treatment of gastric metastasis from the lung are not satisfactory. Therefore, gastric metastasis from lung cancer is associated with dismal outcomes. The aim of this study was to report the clinical characteristics and outcomes of our patient with special emphasis on treatment after a review of the literature.

CASE REPORT

A 71-year-old man was referred to our department because of a 20 d history of persistent cough, sputum and sweating. The patient was diagnosed with pneumonia and suspicious lung cancer of the right lower lobe at a community hospital. He had a history of smoking 50 packs a year and stable pulmonary tuberculosis on both upper lung fields. Recently, the patient had experienced easy fatigue and had a weight loss of about 7 kg/mo. Chest radiography showed a solitary mass with solid opacity in the right lower lung (RLL) (Figure 1A, arrow). Chest computed tomography (CT) scan demonstrated an irregular tumor mass measuring 5.8 cm in size with central necrosis at RLL and a biopsy was performed (Figure 1B, arrow). The biopsy showed syncytial growth of polygonal shaped poorly differentiated cells which were strongly positive for p63 and consistent with squamous cell carcinoma (Figure 2). A complete blood cell count revealed hemoglobin 8.6 g/dL, hematocrit 25.3%, platelets 341000/μL and white blood corpuscles 6000/μL. Tumor marker study revealed that alpha fetoprotein was 1.8 ng/mL, carcinoembryonic antigen was 4.9 ng/mL, and carbohydrate antigen 19-9 was 5.5 U/mL. A gastroduodenoscopy was performed for evaluation of anemia. On gastroduodenoscopy, there was a huge ulcer with easy bleeding from the mid to lower body of the stomach and a biopsy was performed. The patient had no symptoms associated with an ulcer and no history of *Helicobacter pylori* infection.

Initial gastric ulcer biopsy specimen revealed multiple lymphatic invasion of carcinoma and chronic gastritis (Figure 2D). In additional immunohistochemical stains, cells were positive for p63, CK5/6 and carcinoembryonic antigen, which were indicative of metastasis of pulmonary carcinoma. Therefore, the gastric lesion was diagnosed as a squamous cell carcinoma consistent with metastasis from primary lung carcinoma.

Simultaneously performed abdominal CT showed an encircling mass at the body of the stomach with multiple enlarged perigastric lymph nodes, exophytic mass of the pancreatic tail, and splenic hilar invasion (Figure 1D). Positron emission tomography using [^{18}F]-fluoro-2-deoxy-*D*-glucose (FDG-PET)/CT showed a FDG-avid mass on the right lower lobe, mediastinum, stomach and splenic hilum (Figure 1C).

We performed a palliative total gastrectomy, splenectomy and distal pancreatectomy due to bleeding and dysphagia. Macroscopically, there was an ulcerovegeta-

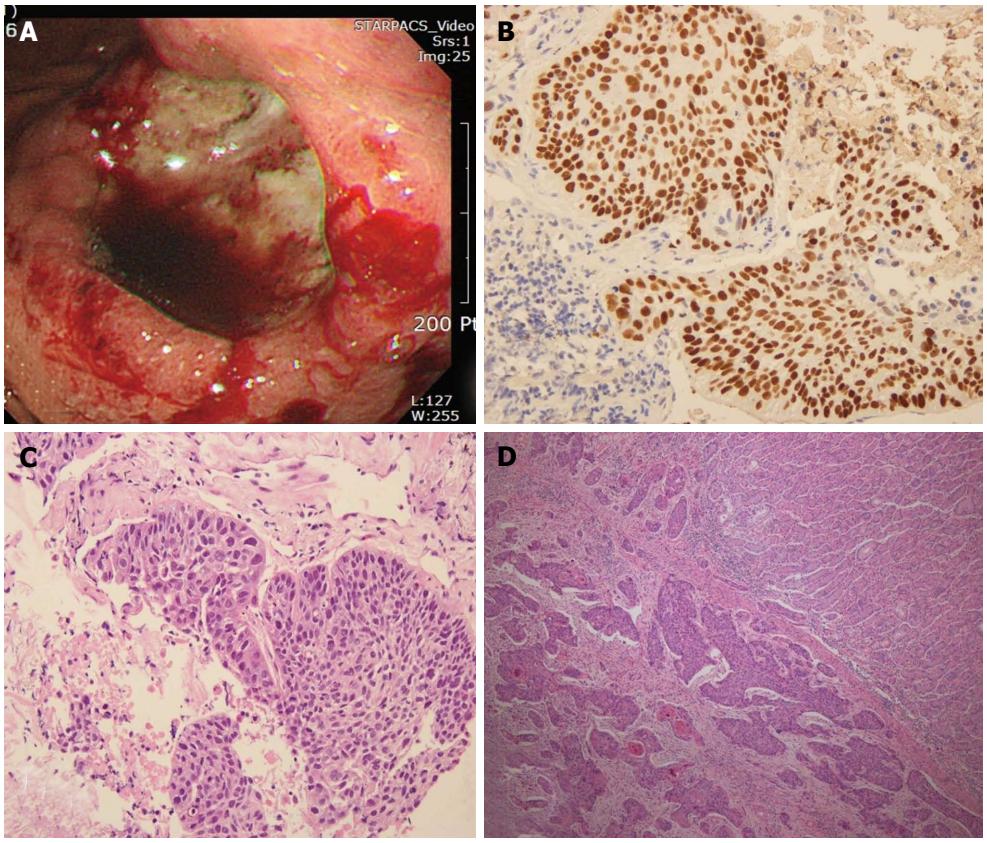

Figure 2 The biopsy showed syncytial growth of polygonal shaped poorly differentiated cells. A: Macroscopically, there was an ulcerofungating 4.0 cm × 3.5 cm lesion on the body; B, C: The bronchoscopic biopsy showed growth of polygonal shaped cells which were strongly positive for p63 and consistent with squamous cell carcinoma; D: Gastric ulcer specimen revealed multiple lymphatic invasion of carcinoma and chronic gastritis.

tive 4.0 cm × 3.5 cm lesion on the body and its side (Figure 2A). In 22 lymph nodes, carcinoma metastases were detected in seven nodes. Metastatic carcinoma invasion was noted in the spleen as well as the pancreas. The patient made an uneventful postoperative recovery and did not receive any adjuvant chemotherapy due to his refusal. The patient was controlled conservatively and survived for 11 mo after surgery.

DISCUSSION

Lung carcinoma is the leading cause of cancer death and about 50% have distant metastasis at the time of diagnosis. The brain, liver, adrenal glands and bone are the most likely sites of extra-thoracic metastasis[8]. The common metastatic site of the gastrointestinal tract is the small bowel with sporadic case reports involving the stomach[9-16]. Gastrointestinal metastases were detected in 10 (0.19%) of 5239 lung cancer patients. The prognosis of gastrointestinal metastasis was poor, with a median survival of 96.5 d after diagnosis[3]. Hematogenous metastasis to the stomach is a rarer event. The most frequent tumors involved in secondary gastric sites are melanoma, breast and lung cancer, with its incidence being reported as 1.7%-29.6%[6,8]. However, the actual incidence of lung cancers metastasizing to the gastrointestinal tract is expected to be higher. The reasons are: (1) the increased incidence of lung cancer in women; (2) the recent increase in the number of endoscopic examinations performed in general hospitals; and (3) the use of immunostains by pathologists in neoplasms showing an undifferentiated morphology[17]. Furthermore, gastrointestinal metastasis has probably been underdiagnosed in living patients because it is frequently regarded as part of generalized metastatic disease or the lesions are considered side effects of chemotherapy, such as ulcers, enteritis or colitis[17].

Most patients with gastric metastasis are asymptomatic. Only a few symptomatic cases have presented with non-specific symptoms of epigastralgia, chronic bleeding, anemia and hematemesis after a considerable growth of the metastatic tumor. Therefore, we should pay more attention to gastrointestinal signs since they are commonly related to an advanced metastatic tumor.

The bull's eye sign (volcano-like or umbilicated on the tip) is a well known characteristic of the radiographic findings of metastatic lesions[6]. However, it is not always the typical configuration. Therefore, some cases resemble early or advanced gastric cancer. Also, the differential diagnosis of lymphoma, ectopic pancreas, carcinoid tumor, eosinophilic granuloma, Kaposi's sarcoma and gastric ulcer should be considered[2].

Although gastric metastasis from lung cancer is associated with dismal outcomes, a longer survival or more favorable outcome has been demonstrated in patients undergoing palliative surgical resection of the metastatic site[17-20]. Our patient also made an uneventful postopera-

tive recovery and survived for 11 mo after surgery without any adjuvant chemotherapy.

In conclusion, surgical resection may provide an option of safe palliative treatment and gives longer survival with improved quality of life. However, considerable improvements in the understanding and therapeutic strategies for metastatic disease are needed to improve the clinical outcome.

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CASE REPORT

Rapunzel syndrome: A rare presentation with multiple small intestinal intussusceptions

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Abstract

Bezoars are usually confined to the stomach which is seen in individuals with psychiatric illness like trichotillomania, trichophagia and gastric dysmotility. Long standing bezoars may extend into the small intestine leading to a condition known as Rapunzel syndrome. Diagnosis can be established by endoscopy, ultrasonography and computed tomography scan. Treatment includes improvement of general condition and removal of bezoar by laparoscopic approach or laparotomy. Psychiatric consultation is necessary to treat and prevent relapse. We report a case of Rapunzel syndrome in a 16-year-old girl with trichotillomania. She presented with history of epigastric mass for three months and recent onset of pain abdomen, vomiting and early satiety. Skiagram of abdomen was showing distended stomach and endoscopy revealed trichobezoar. At laparotomy, stomach was distended with trichobezoar and there were multiple small intestinal intussusceptions. Gastrotomy and manual reduction of intussusceptions with the removal of trichobezoar with its tail was done. Patient recovered completely after the procedure.

Key words: Rapunzel syndrome; Trichobezoar; Trichotillomania; Intussusception

Core tip: Rapunzel syndrome is a rare condition which occurs in younger age group with trichotillomania and trichophagia. When trichobezoar is diagnosed further work up has to be carried out to rule out the presence of its tail extending into the small intestine causing complications such as intestinal obstruction, bleeding, malnutrition and perforation. We report a case where multiple intussusceptions were present which is rare. Though gastrotomy with enterotomy is advised to remove bezoar, we were able to remove the entire length of intestinal tail through gastrotomy itself and there was no need for enterotomy to remove the intestinal part of bezoar.

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INTRODUCTION

Trichobezoar is a condition where in swallowed hair starts accumulating in the stomach over a period of time to form a concretion which presents later with features of malnutrition and intestinal obstruction. These patients will usually have psychiatric conditions such as trichotillomania and trichophagia. When the bezoar extends into the small intestine it is called as Rapunzel syndrome which was first reported in 1968 by Vaughan *et al*[1]. It can

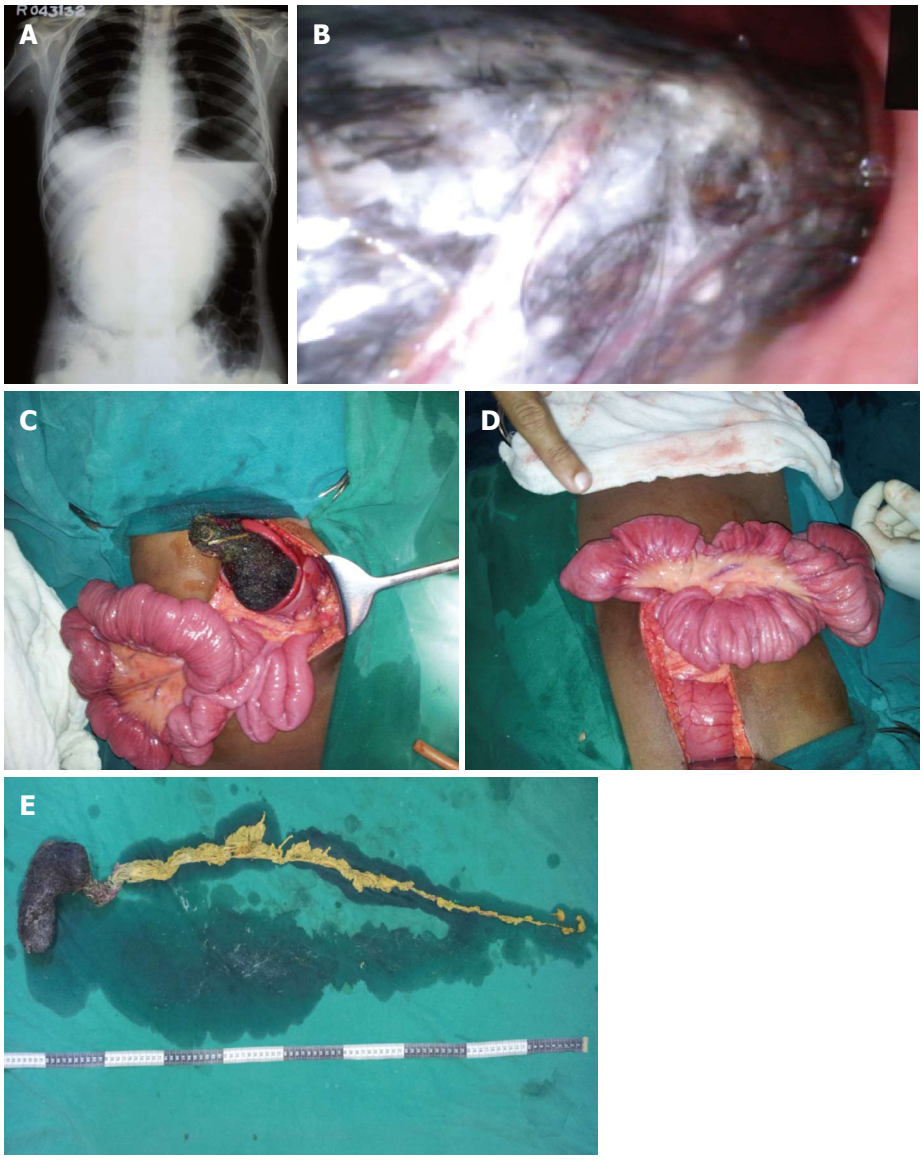

Figure 1 Treatment process. A: Skiagram of thorax and abdomen showing grossly distended stomach; B: Endoscopic view of trichobezoar; C: Gastrotomy showing ball of hair being removed; D: Multiple small bowel intussusceptions; E: Retrieved trichobezoar with its intestinal tail.

even present with complications like intestinal obstruction, perforation and peritonitis. Here we present a rare case of Rapunzel syndrome with multiple small intestinal intussusceptions in an adolescent girl.

CASE REPORT

A 16-year-old girl presented with history of mass in epigastric region for three months duration, abdominal pain for one month and vomiting for three days. The patient had delayed developmental milestones and poor performance at school. There was history of pulling and swallowing hair for three years for which tonsuring was done one year earlier. The patient had received psychiatric treatment for these complaints.

On examination, the patient was conscious, cooperative, pale and haemodynamically stable. Abdominal examination revealed a firm epigastric mass measuring 15 cm × 10 cm. Laboratory investigations revealed hemoglobin of 7.8 g/dL, serum total protein of 4.5 g/dL and serum albumin of 2.5 g/dL. Ultrasound examination of the abdomen was normal. Skiagram of the abdomen showed grossly distended stomach (Figure 1). Upper gastrointestinal endoscopy revealed presence of trichobezoar (Figure 1). The patient was given one packed cell transfusion to correct anemia and was posted for elective laparotomy.

On exploration, the stomach was distended and there were multiple intussusceptions in the jejunum and proximal ileum (Figure 1). The tail of bezoar was palpable throughout the jejunum and proximal ileum. Intussusceptions were manually reduced and gastrotomy along the body of the stomach parallel to greater curvature for a length of 10 cm was carried out. The trichobezoar made of bile stained foul smelling hair and cotton thread was removed along with the tail part (Figure 1). Gastrotomy was closed in two layers. Post operative period was un-

eventful and she was discharged with psychiatric counseling. At the follow-up examination two weeks following surgery, the patient was found to be free of abdominal symptoms and there was an improvement in her hemoglobin and serum total proteins when compared to the preoperative levels.

DISCUSSION

The term "bezoar" is derived from the Persian word "Padzahr" which means antidote[2]. There are various types of bezoar including trichobezoar (hair), phytobezoar (vegetable material), lactobezoar (milk products), pharmacobezoar and bezoars of honey comb, and cotton fibers. This condition is common in teenage girls with trichotillomania and trichophagia and patients with gastric motility problem. Debakey and Oschner suggested that the slippery nature of hair and its entrapment within gastric folds could be the reason for bezoar formation[3]. Over a period of time, hair gets matted with each other and with other indigestible materials like cotton fibers and vegetable matter to assume the shape of the stomach. Sometimes its tail may extend into the small intestine.

Bezoars can present with mass in the abdomen, abdominal pain, nausea, vomiting, weakness, weight loss, constipation, diarrhea and malnutrition[4]. In the present case, the patient had mass per abdomen associated with pain and vomiting. Rarely it may present with complications like intestinal obstruction, bleeding, perforation and obstructive jaundice, pancreatitis and appendicitis[5]. Intestinal obstruction can be the direct effect of the bezoar or secondary to intussusception. The clinician must consider the possibility of Rapunzel syndrome when patient with trichobezoar presents with features of intestinal obstruction[5]. The diagnosis can be made out by ultrasound, computerized tomography, barium meal and endoscopy.

Endoscopic retrieval of gastric trichobezoar is less invasive and cost effective than surgical removal[6]. But it is successful in only few patients and there are instances of respiratory arrest due to airway obstruction while attempting to remove trichobezoar[7]. When Rapunzel syndrome is suspected endoscopic retrieval should not be tried. Large gastric bezoars can be removed with laparoscopic approach safely but at the rate of prolonged operative time[8]. There are instances where Rapunzel syndrome has been managed laparoscopically[9].

In the present case, although the bezoar was extending into the small bowel as a lead point causing multiple intussusceptions, the patient did not have classical features of intestinal obstruction except for non bilious vomiting.

In cases with the bezoar extending into the intestine, usually enterotomy is advised to remove the bezoar. But in the present case the complete trichobezoar could be delivered out through a gastrotomy after reducing the intussusceptions at multiple levels in jejunum and ileum. It is a potentially life threatening condition where early diagnosis, surgical intervention has its role. Unless psychiatric counseling and follow up is done, this condition can recur[10].

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LETTER TO THE EDITOR

Left sided Amyand's hernia

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Abstract

The presence of the appendix in an inguinal hernia sac has been referred to as Amyand's hernia. Vermiform appendix located in an external hernia sac is not an uncommon condition, and the incidence of these cases is approximately 1%. In Amyand's hernias, appendices are frequently found in the hernia sac; but an incarceration particularly on the left side is a very unusual sight. In this report we present 32-year-old male with Amyand's hernia on the left side.

Key words: Amyand's hernia; Appendix; Left sided

Core tip: Patients with Amyand's hernias usually present with signs and symptoms of both appendicitis and obstructed or strangulated hernia. Although a CT scan is not routinely used in the diagnosis of an inguinal hernia, it can demonstrate the malrotation of the cecum, situs inversus as well as the Amyand's hernia

Unver M, Ozturk S, Karaman K, Turgut E. Left sided Amyand's hernia. *World J Gastrointest Surg* 2013; 5(10): 285-286 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i10/285.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i10.285

TO THE EDITOR

Claudius Amyand described the first case of a perforated appendix within the hernial sac in 1735 after his patient had undergone a successful appendectomy. Since then, the presence of the appendix in an inguinal hernia sac has been referred to as Amyand's hernia[1].

In this report we present 32-year-old male with Amyand's hernia on the left side. The main complaint of the patient was an irreducible inguinal mass with pain for three days. The other complaints of the patients were nausea and vomiting. He didn't suffer from any significant medical disease and he had undergone a Lichtenstein hernioplasty 3 years before due to a left sided inguinal hernia. We performed an abdominal computerized tomography (CT) which showed a mobile cecum that switched to the left side of the abdomen, with co-existing inflammatory echogenic findings and a left side inguinal hernia sac including appendix vermiformis (Figure 1). The patient underwent an emergency abdominal exploration via a median inferior abdominal incision. The cecum was mobile and shifted to the left side. The appendix vermiformis was found incarcerated in the left inguinal sac. We performed an appendectomy and repaired the internal ring with primary sutures.

Vermiform appendix located in an external hernia sac is not an uncommon condition, and the incidence of these cases is approximately 1%[2]. In Amyand's hernias, appendices are frequently found in the hernia sac; but an incarceration particularly on the left side is a very unusual sight[3]. The hernia sac commonly contains omentum or small bowel, but unusual contents such as the bladder, a Meckel's diverticulum (Littre hernia), or a portion of the wall of the intestine (Richter hernia) are extremely rare[4]. Also, most of the Amyand's hernias occur on the right side, because of the anatomical position of appendix. On the other hand, left-sided Amyand's hernias may be

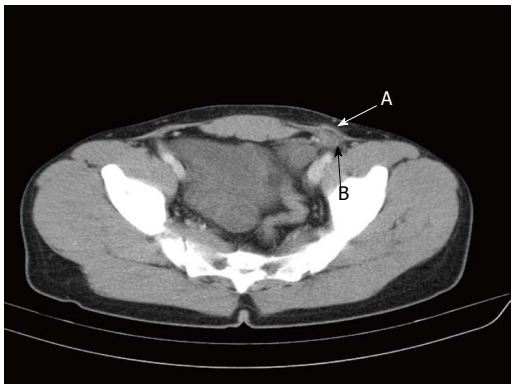

Figure 1 Computerized tomography image of the Amyand's hernia. A: The left sided hernia sac; B: Appendix vermiformis incarcerated in the hernia sac.

associated with situs inversus, intestinal malrotation or a mobile cecum[4,5].

In conclusion, Patients with Amyand's hernias usually present with signs and symptoms of both appendicitis and obstructed or strangulated hernia. Although a CT scan is not routinely used in the diagnosis of an inguinal hernia, it can demonstrate the malrotation of the cecum, situs inversus as well as the Amyand's hernia.

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BRIEF ARTICLE

Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients

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Abstract

AIM: To investigate the clinical relevance and prognosis regarding survival according to the changes of the tumor-node-metastasis (TNM) in gastric cancer patients.

METHODS: We retrospectively studied 347 consecutive subjects who underwent surgery for gastric adenocarcinoma at the Division of General Surgery, Hospital of Busto Arsizio, Busto Arsizio, Italy between June 1998 and December 2009. Patients who underwent surgery without curative intent, patients with tumors of the gastric stump and patients with tumors involving the esophagus were excluded for survival analysis. Patients were staged according to the 6th and 7th edition TNM criteria; 5-year overall survival rates were investigated, and the event was defined as death from any cause.

RESULTS: After exclusion, our study population included 241 resected patients with curative intent for gastric adenocarcinoma. The 5-year overall survival (5-year OS) rate of all the patients was 52.8%. The diagnosed stage differed in 32% of 241 patients based on the TNM edition used for the diagnosis. The patients in stage Ⅱ according to the 6th edition who were reclassified as stage Ⅲ had significantly worse prognosis than patients classified as stage Ⅱ (5-year OS, 39% *vs* 71%). According to the 6th edition, 135 patients were classifed as T2, and 75% of these patients migrated to T3 and exhibited a significantly worse prognosis than those who remained T2, regardless of lymph node involvement (37% *vs* 71%). The new N1 patients exhibited a better prognosis than the previous N1 patients (67% *vs* 43%).

CONCLUSION: 7th TNM allows new T2 and N1 patients to be selected with better prognosis, which leads to different staging. New stratification is important in multimodal therapy.

Key words: Gastric cancer; Tumor-node-metastasis staging system; Survival analysis; Prognostic factor; Lymphadenectomy

Core tip: The 7th edition of the tumor-node-metastasis (TNM) staging system appears to exhibit improved accuracy in staging and prognostic stratification with more precise indication for adjuvant and neoadjuvant therapy in the multimodal treatment era. Our data show the importance of standardization of treatment and the type of surgical lymphadenectomy for comparing different experiences. Further studies are necessary to improve the TNM system, particularly regarding the parameter N and the division into substages.

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INTRODUCTION

In addition to age, comorbidities, lesion site, macro- and microscopic type of tumor, quality of surgery and residual tumors, the main factors that influence the long-term survival of patients with gastric cancer are (1) the depth of tumor penetration into the gastric wall (T parameter); (2) the amount of the metastatic regional lymph nodes involved (N parameter); and (3) the presence of distant metastases (M parameter).

The tumor-node-metastasis (TNM) classification of cancer was developed between 1943 and 1952 by Prof. Pierre Denoix at the Institute Gustave-Roussy. In 1987, the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM classifications were unified. The following are the main objectives of the classifications: to aid the clinician in the planning of treatment, to provide an indication of prognosis, to assist in the evaluation of the results of treatment; to facilitate the exchange of information between treatment centers, to contribute to the continuing investigation of human cancer and to support cancer control activities[1,2]. Since January 1st 2010, the UICC/AJCC TNM 7th edition differs from the previous version regarding some aspects of the T parameter and is completely renewed regarding the N parameter (Table 1).

Particularly, the subserosa infiltration by the tumor, which was previously classified as T2b, is now classified as T3, and the perforation of serosa changed from T3 to T4a. Regarding the parameter N, the UICC/AJCC TNM 7th edition changes the lymph nodes "cut-off". Tumors classified as N1 in the 6th edition with more than 2 positive nodes are classified as N2 in the 7th edition, while N2 is classified as N3a, and N3 is classified as N3b. In the new stratification by stage, the number of substages is increased. According to the 7th edition, only patients with distant metastases are classified as the fourth stage. Another important change to the criteria concerns distant metastases. In the new edition of the TNM staging system, a positive peritoneal cytology is considered as M1.

Several studies, which were mostly performed in eastern countries, have demonstrated the superiority of the 7th edition TNM criteria and highlighted issues still in dispute for improvement.

The aim of the present study is to compare the sixth and the seventh edition of the TNM classification in patients who underwent surgery for gastric cancer in a single center to confirm the superiority of the new edition regarding its prognostic stratification and reliability. We considered the parameters T, N and the lymph node ratio (LNR) individually regardless of stage as additional prognostic parameters. We observed and followed how these changes in the allocation of pT and pN parameters according to the two editions of the classification affect determining the prognosis and the type of treatment for these patients.

Table 1 Tumor-node-metastasis staging system 6th and 7th edition

TNM staging system 6th edition				TNM staging system 7th edition			
Stage	T	N	M	Stage	T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
I A	T1	N0	M0	I A	T1	N0	M0
I B	T1	N1	M0	I B	T2	N0	M0
	T2a	N0	M0		T1	N1	M0
	T2b	N0	M0	II A	T3	N0	M0
II	T1	N2	M0		T2	N1	M0
	T2a	N1	M0		T1	N2	M0
	T2b	N1	M0	II B	T4a	N0	M0
	T3	N0	M0		T3	N1	M0
III A	T2a	N2	M0		T2	N2	M0
	T2b	N2	M0		T1	N3	M0
	T3	N1	M0	III A	T4a	N1	M0
	T4	N0	M0		T3	N2	M0
III B	T3	N2	M0		T2	N3	M0
IV	T4	N1	M0	III B	T4b	N0, N1	M0
	T4	N2	M0		T4a	N2	M0
	T4	N3	M0		T3	N3	M0
	T1	N3	M0	III C	T4a	N3	M0
	T2	N3	M0		T4b	N2, N3	M0
	T3	N3	M0	IV	AnyT	AnyN	M1
	Any T	Any N	M1				

MATERIALS AND METHODS

Patient cohort

We retrospectively studied 347 consecutive patients who underwent surgery for gastric adenocarcinoma at the Division of General Surgery, Hospital of Busto Arsizio (Varese), Italy from June 1998 through December 2009. For the survival analysis, we excluded the following patients: (1) patients with distant metastases; (2) patients who underwent surgery without curative intent; (3) patients with tumors of the gastric stump after gastric resection for benign disease; (4) patients with other tumors at the time of diagnosis; and (5) patients with a large involvement of the esophagus requiring total esophagectomy.

None of the patients considered for inclusion in the study underwent neoadjuvant chemotherapy or radiochemotherapy. Because of the heterogeneous and unsystematic indication for adjuvant chemotherapy, treatment protocols and number of cycles, details of the postoperative chemotherapy were not considered in this study.

Regarding the surgical method, en bloc resection of the primary tumor and lymphatic drainage area was routinely performed. D2 lymphadenectomy was performed in 87% of patients, while the remaining 13% underwent a D1 lymphadenectomy according to the Japanese Guidelines[3,4]. The principles of tumor resection and lymphadenectomy by experienced surgeons were similar among all the resected patients. No local excision was performed.

Follow-up

For all patients, a regular 6th month follow-up within 5

Table 2 Univariate survival analysis of clinicopathologic variables in 241 patients *n* (%)

Variable	*n* (%)	5-year overall survival rate (%)	*P* value
All	241	52.80	
Sex			0.740
Female	116 (48.1)	50.40	
Male	125 (51.9)	54.30	
Age (yr)			0.000
1 (≤ 50)	14 (5.8)	78.60	
2 (51-60)	18 (7.5)	32.00	
3 (61-70)	78 (32.3)	57.50	
4 (71-80)	87 (36.1)	57.30	
5 (> 80)	44 (18.3)	35.20	
Site			0.006
S	40 (16.6)	33.30	
M	50 (20.7)	70.80	
I	150 (62.2)	51.50	
Surgery			0.400
Total gastrectomy	191 (79.3)	53.10	
Subtotal gastrectomy	50 (20.7)	52.60	
Lauren			0.500
Intestinal	150 (62.2)	56.50	
Diffuse	58 (24.0)	48.50	
Mixed	15 (6.2)	33.90	
T stage (6th edition)			< 0.0001
T1	64 (26.6)	86.20	
T2	135 (56.0)	45.40	
T3	37 (15.3)	23.30	
T4	5 (2.1)	0.00	
T stage (7th edition)			< 0.0001
T1	64 (26.6)	86.20	
T2	33 (13.7)	71.00	
T3	102 (42.3)	37.30	
T4	42 (17.4)	20.50	
N stage (6th edition)			< 0.0001
N0	81 (33.6)	77.30	
N1	73 (30.3)	55.70	
N2	50 (20.7)	27.60	
N3	37 (15.4)	22.90	
N stage (7th edition)			< 0.0001
N0	81 (33.6)	77.30	
N1	39 (16.2)	67.50	
N2	35 (14.5)	43.00	
N3	86 (35.7)	25.90	
Stage (6th edition)			< 0.0001
I	87 (36.1)	76.40	
II	59 (24.5)	61.50	
III	55 (22.8)	24.40	
IV	40 (16.6)	21.20	
Stage (7th edition)			< 0.0001
I	70 (29)	85.60	
II	56 (23.3)	61.50	
III	115 (47.7)	27.00	
Lymph node ratio			< 0.0001
I (0)	81 (33.6)	77.30	
II (0.01-0.09)	41 (17.1)	65.40	
III (0.1-0.25)	50 (20.7)	44.50	
IV (> 0.25)	69 (28.6)	21.00	

S: Superior; M: Middle; I: Inferior.

years from surgery consisted of the following procedures: serum tumor biomarker and laboratory biochemical examinations, radiological and UltraSound imaging, endoscopic control (1/year) and physical examination. Annual follow-ups after 5 years were performed until the patients died. In this study, a period of 120 mo was considered as the end of the patient's observation. The median follow-up was 48 mo (range: 0-120 mo).

Statistical analysis

The depth of primary tumor invasion (T) and lymph node involvement (N) were classified according to the 6th and 7th UICC/AJCC edition TNM classification. All patients were restaged using the 6th and 7th editions of the UICC/AJCC TNM staging system. Survival curves were estimated using the Kaplan-Meier method[5]. The overall survival (OS) rates were investigated, and the event was defined as death for any cause. The Log rank test was used to identify the differences between the survival estimates of the different patient groups. Hazard ratio (HR) and 95%CI were also generated. A *P* value of less than 0.05 was considered significant. All tests were two-tailed. Statistical analysis and graphics were performed with MedCalc Software bvba, Mariakerke, Belgium.

RESULTS

From June 1998 until December 2009, a total of 347 patients in our department underwent surgery for gastric adenocarcinoma. After exclusion, the study population consisted of 241 resected patients, and 112 patients are currently alive.

The clinical and pathological characteristics are shown in Table 2. The median age was 71 years (range: 37-94 years), and 51.9% of the patients ($n = 125$) were male.

Total gastrectomy was performed in 191 (79%) patients, and subtotal gastrectomy was performed in 50 (21%) patients.

A D2 lymphadenectomy was performed in 208 (87%) patients. The median number of lymph nodes retrieved was 37 (range: 5-100); the value reached 40 (range: 13-100) in D2 lymphadenectomy and 16 (range: 5-45) in D1. The incidence of positive node patients was 67%. The 5-year overall survival of the 241 patients was 52.8%, and the ten-year overall survival was 34.7%. In the univariate analysis, age, site, T parameter, N parameter and Stage were significantly associated with overall survival.

We also studied the LNR as a prognostic factor among parameters of the univariate analysis. We considered 4 cutoff based on Marchet *et al*[6] (Table 2).

Survival analysis by stage

Stage migration occured in 33% of the patients: 19.5% of the I st stage were reclassified to II nd stage, and 33.9% of the II nd stage patients were reclassified as III rd stage. All the patients we considered as stage IV in the 6th ed. of the TNM staging system were reclassified as III rd stage using the 7th edition TNM staging system.

The patients classified as stage II according to the 6th edition and reclassified as stage III exhibited significantly worse prognosis than the patients who remained in stage II (5-year OS, 71% *vs* 39%; $P = 0.01$, HR = 2.3, 95%CI: 0.9-5.8) (Figure 1).

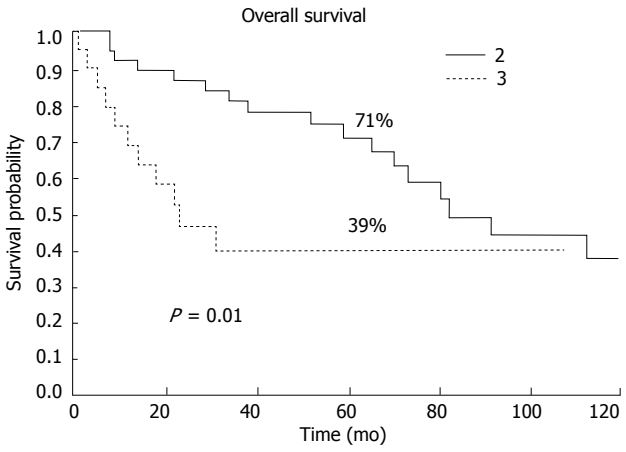

Figure 1 Ⅱ nd stage patients according to the 6th edition of the tumor-node-metastasis staging system reclassified as Ⅱ nd or Ⅲ rd stage according to the 7th edition of the tumor-node-metastasis staging system.

Important changes regarding the survival rates and stage reclassification were observed in our analysis. As shown in Table 3, the patients assigned stages using the sixth edition (orizzontally) exhibit a statistically significant difference in the prognosis when reclassified in a different stage according to the seventh edition criteria. However, a statistically significant difference in the prognosis was not observed when comparing the prognosis of patients assigned stages using the seventh edition criteria (vertically) with the stages assigned using the sixth edition (Table 3).

Regarding the substages in the 7th edition, the 5-year survival rates are comparable between substage Ⅰ B and Ⅱ A (5-year OS 59% *vs* 55%; $P = 0.8$). However, there is a significant difference regarding the survival probability at 5 years among substages Ⅲ A, Ⅲ B and Ⅲ C (5-year OS Ⅲ A: 47%, Ⅲ B: 20%, Ⅲ C: 24%; $P = 0.07$). The patients who belong to substage Ⅲ C exhibit similar survival to M+ patients.

Survival analysis by T category

We also analyzed the T category on T2b patients reclassified as T3 in the new edition of the TNM. In our population, 135 T2 patients were classified according to the 6th edition (56%), and 75% of these patients were reclassified as T3 using the most recent revision of the TNM system. The 5-year survival rates of the migrated patients and the patients who remained as T2 were 71% and 37%, respectively ($P = 0.008$, HR = 2.1, 95%CI: 1.3-3.5) (Figure 2A). The T2aN+ patients exhibited significantly better survival compared with the T2b patients with lymph node involvement (N+) according to the 6th edition (5-year OS 73% *vs* 37%; $P = 0.009$, HR = 2.5, 95%CI: 1.4-4.4) (Figure 2B).

Survival analysis by N category

Patients stratified according to the N-stage using the 6th and 7th editions of the TNM are now classified as N1 with the 7th edition and exhibit a 5-year OS probability of 67%. The N2 patients classified according to the 7th edition. TNM exhibit a 5-year OS of 43% ($P = 0.04$) (Figure 3).

Table 3 Stage migration from the sixth to seventh edition of the tumor-node-metastasis system

		7th edition TNM			
6th edition TNM	Stage (patients)	Ⅰ	Ⅱ	Ⅲ	*P*
	Ⅰ	70	17		0.004
	Ⅱ		39	20	0.040
	Ⅲ			55	
	Ⅳ			40	
	P		0.09	*P* (Ⅱ-Ⅲ) = 0.3 *P* (Ⅳ-Ⅲ) = 0.1	

TNM: Tumor-node-metastasis.

DISCUSSION

In this retrospective study, we focused on the major changes between the 6th and 7th edition of the TNM system regarding gastric cancer. The analysis of this migration reveals the most important prognostic factors and possible modifications introduced in multimodal treatment.

We observed an OS of 52.8%. That goes to 54% of survival in the D2 type of lymphadenectomy that represented 87% of the sample. In our study population, more than 50% of the patients were diagnosed with T2 lesions according to the 6th edition regarding the parameter of infiltration of the tumor in the gastric wall (T parameter). Other studies reported variable incidences of T2 (Sarela *et al*[7]: 30%; Marchet *et al*[8]: 32%; Nitti *et al*[9]: 51.4%; Park *et al*[10]: 30%; Lu *et al*[11]: 40%).

In our study, 102 out of 135 patients (75%) classified as T2 according to the 6th edition of the TNM system were reclassified as T3 based on the 7th edition of the TNM system. The shift exhibits a statistically significant prognostic difference in 5-year OS regardless of nodal involvement (Figure 2).

Our results concerning the prognostic differentiation between T2 and T3 are also confirmed by other studies[12,13]. Sarela *et al*[7] reported a statistically significant difference between patients classified as T2N1 and T3N1, (56% *vs* 44%; $P = 0.3$). Fotia *et al*[14] obtained different results (74% *vs* 67% for T2 to T1 to 5 years; $P = 0.2$).

Recently, Marchet *et al*[8] reported 5-year survival values of 67% for T2 and 52% for T3. When N+ patients were included in their analysis, 5-year survival rates of 66% and 47% were obtained for T2N+ and T3N+. In conclusion, the results of this study emphasize the prognostic value of T2/T3 categories and the importance of identifying subgroups of patients (T2b 6th edition) that may benefit from adjuvant chemotherapy. Based on our results, these patients would also be candidates for neoadjuvant treatment[15-17].

The renewal of the lymph node cut-off (N parameter) has allowed us to select patients with better prognosis

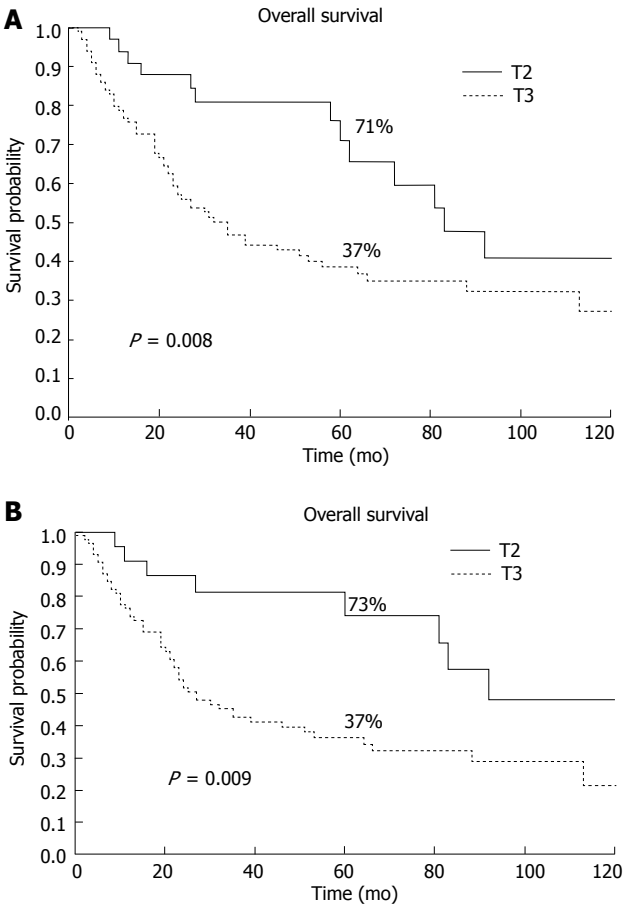

Figure 2 Overall survival. A: T2 patients according to the 6th edition of the tumor-node-metastasis (TNM) staging system reclassified as T2 or T3 with the 7th edition; B: T2N+ patients according to the 6th edition of the TNM staging system reclassified as T2 or T3 with the 7th edition.

(new N1). The involvement of 1-2 lymph nodes was associated with a better prognosis in our cases than patients with N2 (3-6 positive nodes). The 5-year OS rates were 67.5% for N1 and 43% for N2; ($P = 0.04$). Similar results were obtained from the study published by Ahn *et al*[13] (N1: 76.5% *vs* N2: 58%).

In our analysis, we did not investigate the difference between N3a and N3b because of the small sample size. However, according to other reports, a possible reclassification of the N3 category would be desirable because N3a and N3b exhibit significant differences in survival[13,18,19].

The analysis of the LNR (linf+/linftot) showed good prognostic stratification among the 4 curves ($P < 0.0001$). Some studies have described the usefulness of the LNR in Japan and South Korea[20,21].

As demonstrated by the work of Kong *et al*[22], the power of the differential staging of the LNR system was fortified with a higher number of examined lymph nodes and represents appropraite N-staging.

In a retrospective multicenter study of 1853 patients operated for gastric cancer, Marchet *et al*[6] showed that the LNR was an independent prognostic factor regardless of the type of lymphadenectomy.

Wang *et al*[23] showed that the "TNratioM System" may predict survival more accurately in patients who undergo

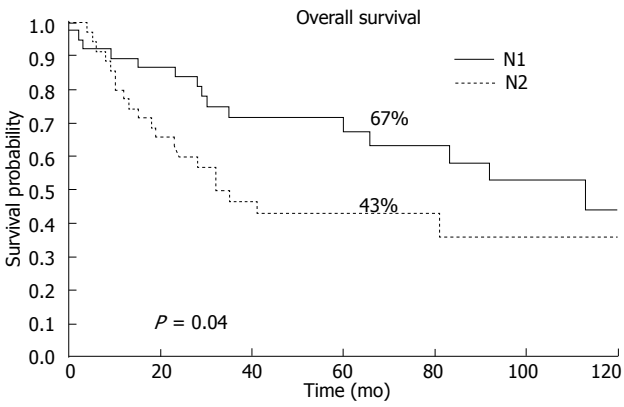

Figure 3 Comparison between N1 patients and N2 patients according to the 7th edition.of the tumor-node-metastasis staging system.

limited lymph node analysis.

The changes in the parameters N and T have generated stage migration, which confirms the superiority of the 7th edition. of the TNM system. The new TNM edition groups patients with similar prognoses and separates subjects with different prognoses better that the previous version of the TNM system (Table 3). Similar rates of survival are shown in the analysis by Marrelli *et al*[24]. Evaluating the substages in our population, we observed that the 5-year survival values were similar between I B and II A. Similar findings were reported in a large series of western patients with gastric cancer[18].

A significant difference regarding the 5-year survival was observed between the substages of stage III (III A, III B and III C). In a study by Wang *et al*[12] on 1503 patients, the tumor size (> 5 cm or < 5 cm) was a determining factor in the differentiation of the prognosis between I B and II A. According to Wang *et al*[12], three subgroups of the fourth stage exhibit different biologic behaviors of relapse or metastasis models and need further analysis.

In conclusion, the 7th edition of the TNM system seems to have improved accuracy in staging and prognostic stratification, the 7th edition provides more precise indication for adjuvant and neoadjuvant therapy in the multimodal treatment era, our data show the importance of standardization of treatment and the type of surgical lymphadenectomy to compare different experiences and further studies are necessary to improve the TNM system particularly regarding the parameter N and the division into substages.

COMMENTS

Background

The Union for International Cancer Control and the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system is the most important classification of tumors. The main objectives of TNM cancer staging are to help the clinician plan the treatment, to give an indication of prognosis and to evaluate the results of treatment. In the new edition of the TNM (7th) staging system, there are important changes in the field of gastric cancer.

Research frontiers

The 7th edition of the TNM system appears to exhibit improved accuracy in staging and prognostic stratification. Different experiences need to be compared to

improve the reliability of the TNM classification system.

Innovations and breakthroughs

The TNM 7th edition differs from the previous version regarding gastric cancer on some aspects of the T and M parameters and is completely renewed regarding the N parameter. Several studies, which were predominantly performed in Eastern countries have demonstrated the superiority of the new edition criteria and the highlighted issues still require improvement.

Applications

The study results suggest that the 7th edition of the TNM system is superior to the previous version regarding prognostic stratification. However, further studies are necessary to improve the TNM system particularly regarding the N parameter and the division into substages.

Terminology

The TNM classification uses three parameters to divide the patients into different stages: depth of tumor penetration into the gastric wall (T parameter), the number of metastatic regional lymph nodes involved (N parameter) and the presence of distant metastases (M parameter).

Peer review

The retrospective study compares the 6th and 7th edition of the TNM classification in a single Italian institution to confirm the superiority of the new edition for prognostic accuracy. According to the experience, standardization of surgical therapy and a multidisciplinary approach are necessary to develop a multimodal tailored treatment.

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BRIEF ARTICLE

Comparative analysis of open and laparoscopic colectomy for malignancy in a developing country

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Abstract

AIM: To compare the short-term, including oncologic, outcomes of open *vs* laparoscopic colectomy for cancer in a developing country.

METHODS: The records of patients who underwent elective open and laparoscopic colectomies for cancer at the University Hospital of the West Indies between January 2005 and December 2010 were retrospectively reviewed. Demographic (age, gender, Charlson comorbidity index score), peri-operative, post-operative and oncologic data were collected for each patient. Specific oncologic variables included lymph node yield, pathologic stage, grade, proximal, distal and circumferential margin involvement. Fisher's exact, Mann-Whitney, and binary logistic regression tests were used for analysis. Significance level was set at $P < 0.05$.

RESULTS: There were 87 cases for open colectomy (OC) and 17 cases for laparoscopic colectomy (LC). Demographics did not significantly differ between OC and LC groups. Intra-operative blood loss and post-operative analgesic requirements did not significantly differ between groups. There was a trend towards longer operating times in OC group and shorter hospital stay in the LC group. Lymph node yield (14 *vs* 14, $P = 0.619$), proximal (10 cm *vs* 7 cm, $P = 0.353$) and distal (8 cm *vs* 8 cm, $P = 0.57$) resection margin distance and circumferential margin involvement (9 *vs* 0, $P = 0.348$) did not significantly differ between groups. Thirty-day morbidity was equivalent between groups (22 *vs* 6, $P = 0.774$). There were 6 deaths within 30 d of initial procedure, all in the OC group (6.9%).

CONCLUSION: Laparoscopic colectomy in a developing country is oncologically safe and represents a option for colonic malignancies in these regions. Such data encourage the continued laparoscopic development.

Key words: Laparoscopy; Colectomy; Cancer; Developing country; Colorectal; Oncology; Short-term; Outcomes

Core tip: The development of laparoscopic colectomy in developing countries has been slow despite strong evidence to support its benefit. The demonstration that laparoscopic procedures can be performed safely in these environments supports and encourages further incorporation of laparoscopy in these environments. Notwithstanding proven feasibility of laparoscopic colectomy for cancer in developing countries, there is the need to demonstrate equivalent oncologic outcomes to open surgery in order to establish safety. This study shows that laparoscopic colectomy for cancer in a developing country is not only feasible but is oncologically safe.

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INTRODUCTION

Laparoscopic colectomy, first described in the early 1990s for diverticular disease, has become a viable option for the management of colorectal cancer. The first case of laparoscopic colonic resection for neoplasia was documented in 1991 following successful resection for a villous adenoma[1]. Subsequently, reports on the successful use of laparoscopic colectomy for cancer cases were increasingly published[2].

Early concerns related to the oncologic equivalence to open colectomy (inadequacy of resection, staging inaccuracies and the possibility of the pneumoperitoneum affecting tumour dissemination) have been dispelled by randomized controlled trials (RCTs)[3-6] and meta-analyses[7]. These have demonstrated similar long-term oncologic outcomes compared to open colectomy, while also demonstrating superior short-term outcomes expected of the laparoscopic approach.

The incorporation of laparoscopic techniques in developing countries has been challenging, due in particular to the high costs of equipment and lack of expertise[8]. Despite these ongoing challenges, the continued use of laparoscopy is still encouraged[8]. Many laparoscopic procedures, including appendicectomy[9], cholecystectomy[10,11] and hysterectomy[12], splenectomy[13], have successful been performed in developing countries. A recent study from our institution demonstrated that laparoscopic colectomy for neoplasms is safe and feasible. Studies from other developing countries such as Argentina[14], China[15,16], Mexico[17] and Turkey[18], have demonstrated the feasibility and safety of laparoscopic colectomy, but have neglected to demonstrate the equivalence to the open approach in these settings. Demonstrating oncologic outcomes similar to those achieved in a developed setting will further support the continued growth of laparoscopy for cancer in a developing country. There are currently limited data referencing the oncologic safety of laparoscopic colectomy in these settings. The present study provides further evidence regarding the oncologic safety of laparoscopic colectomy in a developing country. The primary aim of this study was to compare the short-term outcomes, particularly oncologic outcomes, of laparoscopic versus open colectomy for cancer.

MATERIALS AND METHODS

Ethics

This work has been carried out in accordance with the Second International Helskinki Declaration[19]. This study was ethically approved by the Faculty of Medical Sciences/University of the West Indies Ethics Committee (File number: ECP 04, 13/14).

Setting and operative approach

Surgical procedures were undertaken at a tertiary academic centre in a developing country. All surgeons were trained in Jamaica, while surgeons performing laparoscopic colectomy either had formal laparoscopic training or had undertaken mentorship programmes. The operative details have previously been published by Plummer *et al*[20]. Briefly, the laparoscopic equipment included a standard laparoscopic tower, reusable trocars and reusable bowel graspers. Vascular control was achieved using clips or Ligasure® (when available) as opposed to stapling devices. Bowel mobilization and dissection was achieved using either monopolar cautery or ultrasonic shears (when available). With specific reference to right hemicolectomy, all patients had extracorporeal anastomoses following exteriorization of the colon.

Data collection

This was a retrospective chart review of adult patients who underwent elective open or laparoscopic colectomy for cancer between January 1, 2005 and December 31, 2010 at the University Hospital of the West Indies. Emergency procedures and rectal resections were excluded. All included patients had preoperative colonoscopy with confirmation, by biopsy, of a carcinoma. Cases were grouped according to intention-to-treat: laparoscopic cases converted to open were included in the laparoscopic group. The decision to perform laparoscopic or open colectomies was based on the discretion of the attending surgeon. Demographic [age, gender, Charlson comorbidity index score (CCI)], peri-operative, post-operative and oncologic data were collected for each patient. Specific oncologic variables included lymph node yield, pathologic stage, grade, proximal, distal and circumferential margin involvement.

Statistical analysis

Demographic, intra-operative, pathological, and post-operative variables between open colectomies (OC) and laparoscopic colectomies (LC) were analyzed using Fisher's exact (for categorical variables) and Mann-Whitney (for continuous variables). Logistic regression was used to determine if length of stay was significantly different between OC and LC group, controlling for all potential confounding variables. Significance level for all analyses was set at $P < 0.05$.

RESULTS

Charts of one hundred and four patients were included. Of these, 87 persons underwent OC and 17 underwent LC. Neither gender, age, nor CCI significantly differed between OC and LC groups (Table 1).

Only one laparoscopic case was converted. Intra-operative blood loss did not differ significantly between

Table 1 Demographics for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
Gender	Male	36 (41.4)	9 (52.9)	0.429
	Female	51 (58.6)	8 (47.1)	
Age [median, (5Q-75Q)], yr		66 (59-78)	62 (58-72)	0.363
Charlson score	0	7 (8.0)	1 (6.2)	0.501
	1	14 (16.1)	4 (25.0)	
	2	22 (25.3)	4 (25.0)	
	3	18 (20.7)	5 (31.2)	
	4	17 (19.5)	1 (6.2)	
	5	7 (8.0)	0 (0.0)	
	6	1 (1.1)	1 (6.2)	
	7	1 (1.1)	0 (0.0)	

OC: Open colectomy; LC: Laparoscopic colectomy.

Table 2 Intra-operative outcomes for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
Procedure	RH	42 (48.3)	7 (41.2)	0.801
	Extended RH	9 (10.3)	1 (5.9)	
	LH	11 (12.6)	2 (11.8)	
	Extended LH	1 (1.1)	0 (0.0)	
	Transverse colectomy	1 (1.1)	0 (0.0)	
	Sigmoid colectomy	21 (24.1)	6 (35.3)	
	Total colectomy	2 (2.3)	1 (5.9)	
Conversion		NA	1 (5.9)	
Total OR time (min) [median (25Q-75Q)]		165 (128-195)	195 (143-259)	0.075
Intraop blood loss (mL) [median (25Q-75Q)]		300 (200-600)	275 (188-550)	0.512

OC: Open colectomy; LC: Laparoscopic colectomy; RH: Right hemicolectomy; LH: Left hemicolectomy; NA: Not available.

groups (Table 2). Although there was not a significant difference in operating time between LC and OC, there was a trend towards longer operating times in the LC group (P = 0.075; Table 2). This trend is further supported by the fact that 13 patients, all within the OC group, had another procedure along with their OC: cholecystectomy, liver biopsy, axillary dissection, small bowel resection, splenectomy, cystolithotomy, hysterectomy and oophorectomy. Contrarily, only 1 patient had a combined procedure (bilateral inguinal hernia repair) during LC.

There were no significant differences between OC and LC for any of the pathological outcomes (Table 3). These outcomes included lymph node yield (P = 0.619), proximal (P = 0.353) and distal (P = 0.57) resection margin distance and circumferential margin involvement (P = 0.348).

Controlling for potential confounders, there was a trend towards a shorter length of hospital stay in the LC group (P = 0.083; Table 4). However, 30-d morbidity was equivalent between groups (P = 0.774; Table 4). Complications included anastomotic leak, wound infection,

Table 3 Pathological outcomes for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
Grade of differentiation	Well	9 (10.35)	4 (23.5)	0.166
	Moderate	74 (85.1)	10 (58.8)	
	Poor	4 (4.6)	0 (0.0)	
Proximal margin (cm) [median (25Q-75Q)]		10 (5-16)	7 (7-10)	0.353
Distal margin (cm) [median (25Q-75Q)]		8 (4-13)	8 (6-10)	0.570
CRM involved	Yes	9 (10.6)	0 (0.0)	0.348
	No	76 (89.4)	16 (100)	
LN yield [median (25Q-75Q)]		14 (10-17)	14 (10-15)	0.619

OC: Open colectomy; LC: Laparoscopic colectomy; CRM: Circumferential resection margin; LN: Lymph node.

Table 4 Postoperative outcomes for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
30-d morbidity	No	46 (52.9)	8 (47.1)	0.774
	Yes	22 (25.3)	6 (35.3)	
	Not recorded	19 (21.8)	3 (17.6)	
30-d mortality	No	62 (71.3)	14 (82.4)	0.717
	Yes	6 (6.9)	0 (0.0)	
	Not recorded	19 (21.8)	3 (17.6)	
Parenteral narcotic doses [median (25Q-75Q)]		6 (4-9)	5 (4-7)	0.176
LOS (d) [median (25Q-75Q)]		6 (5-7)	5 (4-8)	0.083

OC: Open colectomy; LC: Laparoscopic colectomy.

fascial dehiscence, prolonged ileus, respiratory failure, pulmonary embolus, left ventricular failure, and atelectasis. Anastomotic leakage occurred in 4 (3.8%) patients. The number of post-operative parenteral narcotic doses did not significantly differ between groups (P = 0.176; Table 4). Despite 6 deaths in the OC group, a statistically significant difference in 30-d mortality was not demonstrated (P = 0.717; Table 4).

DISCUSSION

The present study demonstrates no statistical differences between open and laparoscopic colectomy with respect to short term oncologic outcomes (proximal, distal and circumferential margins and lymph node yield). This study represents the first comparative analysis of this nature from a developing country in the English-speaking Caribbean.

Numerous RCTs have demonstrated superior short-term outcomes in favour of laparoscopy with respect to post-operative pain, return of bowel function, length of hospitalization and cosmesis[3-6]. Furthermore, meta-analyses of multiple RCTs have concluded that laparoscopic colectomy for cancer provides superior short-term benefits and equivalent oncologic outcomes compared to

open colectomy[7]. More recent studies have even shown improved 30-day morbidity[7,21] and mortality[21-23] with laparoscopic colectomy, with some authors questioning whether it should be standard of care[24].

Despite this evidence, open colectomy remains the most common approach to colonic resection in developing countries[8]. A previous study from our institution[20] demonstrated that laparoscopic colectomy could safely be performed for colonic neoplasia in a developing country. However, the study did not specifically evaluate perioperative outcomes, including oncologic safety or compare such outcomes to a cohort of open cases. Lohsiriwat *et al*[25] demonstrated equivalent short-term and oncologic outcomes in a retrospective series of patients undergoing open and laparoscopic right hemicolectomy for cancer in Thailand. Those results echo that of the present study where no statistically significant difference was found for positive margins or lymph node yield ($P = 0.08$) between groups[25].

Our results demonstrated a trend towards longer operative time and shorter length of hospital stay in the LC compared to the OC group. Although these findings are consistent with the literature[3-6], our results are likely confounded by the inclusion of patients undergoing concomitant surgical procedures in the analysis. Thirteen of 14 cases with additional procedures occurred in the OC group. As such, this may have skewed results towards even longer operative times and hospital stay in the OC group. The equivalence seen between OC and LC groups regarding 30-d morbidity and mortality rates is consistent with previous literature[3-5]. Similarly, oncologic outcomes for OC and LC groups, including resection margins and lymph node yield are consistent with previous RCTs[3-6].

This study has several limitations. Firstly, like all retrospective chart reviews, data abstraction may be affected by inconsistencies, and is limited to the information contained in patients' charts. Although nothing can be done to address the latter, the former limitation was addressed by having a second abstractor review 10% of patients' charts to ensure accuracy of the information collected. Secondly, although this study provides evidence supporting the safe use of LC in resource-restricted settings, contextual factors imperative for LC implementation, such as availability of equipment and cost, were not considered.

There was a significant difference in the numbers of OC *vs* LC cases. This is a limitation of the study, which will impact on the ability to make definitive conclusions. In addition, the disparity in numbers suggests persistent barriers to the incorporation of laparoscopy in our setting. A recent survey of surgeons in Jamaica suggested that cost and lack of expertise/training were the main barriers of laparoscopy uptake[26]. However, improved short-term outcomes such as shorter hospital stay, faster return to work, and reduced surgical site infection rates, often offset the upfront costs of laparoscopy[27]. In countries already performing laparoscopic cholecystectomy, no additional basic equipment is usually required for colectomy. Institutional investment in reusable bowel graspers and needle drivers would obviate the need for disposables with some cost reduction. Some disposable equipment, however, have no reusable counterpart. As such, the initial cost of these disposables (including energy devices and staplers) to the institution or patient remains a challenge. Manoeuvres to avoid the need for these expensive devices, such as colonic mobilization with extracorporeal anastomoses, and the use of monopolar cautery and clips[13] have been described. Meta-analyses have failed to demonstrate any significant disadvantages to extracorporeal anastomoses for laparoscopic right sided colectomies[28]. Additionally, there is no evidence to suggest that use of energy devices is superior to monopolar cautery for laparoscopic colectomy[29]. The surgical technique employed in the present study utilized reusable instruments and extracorporeal anastomoses in order to reduce costs. Such techniques did not adversely affect outcomes. Future studies should incorporate these contextual factors when describing LC uptake in a resource-restricted setting.

Lack of expertise and training as a limiting factor for LC uptake underscores the need to incorporate LC in residency training[8,30]. The recent opening of a skills laboratory and the further addition of minimally invasive surgical staff to our institution have been methods instituted to address this issue. Unfortunately, these factors were not considered in this study and should be discussed in future work.

There remain many challenges to the use of laparoscopic colectomy for colonic carcinoma in developing countries. The equivalent short-term outcomes demonstrated between open and laparoscopic groups in the present study demonstrate that this is an oncologically safe approach in our environment. Continued strategies to reduce costs and increase surgeon training are essential to the further development of laparoscopic colectomy in developing countries. Only through these strategies can caseload increase allowing for progressive high-quality research in the field in these environments.

COMMENTS

Background

Laparoscopic colectomy for cancer has been proven to have superior short-term benefits to open colectomy with equivalent oncologic outcomes. These findings are based on large-scale studies conducted developed countries. The practice of laparoscopic colectomy in developing countries is limited. To date, few studies have sought to evaluate the benefit and oncologic safety of laparoscopic colectomy for patients in developing countries.

Research frontiers

Laparoscopic surgery has revolutionized the care of patients worldwide, providing advantages of reduced pain, shorter hospital stay, earlier return to normal functioning and improved cosmesis. For developing countries, the research hotspot is the demonstration of similar outcomes as in developed countries, particularly for the use of laparoscopy in cancer cases.

Innovations and breakthroughs

Previous studies on the use of laparoscopic colectomy in developing countries have demonstrated feasibility and safety. These studies are few as the practice of laparoscopic colectomy in these environments is limited, particularly by resource constraints. Very few studies have evaluated the specific effects of laparoscopy on oncologic outcomes of colon cancer in developing countries.

In the present study, authors compared a cohort of patients undergoing open and laparoscopic colectomy for cancer and found that the short-term oncologic outcomes were equivalent between the two groups.

Applications

The study results suggest that laparoscopic colectomy for cancer can be safely performed, with equivalent short-term oncologic outcomes to open colectomy, in developing countries where resources may be limited.

Terminology

Laparoscopy is a minimally invasive surgical technique where abdominal operations are undertaken through small incisions, thus minimizing bowel handling and causing less tissue trauma. Colectomy refers to the surgical excision of the colon or part thereof. Short-term oncologic outcomes related to colon cancer include proximal, distal and circumferential margin involvement and the numbers of lymph nodes harvested at the time of surgery.

Peer review

The authors present a comparative study between open and laparoscopic approaches for colectomies in a developing country. They should be congratulated for addressing this relevant topic.

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BRIEF ARTICLE

Drainage *vs* no drainage in secondary peritonitis with sepsis following complicated appendicitis in adults in the modern era of antibiotics

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Abstract

AIM: To compare the profile of postoperative outcome in secondary peritonitis with sepsis due to complicated appendicitis in two cohorts (drainage *vs* no-drainage) after appendicectomy in adults in the modern era of effective antibiotics.

METHODS: A retrospective review of all adult patients who were operated for secondary peritonitis with sepsis due to complicated appendicitis was carried out. Total of 209 patients were identified from May 2005 to April 2009 with operative findings of gangrenous or perforated appendix. The patients were divided into two cohorts, those where prophylactic drainage was established (n = 88) and those where no drain was used (n = 121). Abdominal drain was removed once the drainage ceased or decreased (< 10-20 mL/d in closed system of drainage or when once daily dressing was minimally soaked in open system). Broad spectrum antibiotics to cover the gut flora were started in both cohorts at diagnosis and were stopped once septic features resolved. Peritoneal fluid for aerobic culture and sensitivity were routinely obtained intra operatively; however antibiotic regimens were not changed unless patient failed to respond to the antibiotics based on the institutional protocol. The co-morbidities and their influence on primary end points were noted. Immunocompromised patients, appendicitis complicated by inflammatory bowel disorder and tumors were excluded from the study.

RESULTS: Disease stratification and other demographic features were comparable in both cohorts. There was zero mortality in drainage group while as one patient (0.82%) died in the non-drainage group. The median duration (in days) of hospital stay (6.5 *vs* 4); antibiotic use (5 *vs* 3.5); regular parental analgesic use (5 *vs* 3.5) and paralytic ileus (2.5 *vs* 2) was more common in the drainage group. Incidence of major wound infection in patients 14 (15.9%) *vs* 22 (18.18%) and residual intra-abdominal sepsis (inter loop collection/abscess) -7 (8%) *vs* 13 (10.74%) requiring secondary intervention was not significantly different in drainage and non-drainage cohorts respectively. One patient in the drainage cohort had faecal fistula (1.1%).

CONCLUSION: The complicated appendicitis in the modern era of antibiotics does not necessitate the use of prophylactic drain placement which at times may even prove counterproductive.

Key words: Appendicitis; Antibiotics; Drainage; Gangerenous; Peritonitis

Core tip: The routine placement of the drain after appendicectomy irrespective of the severity of the appendicitis increases both the morbidity and the cost of treatment. The surgeons need to do away with the habits of riding on drains perhaps as a soup to their consciences. Post-operative management of the patient with the drain as compared to those without drain is troublesome, requiring increased work and manpower for the hospital.

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INTRODUCTION

The untruthful trust on the functioning of drains as an agent in preventing the intra-abdominal sepsis is deeply seated in the minds of the surgeons. This belief is usually imbibed by the surgeons from their predecessors during their training period and the practice persists from one generation-surgeons to another. Robinson[1] aptly classified surgeons into three categories based on their use of drains: those who believe that all intraperitoneal operations should be drained, those who feel that drain is useless and those who sit on the fence and insert a drain as a safety valve or perhaps as a sop to their consciences. Even though there is enough evidence to discourage the use of prophylactic drains in different areas of gastrointestinal surgery[2] the literature for or against the use of drain after the complicated appendicitis is small and historical. Drainage following "simple" appendicitis has been assessed by two randomized trials[3,4] which do not favour the placement of drains.

There have been only few randomized trials so for to evaluate the role of drains when the appendix was eithe perforated or gangrenous[3-6]. However three of these studies have been reported in 1970s. Though the meta-analysis based on these studies by Petrowsky *et al*[7] did not recommend the use of intraperitoneal drains, no evidence exist as to whether this approach should be extrapolated in adult patients; and in the new era of antibiotics. Although, there is no universally accepted antibiotic regimen, however broad spectrum coverage with multiple drugs has been advocated[8-10].

MATERIALS AND METHODS

The retrospective analysis of the medical records of adult patients who underwent open appendicectomy for complicated appendicitis (gangrenous and perforated appendix) at Sher-i-Kashmir institute of medical sciences Srinagar from May 2005 to April 2009 was done. The total number of patients encountered was 209. Prophylactic drainage was established in 88 patients while as in 121 patients no drain was used. Abdominal drain was removed once the drainage ceased or decreased (< 10-20 mL/d in closed system of drainage or when once daily dressing was minimally soaked in open system). Broad spectrum antibiotics to cover the gut flora were used in both cohorts at diagnosis and were stopped once sepsis got resolved. Peritoneal fluid for aerobic culture and sensitivity were routinely obtained intra operatively. The co-morbidities and their influence on primary end points were noted. Laparoscopic appendicectomy, immunocompromised patients and appendicitis complicated by inflammatory bowel disorder were excluded from the study. The fluid and electrolyte correction was done wherever necessary before surgery. The patients were put on 3rd generation cephalosporin with or without sulbactum plus metronidazole 7.5 mg/kg q8H at the time of diagnosis of complicated appendicitis. Postoperatively parenteral antibiotics were switched to oral therapy for 5 to 7 d when: (1) baseline signs and symptoms of infection were resolving or resolved; (2) resolution of fever (≤ 37.8 ℃) or hypothermia; (3) leukocytosis, leucopoenia resolving or normal; and (4) subjects able to maintain oral intake.

Patients were operated by one of the Registrars (advanced trainees) in 24 h-emergency theatre without much delay after the assessment by a senior consultant. Right iliac fossa standard muscle splitting/cutting transverse or oblique incision was utilised usually for localised peritonitis or for documented case of appendicitis. A right lower lateral para-median incision was usually used for generalised peritonitis or when diagnosis was in question. After appendicectomy stump burial was an individual preference of surgeon. A liberal lavage was performed by luke warm 0.9% normal saline. Drain placement was largely influenced by the surgeons own preference, understanding of the subject and belonging to a particular school of thought. No rigid departmental protocol has been formulated in this context. Drain was placed either in right para-colic gutter or in pelvis. All wounds were closed primarily after a thorough wound wash. Abdominal drain was removed once the drainage has ceased or decreased (< 10-20 mL/d in closed system of drainage or when once daily dressed was minimally soaked in open system).

In the post-operative period patients who failed to improve over a period of time underwent radiological evaluation (ultrasonography and/or computed tomography) of the abdomen and antibiotics were changed as per the culture sensitivity reports wherever necessary. Though only aerobic culture was obtained often but not routinely at the time of primary surgery. Subsequent cultures were drawn from the potential sources (infected wound or intra-abdominal collection) only if patients failed to respond to initial therapy.

RESULTS

Over a period of 4 years there were a total of 209 adult patients who underwent open appendicectomy for com-

Table 1 Preoperative status of the patients

Patient characteristics	Drainage cohort (*n* = 88)	Non-drainage cohort (*n* = 121)
Age[1] (yr)	29 (14-93)	26 (14-78)
Sex[2] (male: female)	1:1.2	1.3:1
Duration of symptoms[2] (d)	2.5 ± 1.3	2.1 ± 1.5
WBC count[2] (× 109/L)	16.8 ± 4.9	16.1 ± 5.3
Febrile %age (> 37.80 C)	68 (77%)	91 (75%)

[1]Expressed as median (years); [2]Expressed as an average with the standard deviation.

Table 2 Postoperative status of the patients *n* (%)

Post operative outcome	Drainage cohort (*n* = 88)	Non-drainage cohort (*n* = 121)
Hospital stay[1]	6.5 (4-8)	4.0 (3-8)
Antibiotic use (parenteral)[1]	5.0 (4-9)	3.5 (3-6)
Regular analgesic use[1]	5.0 (4-9)	3.5 (3-6)
Paralytic ileus[1] (passing of flatus)	2.5 (1-5)	2.0 (1-4)
Major wound infection	14.0 (15.9)	22.0 (18.18)
Residual intra-abdominal collection	7.0 (8)	13.0 (10.74)
Subacute intestinal obstruction	3.0 (3.4)	5.0 (4.13)
Faecal fistula	1.0 (1.1)	-
Incisional hernia	2.0 (2.2)	2.0 (1.6)
Mortality	1.0 (0.82)	

[1]Are expressed as median (d). $P > 0.05$ (insignificant).

plicated appendicitis. All the patients gave history of fever, vomiting and pain which had started initially in the umbilical area and later shifted to right iliac fossa. All the patients were febrile and had a pulse rate of more than 100/min. There was severe tenderness in the right iliac fossa with positive Mcburney's sign. All the patients had leukocytosis with neutroplilia. The patient demographics and disease parameters were not statistically different in drainage and non-drainage cohorts (Table 1). The post-operative outcome in two cohorts is shown in Table 2. Data was analyzed using SPSS version 10 using χ^2 test. A *P* value below 0.05 was considered statistically significant. The hospital stay in the two cohorts was significantly different, with a median of 6.5 and 4 d in the drainage and non-drainage cohorts respectively. The antibiotic use was longer in the drainage cohort as compared to the non-drainage cohort, *i.e.*, median of 5 d (range 4-29) *vs* 3.5 d (range 3-26) respectively. Similarly the regular analgesic use was also prolonged in the drainage cohort as compared to non-drainage cohort, *i.e.*, median of 5 d (range 2-17) *vs* 3.5 d (range 2-14). One 76-year-old obese female patient with a body mass index of 37.4, with diabetes and hypertension in the non-drainage cohort was operated with a delay of 4 d because of subclinical signs and symptoms. After appendicectomy patient continued to be in sepsis and underwent multiorgan dysfunction syndrome which ultimately resulted in death on 28th post-operative day. One 31-year-old male patient in the drainage cohort had a faecal fistula through the main wound after the removal of the drain on the 5th post operative day.

Table 3 Clinico-pathological profile of patients requiring second surgery *n* (%)

Indications	Duration[1] (*n* = 88)	Drainage cohort (*n* = 121)	Non-drainage cohort
Subacute intestinal obstruction	28-35 d	1 (1.1)	1 (0.82)
Incisional hernia	6-11 mo	2 (2.2)	2 (1.60)

[1]Period after the primary surgery.

Patient was managed conservatively and his fistula healed completely after 35 d. Residual intra-abdominal collection was noted in 7 (8%) patients and 13 (10.74%) patients in drainage and non-drainage cohorts respectively on USG and/or CECT abdomen.

Two patients in each cohort required radiological guided drainage and one patient in the non-drainage cohort drained spontaneously through the main wound. The patients who do not show clinical deterioration or whose intra-abdominal collections were not significant enough to be drained radiologically/surgically were managed conservatively. The clinico-pathological profile of the patients who require second surgery is shown in Table 3. One patient in each cohort failed to the conservative management and required multiple admissions for sub acute intestinal obstruction. Adhesinolysis was all that was required and patients were symptom free thereafter. Mesh hernioplasty was done in a patient with incisional hernia.

DISCUSSION

Hippocrates[11] ever since he first reported the use of an abdominal drain in empyema gallbladder, its usage has been extended to almost all surgical procedures. The very purpose of the drains, to reduce the potential source of infection, detect post-operative bleed and anastomotic leakage or to establish the tract for the drainage of the collected material even after its removal may not be always served. Likewise drainage following appendicectomy (one of the commonest gastrointestinal operation) is usually determined by whether the underlying appendicitis is simple/complicated and largely determined by the surgeons' belief.

In the absence of any universally accepted antibiotic regime for appendicitis, traditionally broad spectrum antibiotic coverage is routinely adopted[8-10]. However the choice of antibiotics in complicated appendicitis is largely influenced by the institutional protocols[12]. A commonly followed guideline[9] recommends triple antibiotics. However there has been a recent trend towards single or dual drug regimes in children[12,13], in order to reduce the cost and simplify dosing schedules. While these paediatric trials are not adequately powered[13-16], the randomised trials in adults have failed to show any difference in antibiotic regimes[17]. We have adopted a cost effective policy of two/three drug regimens (3th generation cephalosporin with or without salbactum plus metronidazole 7.5 mg/kg

q8H), which was instituted at the time of diagnosis of complicated appendicitis. It has been seen that post-operative abscesses occurred in patients who had organisms on culture that were sensitive to the treatment antibiotics[18,19]. Unlike Kokoska *et al*[19], Ong *et al*[18] found that culture of the postoperative abscess did correlate with the initial peritoneal culture, although this does not alter management. Contrary to the commonly held belief, recently, the natural history of immunological mechanisms of the peritoneum has been better understood and its natural defence mechanisms to clear the infection have been elucidated[20-23]. These studies highlight the importance of the peritoneal fluid, and its drainage can even prove counterproductive.

Two randomized controlled trials (RCT) investigated the value of prophylactic drainage after open appendicectomy for acute/simple appendicitis[4,24]. Although both arms (drainage, no-drainage) of the trials had a relatively large sample size (> 90 patients each group), the studies were performed without a power and sample size calculation and were therefore ranked as level 2b. One study reported a significantly higher wound infection rate in drained patients with acute/simple appendicitis[23], whereas the other study found similar wound and intra-abdominal infection rates in drained and non-drained patients[4].

In complicated appendicitis (gangrenous/perforated), the role of prophylactic drainage has been studied in five RCTs. Because of the same reasons mentioned above, the level of evidence was classified as 2b in each RCT. The results showed higher wound infection rates in drained patients (range 43%-85%) than in non-drained patients (29%-54%). The pattern of intra-abdominal infection was not uniform among the studies, as two studies reported slightly higher intra-abdominal infection rates in non drained patients[24,25], one study a higher rate in drained patients[4], and another a similar rate in both groups[6]. Interestingly, the development of fecal fistulas was only observed in drained patients with a rate ranging from 4.2% to 7.5%.

Petrowsky *et al*[7] performed meta-analysis including series of gangrenous or perforated appendicitis only. Four RTCs (all level 2b) were included in the meta-analysis with the end point wound infection, whereas data from 3 RTCs were available for the end points intra-abdominal infection and fecal fistula. The analysis calculated an odds ratio for wound infection of 1.75 (CI: 0.96-3.19). The odds ratio for fecal fistula of 12.4 (CI: 1.14-1.35) favours the no drainage group; whereas the odds ratio for the end point intra-abdominal infection of 1.43 (CI: 0.39-5.29) favours neither group.

We observed almost similar incidence of major wound infection in patients in the drainage (15.9%) and non-drainage (18.18%) cohorts which is not statistically significant ($P > 0.05$). Dandapat *et al*[5] also showed that peritoneal drainage does not prevent wound infection. The author believes that protection of the wound during the primary surgery is of utmost priority, and the effective antibiotics compliment to the aseptic precautions in reducing the incidence of wound infection. Ciftci *et al*[15] observed that the most crucial point to avoid the wound infection is the application of antibiotics with aerobic and anaerobic coverage. In our study all the wounds were closed primarily in both the cohorts. There is an apprehension that primary closure of surgical incision after appendicectomy for complicated appendicitis may result in increased incidence of surgical site infection[26,27]. These incisions are often managed with delayed closure. However Rucinski *et al*[28] did a meta-analytic study of 2532 patients with gangrenous and perforated appendicitis. They concluded that primary closure of the skin and subcutaneous tissue after appendicectomy for gangrenous or perforated appendicitis, combined with the use of antibiotics in the perioperative period, is not associated with an increased risk of incision infection when compared with delayed closure.

On the one hand there seems to be a tendency on the part of the treating physician to continue the parental antibiotics and analgesics longer in the drainage cohort than in the non-drainage cohort and thus delay the discharge of the former[29,30]. On the other hand there seems to be tendency on the part of the patient to continue to assume the sick role until the drains are removed. Furthermore the post-operative care of the patients with the drain as compared to those without drain is troublesome, requiring increased work and manpower for the hospital. We had one patient (1.1%) in the drainage cohort whose postoperative course was complicated by the fecal fistulae. The exact cause of the fistulae remained unsolved in our series. However, these drains themselves are also a potential source of infection; may induce anastomotic leakage and may cause damage by mechanical pressure and suction[31,32].

The incidence of paralytic ileus and intra-abdominal collection in the two cohorts is not statistically different in our series. Also the incidence and indications of the second operation is not significantly different in the two cohorts in our series.

In a conclusion, the routine placement of the drain after appendicectomy is not indicated regardless of the severity of the appendicitis. It not only increases the morbidity, but is also not a cost effective method. The surgeons need to shun away the deeply inculcated habits of riding on drains perhaps as a soup to their consciences. The criticism of the study is that it is not a randomised controlled prospective trial and thus cannot generate the level 1 evidence. The results cannot be translated completely into the laparoscopic era, where the profile of postoperative outcome would be certainly different. However the author maintains that these patients were diagnosed and operated as secondary peritonitis with sepsis where the role of laparoscopy is still not fully defined. But the power of the study is adequate enough to validate the end points of the study.

COMMENTS

Background

Although there is lot of evidence that discourages the use of prophylactic drains in different types of gastrointestinal surgeries, enough studies have not been

conducted that would favour or disfavour the use of drain after the complicated appendicitis.

Research frontiers

The principal aim of the study was to compare the postoperative outcome in secondary peritonitis with sepsis due to complicated appendicitis in two groups of patients, one with drainage and another without drainage, after appendicectomy in adults in the modern era of effective antibiotics.

Innovations and breakthroughs

Regardless of the severity of the appendicitis, the routine use of the drain after appendicectomy is not indicated. It not only increases the morbidity, but is also not a cost effective method.

Applications

In the modern era when wide range of antibiotics with a very broad spectrum of action are available, the patients with peritonitis secondary to appendicitis does not necessitate the use of prophylactic drain, rather it may at times may even prove counterproductive.

Peer review

The authors have conducted the present study to evaluate the effectiveness of drain in patients with complicated appendicitis. The results are interesting and may form the basis of further study.

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CASE REPORT

Hemophagocytic lymphohistiocytosis caused by primary Epstein-Barr virus in patient with Crohn's disease

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Abstract

We present a case of a 19-year-old man with a 6-year history of Crohn's disease (CD), previously treated with 6-mercaptopurine, who was admitted to our department for Epstein-Barr virus (EBV) infection and subsequently developed a hemophagocytic lymphohistiocytosis (HLH). HLH is a rare disease which causes phagocytosis of all bone marrow derived cells. It can be a primary form as a autosomic recessive disease, or a secondary form associated with a variety of infections; EBV is the most common, the one with poorer prognosis. The incidence of lymphoproliferative disorders was increased in patients with inflammatory bowel disease (IBD) treated with thiopurines. Specific EBV-related clinical and virological management should be considered when treating a patient with IBD with immunosuppressive therapy. Moreover EBV infection in immunosuppressed patient can occur with more aggressive forms such as encephalitis and diffuse large B cell lymphoma. Our case confirms what is described in the literature; patients with IBD, particularly patients with CD receiving thiopurine therapy, who present 5 d of fever and cervical lymphadenopathy or previous evidence of lymphopenia should be screened for HLH.

Key words: Crohn's disease; Hemophagocytic lymphohistiocytosis; Epstein-Barr virus infection; Immunosuppressive therapy; Thiopurines

Core tip: About the case we're presenting, a literature review showed how this rare disease is often lethal and how low is the percentage of patients who have successful treatment. We show our case history and our management which has permitted to discharge the patient with disease regression.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal disease which causes phagocytosis of all bone marrow derived cells. It can be a primary form as a autosomic recessive disease, or a secondary form associated with a variety of infections; Epstein-Barr virus (EBV) is the most common, the one with poorer prognosis. Patients with inflammatory bowel disease (IBD) are a greater risk of developing secondary HLH due to chronic systemic inflammation condition as well as exposure to immunosuppressive medications[1].

CASE REPORT

A 19-year-old man was moved to our Hospital from a local hospital in London, where he was admitted 10 d

Table 1 Current diagnostic criteria for hemophagocytic lymphohistiocytosis[7]

The diagnosis of HLH may be established by[1]
A molecular diagnosis consistent with HLH (for example, pathologic mutations of *PRF1*, *UNC13D* or *STX11* are identified) or
Fulfillment of five out of the eight criteria listed below:
Fever
Splenomegaly
Cytopenias (affecting at least two of three lineages in the peripheral blood):
Hemoglobin < 9 g/100 mL (in infants < 4 wk: hemoglobin < 10 g/100 mL)
Platelets < 100-103/mL
Neutrophils < 1-103/mL
Hypertriglyceridemia (fasting, 265 mg/100 mL) and/or hypofibrinogenemia (150 mg/100 mL)
Hemophagocytosis in BM, spleen or lymph nodes
Low or absent NK cell activity
Ferritin 500 ng/mL
Soluble CD25 (that is, soluble IL-2 receptor) > 2400 U/mL (or per local reference laboratory)

[1]In addition, in the case of familial HLH, no evidence of malignancy should be apparent. HLH: Hemophagocytic lymphohistiocytosis; NK cell: Natural killer cell; CD: Crohn's disease; IL-2: Interleukin-2; *PRF1: Pore Forming Protein* gene; *UNC13D*: *Unc-13 homolog D* gene; *STX11*: *Syntaxin 11* gene.

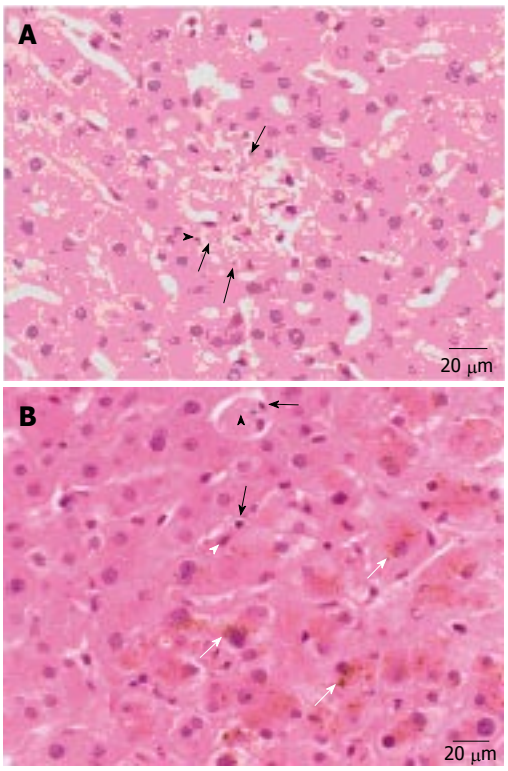

Figure 1 Active Epstein-Barr virus infection with hemophagocytosis not with lymphoma. A: Large histiocytes showing erythrophagocytosis (arrows) and leucophagocytosis (black arrowhead); B: A Kupffer cell (white arrowhead) and a large histiocyte (arrowhead) have phagocytosed a lymphocyte (arrow), moderate cholestasis is present (white arrow).

before with a history of fever, jaundice and weakness on a background of Crohn's disease (CD), which was diagnosed 5 years before and was previously treated with 6-mercaptopurine (6-MP). Diagnosis of EBV infection was performed by serologic exams. During his inpatient stay he developed a progressive pancytopenia (white blood cell 0.5 × 10^9/L, neutrophils 0.7 × 10^9/L, hemoglobin 66 g/L, platelets 236.000/mm^3), 6-MP therapy was therefore suspended and replaced with steroids. On clinical examination a continuous fever of up to 39 ℃ was reported. A bone-marrow biopsy was performed to clarify the cause of pancytopenia and it was positive for HLH; diagnosis was thus confirmed matching the diagnostic criteria for HLH (Table 1). Supportive treatment with granulocyte-colony stimulating factor and antibiotics was started. He had been transfused with packed red cells as necessary.

During his recover in our hospital he developed perirectal bleeding and a flexysigmoidoscopy showed multiple ulcers but a non specific point of bleeding. Due to this, a computed tomography (CT) angiogram was performed and at that time a bleeding point was identified at the splenic flexure. Hepatosplenomegaly was also noted. Consequently embolization of mesenteric artery was attempt but superior and inferior mesenteric arteries runs did not demonstrate any active bleeding. Moreover, a liver biopsy to exclude other liver diseases has been performed and it showed features consistent with active EBV infection with evidence of hemophagocytosis and no evidence of lymphoma (Figure 1). CT chest was performed and it showed diffuse adenopathy (mediastinal, supraclavicular, bilateral axillary). A right axillary core biopsy showed no evidence of lymphoma. HLH 2004 protocol with Etoposide and Rituximab was therefore started ten days after his admission in our Hospital.

The patient clinically improved from a HLH point of view whilst on the HLH 2004 protocol. However increasing cervical lymphadenopathy was noted and a subsequent biopsy demonstrated diffuse large B cell lymphoma (DLBCL) secondary to EBV. He was therefore started on Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone chemotherapy. The patient was noted to have two tonic clonic seizures on the ward, one of which resulted in aspiration pneumonia; transfer in intensive treatment unit for intubation and ventilation was required.

CT head was required to exclude any brain damage

The CT head reported multifocal low attenuation areas of the brain (Figure 2); radiologist report showed as these lesions could have represented central nervous system (CNS) infiltration by the HLH process. However the patient neurological condition was discussed with neurological team and a diagnosis of EBV encephalitis was made. This was treated with Rituximab, Methotrexate, Hydrocortisone and supportive care. His neurological condition improved and the most recent magnetic resonance imaging head showed significant disease improvement. Patient was discharge three months after his admission date.

DISCUSSION

HLH is a rare, often fatal disease in which macrophages

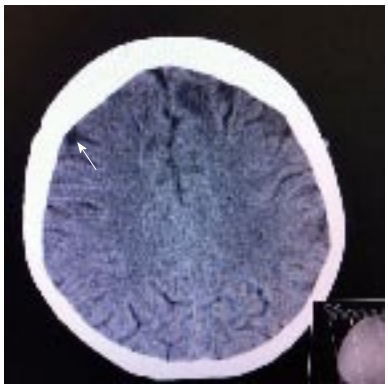

Figure 2 Focal lesion anteriorly in the left parietal lobe.

are inappropriately activated resulting in phagocytosis of all bone marrow derived cells[1].

There are two presentation forms: the first, primary, is an autosomic recessive disease; the second is a secondary HLH which can present at any age and has been documented in association with a variety of infections. While there are a wide variety of micro organisms related to the development of HLH, EBV is the most common, the one with poorer prognosis, and the one benefiting most from early treatment with etoposide[2].

The literature review shows how the incidence of lymphoproliferative disorders was increased in patients with IBD treated with thiopurines[3].

However, thiopurines may interfere with the host's response to a primary EBV infection[1].

EBV can induce HLH; case reports describing HLH and/or lymphoma in patients with CD have also been published[4].

Biank *et al*[1] described 11 additional cases in the literature of HLH in patient with IBD and only 3 of 11 cases reported were associated with an EBV infection. A new review of literature identified 3 further cases; therefore our case is potentially the seventh described in literature. Our patient met diagnostic criteria for HLH (Table 1).

Moreover he developed CNS symptoms with lesions on the CT head which could represent CNS infiltration by the disease process. CNS symptoms occurs in 35%-49% of patients with HLH[5].

In the case we have reported the patient started etoposide 20 d after his first admission. Etoposide may be life-saving, especially in patients with HLH due to EBV infection; mortality was 14 times higher for patients with EBV-associated HLH who did not receive etoposide within the first 4 wk[6].

Our patient also developed a DLBCL secondary to EBV; in literature we founded only one case involving hepatosplenic lymphoma, HLH and EBV infection in a patient with CD undergoing thiopurine and infliximab therapies[3].

Secondary HLH in patients with IBD is often due to EBV infection. Specific EBV-related clinical and virological management should be considered when treating a patient with IBD with immunosuppressive therapy[4].

Particularly, patients treated with thiopurine have greater risk to develop EBV infection, due to inadequate immune system response. Our case confirms what is described in the literature; patients with IBD, particularly patients with CD receiving thiopurine therapy, who present five days of fever and cervical lymphadenopathy or previous evidence of lymphopenia should be screened for HLH[1].

Moreover EBV infection in immunosuppressed patient can occur with more aggressive forms such as encephalitis and DLBCL.

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CASE REPORT

Malignant pheochromocytoma: Hepatectomy for liver metastases

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Abstract

Malignant pheochromocytoma accounts for approximately 10% of pheochromocytoma cases. The main site of distant metastasis is the liver. Hypertensive crisis due to catecholamine oversecretion is potentially fatal. We present a case of malignant pheochromocytoma with multiple liver metastases. A 60-year-old female with repeated hypertensive episodes was diagnosed with malignant pheochromocytoma. She underwent a left adrenalectomy and partial hepatectomy with resection of segment 6. Catecholamine levels remained high after surgery and she received repeated cycles of chemotherapy. Four months after surgery, multiple liver metastases were detected. In spite of ongoing chemotherapy, catecholamine levels eventually became uncontrollable. Serum and urine noradrenaline and vanillylmandelic acid levels increased, but adrenaline and dopamine levels stayed within the normal range. Preoperative liver imaging revealed multiple metastases in all segments except segment 4. Percutaneous transhepatic portal vein embolization (PTPE) of the right and lateral branches of the portal vein was performed. The functional liver volume of segment 4 increased after PTPE. Right hepatectomy, lateral segmentectomy and partial resection of segment 1 were performed 10 mo after the initial surgery. Intraoperative ultrasonography detected two small tumors in segment 4, which were treated with intraoperative microwave coagulation therapy. Noradrenaline levels normalized immediately after the second hepatectomy. As there was increased telomerase activity in the resected specimen, she received adjuvant chemotherapy. She remained in good health for 2 years. However, further metastases eventually occurred and she subsequently died due to a brain hemorrhage. Hepatectomy may be a therapeutic option for reduction of tumor mass in pheochromocytoma with liver metastases.

Key words: Malignant pheochromocytoma; Liver metastasis; Mass reduction; Percutaneous transhepatic portal vein embolization; Hepatectomy

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INTRODUCTION

Pheochromocytoma is an endocrine tumor. Malignant

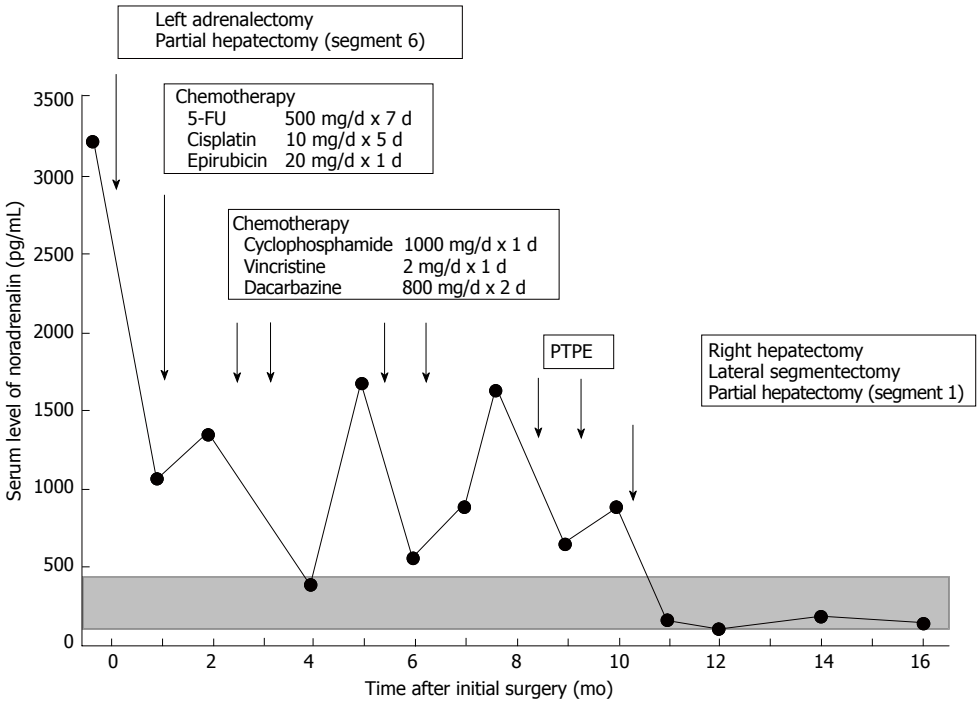

Figure 1 Serum catecholamine levels before and after treatments. Serum catecholamine levels are shown in relation to surgery, chemotherapy and preoperative percutaneous transhepatic portal vein embolization. The shaded area represents the normal range (100-450 pg/mL). PTPE: Percutaneous transhepatic portal.

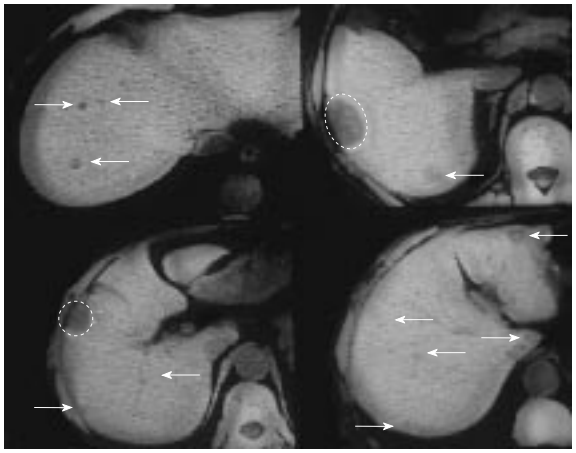

Figure 2 Angio-computed tomography findings. Preoperative image study revealed multiple liver metastases (white arrows) except for segment 4. She underwent the partial hepatectomy of segment 6 at initial surgery (white dotted circle).

pheochromocytoma is diagnosed if a distant metastasis is detected, which occurs in approximately 10% of cases. Hence, pheochromocytoma is commonly called a "10% disease". Hypertension due to the oversecretion of catecholamines may be fatal[1,2]. The main site of distant metastasis is the liver. We present a case of malignant pheochromocytoma treated by hepatectomy to reduce tumor mass. To our knowledge, this is the first case of aggressive hepatectomy for liver metastases requiring preoperative percutaneous transhepatic portal vein embolization (PTPE).

CASE REPORT

A 60-year-old female with repeated hypertensive episodes was diagnosed with malignant pheochromocytoma. She underwent a left adrenalectomy and partial hepatectomy with resection of segment 6. Since her catecholamine levels stayed high after surgery, she received repeated cycles of chemotherapy (5-FU, cisplatin and epirubicin, followed by cyclophosphamide, vincristine and dacarbazine) (Figure 1). Four months later, multiple liver metastases were detected (Figure 2). Even with ongoing cycles of chemotherapy (cyclophosphamide, vincristine and dacarbazine), catecholamine levels eventually became uncontrollable. She was admitted to our institution for surgical therapy. Angio-computed tomography and magnetic resonance imaging findings were consistent with liver metastases, with the tumors showing uptake on meta-iodobenzylguanidine scintigraphy. Serum and urine levels of noradrenaline and vanillylmandelic acid increased, but adrenaline and dopamine levels stayed within the normal range. As preoperative imaging studies revealed multiple metastases in all liver segments except segment 4, PTPE of the right and lateral branches of the portal vein was performed. The functional liver volume of segment 4 increased after PTPE (Figure 3). She underwent a right hepatectomy with lateral segmentectomy and partial resection of segment 1 (Spiegel lobe) at 10 mo after her initial surgery (Figure 4A). Intraoperative ultrasonography detected two small nodules in segment 4, which were treated with intraoperative microwave coagulation therapy (Figure 4B). Intraoperative examination did not detect tumor in the right adrenal gland. Histopathological examination of the surgical specimens was consistent with pheochromocytoma (Figure 5A). The patient's noradrenaline level normalized immediately after the second operation. Telomerase activity in the resected tumor, measured by a modified telomeric repeat amplification protocol, was clearly elevated (Figure 5B).

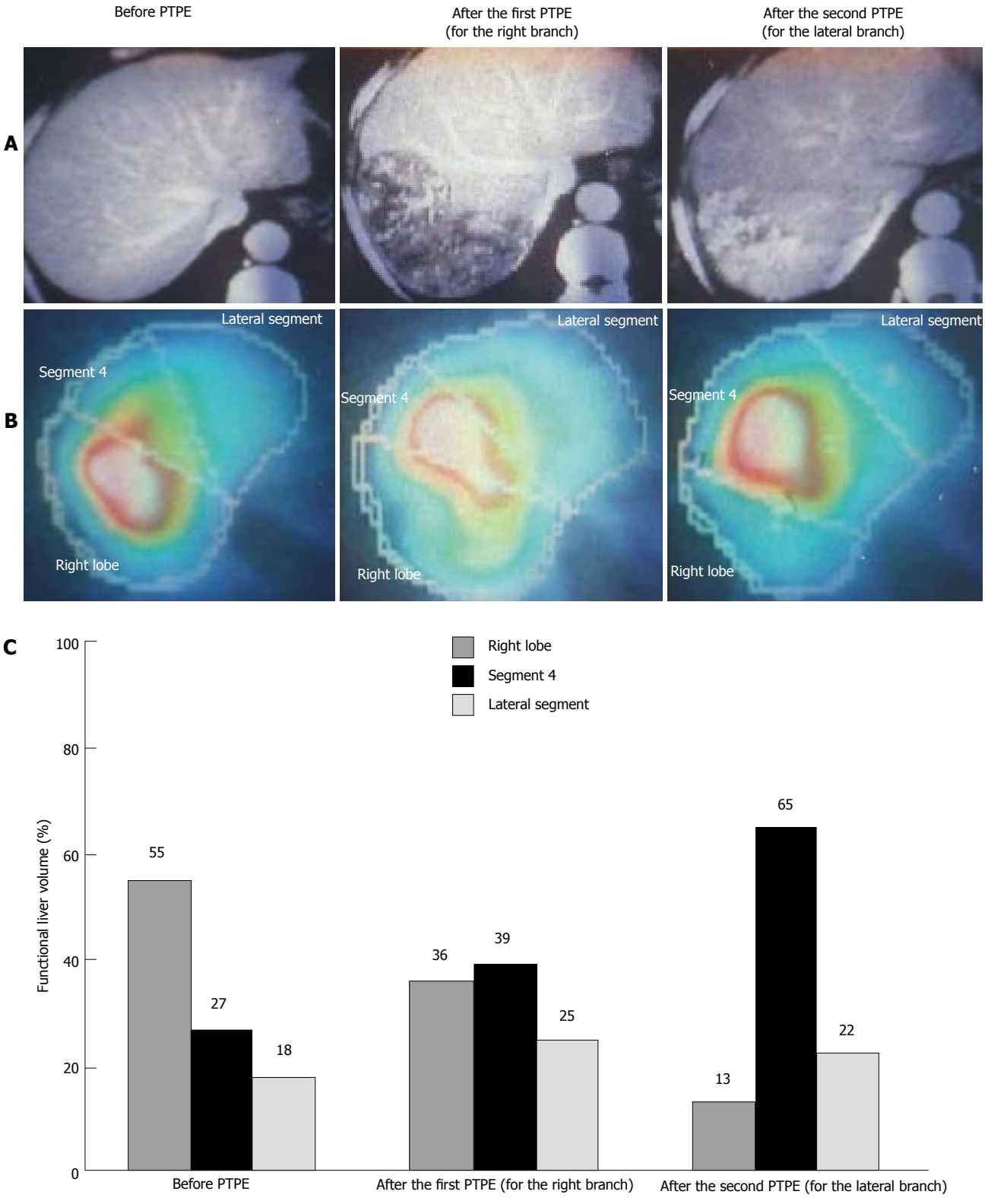

Figure 3 Changes in functional hepatic volume after percutaneous transhepatic portal vein embolization. The angio-computed tomography findings (A), technetium-99m diethylenetriamine pentaacetic acid galactosyl human serum albumin scintigraphy for asialoglycoprotein receptor (B) and the functional hepatic volume (C) were shown in each lobe/segment before and after percutaneous transhepatic portal vein embolization. Functional hepatic volume of each lobe/segment was calculated as a percentage of whole liver volume. PTPE: Percutaneous transhepatic portal.

She received adjuvant chemotherapy (5-FU, cisplatin and epirubicin) and was able to return to her normal physical and social activities. She remained in good health for 2 years after the second operation. However, she eventually developed further distant metastases. The metastatic tumors enlarged and catecholamine levels increased in

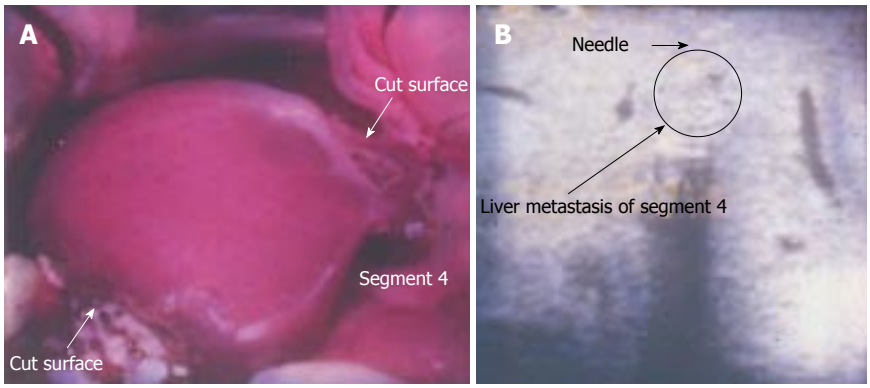

Figure 4 Intraoperative findings. A: She underwent right hepatectomy with lateral segmentectomy and partial resection of segment 1. B: Intraoperative ultrasonography detected two small nodules in segment 4, which were treated with intraoperative microwave coagulation therapy.

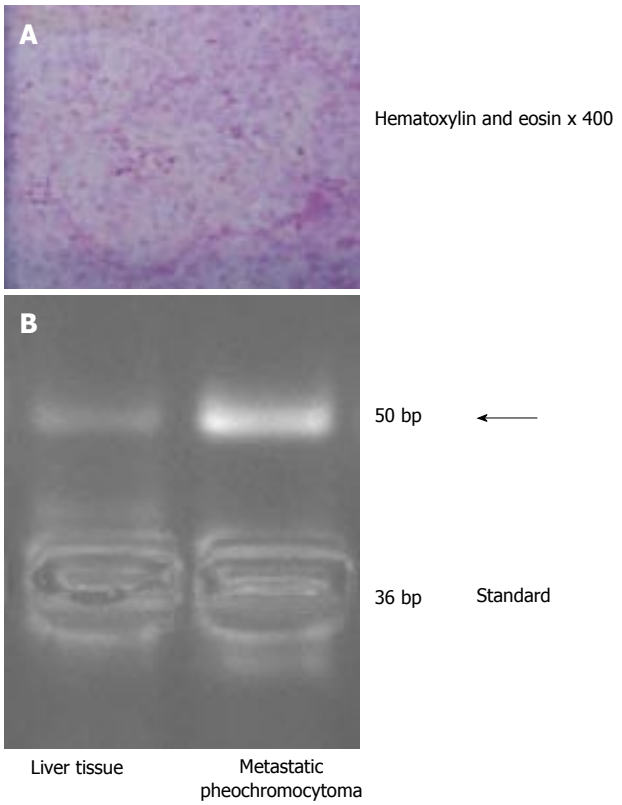

Figure 5 Histopathological finding and telomerase activity in the resected tumor. A: Histopathological examination of the surgical specimens was consistent with pheochromocytoma; B: Real-time polymerase chain reaction clearly revealed increased telomerase activity (arrow) in the resected tumor tissue compared with liver tissue.

spite of ongoing cycles of chemotherapy (cyclophosphamide, vincristine and dacarbazine). She finally died due to a brain hemorrhage triggered by a hypertensive crisis 3 years after the second operation.

DISCUSSION

Pheochromocytoma is an endocrine tumor arising from the chromaffin cells of the adrenal medulla[1]. Distant metastasis occurs in approximately 10% of cases, resulting in a diagnosis of malignant pheochromocytoma. It is important to consider the possibility of malignant disease even if imaging only detects a primary tumor, but it is difficult to predict malignant potential[3,4]. A previous report documented that the expression of telomerase activity clearly suggests malignant behavior of the component cells[3]. We speculate that analysis of telomerase activity in the biopsy or resected specimens may predict the disease course and may be useful for deciding therapeutic strategies, including surgical procedures and postoperative therapy. We understand that liver metastasis should be considered as the systemic disease. We speculate that more aggressive adjuvant chemotherapy will be required in cases with increased telomerase activity, even in the pheochromocytoma without distant metastasis.

Pheochromocytoma may lead to a fatal hypertensive crisis during anesthesia and other stresses[5]. Surgery to resect tumors can cause unexpected oversecretion of catecholamines and severely raise systolic blood pressure[2,5,6], and it is important to try to avoid such hypertension. In our institution, the drainage vein (*i.e.*, the adrenal vein) is ligated as soon as possible during surgery, followed by ligation of the adrenal artery. We suggest that this isolation technique is useful for the prevention of hypertension and in this case, systolic blood pressure stayed less than 200 mmHg.

Close follow-up is crucial for adequate induction of additional therapies after surgery[2,3]. In our institution, catecholamine levels are checked monthly and image studies are scheduled every three months. In this case, we followed this patient more closely, based on the expression of telomerase activity. Malignant potential based on the expression of telomerase activity may be informative for the follow-up schedule in each case.

The fatal manifestation of pheochromocytoma is hypertension due to the oversecretion of catecholamines[1,2]. Current therapies for pheochromocytoma and close long-term follow-up can result in good survival rates[6-8], even although patients with recurrence eventually die due to hypertensive crisis. The liver is the most common site of pheochromocytoma metastasis. Safe techniques for extended hepatectomy and preoperative PTPE are well established. Hepatectomy is a therapeutic option for reduction of tumor mass in patients with liver metastases, even if preoperative PTPE is required for postoperative safety, and may prolong survival or the symptom-free period.

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MINIREVIEWS

"Acute postoperative open abdominal wall": Nosological concept and treatment implications

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Abstract

The so-called "burst abdomen" has been described for many years and is a well-known clinical condition, whereas the concept of the "open abdomen" is relatively new. In clinical practice, both nosological entities are characterized by a complex spectrum of symptoms apparently disconnected, which in many cases poses a great challenge for surgical repair. In order to assess the management of these disorders in a more comprehensive and integral fashion, the concept of "acute postoperative open abdominal wall" (acute POAW) is presented, which in turn can be divided into "intentional" or planned acute POAW and "unintentional" or unplanned POAW. The understanding of the acute POAW as a single clinical process not only allows a better optimization of the therapeutic approach in the surgical repair of abdominal wall-related disorders, but also the stratification and collection of data in different patient subsets, favoring a better knowledge of the wide spectrum of conditions involved in the surgical reconstruction of the abdominal wall.

Key words: Burst abdomen; Open abdomen; Evisceration; Abdominal wall; Mesh; Negative pressure wound therapy; Incisional hernia; Enteroatmospheric fistula

Core tip: Burst abdomen and open abdomen are clinical conditions apparently disconnected. In order to assess the management of these disorders in a more comprehensive and integral fashion, the concept of "acute postoperative open abdominal wall" (acute POAW) is presented. The understanding of the acute POAW as a single clinical process allows stratification and collection of data in different patient subsets, favoring a better knowledge of conditions involved in the surgical reconstruction of the abdominal wall.

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INTRODUCTION

Excluding the defects of the abdominal wall secondary to trauma, tumors or necrotizing infections, the "acute postoperative open abdominal wall" (acute POAW) embracing evisceration and the open abdomen, appears to include a number of heterogeneous and unrelated processes[1]. Different descriptors found in the PubMed data-

base[2] may be applicable to the concept of acute POAW, such as "burst abdomen", "postoperative burst abdomen", "abdominal evisceration", "bowel evisceration", "abdominal wall dehiscence", "abdominal fascial dehiscence", "acute abdominal wound failure", "open abdomen", "abdominal wound dehiscence", "abdominal wall rupture" and "disruption of abdominal wall wounds". In this previous context, definition of what constitutes an acute POAW becomes a maze.

We here propose that acute POAW is a single nosological entity formed by patients with different interrelated categories of treatment approaches. Therefore, the purpose of this article is to present the conceptual frame for an analysis of the acute POAW and their subgroup categories of treatment. For clarity purposes, the information is divided into definition of acute POAW, description and treatment of intentional (planned) and unintentional (unplanned) acute POAW, followed by some concluding remarks.

DEFINITION OF ACUTE POAW

Acute POAW consists of the separation of the cutaneous, muscular and aponeurotic layers of the abdominal wall that occurs immediately or within the first hours or days after laparotomy. It may be considered a unique nosological clinical entity resulting from intentional or unintentional surgical-related actions and composed by different interrelated clinico-therapeutical scenarios.

INTENTIONAL (PLANNED) ACUTE POAW

Intentional acute POAW is the result of a deliberate therapeutic procedure, the so-called "open abdomen"[3,4]. This entity was described for the first time in the context of patients with intra-abdominal infection due to pancreatitis or peritonitis[5,6], but the indications for the use of the open abdomen technique have expanded to patients without intra-abdominal infection[7]. Nowadays the main indications are (1) damage control for life-threatening intra-abdominal bleeding; (2) management of severe intra-abdominal sepsis; and (3) prevention or treatment of intra-abdominal hypertension.

Once the therapeutic objective has been achieved, closure of the musculofascial layers should be performed[3,4,8-10]. However, closure of the open abdomen depends on the method used for temporary abdominal wall closure[3,8,9], the capacity of tissues for healing without tension, and whether or not enteroatmospheric fistulas are present.

The ideal temporary abdominal wall closure should protect the abdominal contents, prevent evisceration, allow removal of infected or toxic fluid from the peritoneal cavity, avoid damage to the musculofascial tissue, preserve the abdominal wall domain, facilitate reoperation for definitive closure and, very importantly, prevent the formation of enterocutaneous fistulas[11]. Different methods for temporary abdominal closure have been used, including among others: skin approximation with towel clips or running suture, application of a plastic silo (the Bogota bag), absorbable synthetic meshes [Safil®Mesh (BBraun, Rubí, Barcelona, Spain); BIO-A Tissue Reinforcement® mesh (Gore and Associates, Flagstaff, AZ)], non-absorbable synthetic meshes (polypropylene, e-PTFE), dynamic methods [ABRA® (Canica Design Inc, Almonte, Ontario, Canada); Wittmann Patch® (Starsurgical, Burlington, WI)], biological implants or negative pressure dressing systems [RENASYS AB® Abdominal Kit (Smith and Nephew, Hull, United Kingdom); ABThera® (KCI International, San Antonio, TX)][12]. The capacity of tissues for healing without tension depends on wound-related factors and the patient's general condition[11]. Independently of the technique used for temporary abdominal wall closure, there is a limited window of 2-3 wk to assess early *vs* delayed closure[8-11,13,14]. Early definitive closure (final closure of the abdominal defect within the window of 2-3 wk) is based on the resolution of interstitial edema and the evidence of non-adherence between the bowel loops and the abdominal wall. In contrast, when the abdominal content adheres to the undersurface of the anterior abdominal wall ("frozen abdomen" generally beyond 2-3 wk), delayed closure ("planned" incisional hernia repair) is the only realistic alternative in the operative management of the open abdomen. There are mixed situations between non-adherent loops and abdominal wall and the "frozen abdomen".

The development of enteroatmospheric fistulas is the most serious and challenging local complication[15], with an overall incidence still reported between 5% and 75%. Mortality of patients with fistula can be still high, up to 42% according to a review of different studies[15].

Treatment options

According to the aforementioned features, we have four different subgroup categories of treatment options: (1) Patients within the 2-3 wk time window with non-adherent bowel loops/abdominal wall and without intestinal fistula are candidates for definitive fascia-to-fascia closure using a continuous slowly absorbable monofilament suture and following the 4:1 suture length (SL): wound length (WL) ratio[16,17]. Also, autologous tissue reconstruction procedures (component separation technique, anterior rectus sheath flaps, oblique muscles) to improve closure or to further reduce tension have been reported[13,18-20]. There are no data in the literature on the usefulness of synthetic (absorbable or non-absorbable) meshes or biological implants to reinforce the repair, which mostly relies on the surgeon's experience and decision and the risk factors present in each individual patient; (2) Patients within the 2-3 wk time window with partially non-adherent bowel loops/abdominal wall and without enteroatmospheric fistula are candidates for a definitive early progressive abdominal wall closure, which will depend on the progressive improvement of the patient's general condition and the interstitial edema. In these cases, combinations of non-absorbable synthet-

ic meshes and negative pressure wound therapy (NPWT) are generally indicated. NPWT and non-absorbable synthetic mesh traction (pleating or serial excision of the mesh as the fascial edges are re-approximated) have been reported to be a practical wound closure system for the treatment of the open abdomen[21-25]. In addition, several types of extracellular matrix-derived biological implants have been used[26,27], although they are not recommended to bridge a fascial defect, and the long-term durability and functional outcome of biological implants is still unknown[28]. Other techniques for progressive closure of the abdominal wall, in combination or not with NPWT, include dynamic wound closure systems based on continuous dynamic tension to achieve re-approximation of the fascial edges of the abdominal wall[29,30] or the use of patches of synthetic material as a temporary, gradual means for abdominal closure[31]; (3) Patients beyond the 2-3 wk window without progress towards closure or improvement of general condition and interstitial edema ("frozen abdomen") and without bowel fistulization. In these cases, the treatment options include skin cover over the defect or allow wound granulation (absorbable synthetic mesh implant, NPWT) and thereafter cover with skin grafts and subsequent definitive delayed closure (after 6-12 mo) in the context of a "planned" incisional hernia repair[32-37]; and (4) Patients with enteroatmospheric fistula. In these cases, the constant leak of enteric contents on the open abdomen aggravates the inflammation and encourages the formation of new fistulas. The control is extremely difficult[3]. Management includes systemic treatment (nutritional support) and temporary local control to prevent spillage of the enteric contents and excoriation of the surrounding skin while planning for definitive closure of the fistula. Due to the large variability of enterocutaneous fistulas, treatment should be individualized[15,38-40].

UNINTENTIONAL (UNPLANNED) ACUTE POAW

Unintentional acute POAW or acute wound failure (also known as burst abdomen, evisceration, wound dehiscence, wound disruption and fascial dehiscence) is a postoperative complication after primary closure of an abdominal laparotomy incision[41]. The incidence of fascial dehiscence ranges between 0.5% and 3% of all laparotomies[42,43]. The morbidity is high, with prolonged hospital stay and an increase in direct costs[44-48]. The dehiscence-associated mortality rate (range 34%-44%) does not appear to be declining[49,50]. Moreover, unintentional acute POAW is associated with a high incidence of subsequent incisional hernia (40%-60%)[49,50]. Wound breakdown may be complete, affecting all layers of the abdominal wall including the skin[51,43] or incomplete when the skin remains intact. Drainage of serosanguinous fluid from the incision precedes dehiscence in up to 84% of cases[41].

Predisposing factors to the development of wound disruption include the technique of wound closure, type of incision, indication for operation (emergency operations, malignant tumors, infectious diseases), raised intra-abdominal pressure (coughing, vomiting, abdominal distension from ileus or vigorous postoperative ventilation), age > 65 years, chronic obstructive pulmonary disease (COPD), hemodynamic instability, malnutrition, diabetes, obesity, ascites, jaundice and steroid use[43]. However, wound infection due to intra-abdominal infection (20%-40% of cases)[52,53] or wound contamination (up to 52% of cases)[52] is the single most important risk factor for abdominal wound disruption[43].

Unintentional acute POAW may occur during the first 24 h after surgery[43], although it may range from 1 to more than 23 d[41,47], with an average of 7 d postoperatively[41]. The preferred treatment of unplanned acute POAW regarding definitive early or delayed closure[43-45,47,48,51-53] should be established according to the possibility of early reclosure without tension during the window period of 2-3 wk (as in planned acute POAW), the identification and proper treatment of intra-abdominal infection including intra-abdominal abscesses (appropriate antibiotic treatment and drainage preferably by the percutaneous route) and the presence or absence of enterocutaneous fistulas.

Treatment options

According to the aforementioned features, we have different subgroup categories of treatment which are also closely interrelated with the subgroup categories of intentional acute POAW. (1) Patients with unintentional acute POAW with complete wound dehiscence shared the same characteristics and should be managed as patients with intentional acute POAW; (2) Patients with incomplete unintentional acute POAW with non-adherent bowel loops/abdominal wall and without fistula are candidates for fascia-to-fascia closure using a continuous slowly absorbable monofilament suture and following the 4:1 SL: WL ratio[16,17,41-48,51-53]. Placement of retention sutures is controversial and negative side-effects of the retention closure technique have been reported[41,54-58]. Development of recurrence of unintentional acute POAW has been described with a 5% incidence and development in long term follow-up of incisional hernia in 40%-60% of the cases[49,50]. For this reason, reinforcement with a synthetic mesh may be useful, especially in the absence of intra-abdominal infection, although mesh closure has also been recommended in clean-contaminated/contaminated wounds[59-63]. Use of absorbable mesh is discouraged by the high incidence of incisional hernias in the long-term[64]. In contaminated/dirty fields, other methods such as NPWT or dynamic wound closure systems are more appropriate[65]. The usefulness and long-term results of biological implants is uncertain and are not recommended in cases of large bacterial inocula[28]; (3) Patients within the 2-3 wk time window with incomplete unintentional acute POAW and partially non-adherent bowel loops/abdominal wall and without enteroatmospheric fistula are candidates for a definitive early progressive abdominal wall closure in the same way as planned acute POAW; (4)

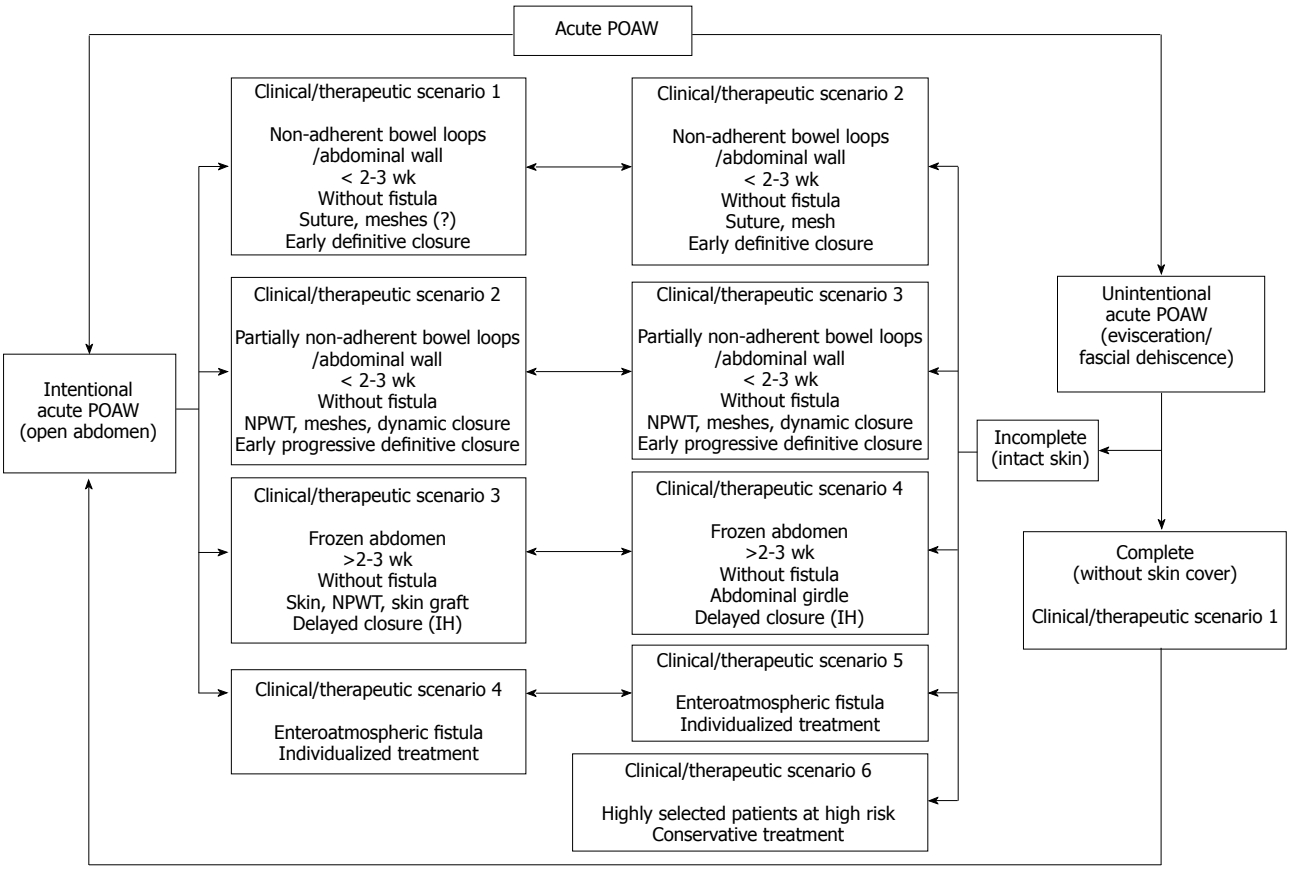

Figure 1 Treatment strategies of acute postoperative open abdominal wall (intentional and unintentional) for the different clinical/therapeutic scenarios. POAW: Postoperative open abdominal wall; NPWT: Negative pressure wound therapy; IH: Incisional hernia.

In patients with incomplete wound dehiscence and bowel loops adherent to the abdominal wall beyond 2-3 wk (frozen abdomen), abdominal girdles may be used before planning a delayed closure method (after 6-12 mo) in the context of an incisional hernia repair[49,50]; (5) Patients with incomplete wound failure and enterocutaneous fistula should be managed individually and the technique of closure of the wound depends on the surgeon's discretion (as in planned acute POAW); and (6) In highly selected patients at high risk for surgery, the use of some type of compression garment (such as a girdle) is recommended and attempts of closure of the musculofascial layers are contraindicated.

Treatment strategies and relationships of acute POAW (intentional and unintentional) for the different clinical/therapeutic scenarios are summarized in Figure 1 and Tables 1 and 2. However, the description of different options do not lead to the definitive concept of "how I do it" in each scenario because of a lack of a systematic approach (low level of evidence) in the management of this serious and heterogeneous surgical problem. In addition, the use of different techniques is still dependent on the individual surgeon's decision and experience.

CONCLUSION

We believe that in daily surgical practice, burst abdomen/evisceration/fascial dehiscence and the open abdomen are viewed as different and unrelated processes, possibly because the first is considered a complication of surgery[41,43] and the second as a procedure of surgery[1,3]. On the other hand, the abdominal wall is a complex and unique biological "organ"/mechanism contributing to the correct maintenance of the organism homeostatic balance through contention of the abdominal viscera in the right position, dynamics of respiratory activity[66], movement of the trunk[67], statics of the spine[68,69] and generation of intra-abdominal pressure for physiological functions such as cough, micturition and defecation. In this context, acute postoperative open abdominal wall as a result of unintended complications of surgery (*i.e.,* burst abdomen/evisceration/fascial dehiscence) or intended surgical options (*i.e.,* the open abdomen) originates from different and interrelated groups of patients with a common characteristic: impaired abdominal wall, which in turn may be grouped together under the term of acute POAW. Conceptual understanding of acute POAW as a nosological entity would allow stratification and collection of data in different patient subsets, favoring a better knowledge and optimization of the therapeutic approach of patients with this kind of abdominal wall-related disorders. In addition, it allows considering the abdominal wall system as an independent "organ" involved in other pathological and/or therapeutic conditions with a final

Table 1 Groups and therapeutic options in complete intentional and unintentional acute postoperative open abdominal wall

Clinical/therapeutic scenario	Intestinal fistula	Non-adherent bowel loops	Free inner abdominal wall	Window ⩽ 2-3 wk	Window > 2-3 wk	Therapeutic option
1	No	Yes	Yes	Yes Early definitive closure	-	Fascia to fascia closure. Continuous slowly absorbable monofilament suture, 4:1 rule
2	No	Partially	Partially	Yes Definitive early progressive closure	-	Vacuum-assisted wound closure and mesh traction or dynamic wound closure systems
3	No	No "Frozen abdomen"	No "Frozen abdomen"	-	Yes Delayed closure	Skin cover or after granulation skin graft "Planned" incisional hernia repair
4	Yes	-	-	-	-	Individualized

Table 2 Groups and therapeutic options in incomplete (intact skin) unintentional acute postoperative open abdominal wall

Clinical/therapeutic scenario	Intestinal fistula	Non-adherent bowel loops	Free inner abdominal wall	Window ⩽ 2-3 wk	Window > 2-3 wk	Therapeutic option
2	No	Yes	Yes	Yes Early definitive closure	-	Fascia to fascia closure, 4:1 No retention sutures Mesh depending contamination Biologics doubtful
3	No	Partially	Partially	Yes definitive early progressive closure	-	Vacuum-assisted wound closure and mesh traction Or dynamic wound closure systems
4	No	No "Frozen abdomen"	No "Frozen abdomen"		Yes Delayed closure	Abdominal girdles Planned incisional hernia repair
5	Yes	-	-	-	-	Individualized
6 High surgical risk	-	-	-	-	-	Abdominal girdle

common challenge: closure of the abdominal wall.

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BRIEF ARTICLE

Timing of chemotherapy and survival in patients with resectable gastric adenocarcinoma

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Abstract

AIM: To evaluate the timing of chemotherapy in gastric cancer by comparing survival outcomes in treatment groups.

METHODS: Patients with surgically resected gastric adenocarcinoma from 1988 to 2006 were identified from the Los Angeles County Cancer Surveillance Program. To evaluate the population most likely to receive and/or benefit from adjunct chemotherapy, inclusion criteria consisted of Stage Ⅱ or Ⅲ gastric cancer patients > 18 years of age who underwent curative-intent surgical resection. Patients were categorized into three groups according to the receipt of chemotherapy: (1) no chemotherapy; (2) preoperative chemotherapy; or (3) postoperative chemotherapy. Clinical and pathologic characteristics were compared across the different treatment arms.

RESULTS: Of 1518 patients with surgically resected gastric cancer, 327 (21.5%) received perioperative chemotherapy. The majority of these 327 patients were male (68%) with a mean age of 61.5 years; and they were significantly younger than non-chemotherapy patients (mean age, 70.7; $P < 0.001$). Most patients had tumors frequently located in the distal stomach (34.5%). Preoperative chemotherapy was administered to 11.3% of patients ($n = 37$) and postoperative therapy to 88.7% of patients ($n = 290$). An overall survival benefit according to timing of chemotherapy was not observed on univariate or multivariate analysis. Similar results were observed with stage-specific survival analyses (5-year overall survival: Stage Ⅱ, 25% *vs* 30%, respectively; Stage Ⅲ, 14% *vs* 11%, respectively). Therefore, our results do not identify a survival advantage for specific timing of chemotherapy in locally advanced gastric cancer.

CONCLUSION: This study supports the implementation of a randomized trial comparing the timing of perioperative therapy in patients with locally advanced gastric cancer.

Key words: Chemotherapy; Gastric cancer; Adjunct therapy; Postoperative therapy; Preoperative therapy; Timing

Core tip: Curative intent surgical resection offers the

best survival potential in conjunction with chemotherapy for patients with gastric cancer. Few studies have evaluated the optimal timing of chemotherapy. This study shows that in the setting of resectable gastric cancer, there is no survival advantage based on the timing of chemotherapy.

Arrington AK, Nelson R, Patel SS, Luu C, Ko M, Garcia-Aguilar J, Kim J. Timing of chemotherapy and survival in patients with resectable gastric adenocarcinoma. *World J Gastrointest Surg* 2013; 5(12): 321-328 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i12/321.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i12.321

INTRODUCTION

Despite an overall decrease in the incidence and mortality in gastric cancer patients in the United States, nearly 22000 patients will be diagnosed with gastric cancer in the United States each year[1]. More alarmingly, gastric cancer remains the 2nd leading cause of cancer-related deaths worldwide accounting for an estimated 436930 deaths in 2013[2,3]. In Western societies, where screening is not routine (compared to Asian countries[4,5]), the majority of patients present with regional or distant disease[6,7], and the 5-year overall survival is 30%-40%[8-10]. In these cases, the only hope for long term survival remains surgical resection with curative intent[11]. Despite aggressive surgical measures, rates of disease recurrence remain high following surgery[12,13]. In fact, approximately 50% to 90% of patients die as a result of disease relapse[14]. As a result, much attention has been placed on the identification of optimal adjunct therapies for gastric cancer.

Adjunct therapies for gastric cancer may be administered in the pre-operative (*i.e.*, neoadjuvant) or post-operative (*i.e.*, adjuvant) settings. Multiple trials have assessed these treatment strategies; and potential benefits have been drawn from both options[14-19]. In a landmark study, the investigators of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial reported an overall survival benefit with a regimen that incorporated neoadjuvant and adjuvant (*i.e.*, perioperative) timing of chemotherapy consisting of epirubicin, cisplatin, and fluorouracil (ECF) when compared to surgery alone[18]. From the Intergroup 0116 trial, investigators reported a 9 mo improvement in survival (27 mo *vs* 36 mo) when adjuvant chemoradiation was administered compared to surgery alone[17]. More recently, the CLASSIC trial investigators reported an overall survival benefit from adjuvant chemotherapy (capecitabine and oxaliplatin) compared to surgery alone[20]. However, there has been no trial that has directly compared neoadjuvant versus adjuvant chemotherapy administration. Using a large, population-based cohort, the objective of this study was to assess whether the timing of chemotherapy affects the survival of patients following surgical resection for gastric cancer.

MATERIALS AND METHODS

Los Angeles County Cancer Surveillance Program

The Los Angeles County (LAC) Cancer Surveillance Program (CSP) is the cancer registry that collects information for all cancer diagnoses in LAC since 1972. As part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program, CSP routinely collects data on patient demographics, primary tumor site, tumor morphology, disease stage at diagnosis, treatment received, and follow-up. CSP monitors the quality of data by performing annual reviews and training of staff. Approval to conduct this study was obtained from the Institutional Review Boards of the City of Hope and the State of California.

CSP tumor coding and study criteria

Using the CSP registry, we identified patients diagnosed with gastric adenocarcinoma from 1988 to 2006. Inclusion criteria consisted of Stage Ⅱ or Ⅲ gastric cancer patients above 18 years of age who underwent curative-intent surgical resection. As Stage Ⅰ disease is more likely to be treated by surgery alone and patients with Stage Ⅳ disease are more likely not to undergo surgery given metastatic/unresectable disease, these patients were excluded from the current study. Therefore, this study was designed to evaluate the population most likely to receive and/or benefit from adjunct chemotherapy (Stage Ⅱ or Ⅲ).

Specifically, we included only gastric cancer patients with International Classification of Diseases for Oncology histology codes for adenocarcinoma: 8140-8145, 8210-8211, 8480-8481, and 8490. In CSP, the location of tumor was categorized as proximal, distal, middle, or whole stomach. For each patient, stage was categorized according to the American Joint Commission on Cancer (AJCC) 7th Edition classification system. Furthermore, size and depth of tumor invasion were categorized by AJCC T-stage as: T1A, T1B, T2, T3, or T4. The presence or absence of nodal involvement was designated by AJCC N-stage as: N0, N1, N2, or N3. Our survival analysis included only patients with AJCC Stage Ⅱ and Ⅲ gastric cancer. Finally, we obtained data regarding the timing of chemotherapy administration (none, preoperative, or postoperative). As the CSP database only codes the date of the first chemotherapy treatment, patients who did receive preoperative (neoadjuvant) chemotherapy may or may not have received subsequent postoperative chemotherapy. Therefore, we could not distinguish between neoadjuvant and perioperative chemotherapy in this database. Thus, this study compares neoadjuvant chemotherapy, adjuvant chemotherapy, and no chemotherapy.

Statistical analysis

Patients were categorized into three groups according to the receipt of chemotherapy: (1) no chemotherapy; (2) neoadjuvant chemotherapy (± postoperative chemother-

Table 1 Comparison of the characteristics of the surgical groups *n* (%)

Characteristic		No chemo *n* = 1191	Received chemotherapy *n* = 327	*P* value
Age, yr	Mean ± SD	71 ± 12	61 ± 14	< 0.0001
Sex	Men	741 (62)	221 (68)	0.0743
	Women	450 (38)	106 (32)	
Race/ ethnicity	Non-hispanic white	438 (37)	118 (36)	0.9833
	Black	112 (9)	33 (10)	
	Hispanic white	322 (27)	88 (27)	
	Asian/pacific islanders	319 (27)	88 (27)	
Tumor location	Proximal	296 (25)	98 (30)	0.0290
	Distal	423 (36)	100 (31)	
	Whole	167 (14)	59 (18)	
	Middle	305 (26)	70 (21)	
Grade	Well differentiated	26 (2)	1 (0)	0.0178
	Moderately differentiated	312 (26)	70 (21)	
	Poorly differentiated	792 (66)	234 (72)	
	Undifferentiated	40 (3)	18 (6)	
	Unknown	21 (2)	4 (1)	
Tumor size	≤ 5 cm	462 (39)	117 (36)	0.6048
	>5 cm	507 (43)	145 (44)	
	Unknown	222 (19)	65 (20)	
T stage[1]	T2	108 (9)	24 (7)	0.1556
	T3	620 (52)	163 (50)	
	T4a	319 (27)	96 (29)	
	T4b	144 (12)	44 (13)	
N stage[1]	N0	334 (28)	38 (12)	< 0.0001
	N1	786 (66)	261 (80)	
	N2	31 (3)	15 (5)	
	N3	40 (3)	13 (4)	
Node status	N-	334 (28)	38 (12)	< 0.0001
	N+	857 (72)	289 (88)	
AJCC7 group	Ⅱ	767 (64)	187 (57)	0.0168
	Ⅲ	424 (36)	140 (43)	

[1]*P* values shown are based on the Jonckheere-Terpstra test for ordinal data. AJCC: American joint commission on cancer.

apy); or (3) adjuvant chemotherapy.

Clinical and pathologic characteristics were compared across the different treatment arms by χ^2 analyses for categorical variables and student's *t* test for continuous variables. Cox-proportional hazards modeling was used to evaluate the role of chemotherapy and other variables on overall survival as represented by hazard ratios (HR) with 95%CI. Variables included in the univariate analyses were age, sex, race/ethnicity, tumor location, AJCC stage, T-stage, N-stage, tumor grade, tumor size, lymph node number, and timing of chemotherapy regimen (neoadjuvant ± adjuvant *vs* adjuvant alone). Variables included in the multivariate analyses were age, AJCC stage, and timing of chemotherapy regimen (preoperative *vs* postoperative). Because tumor size, T stage and lymph node status are multi-collinear with AJCC stage, the multivariate model included AJCC stage alone to represent the staging variable.

Survival was defined as survival throughout the study period (1988-2006). Mortality was defined through the database used as all-cause mortality since date of diagnosis of gastric cancer. Overall survival (OS) for the treatment arms was calculated by the Kaplan-Meier method, and differences in survival were compared by the log-rank test. Proportional hazard assumptions for the Cox models were tested by calculating scaled Schoenfeld residuals with results indicating model fit. Two-sided *P* values < 0.05 were considered to be statistically significant. All statistical analyses were completed using SAS software, (SAS institute Inc. Cary, NC).

RESULTS

Patient and tumor demographics

Of 1518 patients with AJCC Stage Ⅱ or Ⅲ surgically resected gastric cancer between 1988 and 2006, 22% of patients (*n* = 327) received chemotherapy as part of their cancer treatment. The demographics of the study cohort are presented in Table 1. Most tumors were observed in the proximal (26%) or distal stomach (35%) and were poorly differentiated (68%) by histology. The majority (76%) of the study cohort had lymph node positive disease; and most patients had Stage Ⅱ disease (63%) rather than Stage Ⅲ disease (37%). Patients who did not receive chemotherapy were more likely to have lymph node negative disease than those who did receive chemotherapy (28% *vs* 12%, *P* < 0.001).

Comparison of patients by treatment group

As shown in Table 1, patients who did not receive chemotherapy were older than those who did (71 *vs* 61, respectively, *P* < 0.001). Within the chemotherapy groups (Table 2), more patients received adjuvant chemotherapy (*n* = 290, 89%) than neoadjuvant chemotherapy (*n* = 37, 11%, *P* < 0.001). The mean ages of patients receiving chemotherapy were similar (65 and 61 years, neoadjuvant and adjuvant, respectively). The majority of patients were male in both chemotherapy groups. There was no difference in race/ethnicity, tumor location, tumor grade, T stage, N stage, node status or AJCC stage group.

Survival by treatment group and univariate and multivariate analysis

Patients who received chemotherapy were compared according to the timing of administration of chemotherapy (neoadjuvant *vs* adjuvant). By Kaplan-Meier method, a difference in overall survival was not observed between the neoadjuvant *vs* adjuvant chemotherapy groups (Figure 1A). This was consistent when the groups were evaluated by stage of disease as well (Figure 1B and C). Next, univariate and multivariate analyses were performed to identify factors associated with improved survival (Table 3). In univariate analysis, younger age, lower T stage, node negative status and Stage Ⅱ disease were associated with improved survival. On multivariate analysis, older age and Stage Ⅲ disease were independently associated with shorter survival. All other factors fell out of multivariate analysis and were not significant. When grouped by stage, age continued to be an independent predictor of survival in both the Stage Ⅱ and Ⅲ gastric cancer patients (data

Table 2 Comparison of characteristics by chemotherapy groups *n* (%)

Characteristic		Neoadjuvant *n* = 37	Adjuvant *n* = 290	*P* value
Age, yr	Mean (± SD)	65 (± 10)	61 (± 14)	0.0583
Sex	Men	23 (62)	198 (68)	0.4543
	Women	14 (38)	92 (32)	
Race/ ethnicity	Non-hispanic white	18 (49)	100 (34)	0.2885
	Black	3 (8)	30 (10)	
	Hispanic white	6 (16)	82 (28)	
	Asian/pacific islanders	10 (27)	78 (27)	
Tumor location	Proximal	12 (32)	86 (30)	0.9189
	Distal	10 (27)	90 (31)	
	Whole	6 (16)	53 (18)	
	Middle	9 (24)	61 (21)	
Grade	Well differentiated	0 (0)	1 (0)	0.9087
	Moderately differentiated	7 (19)	63 (22)	
	Poorly differentiated	27 (73)	207 (71)	
	Undifferentiated	2 (5)	16 (6)	
	Unknown	1 (3)	3 (1)	
Tumor size	≤ 5 cm	10 (27)	107 (37)	0.2297
	> 5 cm	16 (43)	129 (44)	
	Unknown	11 (30)	54 (19)	
T stage[1]	T2	0 (0)	24 (8)	0.4283
	T3	19 (51)	144 (50)	
	T4a	15 (41)	81 (28)	
	T4b	3 (8)	41 (14)	
N stage[1]	N0	7 (19)	31 (11)	0.2684
	N1	27 (73)	234 (81)	
	N2	1 (3)	14 (5)	
	N3	2 (5)	11 (4)	
Node status	N-	7 (19)	31 (11)	0.1413
	N+	30 (81)	259 (89)	
AJCC7 group	Ⅱ	23 (62)	164 (57)	0.5160
	Ⅲ	14 (38)	126 (43)	

[1]*P* values shown are based on the Jonckheere-Terpstra test for ordinal data. AJCC: American joint commission on cancer.

not shown).

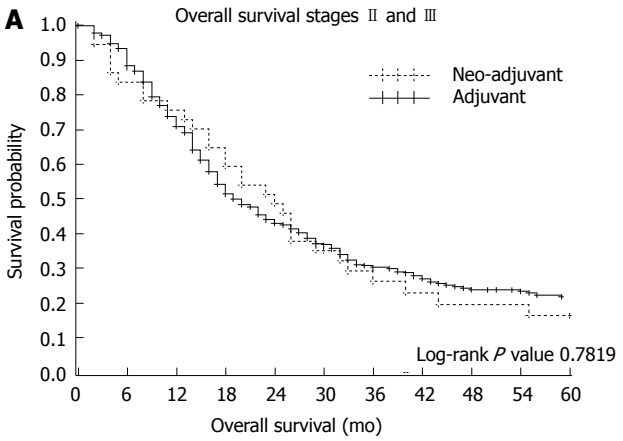
DISCUSSION

Despite advances in medical and surgical therapies, the prognosis of advanced gastric cancers remains poor, with a dismal 5-year relative survival rate of 28%[1]. With locoregional and distant recurrence rates approaching > 70%, an emphasis has been placed on identifying effective adjunct therapeutic regimens[18,17,20-23]. Systemic chemotherapy has been a logical choice, but the optimal timing of its administration remains unclear. In this study we compared the outcomes of Stage Ⅱ-Ⅲ surgically resected gastric cancer patients who received neoadjuvant (± postoperative chemotherapy) versus adjuvant chemotherapy and observed no difference in overall survival between the two treatment groups.

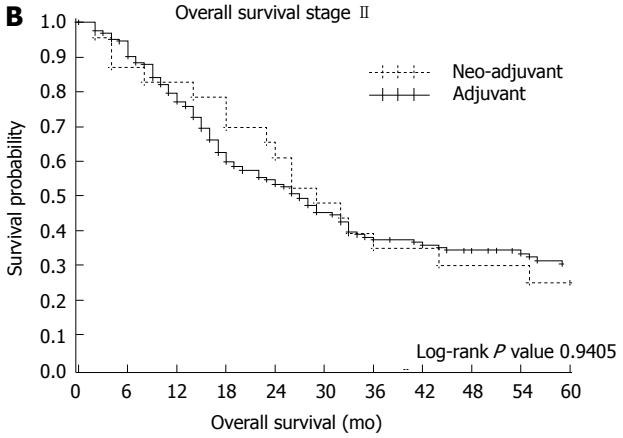
Several trials have examined the use of chemotherapy in the management of gastric cancer. One landmark study, the MAGIC trial by Cunningham *et al*[18], showed that perioperative chemotherapy with ECF decreased tumor size and stage while improving both progression-free and overall survival when compared to surgery alone. In this randomized controlled prospective study, 503 patients were randomly assigned to either perioperative ECF chemotherapy (three cycles preoperative and three cycles postoperative) or surgery alone. Of the perioperative group, only 41.6% completed all six cycles of chemotherapy due to disease progression, toxic effects, or complications[18]. The use of neoadjuvant chemotherapy decreased tumor size (3 cm *vs* 5 cm, $P < 0.001$) and stage of the pathologic surgical specimens. Therefore, by administering chemotherapy neoadjuvantly, the chance of curative resection by downstaging the tumor is increased. Other benefits of neoadjuvant chemotherapy include the elimination of micrometastasis, the improvement of tumor-related symptoms, and the determination of whether the tumor is chemotherapy-sensitive[18]. The MAGIC trial concluded perioperative chemotherapy should be considered in patients with resectable gastric cancers. Although we observed no difference between neoadjuvant and adjuvant timing of chemotherapy, nevertheless our findings suggest that patients with Stage Ⅱ or Stage Ⅲ gastric cancer indeed benefit from chemotherapy in conjunction with surgery. The 3-year OS was 16.6% in the MAGIC trial compared to 35% and 37% in the neoadjuvant and adjuvant arms, respectively, in our study. Given the inherent limitations of our database, we could not assess the effect of neoadjuvant chemotherapy on downstaging the gastric cancer, an outcome also not reported in the MAGIC trial.

The use of adjuvant chemotherapy has also been a treatment choice in the setting of chemotherapy. Adjuvant chemotherapy provides the benefit of removing disease burden upfront with a surgical resection, followed by chemotherapy. The potential downfall of adjuvant chemotherapy is the delay in beginning systemic treatment in the postoperative period for recovery from surgery. Further, downstaging tumor is not possible with adjuvant chemotherapy. Bang *et al*[20] evaluated the use of adjuvant chemotherapy after gastrectomy with D2 lymph node dissection in patients with Stage Ⅱ-ⅢB gastric cancer in the recent CLASSIC (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer) trial. In this phase Ⅲ randomized controlled, multi-institutional study, 1035 patients were randomized to surgery alone or surgery followed by chemotherapy (capecitabine plus oxaliplatin). The CLASSIC trial found a 34% reduction in the risk of death in the chemotherapy arm (HR = 0.66, 95%CI: 0.51-0.85; $P = 0.0015$) and a 5-year overall survival that was significantly increased in the chemotherapy arm (78% chemotherapy arm *vs* 69% surgery alone arm, $P < 0.0029$)[20,24]. However, the CLASSIC trial was reported in an eastern hemisphere patient population and has not been readily accepted in the United States[20,24]. Further, the CLASSIC trial had a 56% rate of grade 3 or 4 adverse effects (neutropenia, nausea, and vomiting) requiring dose modifications in a significant portion of patients, thereby limiting completion of adjuvant therapy[20].

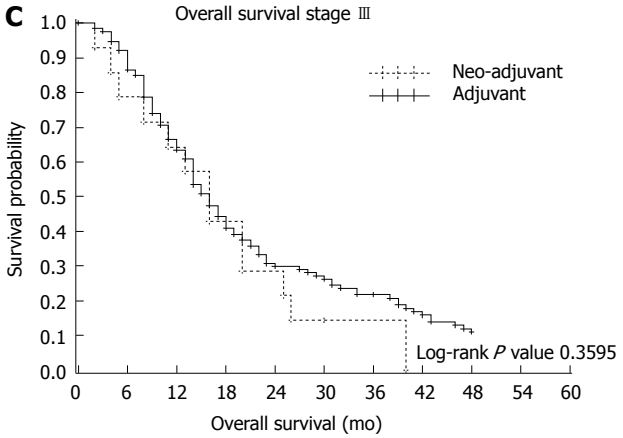
The MAGIC and CLASSIC trials, however, did not



	Neo-adjuvant	Adjuvant
No. of patients	37	290
Death	31 (84%)	219 (76%)
Censored	6 (16%)	71 (24%)
Median OS	24 mo	20 mo
1-yr OS	76%	71%
3-yr OS	26%	30%
5-yr OS	16%	22%



	Neo-adjuvant	Adjuvant
No. of patients	23	164
Death	18 (78%)	111 (68%)
Censored	5 (22%)	53 (32%)
Median OS	29 mo	27 mo
1-yr OS	83%	77%
3-yr OS	35%	37%
5-yr OS	25%	30%



	Neo-adjuvant	Adjuvant
No. of patients	14	126
Death	13 (93%)	108 (86%)
Censored	1 (7%)	18 (14%)
Median OS	16 mo	16 mo
1-yr OS	64%	63%
3-yr OS	14%	22%
5-yr OS	14%	11%

Figure 1 Comparison of Kaplan-Meier survival curves. A: For Stage Ⅱ and Ⅲ gastric cancer patients who underwent preoperative chemotherapy compared to those who had postoperative chemotherapy (MS 24 mo *vs* 20 mo, respectively; $P = 0.7819$); B: Stage Ⅱ gastric cancer patients who underwent neoadjuvant chemotherapy (with or without adjuvant therapy) compared to those who had adjuvant chemotherapy alone (MS 29 mo *vs* 27 mo, respectively; 5-yr operating system (OS) 25% *vs* 30%; $P = 0.9405$); C: Stage Ⅲ gastric cancer patients who underwent neoadjuvant chemotherapy (with or without adjuvant therapy) compared to those who had adjuvant chemotherapy alone (MS 16 mo *vs* 16 mo, respectively; 5-yr OS 14% *vs* 11%; $P = 0.3595$).

examine the role and timing of radiation for gastric cancer. Adjuvant chemoradiation has been shown to improve overall survival in patients with locally advanced gastric cancer. Macdonald *et al*[16,17,25-27] reported in the INT0116 Phase Ⅲ randomized multi-institutional trial of adjuvant chemoradiation compared to surgery alone that adjuvant chemoradiation improved overall survival and disease-free survival. Though Macdonald *et al*[16,17,25-27] evaluated adjuvant chemoradiation to surgery alone, there are no phase Ⅲ trials that directly compare neoadjuvant with adjuvant chemoradiation. With the database used for this study, only receipt of radiation could be determined. Therefore, we could not assess the timing of radiation in relation to surgery and to exclude bias of radiation in our analysis, patients who received radiation were excluded from this current study.

Our study is not without its limitations. Due to the retrospective nature of this study, there may be patient

Table 3 Univariate and multivariate analysis

Factor		*n* (%)	Univariate		Multivariate	
			HR (95%CI)	*P* value	HR (95%CI)	*P* value
Chemo status[1]	Neo-Adjuvant	37 (11)	-	-	-	-
	Adjuvant	290 (89)	0.95 (0.65-1.38)	0.7854	0.97 (0.67-1.43)	0.8961
Age[1], yr	Mean ± SD	61.5 ± 14	1.02 (1.01-1.03)	0.0008	1.02 (1.01-1.03)	0.0006
Sex	Men	221 (68)	-	-		
	Women	106 (32)	1.00 (0.77-1.31)	0.9859		
Race/ethnicity	Non-hispanic white	118 (36)	-	-		
	Black	33 (10)	1.48 (0.96-2.27)	0.0765		
	Hispanic white	88 (27)	1.16 (0.84-1.59)	0.3576		
	Asian/pacific islanders	88 (27)	1.00 (0.73-1.37)	1.0000		
Tumor location	Proximal	98 (30)	-	-		
	Distal	100 (31)	0.90 (0.65-1.24)	0.5173		
	Whole	59 (18)	0.99 (0.69-1.43)	0.9621		
	Middle	70 (21)	0.94 (0.67-1.33)	0.7395		
Grade	Well differentiated	1 (0)	-	-		
	Moderately differentiated	70 (21)	0.38 (0.05-2.73)	0.3338		
	Poorly differentiated	234 (72)	0.48 (0.07-3.43)	0.4642		
	Undifferentiated	18 (6)	0.57 (0.07-4.31)	0.5843		
	Unknown	4 (1)	0.41 (0.04-4.55)	0.4687		
Tumor size	≤ 5cm	117 (36)	-	-		
	> 5cm	145 (44)	1.33 (1.02-1.75)	0.0379		
	Unknown	65 (20)	0.98 (0.66-1.46)	0.9322		
T stage	T2	24 (7)	-	-		
	T3	163 (50)	2.18 (1.17-4.05)	0.0135		
	T4a	96 (29)	2.90 (1.54-5.45)	0.0009		
	T4b	44 (13)	4.86 (2.48-9.53)	< 0.0001		
N stage	N0	38 (12)	-	-		
	N1	261 (80)	1.47 (0.99-2.20)	0.0588		
	N2	15 (5)	1.98 (0.95-4.11)	0.0666		
	N3	13 (4)	1.90 (0.94-3.84)	0.0731		
Node status	N-	38 (12)	-	-		
	N+	289 (88)	1.51 (1.01-2.25)	0.0449		
AJCC7 group[1]	Ⅱ	187 (57)	-	-	-	-
	Ⅲ	140 (43)	1.79 (1.39-2.30)	< 0.0001	1.81 (1.41-2.33)	< 0.0001

[1]Included in multivariate model. AJCC: American joint commission on cancer; Chemo: Chemotherapy.

selection bias. Surgical techniques and chemotherapy options have drastically changed over time. Therefore, resectability criteria have changed in that time period as well. Given the 18-year time period in our study, selection bias could play a role in neoadjuvant chemotherapy determination, surgical resectability criteria used, and adjuvant chemotherapy recommendations. However, we cannot determine in this retrospective study whether these biases would skew the results in any direction. To account for this, we limited our study to patients with Stage Ⅱ and Stage Ⅲ disease given that, in general, they are likely to have resectable disease. Stage I disease was omitted as Stage I patients routinely did not receive chemotherapy. The staging information in the CSP database is based on pathologic staging at the time of surgery. Therefore, we acknowledge that downstaging and decreased tumor burden could have occurred in the neoadjuvant chemotherapy group. However, to limit the potential bias of downstaging disease stage in the cohort that received neoadjuvant chemotherapy, Stage I and Ⅳ disease was omitted from our analysis. In particular, Stage I disease should be treated with surgery first, potentially followed with adjuvant chemotherapy. As such, patients who were documented to have Stage I disease and received neoadjuvant chemotherapy were more likely to have had downstaging of disease.

Another limitation is that although the CSP database provides coding for the receipt of chemotherapy and the first date of chemotherapy, we do not have data on the exact chemotherapy regimen (the type of chemotherapy, number of cycles, dose reductions, *etc.*) or on the successful completion of chemotherapy. Therefore, patients who did have preoperative chemotherapy determined by the first date of surgery could have also received postoperative chemotherapy.

Although the neoadjuvant cohort is smaller than the adjuvant group, our data does not appear underpowered. Prior to the study, a power calculation was performed. Assuming 80% power with a 2-sided log-rank alpha of 0.05 and based on the parameter estimates for neoadjuvant and adjuvant survival in stage Ⅱ patients at 1 year (83% *vs* 77%, respectively), it would take a sample size of 699 patients in each group to find these differences statistically significant. This however, assumes that the 1 year survival curves (neoadjuvant *vs* adjuvant) are parallel and do not cross. Given that the survivals do cross (Figure 1), and due to the fact that the 3 year and 5 year results showing adjuvant survival is longer than neoadjuvant sur-

vival, a larger sample size would not change our overall conclusion.

As the management of gastric cancer continues to evolve, many questions remain unanswered. The extent of surgical resection, choice of adjunct therapy, and timing of therapy remain under debate. In this study, we compared survival following postoperative and preoperative chemotherapy, with similar outcomes observed between the preoperative and postoperative chemotherapy regimens. On the basis of these observations, we propose that a randomized, controlled trial be conducted to define the optimal timing of chemotherapy administration in the management of surgically resectable gastric cancer.

ACKNOWLEDGMENTS

This study was presented at the 7th Annual Academic Surgical Congress held February 14-16, 2012.

COMMENTS

Background

Gastric adenocarcinoma is cancer of the stomach. The outcome of patients diagnosed with gastric cancer is determined by stage of disease. Though surgery remains the best curative-intent treatment, recurrence rates are unfortunately high. Multiple studies have evaluated the benefit of surgery alone or combined with chemotherapy, but there are few studies evaluating the timing of chemotherapy around surgery.

Research frontiers

Multimodality therapies are now being investigated for the treatment of gastric cancer, such as chemoradiation and intraperitoneal chemotherapy; yet these therapies are not standard of care.

Innovations and breakthroughs

The mainstay of treatment is surgical resection either with perioperative chemotherapy or postoperative chemotherapy. Most chemotherapy regimens are either 5-fluorouracil (5-FU) based or cisplatin/oxaliplatin based. Asian studies have also shown benefit with adjuvant S-1, an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine based on a biochemical modulation of 5-FU.

Applications

This study indicates that chemotherapy and surgery provides the best survival benefits for patients with gastric cancer. There was no difference in survival when comparing neoadjuvant chemotherapy to adjuvant chemotherapy alone.

Terminology

Gastric adenocarcinoma: a cancer of the stomach; Neoadjuvant chemotherapy: chemotherapy given prior to surgical resection; Adjuvant chemotherapy: chemotherapy given after surgical resection.

Peer review

The authors investigated outcomes for patients with gastric cancer treated with surgery and chemotherapy using a population-based cancer registry (n = 327). They demonstrated that both chemotherapy and surgical resection are critically important treatment modalities, while reporting no difference in overall survival between patients given neoadjuvant chemotherapy or adjuvant chemotherapy.

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CASE REPORT

Uncommon cause of pneumoperitoneum

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Abstract

Free intraperitoneal air is thought to be pathognomonic for perforation of a hollow viscus. Here, we present a patient with pain in the upper left quadrant, a mild fever and leukocytosis. Free air was suggested under the left diaphragm but during the explorative laparotomy no signs of gastric or diverticular perforation were seen. Further exploration and revision of the computed tomography revealed a perforated splenic abscess. Splenic abscesses are a rare clinical entity. Presenting symptoms are often non-specific and include upper abdominal pain, recurrent or persistent fever, nausea and vomiting, splenomegaly, leukocytosis and left lower chest abnormalities. Predisposing conditions can be very divergent and include depressed immunosuppressed state, metastatic or contiguous infection, splenic infarction and trauma. Splenic abscess should therefore be considered in a patient with fever, left upper abdominal pain and leukocytosis. Moreover, our case shows that splenic abscess can present in an exceptional way without clear underlying aetiology and should even be considered in the presence of free abdominal air.

Key words: Spleen; Abscess; Pneumoperitoneum

Core tip: Free intraperitoneal air is thought to be pathognomonic for perforation of a hollow viscus. Here, we present a patient with pain in the upper left quadrant, a mild fever and leukocytosis. Free air was suggested under the left diaphragm but during the explorative laparotomy no signs of gastric or diverticular perforation were seen. Further exploration and revision of the computed tomography revealed a perforated splenic abscess. Splenic abscesses are a rare clinical entity. Our case shows that splenic abscess can present in an exceptional way without clear underlying aetiology and should even be considered in the presence of free abdominal air.

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INTRODUCTION

Splenic abscess is a rare condition with a reported frequency in autopsy series between 0.1% to 0.7%[1-3]. Presenting symptoms include upper abdominal pain, recurrent or persistent fever, nausea and vomiting, splenomegaly, leukocytosis and left lower chest abnormalities[4,5]. Diagnosis of a splenic abscess is confirmed on ultrasound or computed tomography (CT)-imaging of the abdomen. Splenectomy has been the gold standard treatment for splenic abscess, however more recent percutaneous drainage is also suggested to be safe and effective[1,6,7]. While gas formation in splenic abscess has been described, few have reported pneumoperitoneum as presenting symptom of a ruptured splenic abscess[8-11].

CASE REPORT

A 78-year-old man presented to our Emergency Room with acute abdominal pain located in the upper left quadrant. The pain had presented in the middle of the

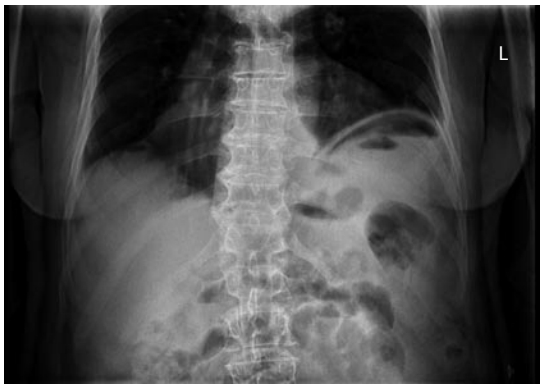

Figure 1 Pneumoperitoneum.

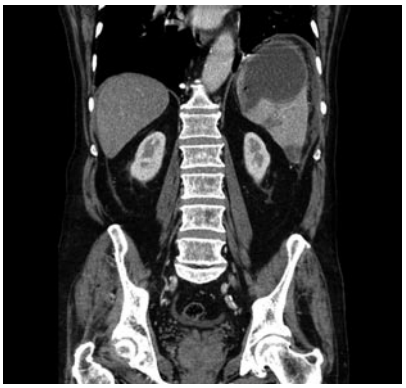

Figure 2 Splenic cyste.

night, waking the patient. No nausea nor vomiting had occurred, but he was experiencing an urge to move. His clinical record mentioned a mild mitralis valve insufficiency, atypical rheumatic complains and diverticulosis. He did not use immunosuppressive medication. Clinical examination reported a painful man with a mild fever and raised pulse. The abdomen was bloated, showed little peristaltic sounds, while percussion of the liver was normal and neither liver nor spleen were palpable. Laboratory findings showed leukocytosis and a raised CRP. On the standing X-ray of the thorax a strong suspicion of free air was suggested under the diaphragm, which was confirmed with an X-ray of the abdomen in left lateral position (Figure 1).

Additional CT showed free air in the upper abdomen with some abdominal fluid left paracolic and in the small pelvis, some left pleural effusion, thickening of the gastric wall and a cyst in the spleen (Figure 2). Therefore, a gastric perforation was suggested. There was no sign of diverticular infiltration or perforation.

After intravenous antibiotics were started on the ER, an explorative laparotomy was performed. No signs of gastric or diverticular perforation were seen. Re-evaluation of the CT in the operation room was performed and the suggestion of an abscess rather than a cyst in the spleen was introduced (Figure 2). Further exploration of the flexura lienalis was performed and pus was evacuated from the upper left quadrant. A ruptured splenic abscess was found and a splenectomy was performed. Cultures remained negative for any grow of bacteria. Pathology report of the spleen revealed an inflammation with abscess and necrosis without micro-organisms or signs of neoplasia. Post-splenectomy vaccinations were prescribed and the patient was discharged 2 wk after admission. Two months after surgery he was in a good clinical condition.

DISCUSSION

Diagnosis of splenic abscess is often not considered due to its rarity and the presence of predisposing conditions which obscure its clinical presentation[6]. Thereby, the aetiology of splenic abscesses is diverse. Three etiological causes of splenic abscesses have been proposed by Kuttner: trauma with secondary infection; per continuitatem; and haematogenous spread[12]. Development by continuitatem has been described in perforated gastric ulcer, perinephric abscess, septic abortion, appendicitis with perforation and in case of concomitant colon carcinoma[1,3,13,14]. Colon carcinoma are also important precursors in the small number of cases in which metastasis of the spleen were secondary infected[15]. Other haematological spread can be caused by retropharyngeal abscess, otitis media, tonsillectomy, infective endocarditis and phlebitis of the calf[3,5,16].

The most common organisms found on bacteriological examination are *Gram Negative Bacillus* (*Klebsiella Pneumoniae*, *Escherichia Coli*) and *Gram Positive Coccus* (*Staphylococcus Aureus*), although a great variety of pathogens have been described[4,17,18].

All studies on this subject stress the strong correlation between splenic abscess and predisposing factors. Direct trauma, infarction or ischemia of the spleen predispose to secondary infection. Especially immunosuppressive state seems to play a great role in the development and rising incidence of splenic abscesses[19]. Furthermore, intravenous drug abuse, human immunodeficiency virus, diabetes mellitus, tuberculosis and neoplasia seem to be contributing diseases[4,8,15,20].

Review of the literature shows only a few cases in which a splenic abscess presented with a pneumoperitoneum[8-11]. In some of these cases the aetiology is clear, but all needed an explorative laparotomy to clarify the diagnosis.

In our case, due to the free abdominal air we expected to find a gastric perforation. The splenic abscess was detected during the explorative laparotomy and only in retrospection the CT-images were interpreted accordingly. Postoperative evaluation revealed no aetiological cause of the splenic abscess. The patient did have diverticulosis, but on operative inspection no inflammation was present. Pathology report of the spleen revealed an inflammation with abscess and necrosis without micro-organisms or signs of neoplasia. Futhermore, blood cultures remained negative in our case. This appears to be the case in approximately 30% of patients with a splenic abscess[4,5]. In conclusion, splenic abscess should be considered in a patient with fever, left upper abdominal pain, and leukocytosis[7]. Moreover, our case shows that splenic abscess can

present in an exceptional way without clear underlying aetiology and should even be considered in the presence of free abdominal air.

COMMENTS

Case characteristics

The presenting symptoms include acute abdominal pain located in the upper left quadrant with and an urge to move.

Clinical diagnosis

The patient had a mild fever and raised pulse, a bloated abdomen which showed little peristaltic sounds.

Differential diagnosis

Based on these findings an extensive differential diagnosis of intra-abdominal pathology arose.

Laboratory diagnosis

Laboratory findings showed a leukocytosis and raised CRP. On the standing X-ray of the thorax free air was suggested and a strong suspicion of perforation of a hollow viscus arose.

Imaging diagnosis

Additional computed tomography showed free air in the upper abdomen with some abdominal fluid left paracolic and in the small pelvis, thickening of the gastric wall and a cyst in the spleen.

Pathological diagnosis

Review of the literature shows only a few cases in which a splenic abscess presented with a pneumoperitoneum. In some of these cases the aetiology is clear, but all needed an explorative laparotomy to clarify the diagnosis.

Treatment

After intravenous antibiotics were started, an explorative laparotomy was performed and a ruptured splenic abscess was treated by a splenectomy.

Related reports

While gas formation in splenic abscesses has been described, few have reported pneumoperitoneum as presenting symptom of a ruptured splenic abscess.

Experiences and lessons

Therefore, splenic abscess should be considered in a patient with fever, left upper abdominal pain and leukocytosis, even in the presence of free abdominal air.

Peer review

This is a very interesting case report.

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CASE REPORT

A gastrointestinal stromal tumor of the third portion of the duodenum treated by wedge resection: A case report

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Key words: Gastrointestinal stromal tumor; Duodenum; Wedge resection; Surgery

Core tip: Duodenal gastrointestinal stromal tumors (GISTs) are uncommon, with a relatively small subset of GISTs whose optimal surgical procedure has not been well defined. Because submucosal spread and local lymph node involvement is infrequent in GISTs, wide margins with routine lymph node dissection may not be required. Various techniques of limited resection for duodenal GISTs have been described, depending on the site and the size of the tumors. Herein, we present a case of GIST involving the third portion of the duodenum successfully treated by wedge resection with primary closure.

Abstract

A 65-year old woman was admitted to our hospital with abdominal pain. Computed tomography showed a tumor measuring about 3 cm in diameter with no metastatic lesion or signs of local infiltration. Gastroduodenal endoscopy revealed the presence of a submucosal tumor in the third portion of the duodenum and biopsy revealed tumor cells stained positive for c-kit. These findings were consistent with gastrointestinal stromal tumors (GISTs) and we performed a wedge resection of the duodenum, sparing the pancreas. The postoperative course was uneventful and she was discharged on day 6. Surgical margins were negative. Histology revealed a GIST with a diameter of 3.2 cm and < 5 mitoses/50 high power fields, indicating a low risk of malignancy. Therefore, adjuvant therapy with imatinib was not initiated. Wedge resection with primary closure is a surgical procedure that can be used to treat low malignant potential neoplasms of the duodenum and avoid extensive surgery, with significant morbidity and possible mortality, such as pancreatoduodenectomy.

Acar F, Sahin M, Ugras S, Calisir A. A gastrointestinal stromal tumor of the third portion of the duodenum treated by wedge resection: A case report. *World J Gastrointest Surg* 2013; 5(12): 332-336 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i12/332.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i12.332

INTRODUCTION

Gastrointestinal tumors are the most common mesenchymal tumors arising within the gastrointestinal tract[1] and the treatment of choice of these tumors is surgical resection[2,3]. The small intestine is the second most common site of gastrointestinal stromal tumor (GIST), of which approximately 20% are found in the duodenum[2]. The optimal surgical procedure for duodenal GIST, however, remains undefined[4] because, while surgical resection clearly confers survival advantage, there is little submucosal spread in GIST and lymphatic involvement is rare. The few reports in the literature addressing the surgical procedures for duodenal GIST include pancreatoduodenectomy, pancreas-sparing duodenectomy, segmental duodenectomy or local resection[4-6]. In this study, we

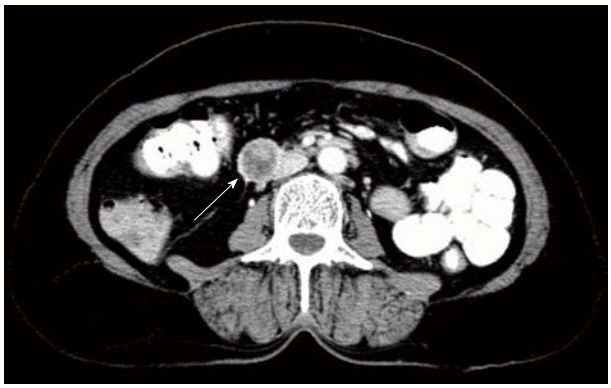

Figure 1 Computed tomography showed a well-demarcated enhancing tumor 4.0 cm in diameter in the third portion of the duodenum (white arrow).

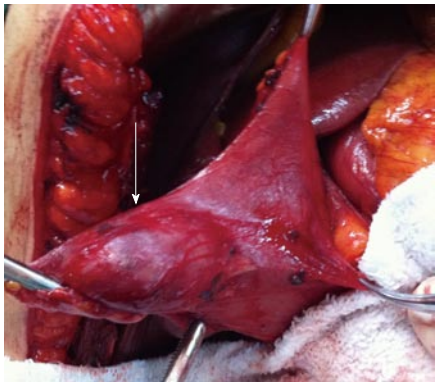

Figure 2 An endophytic gastrointestinal stromal tumor of the third portion of the duodenum (white arrow).

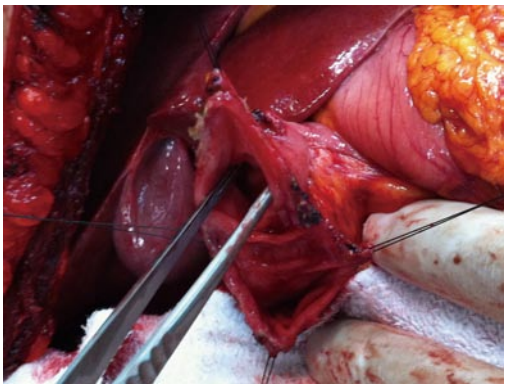

Figure 3 Local limited wedge resection was subsequently performed with clear margins. Surrounding bowel can be seen to be healthy, allowing for a primary anastomosis.

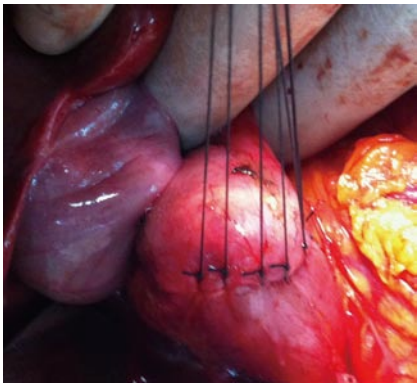

Figure 4 Wedge resection with primary closure.

report a case of GIST involving the third portion of the duodenum successfully treated by wedge resection. This surgical technique is ideal when GIST does not involve the ampulla and has not been previously described for the management of this malignancy.

CASE REPORT

A 65-year old woman presenting with abdominal pain was referred to our hospital. Her medical and family history was unremarkable. She had no history of previous abdominal surgery. On physical examination, mild tenderness was complained of in the right upper quadrant area. Abdominal computed tomography (CT) showed a well-demarcated and enhanced tumor in the third portion of the duodenum, measuring approximately 3.0 cm in diameter. The mass appeared to compress the uncinate portion of the pancreas (Figure 1). From these radiographic findings, we diagnosed a submucosal tumor of the duodenum. She underwent an esophagogastroduodenoscopy, which revealed a submucosal tumor at the second and third portion of the duodenum. A biopsy obtained was reported as GIST. There was no evidence of metastases to her liver or lung. At laparotomy, a 3.0 cm sized solid mass was identified arising from the pancreatic border of the third portion of the duodenum (Figure 2). No evidence of local invasion of the pancreas or of distant metastases was found and the duodenal wall was carefully dissected from the inferior border of the pancreas. Considering that the pancreas and major papilla were not involved, a partial resection was performed, with a 1 cm disease-free margin (Figures 3 and 4). Operative time was 125 minutes and estimated blood loss was 50 mL. Histological examination revealed that the tumor was composed of spindle cells with a mitotic count < 5 mitoses/50 high power fields (Figure 5A and B). Immunohistochemical study revealed positive staining for CD 117 (c-kit) and S-100 (Figure 5C-E). Based on the above findings, the tumor was finally diagnosed as a GIST with low-grade malignancy originating from the duodenum. A molecular genetic analysis for KIT protein mutation was not performed because of its unavailability at our institute. The patient was doing very well with no evidence of disease recurrence when she was last seen, 4 mo after her operation.

DISCUSSION

GISTs are believed to originate from the interstitial cells of Cajal, which are intestinal pacemaker cells or mesenchymal stem cells[7]. A typical feature of virtually all GISTs is a positivity at immunohistochemistry for

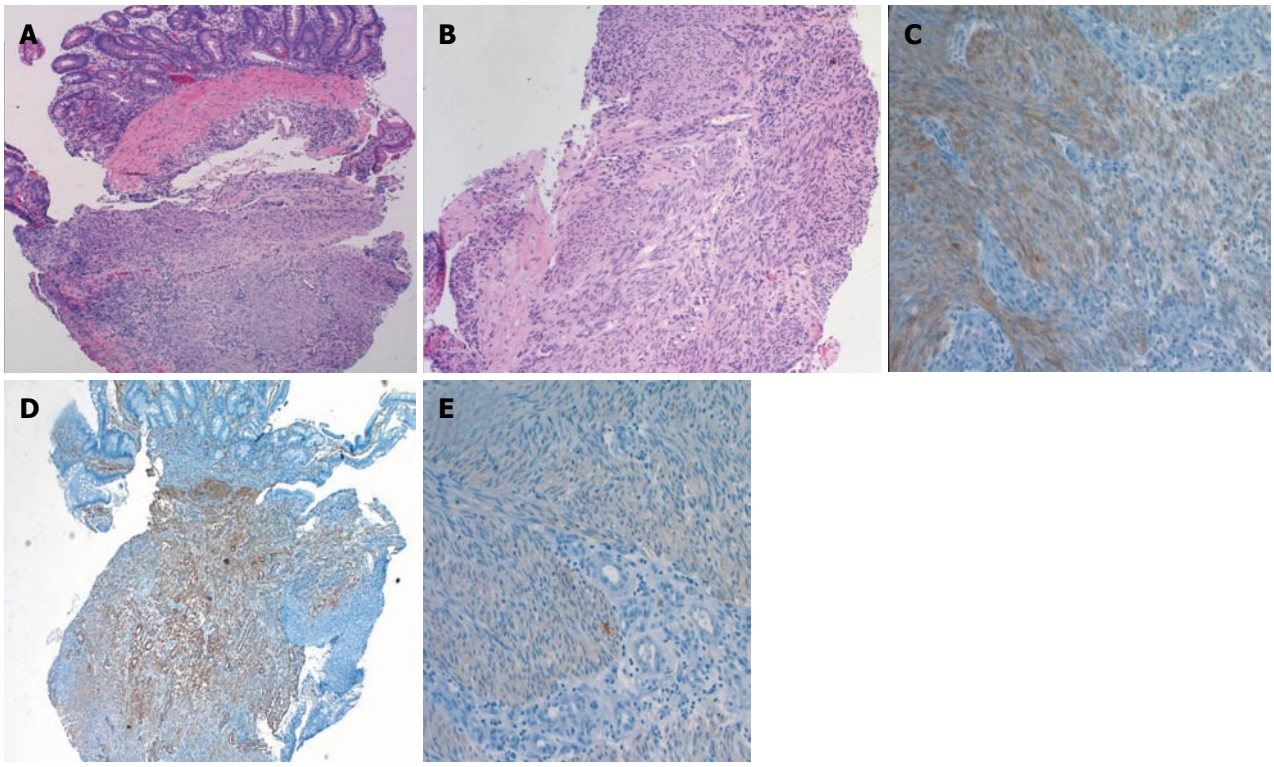

Figure 5 Histology. A: Submucosal tumor tissue is located (hematoxylin-eosin stain, original magnification, × 5); B: Spindle tumor tissue is composed of cells (hematoxylin-eosin stain, original magnification, × 10); C: Tumor tissue widely seen moderately strong staining of CD117 (CD117, original magnification, × 20); D: Tumor tissue widely seen SMA staining (SMA, original magnification, × 5); E: Tumor tissue, common, poor, S-100 staining is observed (S-100, original magnification, × 20).

the KIT protein (CD117), a transmembrane receptor linked to an intracytoplasmic tyrosine kinase[8]. Duodenal GISTs are mainly located in the second portion of the duodenum[9]. The tumors are frequently located in close relationship to the ampulla of Vater, this determining surgical treatment strategy. In the case presented here, the tumor was located 3 cm distal of the papilla. Most duodenal GISTs present with GI bleeding, usually associated with melena and occasionally with massive acute bleeding[9]. Other symptoms like abdominal pain, early satiety, bloating or obstructive jaundice due to involvement of the papilla of Vater were present in our patient. Diagnosis can be made with upper gastrointestinal endoscopy[10]. The tumor is usually exophytic and appears as a submucosal swelling. Sometimes it presents only as an endophytic tumor, as in our case. The biopsy should be deep but may not always be diagnostic. Endoscopic ultrasound can help in delineating the submucosal tumor. Alternative diagnostic means include CT, magnetic resonance imaging (MRI), barium study or ultrasonography[11]. However, CT and MRI seem to be the best imaging modalities for assessment of the primary lesion and detection of metastases[12], although CT scans are not always helpful in specifying the origin of the mass. In several cases reported in the literature, the mass was misdiagnosed as arising from the head of the pancreas[13].

There is currently uniform agreement that the surgical treatment of choice for GISTs is resection of the tumor with clear surgical margins, including adjacent organs as necessary[12]. As local and regional lymph node involvement is infrequent in GIST, routine lymph node dissection is not advocated[11,14,15] and limited resection is frequently performed. The surgical choice depends not only on the size of the tumor, but also on the location in the duodenal wall and the relationship to the ampulla of Vater[12,16,17]. Patients with duodenal GISTs close to the papilla of Vater should be treated by pancreatoduodenectomy. Various techniques of limited resection for duodenal GISTs have been advocated, depending on the site and the size of the tumors. Wedge resection with primary closure can be performed for small lesions if the resulting lumen is adequate and the ampulla can be preserved[9,18]. Segmental duodenectomy with side-to-end or end-to-end duodenojejunostomy can be performed for larger tumors located at the third and fourth portion of the duodenum[18]. Partial duodenectomy with Roux-en-Y duodenojejunostomy can be performed for larger tumors involving the antimesenteric border of the second and third portion of the duodenum[19]. Although a limited operation procedure, such as wedge or segmental resection, is relatively simple to perform, there is a risk of subsequent anastomotic leakage or stenosis development, as well as later tumor recurrence in patients treated by limited operation. By contrast, pancreatoduodenectomy as a treatment for duodenal GISTs can provide a wider surgical margin but may be associated with excessive morbidity, especially in patients with a tumor of low-grade malignancy[20]. It is not clear what the optimal

Table 1 Risk of aggressive behavior in gastrointestinal stromal tumors

Risk	Size (cm)	Mitotic count (mitoses per 50 high powered fields)
Very low risk	< 2	< 5
Low risk	2-5	< 5
Intermediate risk	< 5	6-10
	5-10	< 5
High risk	> 5	> 5
	> 10	Any mitotic rate
	Any size	> 10

Adapted from Fletcher *et al*[22].

surgical margin should be, but a negative one is essential to prevent local recurrence of the tumor. No lymph node dissection is required because they are very unlikely to be involved[18,21]. The outcome depends on the pathological features of the tumor and the completeness of surgical resection. Local recurrence is higher in tumors not completely removed or with a positive microscopic margin. In our patient, no suspicious peritumoral lymph nodes were present. Therefore, in order to minimize operative morbidity, we did not perform a formal lymph node dissection.

Fletcher *et al*[22] established a risk stratification based upon tumor diameter and mitotic activity (Table 1)[22]. The tumor presented in this case belongs to the category determined by size between 2-5 cm and a mitotic count < 5/50 high power fields, which is classified as "low risk". As we performed a wedge resection of the GIST, this indicates a good prognosis for our patient.

Imatinib (Gleevec, Novartis, Basel, Switzerland) is the treatment for locally advanced or metastatic GIST. Imatinib is a signal transduction inhibitor and in particular inhibits the binding of adenosine triphosphate to tyrosine kinase that includes PDGFRA and the c-Kit receptor expressed in GISTs[23]. Recently sunitinib malate, an oral receptor tyrosine kinase inhibitor, was approved for the treatment of GISTs after progression or intolerance to imatinib mesylate. Sunitinib inhibits platelet-derived growth factor receptors and vascular endothelial growth factor receptors, which play key roles in tumor angiogenesis and tumor cell proliferation[24]. As our patient was classified as "low risk", we did not initiate an adjuvant treatment with imatinib.

In summary, we report a case of a duodenal GIST located 3 cm distal of the ampulla of Vater successfully treated by a wedge resection. Wedge resection with primary closure is a surgical procedure that can be used to treat low malignant potential neoplasms of the duodenum and avoid extensive surgery, with significant morbidity and possible mortality, such as pancreatoduodenectomy.

COMMENTS

Case characteristics

A 65 year old woman was admitted to hospital with abdominal pain.

Clinical diagnosis

Gastroduodenal endoscopy revealed the presence of a submucosal tumor in the third portion of the duodenum and biopsy revealed tumor cells stained positive for c-kit.

Imaging diagnosis

Abdominal computed tomography showed a well-demarcated and enhanced tumor in the third portion of the duodenum, measuring approximately 3.0 cm in diameter.

Treatment

The patient underwent an esophagogastroduodenoscopy which revealed a submucosal tumor at the second and third portion of the duodenum.

Related reports

There is currently uniform agreement that the surgical treatment of choice for gastrointestinal stromal tumors is resection of the tumor with clear surgical margins, including adjacent organs as necessary.

Experiences and lessons

Wedge resection with primary closure is a surgical procedure that can be used to treat low malignant potential neoplasms of the duodenum and avoid extensive surgery with significant morbidity and possible mortality such as pancreatoduodenectomy.

Peer review

The manuscript is in general a nice case report but the discussion of the article needs polished.

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CASE REPORT

Fatal aortoesophageal fistula bleeding after stenting for a leak post sleeve gastrectomy

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Abstract

Bariatric surgeries have been used in an effort to curtail the obesity epidemic. The type of surgery used has changed over time, with sleeve gastrectomies being one of the preferred options. This has been associated with some complications, including staple line leaks. We report a 43-year old female who had undergone a laparoscopic sleeve gastrectomy that was complicated by a proximal gastric pouch leak at the gastroesophageal junction. We used self-expandable stents (SEMS) in the management of the leak. Seven weeks after the insertion of the initial SEMS, the patient presented with a massive gastrointestinal bleed that could not be localized due to profuse bleeding. The patient underwent a computerized tomography angiogram and then an angiogram that could not localize the site of the bleed. An emergency laparotomy was performed and identified the source of bleeding to be an aortoesophageal fistula. A graft of the diseased area was attempted but the patient unfortunately did not survive the procedure. An aortoesophageal fistula after an esophageal SEMS insertion for a benign disease has rarely been reported and only in cases where there was a thoracic neoplasm, thoracic aortic aneurism, endovascular stent repair, foreign body or esophageal surgery. To our knowledge, this is the first case that reports an aortoesophageal fistula as a result of a SEMS for the management of a gastric pouch leak after a laparoscopic sleeve gastrectomy.

Key words: Stents; Esophagus; Leak; Surgery; Complication; Aortoesophageal fistula; Endoscopy; Bariatric surgery; Sleeve gastrectomy

Core tip: One modality for managing staple line leaks after laparoscopic sleeve gastrectomies depends on a non-surgical approach, including elimination of oral intake, parenteral nutrition, use of broad spectrum antimicrobial therapy, drainage procedures and the use of esophageal self-expandable metal stents for sealing these leaks and the induction of tissue hyperplasia that would close these defects. Although this seems as a less invasive procedure when compared to a repeated surgical procedure and there is a body of evidence in the literature that supports such an approach, it is not void of complications. Here we report a fatal aortoesophageal fistula as a complication.

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INTRODUCTION

Obesity has become a major public health challenge, associated with a significant morbidity, mortality as well as decreased quality of life. Bariatric surgeries have been used as a modality to treat obesity, preferably after a multidisciplinary assessment. Although such an intervention has been proven to be effective in decreasing the excess weight of patients, it is associated with some complications of which surgical leaks are one of the most unfavorable with a considerable morbidity and mortality[1]. The management of staple line leaks post sleeve gastrectomy has evolved from surgical reinterventions to a less invasive approach with elimination of oral intake, parenteral nutrition, broad spectrum antimicrobial therapy, as well as percutaneous drainage procedures[1]. More recently, the use of esophageal self-expandable metal stents (SEMS) or self-expandable plastic stents (SEPS)[1-3] as method of occluding these leaks has become a more acceptable form of management.

We present an unusual case where a SEMS resulted in a massive gastrointestinal bleed secondary to an aortoesophageal fistula.

CASE REPORT

A 43-year old female was referred to our institution after the development of a proximal gastric pouch staple line leak at the gastroesophageal junction three weeks after a laparoscopic sleeve gastrectomy, which was confirmed by a contrast swallow study. The patient was started on broad-spectrum antibiotics and a percutaneous drainage tube was inserted to treat a subdiaphragmatic fluid collection seen on computer tomography (CT). An esophagogastroduodenoscopy (EGD) showed an opening at the area of the staple line at the gastroesophageal junction (Figure 1A). As one of the preferable modalities to treat staple line leaks post sleeve gastrectomy, a 12 cm fully covered SEMS was inserted (Figure 1B). The patient presented with nausea and vomiting three weeks later. An EGD found the distal end of the SEMS to be narrowed at the antrum angulation, it was removed and a second 15 cm partially covered SEMS was inserted as the staple line leak was still present. Four weeks later, the patient presented with hematemesis, hypotension and tachycardia. She was resuscitated and an EGD showed blood in the stomach but the source of bleeding could not be identified. The patient underwent a CT angiogram (Figure 2) and then an angiogram (Figure 3), but no clear source was found apart from doubtful areas along the left gastric (Figure 4) and gastroduodenal arteries that were coiled, but the patient continued to bleed.

An emergency laparotomy was performed. During exploration, the gastric pouch was opened distally and the stent was removed but the patient continued to bleed proximally, necessitating opening the gastric pouch completely up to the level of gastroesophageal junction where the source of the fresh blood was identified. A small pinpoint hole at the base of a small ulcer in the distal esophagus was bleeding profusely. The diagnosis of an aortoesophageal fistula was made and was confirmed by a left thoracoabdominal incisional approach by a cardiovascular surgeon. A short segment of tense fibrosis between the distal esophagus and aorta with a 2-3 mm opening communicating between them was seen. A graft of the diseased area was attempted but the patient unfortunately did not survive the procedure.

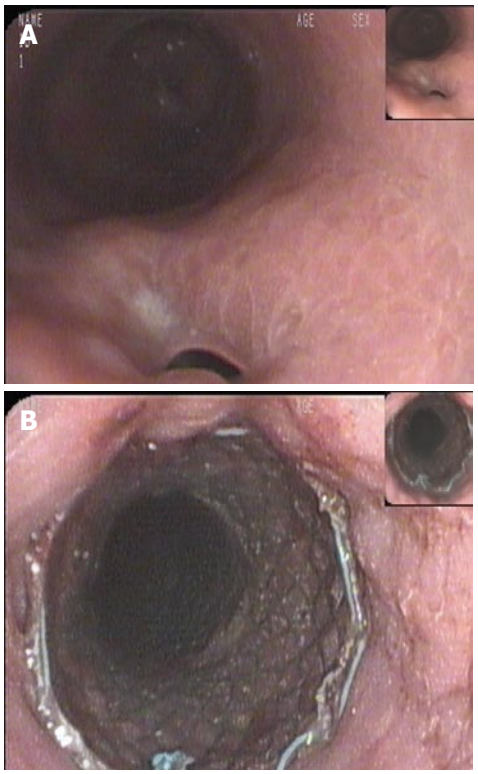

Figure 1 Endoscopic image. A: An opening at the area of the staple line near the gastroesophageal junction; B: A 12 cm fully covered self-expandable metal stent was inserted in the esophagus and overlapped the staple line leak.

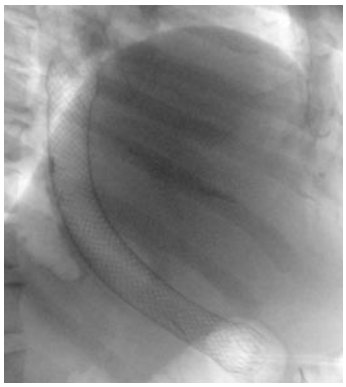

Figure 2 A fluoroscopic image demonstrating the deployed stent in the esophagus with its distal end extending into the stomach remnant.

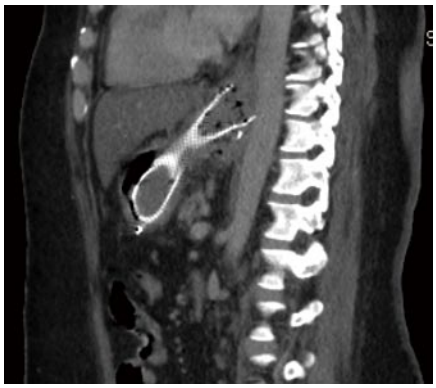

Figure 3 A reconstructed sagittal image of the computed tomography scan demonstrating the proximal aspect of the metal stent in very close proximity to the wall of the descending aorta but there was no evidence of active bleeding.

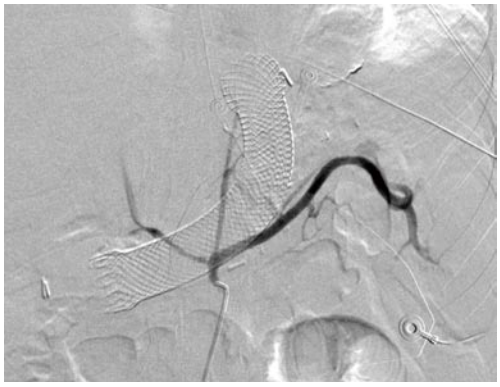

Figure 4 An angiogram of the celiac hepatic and left gastric arteries did not show active bleeding.

DISCUSSION

In two systematic reviews, the incidence of leaks after laparoscopic sleeve gastrectomy was found to be 2.2%[3] to 2.4%[4] and the leaks are usually in the proximal third of the stomach near the gastroesophageal junction in 85%-89%[1,4] of cases, with an associated mortality rate of 6%-14.7%[1]. The use of enteric SEMSs has evolved from the management of malignant diseases to benign strictures as well as leaks. A systematic review incorporating 25 studies with a total of 267 patients demonstrated a success rate of 85% with the use of SEMSs for the management of enteric leaks with no difference in the rate of clinical success between the type of SEMS used, whether partially or fully-covered SEMS or SEPS ($P = 0.97$)[5]. In these studies, the patient population included cases who had esophageal anastomotic leaks or a benign rupture of the esophagus[5]. A second meta-analysis for patients who exclusively had leaks post bariatric surgery and were managed by SEMSs found a success rate of 87.8% (95%CI: 79.4%-94.2%)[6].

An aortoesophageal fistula[7,8] is a rarely reported complication of esophageal SEMS and the majority of reported cases are secondary to thoracic aortic aneurisms, endovascular stent repairs, thoracic neoplasms, foreign bodies, radiofrequency ablation for atrial fibrillation or esophageal surgery. An aortoesophageal fistula after an esophageal SEMS insertion for an esophageal benign disease has rarely been reported and only in cases where there was an esophageal stricture[9,10]. More recently, the management of aortoenteric fistulas has been via thoracic endovascular aortic repair to control bleeding in the acute setting, either as a stand alone procedure or combined with a more definite management in an elective setting[11]. Other management strategies include endovascular aortic repair and subtotal esophageal resection followed by gastroesophageal reconstruction or open thoracic surgery[11]. The advantage of the former approach compared to the stand alone endovascular aortic repair is that, although it controls bleeding acutely, there is a higher probability of graft infection and mediastinitis given that the esophageal defect is not corrected[12]. Even when a diagnosis of an aortoesophageal fistula is reached, the morbidity and mortality is high, reaching up to 40%[13].

In a case series of 52 patients who required SEMSs for enteric leaks, there was a report of a death from severe hemorrhage after the insertion of a fully covered SEMS; the patient refused any intervention and thus the cause of the bleeding was unknown[2]. Also, there was a report of 4 deaths in a series of patients who had stents inserted for leaks after various bariatric surgeries but none were related to the stents[14].

Although the patient had adequate initial resuscitation that permitted the performance of an EGD as well as two radiological procedures, the diagnosis was not easily reached, an emergency surgery was required and even after reaching a definite diagnosis, the patient did not survive the surgery.

This case demonstrates that although the success rate with the use of SEMSs for the management of staple line leaks after laparoscopic sleeve gastrectomies is high, they still have potential complications and a high index of suspicion is required in order to pursue timely management of such complications.

To our knowledge, this is the first case that reports an aortoesophageal fistula as a result of a SEMS for the management of a gastric pouch leak after a laparoscopic sleeve gastrectomy.

COMMENTS

Case characteristics

This is a case of fatal aortoesophageal fistula bleeding after stenting for a leak post sleeve gastrectomy.

Clinical diagnosis

This is the first case that reports an aortoesophageal fistula as a result of a self-expandable stents (SEMS) for the management of a gastric pouch leak after a laparoscopic sleeve gastrectomy.

Experiences and lessons

Although the success rate with the use of SEMSs for the management of staple line leaks after laparoscopic sleeve gastrectomies is high, they still have potential complications and a high index of suspicion is required in order to pursue timely management of such complications.

Peer review

The authors have reported an interesting case of sleeve gastrectomy complication and an alarming finding on metal stent use for treatment of gastro-

esophageal leak.

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