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WJGS

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 9 Number 12 December 27, 2017

REVIEW

233 Advances and challenges in laparoscopic surgery in the management of hepatocellular carcinoma

Ziogas IA, Tsoulfas G

246 Role of oral antibiotics for prophylaxis against surgical site infections after elective colorectal surgery

Cawich SO, Teelucksingh S, Hassranah S, Naraynsingh V

ORIGINAL ARTICLE

Retrospective Study

256 Hepatocellular carcinoma with child Pugh-A Cirrhosis treated with stereotactic body radiotherapy

Hasan S, Thai N, Uemura T, Kudithipudi V, Renz P, Abel S, Kirichenko AV

264 Utility of single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection

Yamamoto M, Urushihara T, Itamoto T

Clinical Practice Study

270 Risk factors for pancreatic fistula following pancreaticoduodenectomy: A retrospective study in a Thai tertiary center

Rungsakulkij N, Mingphruedhi S, Tangtawee P, Krutsri C, Muangkaew P, Suragul W, Tannaphai P, Aeesoa S

CASE REPORT

281 Surgically treated diaphragmatic perforation after radiofrequency ablation for hepatocellular carcinoma

Nagasu S, Okuda K, Kuromatsu R, Nomura Y, Torimura T, Akagi Y

288 Ectopic gastrointestinal variceal bleeding with portal hypertension

Minowa K, Komatsu S, Takashina K, Tanaka S, Kumano T, Imura K, Shimomura K, Ikeda J, Taniguchi F, Ueshima Y, Lee T, Ikeda E, Otsuji E, Shioaki Y

Contents

World Journal of Gastrointestinal Surgery
Volume 9 Number 12 December 27, 2017

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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Advances and challenges in laparoscopic surgery in the management of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma is the fifth most common malignancy and the third most common cause of cancer-related mortality worldwide. From the wide variety of treatment options, surgical resection and liver transplantation are the only therapeutic ones. However, due to shortage of liver grafts, surgical resection is the most common therapeutic modality implemented. Owing to rapid technological development, minimally invasive approaches have been incorporated in liver surgery. Liver laparoscopic resection has been evaluated in comparison to the open technique and has been shown to be superior because of the reported decrease in surgical incision length and trauma, blood loss, operating theatre time, postsurgical pain and complications, R0 resection, length of stay, time to recovery and oral intake. It has been reported that laparoscopic excision is a safe and feasible approach with near zero mortality and oncologic outcomes similar to open resection. Nevertheless, current indications include solid tumors in the periphery < 5 cm, especially in segments Ⅱ through Ⅵ, while according to the consensus laparoscopic major hepatectomy should only be performed by surgeons with high expertise in laparoscopic and hepatobiliary surgery in tertiary centers. It is necessary for a surgeon to surpass the 60-cases learning curve observed in order to accomplish the desirable outcomes and preserve patient safety. In this review, our aim is to thoroughly describe the general principles and current status of laparoscopic liver resection for hepatocellular carcinoma, as well as future prospects.

Key words: Hepatocellular carcinoma; Laparoscopic liver resection; Minimally invasive surgery; Laparoscopic hepatectomy; Liver malignant disease; Surgical excision

Core tip: Hepatocellular carcinoma is the most common primary malignant tumor of the liver and fifth most common malignancy worldwide. Surgical resection is the therapeutic treatment of choice and its laparoscopic version has come into play since 1992. Several matched comparative studies reported its superiority over open

resection regarding operating theatre time and hospital stay, blood loss, need for transfusion and postsurgical opioid analgesics, postoperative pain, morbidity, R0 resection, time to recuperation, time to oral intake and stress response. The high costs of the procedure are offset by the decrease in the length of the operation and hospital stay, while in experienced hands conversion rates and morbidity are even more diminished. Laparoscopic and robotic liver resection is a continuously evolving field of minimally invasive liver surgery with a very promising future.

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INTRODUCTION

Although research in oncology and surgery has achieved some major milestones, hepatocellular carcinoma (HCC) still represents the fifth most common malignant tumor and the third most common cause of mortality related to cancer in the world[1]. In comparison with other malignant cancers, there is a wide variety of treatments in the armamentarium of surgeons, oncologists and radiologists, such as surgical resection, liver transplantation, chemoembolization, microwave and radiofrequency ablation, or even chemotherapy with sorafenib. However, before deciding on which method to choose from, clinicians ought to first define the clinical stage of the patient's HCC, which also defines the prognosis.

Especially for HCC, the three important factors determining the patient's survival are the tumor's characteristics (size, invasion of the vessels, number of nodules), the patient's physiologic reserve (for instance, Eastern Cooperative Oncology Group performance status) and the ability of the liver to function properly (Child-Pugh score)[2-4]. In addition, the issue still remains that there is lack of a common language in terms of HCC staging. Histopathology should also be taken into consideration when it comes to staging a type of cancer, and thus a variety of HCC staging systems, such as the Japanese Integrated Staging score, have adopted the American Joint Committee on Cancer TNM staging system[5]. One significant limitation of this system is the fact that it cannot incorporate the unresectable HCCs, because when relying primarily on the pathological characteristics of the tumor, it is a prerequisite that a surgical specimen is needed. Moreover, it does not include two of the three major survival factors mentioned above: physiologic reserve and liver function.

The staging system that seems to be the most inclusive, as well as the most widely verified, is the Barcelona Clinic Liver Cancer (commonly known as BCLC) staging system[6]. Based on this system, HCC patients are classified into subgroups based on their malignancy's characteristics, the function of the liver and their health in general, and each subgroup is allocated to a different treatment modality according to the treatment algorithm (Figure 1)[7]. On the other hand, a study ranking the different staging systems as to their prognostic value and patient survival, reported the superiority of the Cancer of the Liver Italian Program (commonly known as CLIP) classification and the Chinese University Prognostic Index (commonly known as CUPI)[8]. Although these staging systems differ to a great extent, mostly due to the geographical variation and etiologies of the different HCCs, the EASL-EORTC guidelines suggest that the BCLC classification should be followed when it comes to the management of HCC[9].

In this review, our aim is to thoroughly present the current knowledge around laparoscopic hepatectomy, with a special interest on the indications, general principles and technique, as well as its envisioned future.

Indications for surgical resection for HCC

The fact that HCC arises mostly in a cirrhotic liver, means that any type of treatment of the tumor has to account for factors related to hepatic quality and function. Regarding the liver-related factors, both quantity and quality of the future liver remnant (FLR) should be taken into consideration before performing an excision. One way to achieve hepatic hypertrophy, to ensure adequate liver mass posthepatectomy, is portal vein embolization (PVE), which improves the FLR of the side not embolized[10]. Another important factor is the preoperative liver function status, which can be evaluated by the Child-Pugh classification system (class A patients are suitable for hepatectomy, while class B or C patients are more prone to major complications after surgery due to liver dysfunction)[11]. Nevertheless, a significant contraindication to hepatectomy is high grade portal hypertension, which could be assessed either invasively by measuring hepatic venous pressure gradient (HVPG)[12,13] or noninvasively by measuring the platelet count[14].

The mostly studied tumor-related issues that determine the indications for liver surgical resection are tumor size, number of tumors and vascular invasion. Size alone is not a determining factor for patient survival after surgery, as it has been shown that excision of tumors larger than 10 cm may exhibit equal survival to those smaller than 10 cm, provided that the FLR is sufficient and there is insignificant vascular invasion[15]. Additionally, the management of multinodular HCC is still under discussion, with tumors arising in the cirrhotic liver due to the "field effect" showing improved survival posthepatectomy, in contrast to intrahepatic metastases, which usually present as a sizeable lesion encircled by satellite minor tumor masses[16,17]. Last but not least, it is generally accepted that significant invasion of major vessels remains an important contraindication to surgical

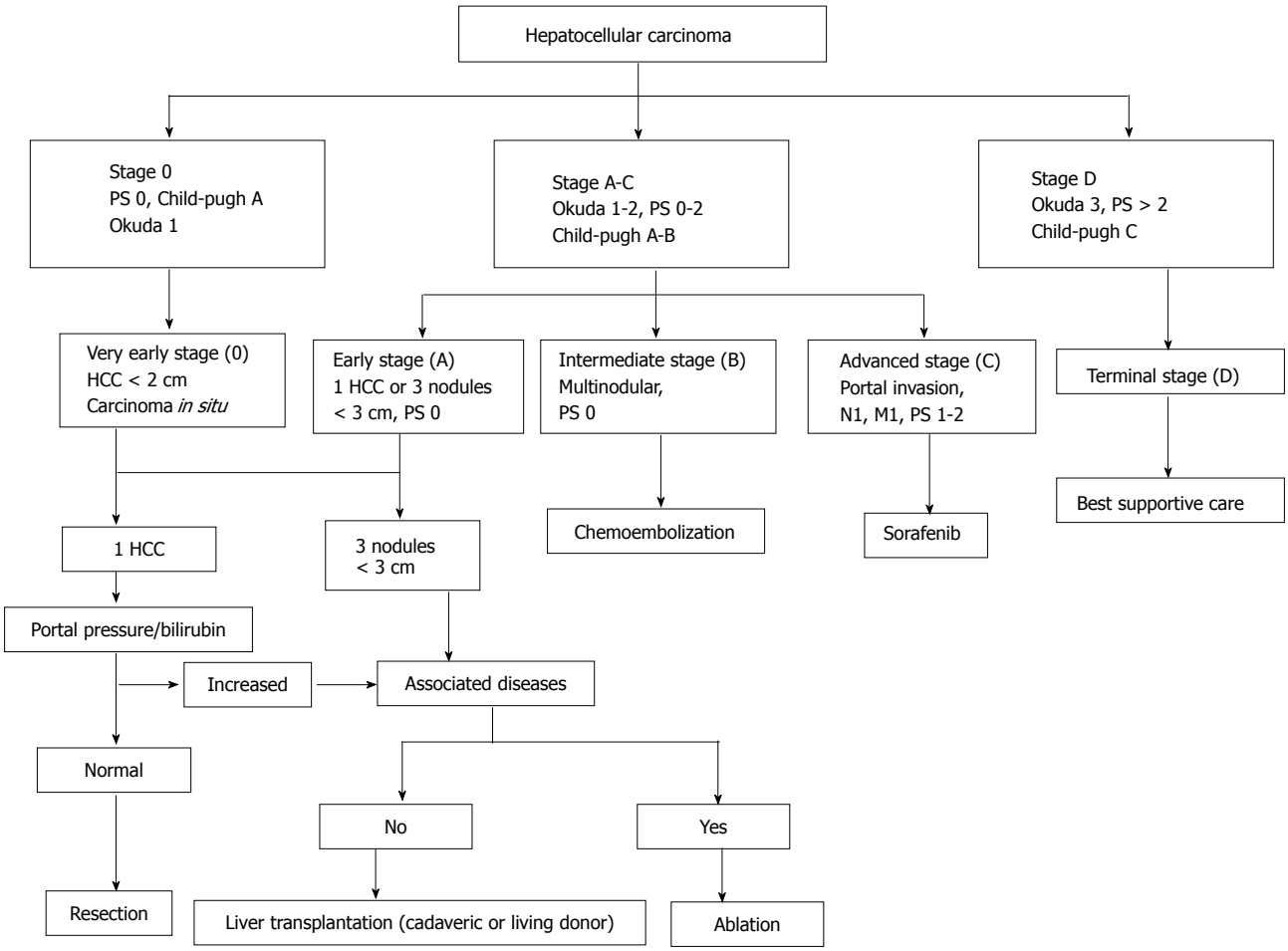

Figure 1 Barcelona Clinic Liver Cancer staging system and treatment algorithm. M: Metastases; N: Nodules; PS: Performance status; HCC: Hepatocellular carcinoma.

resection owing to worse prognosis and early disease recurrence[18].

Laparoscopic liver resection in general

To begin with, there are some challenges in the wider application of laparoscopic surgery. The first one is the loss of tactile sense, such as the margins and staging, but this could be helped by the use of laparoscopic ultrasound and hand-assisted techniques. Another obstacle is that of limited access and instrumentation, which could be solved by hand-assisted maneuvers and improved retractors. The question of bleeding control, while always a significant threat with the liver, can be addressed with devices such as the harmonic scalpel, the vascular stapler and the LigaSure device. In addition, other issues to be addressed include time and money, port side metastases and gas embolism.

Although many studies that compare laparoscopic liver resection (LLR) to open liver resection (OLR) have been carried out to date[19], only one of them was a randomized controlled trial[20]. Despite that, there has been an effort to progress over time from benign to malignant lesions, from smaller to bigger and from normal liver over to the cirrhotic one, by carefully selecting suitable candidates.

Currently, peripheral tumors (segments Ⅱ, Ⅲ, Ⅳb, Ⅴ and Ⅵ) are easier to resect laparoscopically[21]. Regarding larger and deeper located tumors, or those located superiorly or posteriorly, which are more difficult to excise, despite the fact that LLR can be implemented[22-24], it is advisable that hand-assisted or a hybrid technique (laparoscopic-assisted open) are performed[25]. On the whole, LLR is currently indicated, especially for solitary HCCs, 5 cm or less, located in the periphery of the liver, especially in segments Ⅱ through Ⅵ, that allow a wedge excision or a segmentectomy[19,26].

Current status of laparoscopic liver resection for HCC

According to Nguyen and Geller from 1992, when the first LLR was performed till 2009, about 2804 LLRs have been carried out. Half of them involved malignant lesions, while 45% were benign and about 1.7% live donor hepatectomies, with the remaining being undetermined[26]. Regarding the technique used 75% were completely laparoscopic, 17% were hand-assisted and about 2% were hybrid, while as it pertains to the resected specimen 45% of them were wedge or segment resections, 20% were anatomic left lateral sectionectomies and 9% were right and 7% were left hepatectomies[26].

Significantly, only a small percentage of the laparoscopic procedures were converted to open (4.1%) and to

hand-assisted (0.7%).

Safety

LLR is generally thought of as a safe and feasible operation[27,28]. A previously published world review[26] reported a clearly low rate of mortality (0.3%), without any deaths occurring during the procedure. The most common causes of death were liver dysfunction, multiple organ failure, delirium tremens and hemorrhage. Morbidity, on the other hand, was 10.5%, with postoperative bile leak being the most common complication (1.5%), followed by transient liver failure and liver abscess, as well as bleeding, surgical site infection and collection of fluid inside the abdominal cavity. These low rates could possibly be attributed to several factors, though.

It is clear that careful patient selection and high surgical expertise play important roles. Apart from that, the utilization of the hand-assisted method may decrease bleeding more quickly through direct pressure, while laparoscopic sutures could be more safely executed, thus rendering more difficult cases feasible[29]. Moreover, although keeping a low pressure pneumoperitoneum reduces the incidence of air embolism, if it is increased it can be efficacious in reducing venous leakage[29].

The positive effects of pneumoperitoneum do not stop there, as it is helpful in achieving optimal visualization and as a result bloodless parenchymal transection, which decreases the risk of major hemorrhage and the requirements of blood transfusion, therefore also avoiding the unspecified immunosuppression which increases morbidity and cancer recurrence[30]. In addition, a recent meta-analysis reported lower loss of blood and decreased need for transfusion, rapid recovery and significantly decreased postoperative pain[31]. Finally, data suggest that complications are going to decrease more as the surgeon becomes more experienced.

Operative time

In general, operating time, just as blood loss, is quite challenging to calculate due to the high heterogeneity among the wide range of procedures being performed. Despite this, the world review reported that the operating time may vary from 99 min to 331 min[26], while Soubrane *et al*[30] estimated a median operating time of 3 h. Similarly, Cannon *et al*[29] found that for their first 100 patients, the operative time was also 3 h, but as surgeons gained more experience, the time went down to around 2 h for their most recent 100 patients. On the contrary, a meta-analysis of 26 studies showed a significantly increased procedure time as to the open approach[32].

As a matter of fact, OLR involves a larger incision, which needs extra time to be closed; hence, when surgeons become even more expert in this field of hepatobiliary surgery, LLR is not going to be that much more time-consuming. Another meta-analysis found out no difference between LLR and OLR regarding the operative time[28], suggesting that only a minor variance exists. Obviously, the critical factor regarding operative time is the learning curve, something which will also change again in the future as these procedures become more established and they move from the level of the attending to the level of the fellow, and potentially even to the senior resident.

Length of hospital stay

As expected, laparoscopic procedures show a remarkable decrease not only in blood loss and postoperative pain, but also in the length of hospital stay. Specifically, the estimated time for hospital stay is around 2.9 d[29], which is obviously lower than that of the OLR; interestingly, Simillis *et al*[28] reported a decrease of about 2.6 d in patients treated with LLR compared to those undergoing OLR. The world review[26] exhibited a range between 1.2 d to 15.3 d for LLR, which again was proven to be lower than that of OLR. This variance, though, may be due to nuances among the healthcare providers and cultural habits, as well as due to the fact that some studies included liver cyst excisions, while others did not. This kind of cultural bias tends to play a key role in determining the length of the hospital stay as it ranges only between 1.9 d to 4 d in the United States, while in Europe it is about 3.5 d to 10 d and in Asia 4 d to 20 d for LLR; even so, a constant decrease of about 50% was observed in LLR when compared to OLR[33].

Efficiency

At first, there was great concern regarding LLR and the risk of positive margins, potential tumor seeding and port-site metastasis, which impeded its wide implementation. The results reported by Nguyen *et al*[26] state categorically that there is no reason for not adopting LLR, as resection with tumor-free margins can be accomplished, and neither significant tumor seeding nor port-site cancer recurrence have ever been reported. The only exception is a patient whose renal cell carcinoma ruptured before the operation, which clearly had nothing to do with the LLR[34]. Moreover, both approaches are equal in terms of oncological survival outcomes[26].

Many studies including patients with HCC or colorectal metastases reported promising survival rates; and, specifically the 5-year survival for colorectal metastases to the liver ranged between 50%-64%, while R0 excision percentages were about the same as those of OLR[21,35]. As to HCC, a study showed that 1-, 3- and 5-year survival rates were 95.4%, 67.5% and 56.2%, respectively, after LLR *vs* 100%, 73.8% and 53.8% after OLR[36]. Soubrane *et al*[30] also published a LLR study, in which they achieved R0 marginal resection in 92% of their patients, while 1-, 3- and 5-year overall survival was 90.3%, 70.1% and 65.9%, respectively, and 1-, 3- and 5-year progression-free survival was 85.2%, 55.9% and 40.4%, respectively. In this study, they also proved that LLR fulfills the criteria established by the EASL-EORTC guidelines; hence, it should be used widely for the resection of HCC.

Conversion

Laparoscopic liver resection can be converted to laparotomy if the anatomy is not clear or so as not to endanger patient safety. Although some studies report a high rate of conversion of 13%-17%[30,37], generally rates tend to be as low as about 4%-7%[26,38-40]. Excessive bleeding is the most common cause of conversion, while adhesions, gas embolism, poor visualization and anatomic disorientation or nearby large vessels are some other common causes[26,37,39,40]. Resection of postero-superior segments was found to be an independent factor for conversion, as indicated by a multivariate analysis; major hepatectomy was another significant factor for conversion *vs* minor hepatectomy[39]. It would be wrong not to mention the relationship between conversion and learning curve. The considerable learning curve indicates that less experienced surgeons may not be able to deal with the numerous difficulties a LLR involves; hence, it has been observed that only after performing about 60 LLRs will the risk of converting LLR to OLR decrease[41].

It is obvious that when a laparoscopic procedure is converted to open, every advantage of the laparoscopic technique is immediately lost. This does not mean, though, that the surgeon should exceed his/her level of competency in order to avoid a conversion, because if it is delayed in some challenging cases, length of hospital stay may increase and complications may be more numerous and devastating[42]. As a result, the hepatobiliary surgeon must first become competent enough in performing LLR, so as to know when to convert or not.

The main reason for conversion, as mentioned previously, has been bleeding. In order to laparoscopically deal with major hemorrhage, the surgeon can intermittently use the Pringle maneuver, compress with gauzes, use clips or staplers or even the hand-assisted approach[43,44]. It is generally advisable that in case of acute bleeding, laparoscopic sutures should be placed after snatching the vessel, which can lead to less blood loss during conversion, and then saline solution should be used in the abdominal cavity when the converting incision is made[39]. The hand-assisted technique is an "in-between" technique used when there is an urgent need to stop bleeding and the decision to convert or not has not yet been made. The other important cause of conversion, gas embolism, can be managed by shifting the operating table into the Trendelenburg position, which increases central venous pressure in case of a damaged vessel[45]. Finally, when resecting a lesion in a postero-superior segment, which represents a higher risk of conversion, robotic-assisted resection is suggested to decrease the risk of conversion[39]; however, a systematic review reported a 6.6% rate of conversion for the robotic procedure[46] and, thus, more research is necessary.

Comparison with the open technique

When comparing techniques, it is important to ensure patient similarity between the different groups. Aiming to prove the advantages of a laparoscopic approach, Ito *et al*[47] matched 65 patients that received LLR to 65 OLR patients from their archive and then compared them. The results, especially for the short-term, were significantly in favor of the laparoscopic approach, showing a decrease in bleeding, need for transfusion, frequency of the Pringle maneuver, postoperative complications, time to recuperation, length of stay in the hospital and cases of surgical site herniation. As far as the oncologic outcomes are concerned, free-marginal resection and lack of surgical site recurrence were accomplished in both groups, while cancer recurrence rates were also similar. Also, the first study comparing the two techniques for a major liver excision showed that they are equal regarding operative time and postoperative complications, but blood loss, length of hospital stay and general morbidity were significantly reduced in the case of LLR[48].

A meta-analysis comparing the two methods, particularly comparing small resections for solitary tumors in the left lateral lobe or right peripheral subcapsular area, reported that LLR is superior to OLR in short-term outcomes (*i.e.,* loss of blood and postsurgical morbidity), while long-term outcomes (*i.e.,* severity of complications) were similar between the two approaches[49]. Besides, a comparative study reviewing 12 primary studies observed similar mortality rates between the laparoscopic (0.3%) and the open (0.4%) techniques, while liver failure was the most common cause of death in both groups[50].

Other major advantages of the laparoscopic method have to do with improved patient satisfaction and comfort. It is well known that a laparoscopic technique causes less surgical stress than an open one, and this can lead to decreased postsurgical pain, cosmetic advantages (almost no scar) and shorter length of stay in the hospital[51]. Also, time to oral intake and need for opioid analgesics may be reduced[52], the patient may recover faster and get back to his previous activities[53].

A meta-analysis published in 2017 also compared LLR to OLR in terms of short- and long-term outcomes[31]. To elaborate this, the open method showed increased rates of blood loss, requirements for blood transfusion and length of hospital stay, while the only insignificant difference was observed regarding the operating time. Free-marginal resection and width of marginal resection were found to be increased in LLR generally. This study also highlighted the decrease in postsurgical morbidity and in 30-d mortality, in favor of the laparoscopic operation.

Concerning long-term outcomes, although 1-year overall survival was significantly increased in LLR, there was no noticeable difference between the two groups in the 3- and 5-year overall survival. Disease-free survivals after 1, 3 and 5 years, as well as cancer recurrence rates, were also similar for the two methods. Unfortunately, except for one randomized controlled trial from China[20], all the studies included in the meta-analysis are non-randomized comparative studies, which are also

characterized as "methodologically adequate". Although since meta-analysis may over-estimate the effect of sizes in comparison to a meta-analysis of randomized controlled trials[54], the big picture emerges despite the lack of high-quality evidence-based research in LLR. Even though there is a large heterogeneity among the studies regarding surgical expertise, patient selection and tumor-related parameters, this helpful meta-analysis emphasizes the superiority of LLR over OLR for small HCCs.

Cost

Although at first glance one would expect the LLR to be more expensive, given the use of the laparoscopic instruments, this is not necessarily the case. When addressing the issue of cost analysis, the clinical aspect should be taken into consideration and "cost-effectiveness" should be the key concept. Specifically, although using an endoscopic stapler for liver resection is significantly more expensive than the "finger fracture" technique used in an open procedure, the operating room time saved could potentially make up for the difference. Even though, a study reported that the costs of trocars and staplers did not differ between the two groups[55], another from the United Kingdom showed that the devices and disposables utilized in the LLR group were more costly indeed than those in the OLR group[56].

A Canadian study reported no difference in the operative time between the laparoscopic and the open group, which was around 140 min, but an overall theatre time of more than 200 min was documented and the nonsurgical time was occasionally higher than the operative one[55]. Besides, it has been proposed that the theatre usage time is a better indicator of the cost-effectiveness of a procedure than the operative time. This nonsurgical time, though, was similar for the two techniques and was not a result of placing an epidural catheter in the OLR group. However, the aforementioned United Kingdom study[56] showed that although the placement of an epidural anesthesia is beneficial to patients receiving the open operation, it does increase the cost of the procedure compared to the laparoscopic one. As a result, if we add the shorter time of anesthesia and the reduced need for a high-dependency unit admission to the faster recovery time, ambulation time and reduced surgical ward stay observed in the laparoscopic group, it can be seen how the cost of LLR could be lower than that of OLR[56,57]. Additionally, the patient can return to his previous activities quicker, with reduced morbidity, and go to work sooner[58].

In contrast, this financial benefit is not observed in more complex and difficult cases. Specifically, Cannon *et al*[59] reported that although laparoscopy in general is less expensive than the OLR, when performing a right hepatectomy, which is clearly characterized by higher complexity, the cost-effectiveness of LLR is lost. Nevertheless, segmentectomy and bisegmentectomy clearly emphasize the cost-effectiveness of the laparoscopic approach, as the total hospital cost was lower by around £2.571 (~$3.800) compared to the open approach[56]. Similarly, Koffron *et al*[38] compared carefully selected and matched patients that received partial and right hemihepatectomy, excluding the outliers, and reported that the overall hospital cost for the laparoscopic group was 98% and 66%, respectively, of that of the open group. Also, they found that the operating room cost for those resections done laparoscopically was 51% and 47% of the overall hospital cost compared to 39% and 36%, respectively, in the case of an open operation.

Vanounou *et al*[60] used the deviation-based cost modeling to clinically and economically compare the two approaches and showed that the weighted-average median cost of LLR was reduced by about $2.939 in comparison with OLR ($15.104 *vs* $18.043, respectively). They also expanded this comparison to include malignant disease and they proved again that LLR is more cost-effective than OLR, by about $1.527. On the whole, it is clearly understood that the shorter duration of hospital stay accompanied by the lower morbidity rates, offset the higher intraoperative costs reported in the laparoscopic technique, thus ensuring cost-effectiveness.

SPECIAL SITUATIONS

Patient with cirrhosis

Cirrhosis is seen commonly in patients with HCC, and a different approach may be in order in these patients. The most common postoperative complication observed in cirrhotic patients is ascites, seen even in minor surgeries[61,62]. This could be prevented by the utilization of LLR, which also improves the postsurgical status of those patients in general. The reasons for that are: (1) The less traumatic insult to the abdominal wall and the round ligament, which prevents collateral circulation; (2) the protection of visceral organs from exposure to the atmosphere, which decreases the loss of electrolytes and the need for extra fluid administration; and (3) the restricted loss of blood during the operation[50]. In addition, LLR does not require the total emptying of ascites in the cirrhotic patient, therefore reducing the risk of postsurgical ascites and fluid and electrolyte disturbances[48,63]. Another frequent health issue that patients with cirrhosis usually face is bleeding from intra-abdominal varices. Some experts suggest that such a bleeding incident could be prevented thanks to the pneumoperitoneum produced during a LLR, owing to the tamponade effect[64]. Moreover, as we know, liver transplantation is the only therapeutic modality for cirrhosis. In conjunction to this, a study proved that when resecting a hepatic lesion from a potential future liver transplant candidate, LLR should be adopted over OLR, because it can facilitate liver transplantation due to a lesser degree of postoperative adhesions[65].

On the other hand, a LLR in cirrhotic liver has its own challenges. It is necessary that patient selection criteria are established, so that the early learning curve does not cause more harm than good. In other words, some

surgeons suggest that the lesions which are going to be excised should be in the left or anterior right segment of the liver, in order to achieve optimal accessibility, while the lesion's size should not exceed the 5 cm diameter[64]. This concept is included in the international consensus conference on LLR, and the laparoscopic approach is advocated for surgeons with appropriate expertise and in the beginning for peripherally located solitary lesions that do not exceed 5 cm in diameter[66].

Laparoscopic liver resection, immune system and stress response

Surgery initiates a complex systemic response involving multiple cytokines, immune cells, messenger molecules and metabolic pathways. All of these start with the abdominal trauma induced by the scalpel, but what if we could minimize this incision-induced stress reaction? This is where minimally invasive surgery and laparoscopy come into play.

The utilization of LLR leads to a smaller abdominal incision and decreased damage to the tissues. The initiated stress response is assessed by several measures, such as tumor necrosis factor alpha (TNF-α) and interleukins (IL-1β, -2, -6, -8, -10, -12), C-reactive proteins (CRPs), hormones deriving from the adrenals, lymphocytes in the periphery and by the implementation of delayed-type hypersensitivity skin tests[67,68]. The early stress response to the surgical wound is thought to be mediated by IL-6 produced by monocytes, macrophages and endothelial cells, while the severity of tissue damage can also be evaluated by high serum levels of IL-6[69]. In fact, a study suggested that approaches lowering IL-6 levels, such as laparoscopy, may be more beneficial in the future[70].

LLR, compared to OLR, has shown a decrease in postoperative complications, pain, hospital stay, bleeding and need for blood transfusion, time to oral intake, postoperative need for opioid analgesics and more rapid recovery. All these factors clearly highlight the reduced surgical stress response observed in the laparoscopic group and its superiority over the open method.

Diagnostic laparoscopy in HCC patients prior to resection

Apart from clinical and laboratory examinations, imaging plays a key role in the preoperative work-up and evaluation of HCC. Transabdominal ultrasound, three-phase computerized tomography and magnetic resonance imaging are some of the imaging examinations included in the preoperative work-up. However, as HCC is usually associated with cirrhosis and hepatitis, those may underestimate the level of cirrhosis and the regenerative nodules or peritoneal spread of the tumor, which can be more clearly identified only under direct vision[71]. Indeed, Klegar *et al*[71] utilized diagnostic laparoscopy in HCC patients undergoing resection, and it changed the decision made to a significant extent in 9 out of 20 cases (45%). The main reasons for this change were advanced level nodular cirrhosis, incorrect evaluation of intrahepatic metastases, difficulty in recognizing a HCC, peritoneal carcinomatosis and intolerability to general anesthesia. Consequently, diagnostic laparoscopy may be kept in mind for the preoperative imaging assessment of HCC.

Ablation

In the beginning of our review we stated that candidates for surgical resection need to fulfill some specific criteria. In the case of the patients that are excluded, a non-surgical approach, such as transarterial chemoembolization, percutaneous ethanol injection, percutaneous radiofrequency and microwave ablation, can be used. Unfortunately, some HCC patients are not suitable even for percutaneous ablation due to liver dysfunction or tumor characteristics necessitating a more controlled approach, and as a result the implementation of laparoscopic ablation could be helpful.

Laparoscopic radiofrequency ablation is a safe procedure used as an alternative to the percutaneous method in subcapsular tumors or in those in contact with adjacent organs. A European study confirmed the safety and efficacy of this procedure, as the reported initial complete response percentage was 94%, while the sustained one was 70% after the follow-up period[72]. Additionally, overall survival rates at 1, 3 and 5 years were 92.6%, 64.5% and 43%, respectively. Buell *et al*[73] compared laparoscopic radiofrequency ablation to LLR and noticed similar unwanted events and mortality rates (11% *vs* 16%, respectively and 1.5% *vs* 1.6%, respectively). Although the rates of overall recurrent disease were equal between the two techniques (24% *vs* 23%, respectively), local recurrence was more frequently observed in the radiofrequency group (6.3% *vs* 1.5%, respectively).

An Italian study evaluated the use of laparoscopic microwave ablation in 42 patients and had promising results[74]. Specifically, there was 0% mortality, but the morbidity rate was 24%, while survival and recurrence rates after 2 years were 79% and 55%, respectively. After matching 28 of these patients with 28 others receiving laparoscopic radiofrequency ablation, the 2-year recurrence percentages reported were 55% and 77%, respectively.

Microwave thermosphere ablation is a new method utilizing a single antenna so as to ablate spherical areas. Zaidi *et al*[75] evaluated microwave thermosphere ablation laparoscopically in 45 patients and reported a morbidity and mortality rate of 11.3% and 0%, respectively. Significantly, the 99.3% complete tumor ablation percentage and the 0.7% local recurrence rate indicate how promising this new technological advance can be in the future.

Learning curve

The combination of technology and technical challenges make the learning curve a critical part of LLR. He *et al*[76] noticed that the increase in volume of LLRs performed in 2009-2012 *vs* 2000-2008 may be partially attributed

to the Louisville 2009 Consensus[66]. They also observed a decrease in length of hospital stay over time, but no difference regarding morbidity and mortality. Issues that need to be addressed are the qualifications necessary to perform the procedure and the path required to learning it. As expected, the vast majority of LLRs have been performed in liver cancer and liver transplantation centers by experienced surgeons with great knowledge and skills in both laparoscopic and hepatobiliary surgeries. Therefore, Tsinberg *et al*[77] proposed the formation of a dynamic duo, a laparoscopic surgeon and a hepatobiliary surgeon, who could work together and learn from each other. They also suggest that a surgeon with little experience should start from laparoscopically resecting peripherally located lesions (*i.e.*, segments Ⅱ, Ⅲ, Ⅳb, Ⅴ and Ⅵ), as well as benefiting from the usage of the hand-assisted technique.

A study assessing the outcomes of LLR in three different groups in three different eras showed that the last group included more complex and demanding cases, as well as more cirrhotic patients, thus indicating the increased comfort and expertise of surgeons performing LLR during a period of time[29]. Even though cases gradually became more and more complex, operating time was reduced for about 3/4 of an hour from the first till the last group. Blood loss, 30-d mortality and length of hospital stay were similar among the three groups. Vigano *et al*[41] also evaluated LLRs performed in three different periods of time and concluded that the volume of LLRs increased, rate of conversion, operating time and loss of blood decreased, but most significantly, after adjusting for case-mix, cumulative sum analysis showed that LLRs required a learning curve of 60 patients. On the other hand, a study assessing the LLR learning curve of a single surgeon again in three periods, reported that 50 cases were required, so that a significant reduction in blood loss was observed, while no less than 160 cases were needed so as to perform a wide range of different LLR with safety[78].

There are issues regarding the nature of the learning curve. Even though it is thought of as an "idealized" curve, gradually progressing until reaching a plateau, Villani *et al*[79] could not but notice several improvements and regressions regarding complications, operative time and blood loss, associated partially to the constantly increasing complexity of the procedures attempted. As a consequence, they proposed the model of the "true" learning curve for LLR, which is characterized by a pattern of "ups and downs" until surgeons become experienced, when their performance reaches peak and the beneficial outcomes are constantly seen.

Koffron *et al*[38] commented on the need for randomized controlled trials, saying that patients would hesitate to enroll in these studies due to the fear of having OLR. On the contrary, the authors suggested that LLR may become the technique of choice, just as laparoscopic cholecystectomy, and propose a way to deviously avoid the learning curve of LLR. Thus, an inexperienced surgeon should start with using the hybrid method, initially for wedge excision of peripherally located lesions, and as time goes by and he/she becomes more comfortable with it, it is advisable to turn to the hand-assisted approaches. When the surgeon reaches a high level of expertise regarding the laparoscopic skills, it is time to gradually move on to the pure laparoscopic method, again initially for peripheral lesions.

FUTURE PROSPECTS

Nowadays, the swift advances in technology have led to several novel instruments and machines in the everyday surgical routine. Robotic surgery is just one of them. In general, help provided by the robot facilitated a new era for minimally invasive surgery including minor incisions, reduced estimated blood loss, postsurgical pain and length of hospital stay, while concurrently expediting the learning curve for transitioning from the open to minimally invasive approach[80,81]. Inevitably, the da Vinci robot (da Vinci Surgical System; Intuitive Surgical, Inc, Sunnyvale, CA, United States) entered the world of hepatobiliary surgery with increasing popularity. LLR is widely adopted, but mostly for left lateral segmentectomy and less for left and right hepatectomies. Thus, the robotic liver resection through its 3D imaging and advanced-mobility instruments may accommodate such resections[82] and promises to play a key role in the evolution of LLR. However, a study comparing robotic to laparoscopic left lateral sectionectomy reported in the robotic group more admissions to the intensive care unit and more minor complications, as well as increased length of hospital stay and indirect costs[83].

To our knowledge, up to this time, Giulianotti *et al*[84] have published the largest series for robotic major hepatectomy, consisting of 27 patients (20 right hepatectomies, 5 left hepatectomies and 2 right trisegmentectomies), 74% of which had malignant liver disease. Their median operating time was 313 min, the rate of conversion to open was 4%, while morbidity and mortality rates were 30% and 0%, respectively. Spampinato *et al*[85] published another large study of 25 patients, 68% of which had malignant disease, with a median operative time of 430 min, 4% conversion rate, but reduced transfusion rate, blood loss and morbidity in contrast to Giulianotti *et al*[84]. Both studies had a similar length of hospital stay, of 8 d.

Moreover, the largest study, to the best of our knowledge, regarding robotic minor hepatectomy was from Kingham *et al*[86] in 2016 from the Memorial Sloan Kettering Cancer Center, which included 65 patients (78% with malignant disease). Median operative time was 163 min, conversion rate was 6.3%, morbidity rate was 11% and mortality rate was 2%. Giulianotti *et al*[84] included 43 cases of robotic minor hepatectomy and reported a median operative time of 198 min, conversion rate of 7%, while morbidity and mortality rates were 16% and 0%, respectively. Data suggest that most published series of robotic major or minor hepatectomy achieved a near 100% R0 resection[87].

The interesting approach of robotic-assisted laparo-

scopic anatomic hepatectomy has been reported in a study from China[88]. Although this technique was characterized by increased operating time and hospital costs when compared to laparoscopic or open hepatectomy, it was superior in terms of blood loss, transfusion rate and morbidity, hence proving its safety and feasibility over the other two methods. This significant technique is promising because it can overcome the increased surgical trauma, postoperative pain, loss of blood and diminished recovery of the open approach, but simultaneously expand the indications of LLR, therefore representing an efficient combination. The robot's advantages are the elimination of tremor produced by the surgeon, the accurate resemblance of human wrist movements, the scaling of hand motions into micro-motions, as well as the 3D visualization, which further enhances hand-eye coordination[89,90].

Notably, this robotic-assisted laparoscopic technique can be very helpful when performing hilar dissection, transection of hepatic parenchymal tissue and control of liver outflow, and when dealing with posteriorly located hepatic lesions. Also, robotic surgery can more easily manage bleeding during parenchyma transection, the most common cause of laparoscopic to open conversion[88]. However, there are also disadvantages. For instance, lack of tactile feedback is prominent due to absence of haptic sensors, but the 3D imaging may offset this problem. Additionally, the robotic cart and arms take a great deal of space in the operating room, which may impede additional non-robotic surgical movements or even make the work of the anesthesiologist inconvenient[91]. Robotic surgery is completely different from traditional surgery and many adjustments need to be made, including robotic port placement, development of more advanced surgical instruments and training of table-side surgeons, while hospital costs should always be taken into consideration.

There are other applications of minimally invasive surgery in hepatic surgery. Specifically, the shortage of liver donor grafts is widely known as a major issue in liver transplantation and, thus, many patients resort to live donor liver transplantation, which is a unique procedure given the significant health risk to the living donor; we have to remind ourselves that this is a healthy individual undergoing a high-risk surgery for no benefit to the donor. Consequently, a study compared open to laparoscopic live donor left lateral sectionectomy and reported that the laparoscopic group exhibited a diminished length of hospital stay and time to oral intake, while operative time, estimated blood loss and costs were similar between the two groups with zero mortality observed in both[92]. The same surgical team published in 2017 a study of three pure laparoscopic living donor right hepatectomies, which are very rarely performed, and reported zero complications, reduced surgical trauma morbidity and more rapid recuperation[93]. In 2017, a Japanese study published was the first one to compare laparoscopic to laparoscopy-assisted donor hepatectomy[94]. It showed that although the pure laparoscopic approach may take longer than the laparoscopy-assisted one, it is associated with decreased loss of blood, better cosmetic outcomes and similar complication rates and acceptable liver allograft results.

On the whole, LLR is a challenging procedure requiring a lot of experience, which is not easy to accomplish. Nevertheless, even experienced surgeons may face difficulties intraoperatively. As a result, improved liver and surgical site visualization is needed so as to achieve optimal outcomes. Thus, a surgical simulation 3D system has been developed in order to facilitate surgeons in recognizing vascular structures and the location of the tumor[95]. The aim of this system is to facilitate surgical training, as well as to ultimately provide navigation guidance in real time intra-operatively. Moreover, we have witnessed the evolution of an open liver imaging system to a laparoscopic one, mainly through clinician feedback, which accommodates a high quality intra-operative 3D image, especially useful in LLRs[96]. The future seems quite promising for laparoscopic liver surgery, both in terms of surgical technique, as well as in terms of navigation guidance in the operating room.

CONCLUSION

In conclusion, minimally invasive surgery has made tremendous strides in hepatobiliary surgery, starting with cholecystectomy and ultimately dealing with liver resection. Laparoscopic liver resections have proven to be superior to the traditional open approach in respect to decreased loss of blood, transfusion rate, surgical trauma-induced stress response, postoperative pain and morbidity, time to recovery, time to oral intake, need for postsurgical opioid analgesics, operating theatre time, length of hospital stay, R0 resection and similar mortality and oncologic outcomes, let alone cost-effectiveness.

The majority of the resections are wedge and left lateral segmentectomies, because major (right or left) hepatectomies are more challenging and difficult to perform and are attempted only by highly skilled and experienced surgeons in tertiary centers. Current indications for laparoscopic liver resections involve peripheral solitary tumors not exceeding 5 cm in diameter, particularly in segments II through VI, according to the 2008 Consensus Louisville Conference.

Unfortunately, as indicated by a 2017 meta-analysis, only one randomized controlled trial has been published and thus most data come from matched comparative studies and meta-analyses. Those studies, though, are subject to publication bias, as those with positive and more significant results are more easily published in world class English journals in comparison with the negative results published in local journals, if ever. Selection and attrition bias may also influence the results of meta-analyses. Consequently, we cannot but wait for more high quality and methodologically well-designed studies that will facilitate the adoption of laparoscopic liver resection as the treatment of choice not only for HCC, but also for many other lesions.

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REVIEW

Role of oral antibiotics for prophylaxis against surgical site infections after elective colorectal surgery

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Abstract

Over the past few decades, surgeons have made many attempts to reduce the incidence of surgical site infections (SSI) after elective colorectal surgery. Routine faecal diversion is no longer practiced in elective colonic surgery and mechanical bowel preparation is on the verge of being eliminated altogether. Intravenous antibiotics have become the standard of care as prophylaxis against SSI for elective colorectal operations. However, the role of oral antibiotics is still being debated. We review the available data evaluating the role of oral antibiotics as prophylaxis for SSI in colorectal surgery.

Key words: Colorectal; Anastomosis; Leak; Antibiotics; Bowel preparation

Core tip: The role of oral antibiotics to reduce surgical site infections (SSI) after elective colorectal surgery is not yet settled. The research in this area has been overshadowed by studies examining mechanical bowel preparation (MBP) and intravenous antibiotics. Existing data show that intravenous antibiotics are now considered standardized prophylaxis, and MBP is on the verge of being eliminated altogether. We review the available data evaluating the role of oral antibiotics as prophylaxis for SSI in colorectal surgery.

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INTRODUCTION

Even in this modern era, surgical site infections (SSI) still occur in 26% of patients after elective colorectal resections[1]. When a SSI develops, it lengthens hospital stay, prolongs the recovery period and delays the commencement of adjuvant systemic therapy for malignancies[1]. In addition, the associated health care expenditure increases on average by $11000-40000.00 United States dollars[2]. Therefore, SSI prevention is an important area of medical research.

Despite the existence of evidence-based recommendations for prophylaxis[1-9], there is still a wide variation of clinical practices to prevent SSIs after elective colorectal surgery. Less than a decade ago, the combination of mechanical bowel preparation (MBP) and intravenous antibiotic was the commonest form of prophylaxis in the elective setting. However, the role of MBP is now questionable since several good quality studies have challenged its value[9-19]. If the present trend continues, it appears that patients undergoing elective colorectal surgery may not need any specific intervention to reduce infectious morbidity, except for a single dose of intravenous antibiotics at induction.

On the other hand, there are other interventions that might have been overlooked and it may be worthwhile to re-visit them in order to establish their value in the current era. In this review, we discuss the available methods of SSI prophylaxis in elective colorectal surgery comprehensively by analysing their historical evolution as well as their current value. The role of oral antibiotic prophylaxis is examined in this context.

LITERATURE SEARCH

A systematic literature search was conducted using medical archiving platforms, including Pubmed, Medline, Google Scholar and the Cochrane database of Systematic Reviews. We searched for studies evaluating SSI prophylaxis in elective colorectal surgery using the following search terms: "surgical site, infection, prophylaxis, antibiotics, mechanical preparation, bowel, surgery, elective" and "oral antibiotics". The data is discussed below from a chronological perspective so that the reader will understand the evolution of SSI prophylaxis in elective colorectal surgery.

History of antibiotics in colorectal surgery

In the pre-antibiotic era, elective colorectal surgery was plagued by infections and high overall morbidity. This contributed to mortality rates in excess of 40% in the 19th century. Since faeces was known to be heavily laden with bacteria, it appeared logical that reducing faecal load would reduce infectious complications. This was initially achieved using a diverting stoma proximal to the anastomosis and by leaving the surgical wound open for healing by secondary intention.

At the turn of the 20th century, surgeons also began to manipulate dietary intake and administer oral agents such as charcoal. Over the subsequent decades, MBP evolved and by the mid-20th century became standard practice in elective colorectal operations, although there was no clear evidence of its effectiveness.

During this era, antibiotics had not yet been developed. It was not until 1928 that Alexander Fleming discovered penicillin[20] - and its first recorded clinical use was on February 12, 1941 when it was administered to 43-year old Albert Alexander to treat a facial abscess in the United Kingdom[21]. The clinical application of this discovery ushered in the antibiotic era, when significant research into new antibiotics was launched.

In the next two decades, three classes of antibiotics were discovered that shaped the future of colorectal surgery: Aminoglycosides in 1943[22], macrolides in 1952[23,24] and polymixins in 1958[25]. These antibiotics all had poor enteral absorption and exerted their actions primarily in the bowel lumen.

Albert Schatz discovered streptomycin, the first aminoglycoside, which he isolated from Streptomyces griseus on October 19, 1943[25]. By binding to the 30S sub-unit of bacterial ribosomal RNA, streptomycin interferes with the coupling of tRNA, leading to inhibition of protein synthesis[25]. Its efficacy to treat tuberculosis was proven conclusively by the very first randomized, double-blinded, placebo-controlled trial on record, designed by Sir Geoffrey Marshall of the MRC Tuberculosis Research Unit[26]. It was also used to sterilize the colon as a part of MBP, but when Lockwood *et al*[27] evaluated its efficacy by culturing stool samples in 24 patients who were treated with oral streptomycin, they found that the reduction in intestinal flora was unreliable. There were insignificant reductions in 39% of clostridia, 50% of coliforms and 88% of streptococci[27]. More importantly, they demonstrated rapid development of resistant strains of *Escherichia coli* (*E. coli*) in the patients who showed a favourable early response[27]. Based on these results Lockwood *et al*[27] recommended reserving streptomycin for tuberculosis treatment rather than expend the drug to sterilize the bowel for surgery. When Selman Waksman isolated the second aminoglycoside, neomycin, from streptomyces fradiae in 1944[22], it naturally became the choice for bowel sterilization. It also found application in the treatment of hepatic encephalopathy by killing ammonia-producing bacteria in the gastrointestinal tract.

Colistin, the first polymixin to be discovered, was isolated from Bacillus polymyxa var. colistinus in 1949[25]. It acts by disrupting lipopolysaccharides in the bacterial cell membrane. It was popular to sterilize bowel because it was poorly absorbed enterally and quite effective against luminal gram-negative bacilli such as *E. coli, Klebsiella Spp* and *Pseudomonas Spp*.

McGuire *et al*[23] isolated Erythromycin, the first macrolide, from strains of streptomyces erythreus in 1952. Erythromycin, through an incompletely understood mechanism, also binds to bacterial rRNA and interferes with aminoacyl translocation, preventing coupling of tRNA and so inhibiting protein synthesis[24,28]. It was attractive

for colorectal surgery since it was poorly absorbed from the gut[28].

The discovery of these three new classes of antibiotics that were poorly absorbed from the gastrointestinal tract provided a new opportunity to reduce the colonic bacterial counts because they exerted their action primarily in the bowel lumen. But there were mixed results to control SSIs in this era because most of the drugs were only effective against gram-negative bacteria with little anti-anaerobic effect[29,30]. Therefore, the use of oral antibiotic prophylaxis was slow to gain traction. It was not until the 1970s that reproducible results were obtained showing benefit from oral antibiotic prophylaxis.

In 1973, Nichols *et al*[31] published their landmark paper in which the oral neomycin-erythromycin combination was administered in three doses over 19 h preoperatively. They randomized 20 patients undergoing elective colorectal surgery to MPB with and without the oral antibiotic regime. All patients had colonic samples taken intra-operatively for culture. Nichols *et al*[31] reported "luxuriant growth of aerobes and anaerobes" in the patients who had MBP alone with mean concentrations that were "similar to those normally found in stool". However, addition of the oral antibiotic regime significantly reduced colonic anaerobes, total aerobes, coliforms, streptococci, bacteroides and peptostreptococci[31]. It was not surprising, then, that the incidence of wound infections was significantly greater with MBP alone (30% *vs* 0%) - and cultures revealed that they were all due to *E. coli* and *Bacteroides fragilis*[31]. *Peptostreptococci* and *Clostridia* were also common pathogens in Nichols' subsequent study where they retrospectively evaluated erythromycin/neomycin regimes in 98 elective colectomies in a case-control study[31]. There was also a greater incidence of wound infections when MBP was used alone, without antibiotics, in this study (17% *vs* 0%)[31].

In 1978, Bartlett *et al*[3] carried out a prospective randomized trial across 10 Veterans Administration Hospitals to compare the oral neomycin/erythromycin regime *vs* placebo. The oral antibiotics significantly reduced the incidence of SSIs from 35% to 9% and anastomotic leaks from 10% to 0%[3]. Cultures of luminal contents showed that oral antibiotics significantly reduced the concentrations of both aerobes and anaerobes by approximately 10^5 bacteria/mL at the time of operation and there was no notable emergence of resistant forms on post-operative samples[3].

There was now an accumulation of data to show that when oral antibiotics were administered after the colon was cleansed by MBP, there was a measurable decrease in SSIs associated with colorectal operations[3,32-35]. The findings were so impressive that in 1979, Proud and Chamberlain[36] wrote "there is no justification for including a placebo in trials of this nature. Nor is mechanical preparation of the bowel alone sufficient for patients about to undergo elective colonic surgery". By the late 1970s, there was wide acceptance of oral antibiotics for SSI prophylaxis. However, continued developments in intravenous antibiotics would soon dampen the enthusiasm for oral antibiotics.

clavulanate in 1981[37]. By the mid-1990s, intravenous antibiotics were rapidly being popularized. With convenient dosing regimes, reliable bioavailability profiles and a wider spectrum of coverage, these newer agents overshadowed the oral non-absorbable antibiotics.

Although Benjamin Duggar discovered aureomycin, the first tetracycline, in 1945[38], it was not available for clinical use until 1955[39] and only became popular as a broad-spectrum antibiotic in the 1970s[39]. Metronidazole had been used since 1959 for parasitic infestations but the anti-bacterial effect was not appreciated until 1962 when it was prescribed for trichomonal vaginitis and cured the patient of bacterial gingivitis[40]. Similarly, it was not until the 1970s that metronidazole became used as an anti-anaerobic drug[41] after Nastro *et al*[42] demonstrated an *in vitro* effect and Whelan *et al*[43] proved an anti-anaerobic effect in humans. By the late 1970s, intra-venous metronidazole and tetracycline regime were becoming popular for SSI prophylaxis.

Further change came with the development of the cephalosporins, a group of antibiotics that inhibited cell wall synthesis. Cephalothin, the original cephalosporin, became available in 1964[44] and was soon followed by second-generation cephalosporins that had a wider spectrum of gram-negative cover[45]. The cephalosporins became popular due to the powerful effects against gram-positive and gram-negative bacteria, especially with the extended spectrum of second and third generation drugs in the late 1970s. They were also attractive for patients with penicillin and tetracycline allergies because they had low cross-reactivity rates[46]. Campagna *et al*[46] reported that patients with penicillin allergies had 1% cross-reaction with first generation cephalosporins and "negligible" cross-reactivity with second-generation cephalosporins[46].

Aminopenicillin was the first β-lactam to be identified in 1961 but the clinically useful derivative, amoxicillin, only became available in 1972[37]. By inhibiting peptidoglycan cross-linking in bacterial cell walls, β-lactam antibiotics have activity against a moderate spectrum of gram-positive and gram-negative organisms. Amoxicillin fell out of favour when resistance emerged due to its susceptibility to β-lactamase produced by some organisms[37]. But in 1972 a potent β-lactamase inhibitor, clavulanic acid, was isolated from Streptococcus clavuligerus[37]. It was combined with amoxicillin to produce a combination that became available for clinical use in the United Kingdom as oral preparations in 1981 and intravenous preparations in 1985[37].

In the next few years, these new intravenous broad-spectrum agents were quickly adopted for prophylaxis against SSI at the expense of oral non-absorbable antibiotics[8].

MBP

MBP was in routine use by the mid-20th century. A

variety of methods were employed including enemas, whole gut irrigation and/or cathartics. Several theories were proposed as the mechanisms through which MBP could reduce infectious morbidity: the empty colon was easier for the surgeon to handle, so improving technical creation of the anastomosis[47]; there would be no faecal bulk to mechanically shear the fresh anastomosis[48]; the absence of faeces would avoid intra-operative contamination that led to SSI[49]; the reduced colonic bacterial load would leave less organisms with opportunity to cause SSI[49,50]; and the resultant drop in luminal pH would reduce ammonia production that had a cytotoxic effect on colonic anastomoses[51,52].

Evidence supporting these concepts came primarily from small animal studies suggesting that MBP increased anastomotic bursting pressure (intra-luminal pressure needed to mechanically disrupt an anastomosis)[51-53] and reduced anastomotic leaks on imaging or *ex-vivo* inspection[53]. Perhaps the most convincing evidence to support MBP was published by O'Dwyer *et al*[53] in 1989. They randomized 36 dogs to low anterior resection with or without MBP. At post-operative day 9, dogs subjected to MBP had significantly less anastomotic leaks (13% *vs* 47%) and pelvic abscesses (6% *vs* 29%).

But in the latter part of the 20th century, anastomotic failure rates still ranged widely from 5%-30% despite routine MBP[54]. It also became increasingly apparent that there were undesirable effects from MBP, including fluid shifts, electrolyte disturbances, nausea, vomiting, abdominal pain and poor patient tolerability[55-57]. But it was the growing trauma experience with emergency surgery for penetrating colon injuries that prompted surgeons to seriously question MBP. Multiple reports surfaced revealing good outcomes after emergent surgery in unprepared colon with irregular lacerations, faecal contamination and significant delay before repair[58-60]. A Cochrane Systematic Review of all randomized controlled trials evaluating diversion *vs* primary repair for penetrating colon injuries settled this issue by showing that primary repair in unprepared bowel significantly reduced overall morbidity, infectious complications, dehiscence and wound complications[61].

These good outcomes prompted investigators to design prospective randomized blinded trials to evaluate MBP for elective colorectal surgery[55,62-69]. Three trials actually suggested that MBP was harmful[55,67,68]. Santos *et al*[67] randomized 149 patients to elective colorectal surgery with and without to MBP. They reported that MBP led to significantly more wound infections (24% *vs* 12%, $P < 0.05$) and a worrisome trend toward increased anastomotic leaks (10% *vs* 5%). Bucher *et al*[55], in their multicentre prospective randomized trial of 153 patients, also reported that the MBP group had significantly more wound abscesses (13% *vs* 4%; $P = 0.07$; RR = 1.58; 95%CI: 0.97-2.34), infectious morbidity (22% *vs* 8%; $P = 0.028$; RR = 1.58; 95%CI: 1.16-2.14), extra-abdominal complications (24% *vs* 11%; $P = 0.034$; RR = 1.5; 95%CI: 1.11-2.04) and prolonged hospital stay - even in the sub-group without complications (11.7 ± 5.2 d *vs* 9.1 ± 2.7 d; $P = 0.001$). Bucher *et al*[68] histologically examined macroscopically healthy colon at the proximal resection margins in 50 patients who had MBP in a blinded prospective randomized trial. They noted that MBP produced potentially deleterious microscopic changes, including greater loss of superficial mucus (96% *vs* 52%; $P < 0.001$), loss of epithelial cells (88% *vs* 40%; $P < 0.01$), significant mucosal inflammation (48% *vs* 12%; $P < 0.02$) and infiltration of polymorphonuclear cells (52% *vs* 8%; $P < 0.02$)[68].

Several large meta-analyses were then commissioned to evaluate the available data from the prospective trials that randomized patients to elective colorectal surgery with or without MBP[10-19,70]. The first few meta-analyses also suggested that MBP was harmful[10-13,70]. Three meta-analyses independently demonstrated a statistically significant increase in anastomotic leaks with MBP[11-13]. One meta-analysis demonstrated a significant increase in wound infections with MBP[70] and another demonstrated a significant increase in post-operative cardiac events[10]. More recent meta-analyses, however, that have included larger patient numbers and better trial designs have not corroborated the harmful effects, although they do provide robust level I evidence that there is no benefit to MBP prior to elective colorectal surgery[15-19].

Although it initially appeared logical that reducing faecal load in the colon would reduce infectious morbidity and anastomotic failures, current data does not support this logic. The prevailing theory to explain this is that a fundamental difference exists between in intra-luminal bacteria and mucosa-associated bacteria. Mucosa-associated bacteria are found within the epithelium and they may be adherent to or trapped in mucus lining the colonic wall. While MPB physically evacuates faeces and bacteria from the lumen, there is insignificant effect on mucosa-associated bacteria[71]. Smith *et al*[72] used animal models to study intra-operative colonic lavage. In their study, they used tissue cultures to quantitatively assess the counts of intraluminal and mucosa-associated bacteria. They demonstrated 10000-fold reductions in intraluminal bacteria but insignificant changes in mucosa-associated bacteria[72]. This strengthened the theory that the intra-mucosal environment was a separate ecologic niche[72].

The overwhelming data from well-designed good quality studies demanded that MBP be abandoned as a part of modern colorectal surgery. Currently MBP is relegated only to specific circumstances for patients with: Tumours < 2 cm diameter that may not be easily appreciated intra-operatively, intra-operative colonoscopy is required, a laparoscopic approach is used or restorative proctectomy is scheduled[55]. However, this paradigm change depleted the armamentarium in the quest to minimize infectious morbidity. In our search for other interventions to combat infection, it may be worth re-considering the use of non-absorbable antibiotics.

Firstly, surgeons reported encountering undigested capsules in the colon intra-operatively[73]. They argued that the timing, absorption and dose of oral antibiotics

were not sufficiently refined to allow for reliable tissue concentrations intra-operatively[73]. The mixed results from early trials gave credence to this argument and there was no available data to counter this argument.

Secondly, it became increasingly recognized that anaerobes were being cultured in 50%[74] to 90%[75] of SSIs after elective colonic operations[76-78]. However, effective anaerobic agents were not available until Nastro *et al*[43] demonstrated the anti-anaerobic effect of metronidazole *in vitro* in 1972, and in 1973 when Whelan *et al*[44] demonstrated the *in-vivo* effect against *Bacteroides fragilis* and *Clostridium welchii* from the colon. But this coincided with the advent of intravenous agents and the oral preparations were overshadowed as clinicians' focus shifted toward intravenous metronidazole coupled with the newer broad-spectrum agents.

The cephalosporins, β-lactams and clauvulanic acid were rapidly being developed in the 1970's and 1980's. They were more attractive than oral antibiotics because of their powerful action against a wide spectrum of gram-positive and gram-negative organisms, predictable drug kinetics and better bioavailability[73]. Oral antibiotics sustained a serious blow in 1998 when Song and Glenny[4] carried out a meta-analysis of all randomized controlled trials between 1984 and 1995 that evaluated antimicrobial prophylaxis against postoperative SSI after colorectal surgery. After evaluating many regimes, they declared that the following regimes were ineffective: Metronidazole alone, doxycycline alone, piperacillin alone, and oral neomycin-erythromycin combinations[4]. Song and Glenny[4] recommended prophylaxis with a single pre-operative dose of intravenous second generation cephalosporin coupled with metronidazole.

With the increasing complement of antibiotics, concerns over drug resistance deepened. Lockwood *et al*[27] had already demonstrated that *E. coli* rapidly developed resistance after brief exposure to oral streptomycin. In the 1970s Nichols *et al*[79], having popularized the erythromycin-neomycin regime[29-31], warned that it could suppress endogenous organisms leading to overgrowth of resistant organisms. In the 1980's reports of *Clostridium difficile*-related pseudomembranous colitis "due to intestinal antiseptics such as oral neomycin" began to surface[80,81]. Although several studies have since disproved the significance of the potential overgrowth of resistant organisms[31,82-84], the suggestion that oral antibiotics could be harmful certainly slowed the enthusiasm for its use.

The final blow came in the late 1990s with the surmounting challenges to MBP. Up to this point, oral antibiotics were administered after mechanical cleansing of the colon. So oral antibiotics fell further into disuse in the late 1990's when MBP was seriously challenged in emergency[38,39,61,85] and elective colorectal surgery[10-13,15-19,71]. Without prior MBP, the prevailing thought was that oral antibiotics could not clear organisms effectively if faeces remained in the lumen.

Because of these factors in the late 1990's, oral antibiotics were over shadowed and debate raged on about the optimal choice of Ⅳ antibiotics and MBP. Therefore, it was not surprising that the use of oral antibiotics in colorectal operations steadily declined over the past three decades from 86% in the 1990s[86] to 36% in 2010[87].

At the turn of the 21st century, a few prospective randomized trials attempted to evaluate the role of oral antibiotic prophylaxis[3,5,31,88-92]. However, there was great heterogeneity between the studies in antibiotic selection, methods of administration, dosing schedules and study protocols. Therefore, mixed results were obtained. Some prospective randomized trials showed no further reduction in SSI when oral antibiotics were added to MBP plus intravenous antibiotics[90,91]. However, when Lau *et al*[89] randomized 194 patients to MBP with either the standard oral erythromycin/neomycin combination, intravenous metronidazole/gentamicin or both oral plus intravenous antibiotics, they found a significantly greater incidence of SSI with MBP and oral antibiotics (27.4%) compared to intravenous antibiotics alone (11.9%) or combined intravenous-oral preparations (12.3%). This study provided conflicting results by now suggesting that oral antibiotics were harmful[89]. The findings also conflicted with the results of prospective randomized trials[3,5,31,88,92] that suggested significant reductions in SSI rates when oral plus intravenous antibiotics were used for prophylaxis. The presence of multiple randomized controlled trials with conflicting results prompted three groups to perform meta-analyses[1,5,8]. Table 1 evaluates the data from recent published meta-analyses evaluating oral antibiotic prophylaxis.

Lewis[5] published a meta-analysis in 2002 in which they examined randomized, controlled trials that compared 1077 patients receiving systemic antibiotics alone *vs* combined oral and intravenous antibiotics in 988 patients in order to prevent SSI in elective colorectal surgery between 1979 and 1995. They recorded SSIs in 6.88% of patients who received combined prophylaxis compared to 13.56% with intravenous antibiotics alone. The overall trend favoured combination therapy for prophylaxis, with a weighted mean risk difference for SSI of 0.56.

Bellows *et al*[1] published a meta-analysis in 2011 that included newer prospective randomized blinded trials[25] and only those that evaluated non-absorbable oral antibiotics. They evaluated 2669 patients across 16 randomized controlled trials comparing combined oral non-absorbable plus intravenous antibiotics *vs* intravenous antibiotics alone in elective colorectal surgery[1]. They found that the combination of oral non-absorbable plus intravenous antibiotics significantly reduced the risk of superficial and deep SSI compared to intravenous antibiotics only, although there was no effect on organ space infections or anastomotic leaks. Bellows *et al*[1] came to the same conclusion endorsing combined oral and intravenous antibiotics as prophylaxis during elective colorectal surgery.

Nelson *et al*[8] evaluated the effect of prophylactic

Table 1 Published meta-analyses evaluating the use of oral antibiotics for surgical site infection prophylaxis in elective colorectal surgery

Ref.	Summary	Surgical Site Infections in patients who received antibiotic prophylaxis *via*			Strength/weakness of study	Conclusion
		Combined oral + IV routes	IV route alone	Oral route alone		
Lewis *et al*[5] (2002)	Meta-analysis of randomized trials comparing Ⅳ *vs* combined antibiotic prophylaxis in 2065 patients	68/988 (6.88%)	146/1077 (13.56%)	0	The major criticism was that they included studies that used absorbable and non-absorbable oral antibiotics.	Combination therapy significantly reduced overall SSI rates (RR = 0.51, 95%CI: 0.24-0.78; $P < 0.001$) *vs* Ⅳ antibiotics alone
Nelson *et al*[8] (2014 revision)	Metanalysis of 2929 patients across 15 randomized studies compared combined *vs* Ⅳ alone	100/1456 (6.87%)	188/1473 (12.76%)	0	All 13 trials were randomized controlled trials but only 5 were blinded studies Some included MBP Antibiotics not standardized Included absorbable oral antibiotics	Combination therapy significantly reduced SSI rates (RR = 0.55, 95%CI: 0.43 to 0.71; $P = 0.0001$) compared to Ⅳ alone
Nelson *et al*[8] (2014 revision)	Metanalysis of 1880 patients across 9 randomized studies comparing combined oral + IV antibiotics *vs* oral alone	39/943 (4.14%)	0	74/931 (7.95%)	7 studies used adequate randomization and 4 were blinded studies Many study variables Some included MBP Antibiotics not standardized Included absorbable oral antibiotics	Combination therapy significantly reduced SSI rates (RR = 0.52, 95%CI: 0.35 to 0.76; $P = 0.0003$) *vs* oral alone
Bellows *et al*[1] (2011)	Metanalysis of 2669 patients across 16 randomized trials comparing combined oral + Ⅳ antibiotics *vs* Ⅳ antibiotics alone	91/1352 (6.73%)	159/1317 (12.07%)	0	Only evaluated recent studies using non-absorbable oral antibiotics 7 were blinded studies 7 studies followed patients for hospital duration only	Combination therapy significantly reduced rates of superficial and deep SSI [RR = 0.57 (95%CI: 0.43–0.76), $P = 0.0002$; risk difference, -0.05 (95%CI: -0.08 to -0.02), $P = 0.0003$] *vs* IV alone No difference in organ space infections [RR = 0.71 (95%CI: 0.43–1.16), $P = 0.2$] or anastomotic leaks [RR = 0.63 (95%CI: 0.28–1.41), $P = 0.3$]

SSI: Surgical site infections; MBP: Mechanical bowel preparation.

antibiotics on SSIs in patients who underwent colorectal surgery in 24 randomized controlled trials. The latest 2014 revision of the Cochrane Systematic Review[8] proved that combined regimes of oral plus intravenous antibiotics provided better SSI prophylaxis than intravenous antibiotics alone or oral antibiotics alone. However, some of the individual studies that evaluated oral antibiotics were flawed, many including varied antibiotics and absorbable oral antibiotics and/or MBP. Nevertheless, Nelson *et al*[8] recommended the use of antibiotics covering aerobic and anaerobic bacteria to be delivered orally and intravenously prior to colorectal surgery for SSI prophylaxis.

Therefore, all 3 recently published meta-analyses[1,5,8] suggested that combined oral and intravenous antibiotics should be used for prophylaxis in elective colorectal surgery. Since these meta-analyses were published, further studies supporting the use of oral antibiotic prophylaxis[93-95] have been reported.

Toneva *et al*[93] retrospectively evaluated the post-operative course of 1161 patients who were readmitted to hospital after elective colorectal resections from 2005-2009. When they evaluated readmissions according to the type of prophylaxis used, it was noted that the patients who had oral antibiotic preparation had significantly less 30-day readmissions for infections (3.9% *vs* 5.4%; $P < 0.001$; OR = 0.81; 95%CI: 0.68-0.97) and a lower than average post-operative hospital stay than those who had MBP alone[93].

Canno *et al*[94] retrospectively studied 9,940 patients who underwent colorectal operations from 2005-2009 across 112 Veterans Affairs Hospitals where SCIP protocols were followed. They reported a significantly lower incidence of SSIs in the patients who had oral antibiotics alone (8.3%) compared to those who had MBP alone (18%) and those receiving no MBP (20%). This represented a 67% decrease in SSI (OR = 0.33; 95%CI: 0.21-0.50) when oral antibiotics were used. The use of oral antibiotics plus MBP resulted in 9.2% SSI rates, representing a 57% reduction in SSI occurrence (OR = 0.43; 95%CI: 0.34-0.55).

Sadahiro *et al*[95] evaluated 310 patients who underwent colonic resections for malignant disease who had MBP and intravenous flomoxef that were randomized to non-absorbable antibiotics antibiotics, probiotics or neither. They showed that oral non-absorbable antibiotic group had a significantly lower incidence of SSI (6.1% *vs* 18% *vs* 17.9% respectively). These patients also had a lower incidence of anastomotic leaks (1% *vs* 12% *vs* 7.4% respectively).

There is level Ⅰ evidence proving that intravenous

antibiotics are efficacious in reducing the incidence of SSI during elective colorectal surgery**.** Ideally, they should be administered intravenously, within 60 min of the surgical incision. A single pre-operative dose of a second or third generation cephalosporin (for extended gram negative coverage) combined with metronidazole (for anaerobic cover) is recommended for prophylaxis in elective colorectal surgery.

Good-quality data has now emerged supporting the role of oral antibiotics, in combination with intravenous antibiotics, for SSI prophylaxis. The existing data suggest that combination therapy is more effective than oral antibiotics alone and intravenous antibiotics alone. Therefore, in addition to the above intravenous regime, we also recommend administration of non-absorbable oral agents, such as neomycin sulphate with erythromycin, in the 18-h period prior to elective colorectal surgery.

We do recognize that the choice of antibiotics is still not yet settled, but it should include appropriate gram negative, gram positive and anaerobic coverage, with non-absorbable agents administered orally. The chosen regime should be guided by institutional antimicrobial protocols, taking into account the spectrum of microbes in the local environment, their resistance patterns and the availability of the individual agents.

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ORIGINAL ARTICLE

Retrospective Study

Hepatocellular carcinoma with child Pugh-A Cirrhosis treated with stereotactic body radiotherapy

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Abstract

AIM

To evaluate the control, survival, and hepatic function for Child Pugh (CP)-A patients after Stereotactic body radiotherapy (SBRT) in hepatocellular carcinoma (HCC).

METHODS

From 2009 to 2016, 40 patients with Barcelona Liver Clinic (BCLC) stages 0-B HCC and CP-A cirrhosis completed liver SBRT. The mean prescription dose was 45 Gy (40 to 50 Gy in 4-5 fractions). Local relapse, defined as recurrence within the planning target volume was assessed with intravenous multiphase contrast computed tomography or magnetic resonance imaging every 4-6 mo after completion of SBRT. Progression of cirrhosis was evaluated by CP and Model for End Stage Liver Disease scores every 3-4 mo. Toxicities were graded per the Common Terminology Criteria for Adverse Events (v4.03). Median follow-up was 24 mo.

RESULTS

Forty-nine HCC lesions among 40 patients were analyzed in this IRB approved retrospective study. Median tumor diameter was 3.5 cm (1.5-8.9 cm). Six patients with tumors ⩾ 5 cm completed planned selected transarterial chemoembolization (TACE) in combination with SBRT. Eight patients underwent orthotropic live transplant (OLT) with SBRT as a bridging treatment (median time to transplant was 12 mo, range 5 to 23 mo). The Pathologic complete response (PCR) rate in this group was 62.5%. The 2-year in-field local control was 98% (1 failure). Intrahepatic control was 82% and 62% at 1 and 2 years, respectively. Overall survival (OS) was 92% and 60% at 1 and 2 years, with a median survival of 41 mo per Kaplan Meier analysis. At 1 and 2 years, 71% and 61% of patients retained CPA status. Of the patients with intrahepatic failures, 58% developed progressive cirrhosis, compared to 27% with controlled disease (P = 0.06). Survival specific to hepatic failure was 92%, 81%, and 69% at 12, 18, and 24 mo. There was no grade 3 or higher toxicity. On univariate analysis, gross tumor volume (GTV) < 23 cc was associated with freedom from CP progression (P = 0.05), hepatic failure-specific survival (P = 0.02), and trended with OS (P = 0.10).

CONCLUSION

SBRT is safe and effective in HCC with early cirrhosis and may extend waiting time for transplant in patients who may not otherwise be immediate candidates.

Key words: Stereotactic body radiotherapy; Hepatocellular carcinoma; Child-Pugh A; Cirrhosis; Hepatoma; Local control; Radiotherapy; Radiation

Core tip: This retrospective review demonstrates excellent long term local control of hepatocellular carcinoma (HCC) in early stage cirrhosis treated by Stereotactic body radiotherapy (SBRT), while retaining hepatic function. However, the overall prognosis of HCC remains poor despite successful local therapy and transplant remains the standard of care. Given the rising incidence of HCC, liver procurement and selection of candidates for transplant will become increasingly stringent. The long term control and maintenance of hepatic reserve demonstrated in this series suggests that SBRT as a bridging therapy may extend waiting time for transplant in patients who may not otherwise be immediate candidates for it.

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INTRODUCTION

Accounting for the second most cancer-related deaths worldwide, hepatocellular carcinoma (HCC) is an aggressive malignancy that is diagnosed in at least 6 of every 100000 Americans, a rate nearly triple that of thirty years ago[1,2]. In the United States, Chronic Hepatitis C (HCV), alcohol abuse, and non-alcoholic steatohepatitis (NASH) are the leading causes of HCC, which is diagnosed at a growing rate in light of more sophisticated imaging and vigilant surveillance with serum markers[3-5]. Liver transplant remains the gold standard for definitive treatment, however the vast majority of patients fail to meet the surgical or medical criteria for transplant, with high mortality rates if not properly selected[6]. Further complicating management is the cirrhosis that accompanies HCC, which often renders patients medically inoperable or at high risk for surgery.

Therapeutic alternatives include partial hepatectomy, radiofrequency ablation, trans-arterial chemoembolization (TACE), and radioembolization among others. Each treatment modality is associated with procedural complications especially in patients with portal hypertension. In non-cirrhotic patients, partial hepatectomy or surgical resection of hepatocellular carcinoma is potentially curative, with average long-term intrahepatic control rates over 40% and 5-year survival over 60%[7,8]. However, cirrhotic patients must be carefully selected for partial resection to avoid access perioperative mortality[9,10]. Further limiting patient selection for resection are tumors with vascular invasion or those in a centralized location, even in otherwise healthy livers[11]. Ultimately, 15%-30% of HCC patients are eligible for curative partial hepatectomy[12,13]. Other widely used modalities such as TACE and RFA in non-surgical candidates have shown a control and survival benefit, however selection is limited by vascular invasion and biliary obstruction with TACE[14], and by size (< 3 cm) and location (infradiaphragmatic or adjacent to large vessels) with RFA[15,16].

Stereotactic body radiotherapy (SBRT) has emerged as non-invasive treatment that serves as another alternative for local tumor control or used as a bridge to liver transplant. SBRT by definition is an ultraconformal radiotherapy technique administering high radiotherapy doses in 1-5 fractions. It uses multiple external radiation beams/arcs deliver an ablative tumoricidal dose with sharp dose fall-off which limits unacceptable dose to the liver as well as adjacent vasculature, gallbladder, chest wall, kidney or diaphragm.

Several prospective studies have shown that SBRT can be delivered safely in Child Pugh A patients with local control rates between 75%-90% for median tumor size between 20 - 30 cc[17,18].

Although the data for SBRT in HCC is promising, current guidelines recommend it only when patients are

not amenable to, or have failed, other local therapies. Furthermore, while a favorable short-term SBRT-related toxicity profile in early cirrhotic patients is well documented, its long-term impact on progression of hepatic failure is not widely reported. The objective of this retrospective study is to analyze the tumor control, survival, toxicity and preservation of hepatic function, in HCC patients with Child-Pugh A cirrhosis treated with SBRT.

MATERIALS AND METHODS

Patient selection

Between 2009 and 2016, 49 intrahepatic lesions among 40 patients with BCLC stages 0-B hepatocellular carcinoma and Child-Pugh class A cirrhosis were treated with SBRT at a single institution in this IRB approved study. Patients who were treated with palliative intent at a dose range below 30 Gy, had large multinodular tumors (aggregate > 9 cm), metastatic disease, or an ECOG performance status > 2 were excluded from this study. No patients had previous external beam radiation or Yttrium-90 radioembolization. Six patients with large tumors (median diameter 5.4 cm) received planned TACE prior to SBRT for radiosensitization. All patients were evaluated for hepatectomy and transplant in a multidisciplinary setting prior to undergoing SBRT.

Treatment

Treatment planning consisted of a IV contrast-enhanced free breathing helical computed tomography (CT) scan with 3 mm slice thickness, followed by immediate 4-D CT simulation utilizing a Siemens Somatom Sensation Open scanner (Siemens Medical) with an Anzai belt (AZ733V, Anzai Medical) and immobilization with a Vac-Loc® vacuum bag (Bionix, Toledo, OH, Spain). An internal target volume (ITV) was generated based on hepatic motion during the respiratory cycle, with a planning target volume (PTV) generated in the standard fashion around this volume. PTV included the ITV with a 0.3-0.5 cm margin. SBRT dose was prescribed to the isodose line encompassing the PTV (generally 80%-90% isodose line) allowing up to 20% higher dose to the target volume. Dose per fraction varied based on tumor size, location, and normal tissue tolerance. Twenty-two of the 38 patients utilized 4DCT co-registered with 99mTc-sulfur colloid Single Photon Emission Computed Tomography (SPECT) for visualization and conformal avoidance of best perfused hepatic parenchyma. Details of SPECT/CT co-registration and treatment planning have been previously reported for liver SBRT in cirrhotic HCC patients[19,20]. Dose limits were set such that at least 35% of predicted liver volume by SPECT imaging received $\leqslant$ 18 Gy in 5 fractions or $\leqslant$ 16 Gy in 4 fractions. The median dose to the PTV was 45 Gy (range 40 to 50 Gy) at a median dose per fraction of 9 Gy. Median biologic equivalent dose (BED_{10}) was 85.5 Gy (range 72-105.6 Gy).

Outcome assessment

Local response with contrast-enhanced triple phase CT or MRI was documented every 4-6 mo following radiotherapy as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria[21]. Failures were considered local if within or on the edge of the PTV. Intrahepatic failures were defined as radiographic evidence of progressive hepatocellular carcinoma within the liver and outside of the PTV. Fluctuations in alpha-feto protein (AFP) levels were not considered when assessing response or tumor control. The progression of cirrhosis was evaluated by Child-Pugh and End Stage Liver Disease (MELD) scores at least every 4 mo. Potential prognostic correlates including initial stage, tumor size, radiation dose, performance status, and initial MELD stage were analyzed against intrahepatic control, overall survival, and hepatic-failure specific survival, which we define as the portion of patients who did not die from liver failure. We also evaluated potential correlates of freedom from C-P progression, which we define as advancing from the Child Pugh A to the Child Pugh B classification[22]. Toxicities were graded per the Common Terminology Criteria for Adverse Events (CTCAE) (v4.03). Survival and tumor control analyses are based on Kaplan Meier (KM) methodology, and univariate analysis was conducted *via* Cox proportional hazard regression models using MedCalc.

RESULTS

Patient characteristics

Thirty-two males and eight females with HCC and CP-A cirrhosis who completed liver SBRT were analyzed with a median follow up of 24 mo (4 to 64 mo). Seven of the 40 patients had two tumors treated simultaneously, and one patient had 3 treated at the same time. The maximum tumor diameter ranged from 1.5 to 8.9 cm, with a median of 3.5 cm. Gross tumor volume varied between 2.6 to 220.1 cc with median 23 cc, and the corresponding planning target volume was between 11.5 and 351 cc (median 67.6). BCLC stages 0 (very early), A (early), and B (intermediate) comprised of 6, 10, and 24 patients, respectively. This corresponds to American Joint Committee on Cancer (AJCC) stages Ⅰ (n = 6), Ⅱ (n = 12), ⅢA (n = 8) and ⅢB (n = 8). SBRT was used as a bridging therapy for orthotropic liver transplant in eight patients. The causes of HCC include Hepatitis C (n = 17), alcohol abuse (n = 8), a combination of both (n = 8), NASH (n = 4), biliary cirrhosis (n = 1), immunosuppression following kidney transplant (n = 1), and one was cryptogenic. Eastern Cooperative Oncology Group (ECOG) performance status was equal to 0, 1, and 2 in 21, 14, and 3 patients respectively (2 unknown). Although all patients were classified as Child Pugh A, 9 of the 40 patients had a MELD score of 10 or higher. A summary of patient characteristics is demonstrated on Table 1.

Control

At last follow up, 48 of 49 lesions (98%) were controlled locally (within the PTV). The one failure was a 4.3

Table 1 Patient characteristics

	Number	Percentage
Gender		
Male	32	82%
Female	8	18%
ECOG performance status[1]		
0	21	55%
1	14	37%
2	3	8%
Etiology of hepatocellular carcinoma[2]		
Hepatitis C	17	46%
Alcohol	8	22%
Combination of Hepatitis C/alcohol	8	22%
NASH	4	8%
BCLC Stage		
0 (very early)	6	15%
A (early)	10	25%
B (intermediate)	24	60%
Previous treatment		
None	34	85%
TACE	6	15%
Number of treated lesions		
Single	32	80%
Multiple[3]	8	20%
Initial MELD score		
< 10	31	78%
> 10	9	22%
Median tumor size (range)	3.5 cm	(1.5 to 8.9 cm)
Median gross tumor volume (range)	23 cc	(2.6 to 220.1 cc)
Median planning target volume (range)	67.6 cc	(11.5 to 351 cc)

[1]2 patients unknown; [2]1 patient with biliary cirrhosis and 1 immunosuppressed; [3]7 patients with 2 lesions and 1 with 3 lesions. ECOG: Eastern cooperative oncology group; NASH: Non-alcoholic steatohepatitis; BCLC: Barcelona liver clinic; TACE: Transarterial chemo-embolization; MELD: Model for end stage liver disease.

cm tumor with a GTV of 80 cc treated to 4500 cGy in 5 fractions. The recurrence occurred 10 mo after completing SBRT. Intrahepatic control, defined as no evidence of disease within the entire liver was 82%, 77%, and 62% at 12, 18, and 24 mo, respectively, with a median time to progression of 47 mo per KM analysis. Five of the intrahepatic failures were treated with additional SBRT and five were salvaged with either TACE (1), Y-90 (2), or resection (1). Distant metastases occurred in the peritoneum, bone, and lungs among 6 patients. SBRT served as bridge for orthotropic liver transplant in 8 patients, 5 of whom demonstrated a pathologic complete response (62.5%). The median time to transplant was 12 mo (5-23 mo). One patient developed an intrahepatic failure which was successfully treated with a second SBRT prior to transplant. No patient developed recurrence after transplant.

Survival

Twenty-three of 40 (58%) patients were alive at last follow up. Three patients died from perioperative complications after liver transplant, all of whom retained Child Pugh A status and had a pathologic complete response. The remaining 5 transplant patients were all long term survivors. One (89% *vs* 88%) and two-year survival (60% *vs* 63%) was similar for patients who received SBRT with or without transplant. Progressive HCC was the cause of death in 9 patients treated with SBRT, and five patients died without evidence of recurrence, 3 of whom had progressive cirrhosis, one with heart disease, and one with metastatic lung cancer.

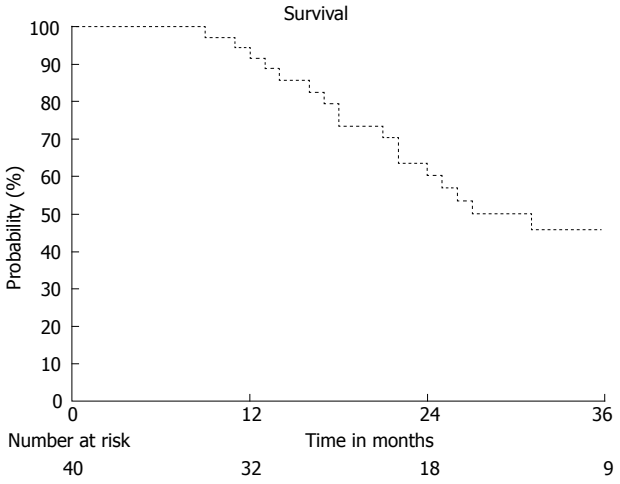

Figure 1 Overall Survival of all patients.

The median survival was 41 mo with a 1-year, 18-month, and 2-year overall survival rate of 92%, 74%, and 60%, respectively. Disease-free survival was 79%, 58%, and 44% at 1 year, 18 mo, and 2 years. Hepatic failure-specific survival was 92%, 81%, and 69% at 1 year, 18 mo, and 2 years, respectively. Univariate analysis suggested that a GTV > 23 cc correlated with a decreased hepatic failure-free survival (HR = 5.72, P = 0.01) and trended towards a decreased overall survival (HR = 2.14, P = 0.10). Advancing Child Pugh cirrhosis also strongly correlated with survival (HR 5.05, P = 0.01) (Figures 1-3).

Hepatic function and toxicity

Of the 40 patients treated, 24 retained Child Pugh A class cirrhosis (63%) and 27 maintained their initial MELD score (68%) at the time of last follow up. The median time to progression within Child Pugh category was 37 mo, with a freedom from Child Pugh progression rate of 89%, 71%, and 62% at 6, 12, and 18 mo respectively (Figure 2). The median time to progression of MELD score was 33 mo with a freedom from MELD progression rate of 95%, 88%, and 79% at 6, 12, and 18 mo respectively. Of the patients with intrahepatic failures, 58% also developed progressive cirrhosis, compared to 27% whom were regionally controlled (HR = 3.8, P = 0.06). As with survival, a GTV > 23 cc (median 60 cc, up to 220 cc) correlated with an increased rate of Child Pugh progression (HR = 2.89, P = 0.05) (Figure 3). There was no incidence of grade 3 or higher toxicity, and 3 patients had grade 2 fatigue. Grade 1 elevation in transaminases was seen in 9 patients, and 1 patient developed grade 2 rise in Alkaline Phosphatase, without any incidence of radiation induced liver disease (RILD).

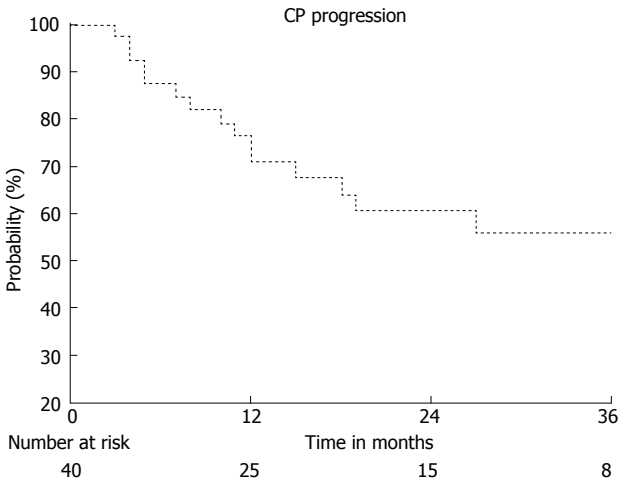

Figure 2 Freedom from child Pugh Progression of all patients. CP progression: Percentage of patients retaining child Pugh A status.

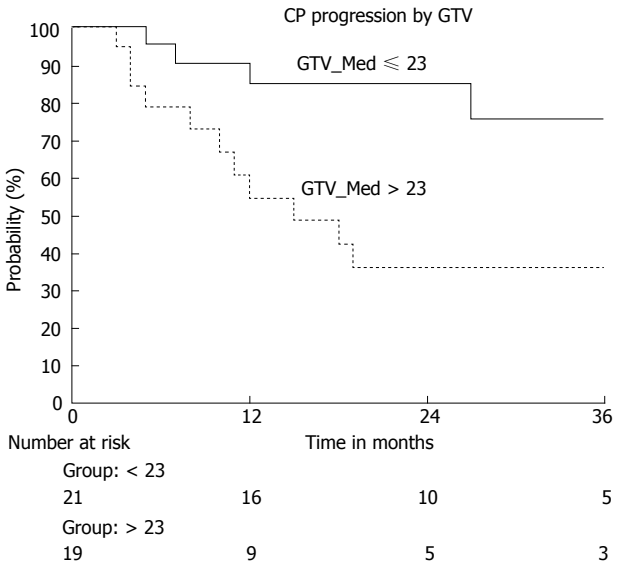

Figure 3 Freedom from child Pugh progression by gross tumor volume. CP progression: Percentage of patients retaining child Pugh A status; GTV: Gross tumor volume in cubic centimeters; Group ⩽ 23: Number of patients with a GTV less than or equal to 23 cc; Group > 23: Number of patients with a GTV greater than 23 cc.

DISCUSSION

Until recently, radiotherapy has been only infrequently used in targeting hepatocellular carcinoma because of the low tolerance of the whole liver to radiation and challenges associated with underlying liver dysfunction. Conversely, dose escalation studies at the University of Michigan with CT-based 3D-conformal radiotherapy planning established a correlation between the irradiated liver volume, the dose delivered, and the risk of radiation-induced liver disease[23]. The liver is a parallel organ and small volumes of liver can tolerate high doses of radiation when the whole liver mean dose can be minimized with techniques such as SBRT. As a result, several prospective SBRT studies have established a dose-response relationship in HCC with early stage cirrhosis, without compromising safety.

Mendez-Romero *et al*[17] and Tse *et al*[24] demonstrated long term local control rates of 75% and 65% with a median dose of 5 Gy x 5 fractions and 6 Gy x 6 fractions, respectively. Dose escalation to 48 Gy in 3 fractions yielded an 87% local control rate for CPA patients in a phase Ⅰ/Ⅱ study by Lasley *et al*[25] Similarly, Bujold *et al*[33] found that doses over 30 Gy (in 6 fractions) improved local control rates. Building on these and other data, the patients in our study were treated to a median BED_{10} of 85.5 Gy (45 Gy in 5 fractions). The 98% local control rate in this study compares favorably to already excellent historical controls, and the overall survival falls within the wide range of reported outcomes in the current literature (Table 2).

In this report of CP-A patients with limited HCC treated with SBRT, 1 and 2 year survival was similar for patients with and without transplant. Given the inherent perioperative mortality risk of liver transplantation, these well selected early CP-A cirrhotic patients with limited extent of HCC may benefit from watchful waiting, reserving orthotopic liver transplantation at the time of further intrahepatic progression or following their natural cirrhosis progression to higher MELD scores. Such a preposition has been suggested by Merion and Wedd *et al*[26,27] whose large retrospective studies independently reported no detriment in survival when delaying transplant in very early stage cirrhosis. Accordingly, close follow-up and careful selection is essential with a watchful waiting approach. Additionally, with 2 year follow up survival is similar with or without transplant, yet long term cure of both HCC and cirrhosis with transplant, may yield a separation of survival curves with longer follow up.

Among the most important aspects of patient selection in HCC is the risk stratification based on hepatic function, such as the Child-Pugh or Model for End Stage Liver Disease (MELD), as patients with worse baseline cirrhosis are at higher risk for therapeutic toxicity. Teh and Cucchetti *et al*[28,29] have shown that a MELD score over 9 preceding partial liver resection is associated with increased perioperative mortality and decreased survival Other studies corroborate a link between initial MELD or Child Pugh score and survival in hepatocellular carcinoma[21,27]. Even in early stage cirrhosis, HCC has been known to accelerate the natural progression of liver failure, which can be impacted regardless of its initial severity[30]. It has also been suggested that a linear progression of liver failure, or serial trend in increasing MELD score, is a better predictor of outcome compared to initial MELD score[31]. These data underline the importance of preserving hepatic function while treating the malignancy that exacerbates it, even at an early stage.

Unsurprisingly, in this study, intrahepatic failure correlated strongly with progressive liver disease, which consequently correlated with overall mortality. Among

Table 2 Summary of prospective stereotactic body radiotherapy studies in hepatocellular carcinoma patients with Child Pugh-A cirrhosis

Study	No of lesions	Median dose-fractionation	Median GTV (cc)	Local control	Overall survival	Grade 3+ toxicity	Median follow-up (m)
Mendez-Romero *et al*[17], 2006	11[1]	5 Gy × 5	22.3	75% (22 mo)	75%, 40% (1, 2 yr)	36%	12.9
Tse *et al*[24], 2008	21	6 Gy × 6	173	65% (1 yr)	48% (1 yr)	12%	17.6
Lasley *et al*[25], 2012	39	16 Gy × 3	-	91% (2 yr)	72% (2 yr)	4.60%	33.3
Bujold *et al*[33], 2013	102	6 Gy × 6	117	87% (1 yr)	55%, 34% (1 yr, 2 yr)	2%	31
Current study	47	9 Gy × 5	23	98% (2 yr)	92%, 60% (1 yr, 2 yr)	None	24

[1]Study includes Child Pugh B patients. GTV: Gross tumor volume; cc: Cubic centimeters; Gy: Gray.

patients treated with SBRT with controlled disease in the liver, 73% retained long term hepatic function which compares favorably to the natural progression of cirrhosis[32]. Three patients advanced to Child Pugh B cirrhosis within 6 mo of SBRT, none of whom had radiographic evidence of HCC. There was no evidence of classic RILD or radiation-induced grade 2 or higher toxicity.

This retrospective review demonstrates excellent long term local control of HCC in early stage cirrhosis treated by SBRT, while retaining hepatic function at a rate similar to historical norms. Unfortunately, the overall prognosis of HCC remains poor despite successful local therapy. Liver transplant remains the standard of care for definitive management. However, with the rising incidence of HCC, demand for healthy livers may outpace supply, and consequently, the selection of appropriate candidates for transplant will become more stringent. The long term local control and maintenance of hepatic reserve demonstrated in this series suggests that SBRT as a bridging therapy may extend waiting time for transplant in patients who may not otherwise be immediate candidates for it, such as those with Child-Pugh A cirrhosis and early stage HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is an aggressive malignancy that is diagnosed in at least 6 of every 100000 Americans, a rate nearly triple that of thirty years ago. Liver transplant remains the gold standard for definitive treatment, however many patients fail to meet the surgical or medical criteria for transplant, with high mortality rates if not properly selected. Stereotactic body radiotherapy (SBRT) has emerged as non-invasive treatment option for HCC to achieve local tumor control and may be used as a bridge to liver transplant. Multiple external radiation beams/arcs delivered ablative doses with sharp dose fall-off at surrounding normal tissues allowing SBRT to be administered without limitations of unacceptable toxicity to the liver and adjacent vasculature, gallbladder, chest wall, kidney or diaphragm. Several prospective studies have shown that SBRT can be delivered safely in Child Pugh A patients with local control rates between 75%-90%.

Research motivations

Although the data for SBRT in HCC is promising, current guidelines recommend it only when patients are not amenable to, or have failed, other local therapies. Furthermore, while short-term SBRT-related toxicity in early cirrhotic patients is well documented, its long-term impact on hepatic failure progression is not widely reported.

Research objectives

The objective of this retrospective study is to analyze the tumor control, survival, toxicity and preservation of hepatic function, in HCC patients with Child-Pugh A cirrhosis treated with SBRT.

Research methods

We retrospectively reviewed 40 patients with Barcelona Liver Clinic (BCLC) stages 0-B HCC and CP-A cirrhosis completed liver SBRT from 2009-2016. Local relapse, defined as recurrence within the planning target volume was assessed with intravenous multiphase contrast CT or MRI every 4-6 mo after completion of SBRT. Progression of cirrhosis was evaluated by CP and Model for End Stage Liver Disease (MELD) scores every 3-4 mo. Toxicities were graded per the Common Terminology Criteria for Adverse Events (v4.03). Median follow-up was 24 mo.

Research results

The 2-year in-field local control was 98% (1 failure). Intrahepatic control was 82% and 62% at 1 and 2 years, respectively. Overall survival (OS) was 92% and 60% at 1 and 2 years, with a median survival of 41 mo. At 1 and 2 years, 71% and 61% of patients retained CPA status. Of the patients with intrahepatic failures, 58% developed progressive cirrhosis, compared to 27% with controlled disease (P = 0.06). Survival specific to hepatic failure was 92%, 81%, and 69% at 12, 18, and 24 mo. There was no grade 3 or higher toxicity. On univariate analysis, gross tumor volume (GTV) < 23 cc was associated with freedom from CP progression (P = 0.05), hepatic failure-specific survival (P = 0.02), and trended with OS (P = 0.10). Eight patients underwent orthotropic live transplant (OLT) with SBRT as a bridging treatment (median time to transplant was 12 mo, range 5 to 23 mo). The Pathologic complete response (PCR) rate in this group was 62.5%.

Research conclusions

This retrospective review demonstrates excellent long term local control of HCC in early stage cirrhosis treated by SBRT, while retaining hepatic function. However, the overall prognosis of HCC remains poor despite successful local therapy and transplant remains the standard of care. Given the rising incidence of HCC, liver procurement and selection of candidates for transplant will become increasingly stringent. The long term control and maintenance of hepatic reserve demonstrated in this series suggests that SBRT as a bridging therapy may extend waiting time for transplant in patients who may not otherwise be immediate candidates for it.

Research perspectives

Further prospective studies utilizing SBRT for HCC as a bridge to transplant are warranted.

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ORIGINAL ARTICLE

Retrospective Study

Utility of single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection

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Abstract

AIM

To study the utility of single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection.

METHODS

A 2 cm transverse skin incision was made in the umbilicus, extending to the intraperitoneal cavity. Carbon dioxide was insufflated followed by insertion of laparoscope to observe the intraperitoneal cavity. The type of hernia was diagnosed and whether there was the presence of intestinal incarceration was confirmed. When an intestinal incarceration in the hernia sac was found, the forceps were inserted through the incision site and the intestine was returned to the intraperitoneal cavity without increasing the number of trocars. Once the peritoneum was closed, totally extraperitoneal inguinal hernia repair was performed, and finally, intraperitoneal observation was performed to reconfirm the repair.

RESULTS

Of the 75 hernias treated, 58 were on one side, 17 were on both sides, and 10 were recurrences. The respective median operation times for these 3 groups of patients were 100 min (range, 66 to 168), 136 min (range, 114 to 165), and 125 min (range, 108 to 156), with median bleeding amounts of 5 g (range, 1 to 26), 3 g

(range, 1 to 52), and 5 g (range, 1 to 26), respectively. Intraperitoneal observation showed hernia on the opposite side in 2 cases, intestinal incarceration in 3 cases, omental adhesion into the hernia sac in 2 cases, severe postoperative intraperitoneal adhesions in 2 cases, and bladder protrusion in 1 case. There was only 1 case of recurrence.

CONCLUSION

Single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection makes hernia repairs safer and reducing postoperative complications. The technique also has excellent cosmetic outcomes.

Key words: Inguinal hernia; Intestinal incarceration; Totally extraperitoneal inguinal hernia repair; Intraperitoneal inspection; Single incision

Core tip: Single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection (iSTEP) makes hernia repairs safer and more effectively. Totally extraperitoneal inguinal hernia repair had the disadvantages for difficulty with confirming the type of hernia as well as difficulty with large indirect inguinal hernia, intestinal incompetence and postoperative prostatectomy. However, iSTEP can be used to diagnose the type of hernia easily. It enables observation of the opposite side and reconfirmation of treatment after mesh repair making the technique safer and reducing postoperative complications. The technique also has excellent cosmetic outcomes.

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INTRODUCTION

Prudent observation of inguinal hernia is recommended for asymptomatic patients according to the guideline for inguinal hernia treatment released by the European Hernia Society[1]. However, surgery is the standard treatment. The surgical techniques used for inguinal hernia consist of the traditional anterior technique and laparoscopic surgery. Two approaches are utilized in laparoscopic surgery: Transabdominal preperitoneal approach (TAPP) and totally extraperitoneal hernia repair (TEP). In cases of intestinal incarceration, intraperitoneal observation may be necessary to confirm the presence of intestinal damage after reduction, but many inguinal hernias can be repaired without entering the abdominal cavity. TEP shortens the operation time, enhances patient satisfaction, and reduces postoperative pain[2]. However, using conventional TEP, only the hernia on one side can be identified, and there is a possibility of missing occulting inguinal hernia on the opposite side. By combining TEP with intraperitoneal observation, it is possible to diagnose the type of hernia, confirm repair after covering the hernia with mesh, and perform both procedures safely and reliably. We report herein our experiences with single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection (iSTEP), which was performed on 75 patients.

MATERIALS AND METHODS

From April 2009 when iSTEP was first introduced until May 2016, the 75 patients who underwent the procedure at the Prefectural Hiroshima Hospital were enrolled. All surgeries were performed by the same experienced surgeon. Data on patient demographics, clinical data, intraoperative findings, and postoperative course were prospectively collected. All patients underwent surgery after providing informed consent. The procedure was approved by the Ethics Committee at the Prefectural Hiroshima Hospital and the study was performed in accordance with the Declaration of Helsinki. We excluded patients who met the following criteria: History of prostate surgery, giant inguinal hernia, young patients with small indirect inguinal hernia, strangulated hernia, and patients who could not tolerate general anesthesia, which was employed for laparoscopic hernia repair at our hospital.

During the surgery, the patient was placed in a supine position under general anesthesia. A 2 cm transverse skin incision was made in the umbilicus, followed by an incision in the peritoneum from the fascia defect to the abdominal cavity. A trocar attached to an access port was inserted and carbon dioxide was insufflated to 8 mmHg (Figure 1). The type of hernia was diagnosed and the presence of intestinal incarceration was confirmed in the intraperitoneal cavity (Figure 2). The trocar was removed and the peritoneum was closed after inserting a catheter to degas the cavity. The peritoneum was ligated by 3-0 Vicryl, once the peritoneum was closed (the ligation was unfolded at the time performing intraperitoneal observation). TEP was then started. The subcutaneous tissue was dissected to the rectus abdominis anterior sheath and a transecting incision was made at the anterior sheath. The rectus abdominis was split and the posterior sheath was exposed. Blunt dissection using an electrical scalpel or a finger was performed between the muscle and the posterior sheath to create a preperitoneal space. A multi-channel access port (GelPOINT MINI; Applied Medical, Rancho Santa Margarita, CA, United States) was installed and carbon dioxide was insufflated to 8mmHg again (Figure 3). The preperitoneal space was dissected using a bipolar forceps by grasping the forceps and pulling toward the Retzius cavity and the peritoneal edge was checked. The cord structures were freed from the hernia sac and parietalisation was performed gently without perforation of the peritoneum. The hernia sac was extracorporeally ligated with a Fisherman'

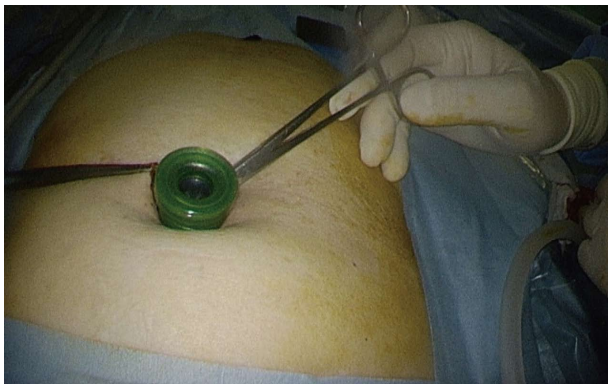

Figure 1 A 2 cm skin incision was made in the umbilicus. A trocar attached to an access port was inserted into the abdominal cavity and carbon dioxide was insufflated.

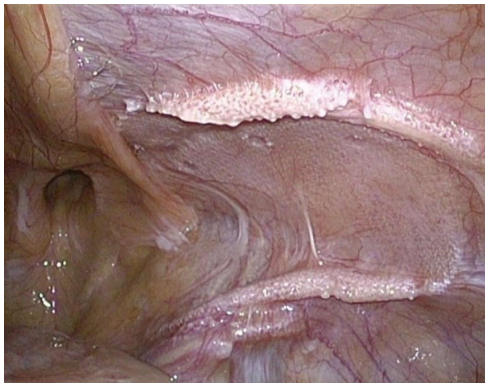

Figure 2 The hernia was viewed and diagnosed within the intraperitoneal cavity. This patient had recurrent hernia at the median part of the Kugel Patch.

s knot using 2-0 Prolene and dissected. The edge of the peritoneum was grasped and dissected toward the dorsal side and the lateral side to secure a space for mesh. The Gel Seal CAP was detached and an artificial patch (3D Max light Mesh L size; Bard, Murray Hill, NJ, United States) (10.8 cm × 16 cm) or TiLENE Mesh; pfm medical, Koln, Germany) (10 cm × 15 cm) was inserted through the incision. After the mesh was positioned to cover the Hesselbach triangle, femoral rings, and inguinal ring, it was fixed to the Cooper's ligaments. The interior and lateral sides of the mesh were secured using a tracking device (Pro Tack; Medtronic, Fridley, MN, United States), applied carefully to avoid injury to the inferior epigastric vessels. Finally, the abdominal cavity was observed to confirm that the repair was complete (Figure 4). The peritoneum, anterior rectus sheath and skin were each closed.

RESULTS

iSTEP hernia repair was successfully completed in 75 patients. Patient demographics and characteristics are summarized in Table 1. There were 66 men and 9 women. The median age of the patients was 68 years (range, 17 to 82 years), median weight was 63 kg (range, 38 to 106 kg), and median body mass index was 23.0

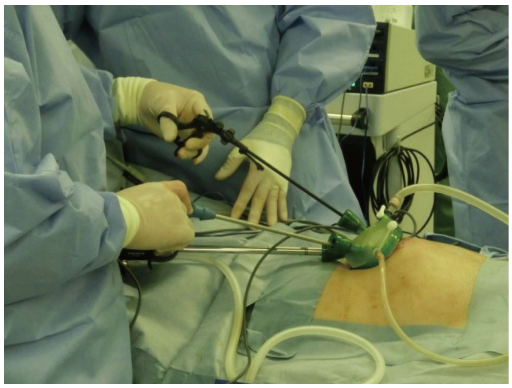

Figure 3 GelPOINT MINI was installed and carbon dioxide was insufflated to 8 mmHg before starting totally extraperitoneal hernia repair.

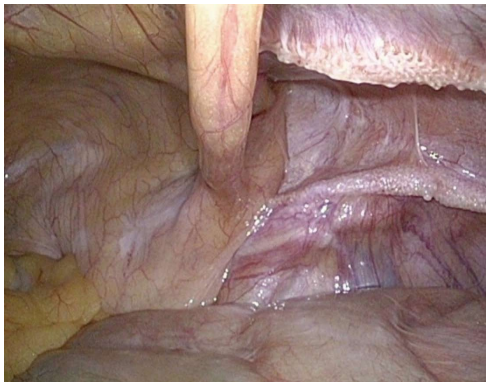

Figure 4 The intraperitoneal cavity was viewed again to confirm the repair.

kg/m^2 (17.3 to 32.7 kg/m^2). The number of patients with a physical status of ASA Ⅰ, Ⅱ, and Ⅲ according to the American Society of Anesthesiologists classification was 25, 49, and 1, respectively. The subjects included smokers, individuals with hypertension, diabetes, respiratory disease, coronary artery disease, or taking anticoagulant/antiplatelet medicine. Fifty-eight hernias were on one side, 17 were on both sides, and 10 were recurrences. The median operation time for these 3 groups of patients was 100 minutes (range, 66 to 168), 136 min (range, 114 to 165), and 125 min (range, 108 to 156) and the median bleeding amount was 5 g (range, 1 to 26), 3 g (range, 1 to 52), 5 g (range, 1 to 26), respectively (Table 2). Intraperitoneal observation showed hernia on the opposite side in 2 cases, intestinal incarceration in 3 cases, omental adhesion to the hernia sac in 2 cases, severe postoperative intraperitoneal adhesions in 2 cases, and bladder protrusion in 1 case. Postoperative hemorrhage and wound infection were not observed, and there was only 1 case of recurrence.

DISCUSSION

Compared to the conventional anterior approach, TEP results in less postoperative pain, fewer postoperative complications, lower recurrence rates, early discharge, and faster return to daily life[3]. TEP is classified as Level 1A treatment in the European hernia guidelines[1].

Table 1 Patient demographics

Variable	*n* (%)
Number of patients	75
Male	66 (88)
Female	9 (12)
Median age, yr (range)	68 (17-82)
Median body weight, kg (range)	63 (17.3-32.7)
Median BMI, kg/m^2 (range)	23.0 (17.3-32.7)
ASA score	
Ⅰ	25 (33.3)
Ⅱ	49 (65.3)
Ⅲ	1 (1.4)
Site of hernia	
Right	33 (44)
Left	25 (33.3)
Both	17 (22.7)
Smoking	37 (49.3)
Hypertension	26 (34.7)
Diabetes mellitus	7 (9.3)
Respiratory disease	10 (13.3)
Coronary artery disease	6 (8)
Anticoagulant/antiplatelet medicine	7 (9.3)

BMI: Body mass index; ASA: American Society of Anesthesiologists.

Table 2 Perioperative data

Variable	Value	%
Operative time		
Unilateral (min)	100 (66-168)	
Bilateral (min)	136 (114-165)	
Recurrence (min)	125 (108-156)	
Bleeding volume (mL)	4 (1-52)	
Conversion to multi-port or open	0	0
Intraoperative complication	0	0
Postoperative complication		
Seroma	0	0
Wound infection	0	0
Chronic pain	0	0
Recurrence	1	1.4

Moreover, it has a superior cosmetic outcome as it is performed through single-incision laparoscopic surgery[4]. Coupled with intraperitoneal observation, it is possible to diagnose the type of hernia, restore the intestinal tract incompetence and confirm the repair afterward. Hernia repairs can therefore be performed more safely and effectively.

A minimally invasive surgical technique for the repair of inguinal hernia, TEP was introduced for laparoscopic hernia repair in the early 1990s[5] and many studies involving the procedure have been reported since. Advantages of TEP include a wide range of exfoliation, ease of mesh placement, short operation time, and no need to perform peritoneal closure. Furthermore, by conducting TEP with single-incision laparoscopic surgery, it is possible to obtain excellent cosmetic outcomes as reported by Filipovic-Cugura *et al*[6] in 2009. However, the disadvantages of the procedure include difficulty with confirming the type of hernia as well as difficulty with large indirect inguinal hernia, intestinal incompetence and postoperative prostatectomy.

We complemented STEP with intraperitoneal observation to compensate for these drawbacks and obtained good results. Although the operation time is longer than that of the conventional procedure and the multiport laparoscopic surgery, the bleeding volume is equivalent, and the outcome is excellent with respect to postoperative complications[7-9]. Cost is also equal because special equipment is not required. Furthermore, compared to single-incision TAPP, STEP is easier in terms of exfoliation and thus the operation time can be shortened[2]. For patients with recurrent hernia, however, the surgical time was longer because of difficulties with the exfoliation procedure, but there was no conversion to TAPP at our hospital.

By using intraperitoneal observation in combination with STEP, it is possible to view the inguinal region without overlooking coexisting lesions, for example, the presence of hernia on the opposite side (Figure 5). Through intraperitoneal observation, it is possible to confirm the mesh coverage in cases where the hernia extends not only to direct and indirect inguinal lesions but also to femoral and obturator lesions. We could confirm the herniated gates extended to the femoral and obturator in 2 of our patients and could perform the necessary repairs reliably. A small hernia was also detected on the opposite side in some of the patients and this was treated simultaneously by performing hernia repair on both sides. In recurrent cases, iSTEP facilitates reliable repair due to reliable identification of the hernia gates.

In addition, if an intestinal incarceration in the hernia sac was found in the intraperitoneal cavity, forceps were inserted through the incision site and the intestine was returned to the abdominal cavity without increasing the number of trocars. Moreover, the presence of intestinal damage could be confirmed. The intestine protruded into the sac in 3 patients. In all 3 cases, we returned the intestine to the abdominal cavity, confirmed that there was no damage, and then performed TEP safely. If it was difficult to perform hernia repair using TEP, we could easily switch to TAPP. We used TAPP for patients that underwent prostate surgery and had severe adhesion in the preperitoneal space. However, we used TEP for 2 patients for whom TAPP would have been difficult due to severe adhesion in the abdominal cavity after abdominal surgery. Since the mesh is located in the preperitoneal space, even if there is adhesion in the abdominal cavity, the adhesion causes no issues during surgery and the risk of organ damage is low.

In cases of large direct inguinal hernia, it is difficult to identify the hernia gate using the anterior approach and it is difficult to dissect the medial and ventral sides using TAPP. Both sides can be dissected easily with TEP. When using the mesh recommended by the European Hernia Society, which is 15 cm × 10 cm in size[1], it is necessary to secure a sufficient dissection range, which is easy to do with TEP. In addition, peritoneal closure is difficult when performing TAPP through a single-incision procedure. Compared to TAPP, the advantages of TEP

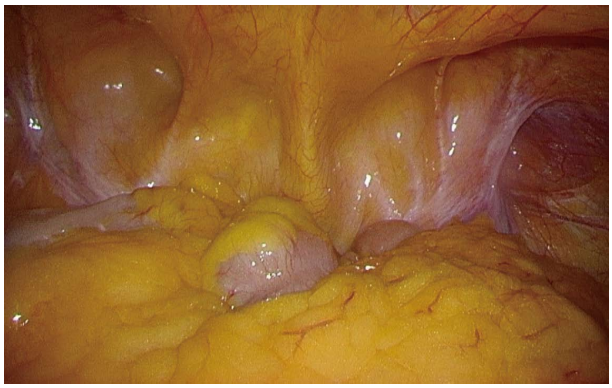

Figure 5 By using intraperitoneal observation simultaneously, it was possible to observe the inguinal region without overlooking the opposite side.

Figure 6 We could obtain better cosmetic outcomes.

are that it does not require intraperitoneal manipulation and adhesion exfoliation can be omitted.

Postoperatively, there is a risk of bowel obstruction caused by intraperitoneal operation using TAPP and adhesion at the peritoneal closure region. The risk of intestinal obstruction after inguinal hernia repair using TAPP or TEP is 2.8 and 0.6 times the risk using the Lichtenstein method, respectively[10]. Additionally, by observing the interior of the abdominal cavity again after hernia repair, it can be confirmed that the fragile portion is covered by mesh and the risk of recurrence can be reduced. By conducting hernia repair with single-incision laparoscopic surgery, we could obtain excellent cosmetic outcomes (Figure 6). As demonstrated above, STEP with intraperitoneal inspection is a very useful technique because diagnosis and reinforcement can be performed reliably and the cosmetic outcome is excellent.

The present study has several limitations. First, this study was carried out at a single high-volume center and was retrospective in nature; hence, patient selection bias may have been inevitable. Patients who met the exclusion criteria were excluded. Second, the population number was small. Further studies on a larger scale are necessary.

ARTICLE HIGHLIGHTS

Research background

Surgery is the standard treatment for inguinal hernia. The surgical techniques used for inguinal hernia consist of the traditional anterior technique and laparoscopic surgery. One type of laparoscopic surgery has totally extraperitoneal hernia repair (TEP). The outcome of TEP is superior to the conventional anterior approach; less postoperative pain, fewer postoperative complications, lower recurrence rates, early discharge, and faster return to daily life and superior cosmetic outcome. The authors cannot observe intraperitoneal cavity on TEP, so the opposite side hernia might be overlooked if the hernia is present. And it is difficult to perform the procedure for patients with intestinal incarceration in the hernia sac.

Research motivation

It is difficult to repair hernia by TEP for patients with large indirect inguinal hernia, intestinal incarceration and postoperative prostatectomy. The authors must compensate for these drawbacks of TEP.

Research objectives

By using intraperitoneal inspection (iSTEP), it is possible to view the inguinal region without overlooking coexisting lesions if the hernia present on the opposite side. And when an intestinal incarceration in the hernia sac was found, we can return the intestine and confirm the presence of intestinal damage. iSTEP is a very useful technique because diagnosis and reinforcement can be performed reliably.

Research methods

Seventy-five patients who underwent iSTEP at the Prefectural Hiroshima Hospital were enrolled. Small skin incision was made in the umbilicus, extending to the intraperitoneal cavity. First of all, insert the laparoscope into the abdominal cavity to observe the intraperitoneal cavity. The type of hernia was diagnosed and whether there was the presence of intestinal incarceration was confirmed. Once the peritoneum was closed, STEP was performed, and finally, intraperitoneal observation was performed to reconfirm the repair. And data on patient demographics, clinical data, intraoperative findings, and postoperative course is prospectively collected.

Research results

The authors performed iSTEP for 75 hernias, 58 were on one side, 17 were on both sides, and 10 were recurrences. The respective median operation times were 100 min (range, 66 to 168), 136 min (range, 114 to 165), and 125 min (range, 108 to 156), with median bleeding amounts of 5 g (range, 1 to 26), 3 g (range, 1 to 52), and 5 g (range, 1 to 26), respectively. Intraperitoneal observation showed hernia on the opposite side in 2 cases, intestinal incarceration in 3 cases, omental adhesion into the hernia sac in 2 cases, severe postoperative intraperitoneal adhesions in 2 cases, and bladder protrusion in 1 case. There was only 1 case of recurrence. Compared with previous reports which repaired by conventional method and TEP, the operation time is longer, but the bleeding volume is equivalent, and the outcome is excellent with respect to postoperative complications. Cost is equal because special equipment is not required.

Research conclusions

Single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection is very useful technique and makes hernia repairs safer and reducing postoperative complications.

Research perspectives

This study suggests that iSTEP is a very useful technique for inguinal hernia repair without history of prostate surgery, giant inguinal hernia, young patients with small indirect inguinal hernia, strangulated hernia, and patients who could not tolerate general anesthesia. The study described a modification of conventional TEP approach with the addition of intraperitoneal observation. We suggested advantage of inspecting the contralateral side for hernia and the possibility to examine incarcerated bowel. It also allowed easy conversion between TEP and TAPP when necessary. The authors will compare with iSTEP

and conventional SILS-TEP and so we report that results.

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ORIGINAL ARTICLE

Clinical Practice Study

Risk factors for pancreatic fistula following pancreaticoduodenectomy: A retrospective study in a Thai tertiary center

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Abstract

AIM

To analyze the risk factors of postoperative pancreatic fistula following pancreaticoduodenectomy in a Thai tertiary care center.

METHODS

We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital from January 2001 to December 2016. Pancreatic fistula were classified into three categories according to a definition made by an International Study Group on Pancreatic Fistula. The risk factors for pancreatic fistula were analyzed by univariate analysis and multivariate logistic regression analysis.

RESULTS
Pancreatic fistula were detected in 88/179 patients (49%) who underwent pancreaticoduodenectomy. Fifty-eight pancreatic fistula (65.9%) were grade A, 22 cases (25.0%) were grade B and eight cases (9.1%) were grade C. Clinically relevant pancreatic fistula were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179 patients). Multivariate logistic regression analysis revealed that soft pancreatic texture (odds ratio = 3.598, 95%CI: 1.77-7.32) was the most significant risk factor for pancreatic fistula. A preoperative serum bilirubin level of > 3 mg/dL was the most significant risk factor for clinically relevant pancreatic fistula according to univariate and multivariate analysis.

CONCLUSION
Soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Key words: Risk factors; Pancreatic fistula; Pancreas; Pancreatectomy; Pancreaticoduodenectomy

Core tip: Pancreaticoduodenectomy is a high morbidity operation. The most common perioperative complication is postoperative pancreatic fistula. We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital. We found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

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INTRODUCTION

Pancreaticoduodenectomy (PD) is the standard treatment for resectable periampullary and pancreatic tumors. PD is an example of major surgery and is a complicated operation to perform for the general surgeon. Current mortality rates are low; previous reports have suggested a perioperative mortality rate of less than 5%[1-3]. However, high morbidity rates have also been reported, some reaching up to 50%[3-7]. The most common complication following PD is postoperative pancreatic fistula (POPF). POPF is the major cause of complications such as delayed gastric emptying (DGE), postoperative hemorrhage, intra-abdominal infection and increased length of hospital stay (LOH)[8].

Many risk factors have been reported for POPF, including obesity, soft pancreatic texture, small pancreatic duct and low volume center[9-15]. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct[16,17], pancreatogastrostomy[18-20], omental roll-up around pancreaticoenteric (PE) anastomosis[21], application of fibrin sealants around PE anastomosis[22,23] and prophylaxis with somatostatin analogs[24-25]. However, the outcomes of these different methods remain controversial.

Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF[9-13]. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

MATERIALS AND METHODS

Patients

From January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand and were considered for inclusion in the study. Patients who underwent a concomitant hepatic resection were excluded; in the end, a total of 179 patients were included. Patient data were retrospectively reviewed. These included age, gender, weight, BMI, underlying disease, serum albumin, preoperative total bilirubin levels and preoperative biliary drainage (PBD). In addition, we recorded the use of percutaneous transhepatic biliary drainage or placement of an endoscopic internal biliary stent. We also reviewed the type of operation, pancreatic texture, pancreatic duct size, type of PE anastomosis, use of trans-anastomotic pancreatic duct stent, pathological diagnosis, operative time and operative blood loss. Ethical permission for this study was obtained from the hospital's ethics committee.

Preoperative evaluation

The general condition of patients and any co-morbid conditions were preoperatively assessed by a physician, surgeon and internist. The diagnosis and clinical staging of the disease were reviewed preoperatively by a multidisciplinary team including surgeons, radiologists and gastroenterologists.

Operative approach

Routine antibiotic prophylaxis was administered 30 min before the incision. PD is classified into classical PD and pylorus-preserved PD (PPPD) and the type of surgery depended on the surgeon's own preference. Reconstruction after resection was performed using

Child's technique, starting with a pancreaticojejunostomy (PJ). A PJ can be performed using either a invagination or duct to mucosa technique and this was decided based on the surgeon's preference. A trans-anastomotic pancreatic duct stent was placed in selected patients, depending on surgeon's preference. The trans-anastomotic pancreatic duct stent was either internal (in the jejunum) or external (partly outside the body). After PJ, biliary-enteric anastomosis was performed followed by a gastro-jejunostomy or duodeno-jejunostomy. A Braun loop jejunojejunostomy was performed in some patients, according to the surgeon's preference. Pancreatic texture was classified into hard, firm or soft consistency based on palpitation by the surgeon. A closed peri-anastomotic drainage system was placed routinely.

Postoperative complications

After surgery, patients were transferred to a critical care unit or intermediate ward. Routine biochemical analyses of patients' blood were performed. An oral diet was started as soon as the output gastric content was < 400 mL and a positive bowel movement occurred. Parenteral nutrition was initiated if the patients did not have a bowel movement or the gastric content was > 400 mL after postoperative day (POD) 3.

POPF was defined according to International Study Group of Pancreatic Fistula (ISGPF) guidelines by amylase levels that were three times higher in the drainage fluid than the serum. POPFs were classified into three categories: (1) Grade A: Transient pancreatic fistula with no clinical impact; (2) grade B: Required a change in management or adjustment of the clinical course; and (3) grade C: Required a major change in clinical management or deviated from the normal clinical course[26]. Combined grade B + C fistulas were defined as "clinically relevant pancreatic fistula" (CR-POPF). DGE was defined as either nasogastric tube insertion after POD 3 or as the inability to tolerate solid food intake by POD 7. Chyle leakage was defined as a milky drain output or triglyceride levels of > 110 mg/dL in the drain fluid on any POD. Postoperative mortality was recorded as the 30-d mortality and in-hospital mortality.

Statistical analysis

Patient characteristics were compared by *t*-test, Wilcoxon Mann-Whitney test, χ^2 test and Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant. Risk factors were analyzed by univariate and multivariate methods using binary logistic regression analysis. Independent risk factors were expressed as odds ratios (ORs) with 95%CI.

RESULTS

Patient characteristics and perioperative status

A total of 179 consecutive patients (95 males, 84 females) that underwent PD were included. One hundred and twenty-eight (71.5%) patients had classical PD and 51 (28.5%) patients had PPPD. Malignancy was diagnosed in 145 patients (79.9%) as follows: 62 ampullary carcinoma patients (44.8%), 40 pancreatic cancer patients (27.6%), 18 cholangiocarcinoma patients (12.4%) and 11 duodenal cancer patients (7.6%) (Table 1).

Patient characteristics and operative outcomes in patients with and without POPF

POPF were detected in 88 patients (49%). Fifty-eight patients (65.9%) had grade A POPF, 22 patients (25%) had grade B POPFs and eight patients (9.1%) had grade C POPFs. CR-POPF were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179). Table 1 compares the post-PD complications between POPF and no POPF groups. Age, serum albumin levels, operative blood loss, gender, diabetes mellitus and PBD were not statistically different between the two groups. However, statistically significant differences were observed in BMI, preoperative total serum bilirubin, pancreatic duct diameter, operative time, cardiovascular disease, pancreatic texture and trans-anastomotic stent between the two groups. The POPF group had a higher rate of other complications (5.5% *vs* 25%, $P < 0.001$) and a longer LOH (15 d *vs* 25 d, $P < 0.001$).

Risk factors for POPF

Univariate and multivariate analyses were used to identify risk factors for POPF (Table 2). Univariate analyses of the 88 patients with pancreatic fistula revealed the following risk factors for POPF: BMI > 25 (OR 2.38, 95%CI: 1.13-5.03, $P = 0.005$), pancreatic duct diameter (OR 2.765, 95%CI: 1.47-5.18, $P = 0.002$), operative time (OR 2.39, 95%CI: 1.26-4.55, $P = 0.008$), history of cardiovascular disease (OR 3.41, 95%CI: 1.48-7.86, $P = 0.004$), soft pancreatic texture (OR 4.682, 95%CI: 2.47-8.87, $P < 0.001$) and placement of a trans-anastomotic pancreatic duct stent (OR 2.55, 95%CI: 1.31-4.99, $P = 0.006$). Multivariate logistic regression analysis revealed soft pancreatic texture (OR 3.59, 95%CI: 3.01-17.35, $P < 0.001$) as the most significant risk factor for POPF.

Effect of POPF grade on patient characteristics and operative outcomes and predictive factors for CR-POPF

Preoperative total bilirubin and pancreatic reconstruction techniques (duct to mucosa *vs* invagination) were significantly different between grade A POPF and CR-POPF (Table 3). Univariate analysis revealed preoperative total serum bilirubin levels of more than 3 mg/dL as a potential risk factor for grade A POPF (OR 3.749, 95%CI: 1.48-9.51, $P = 0.005$). Multivariate analysis revealed total serum bilirubin levels of more than 3 mg/dL as the most significant predictive factor for CR-POPF (OR 4.50, 95%CI: 1.54-13.15, $P = 0.006$) (Table 4).

DISCUSSION

The most common perioperative complication of PD is

Table 1 Patient characteristics in postoperative pancreatic fistula and no postoperative pancreatic fistula groups

Characteristic data	No POPF (*n* = 91)	POPF (*n* = 88)	*P*-value	95%CI
Age, mean (SD)	60.7 (10.6)	59.1 (11.2)	0.33	58.22-61.44
BMI, median (IQR)	21.4 (20, 23.9)	23.1 (20.8, 25.5)	0.005	22.05-23.22
Albumin, median (IQR)	34.1 (31, 38.3)	34.9 (32, 37.95)	0.667	33.38-35.10
Total bilirubin, median (IQR)	4.1 (1.3, 13.2)	1.3 (0.7, 5.6)	0.002	5.01-7.16
Pancreatic duct diameter (mm), median (IQR)	3 (3, 5)	3 (2, 5)	0.048	3.44-3.99
Operative time, median (IQR)	420 (360, 540)	480 (420, 570)	0.014	448.46-486.23
Blood loss (mL), median (IQR)	1000 (600, 1500)	800 (500, 1500)	0.236	1082-1459.66
LOH day, median (IQR)	15 (12, 20)	25 (17, 39.5)	< 0.001	23.14-32.87
Gender, *n* (%)				
Male	49 (53.8)	46 (52.3)	0.833	
Female	42 (46.2)	42 (47.7)		
DM, *n* (%)				
No	64 (70.3)	69 (78.4)	0.216	
Yes	27 (29.7)	19 (21.6)		
Hx of cardiovascular disease, *n* (%)				
No	82 (90.1)	64 (72.7)	0.003	
Yes	9 (9.9)	24 (27.3)		
PBD, *n* (%)				
No	36 (39.6)	25 (28.4)	0.116	
Yes	55 (60.4)	63 (71.6)		
Pancreatic texture, *n* (%)[1]				
Hard/firm	60 (68.2)	27 (31.4)	< 0.001	
Soft	28 (31.8)	59 (68.6)		
Type of resection, *n* (%)				
PPPD	20 (22.0)	31 (35.2)	0.05	
Classical PD	71 (78.0)	57 (64.8)		
Duct to mucosa *vs* Invagination				
Duct to mucosa	56 (61.5)	63 (71.6)	0.154	
Invagination	35 (38.5)	25 (28.4)		
Stent, *n* (%)				
No	73 (80.2)	54 (61.4)	0.005	
Yes	18 (19.8)	34 (38.6)		
External *vs* Internal, *n* (%)				
External	4 (22.2)	12 (36.4)	0.298	
Internal	14 (77.8)	21 (63.6)		
Malignant, *n* (%)				
No	18 (19.8)	16 (18.2)	0.785	
Yes	73 (80.2)	72 (81.8)		
Final diagnosis, *n* (%)				
CA ampulla	25 (27.5)	37 (42.1)	0.04	
CA pancreas	28 (27.5)	12 (13.6)		
CA duodenal	8 (8.8)	3 (3.4)		
CA distal CBD	7 (7.7)	11 (12.5)		
Other	26 (28.5)	25 (28.4)		
Grading, *n* (%)				
No	91 (100)	0	0	
A	0	58 (65.9)		
B	0	22 (25.0)		
C	0	8 (9.1)		
Other complications				
No	86 (94.5)	66 (75.0)	< 0.001	
Yes	5 (5.5)	22 (25.0)		
30-d mortality, *n* (%)				
No	91 (100)	85 (96.6)	0.117	
Yes	0	3 (3.4)		
Age, *n* (%)				
< 70	73 (80.2)	73 (82.9)	0.637	
⩾ 70	18 (19.8)	15 (17.1)		
BMI, *n* (%)				
< 25	78 (85.7)	63 (71.6)	0.021	
⩾ 25	13 (14.3)	25 (28.4)		
Albumin, *n* (%)				
⩾ 30	75 (82.4)	77 (87.5)	0.342	
< 30	16 (17.6)	11 (12.5)		
Total bilirubin, *n* (%)				
< 3	41 (45.1)	56 (63.6)	0.013	
⩾ 3	50 (54.9)	32 (36.4)		

Pancreatic duct diameter, *n* (%)			
⩾ 5	45 (49.4)	23 (26.1)	0.001
< 5	46 (50.6)	65 (73.9)	
Operative time, *n* (%)			
< 420	39 (42.9)	21 (23.9)	0.007
⩾ 420	52 (57.1)	67 (76.1)	
Blood loss, *n* (%)			
< 1000	45 (49.5)	54 (61.4)	0.109
⩾ 1000	46 (50.5)	34 (38.6)	

[1]*n* = 174 patients. Other complications: DGE, postoperative hemorrhage, chyle leakage. POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

Table 2 Univariate and multivariate logistic regression analysis of postoperative pancreatic fistula risk factors

Variable	Univariate OR (95%CI)	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Age (yr)				
< 70				
⩾ 70	0.833 (0.39-1.78)	0.637		
Body mass index (kg/cm^2)				
< 25				
⩾ 25	2.381 (1.13-5.03)	0.023	2.081 (0.86-5.03)	0.104
Albumin				
⩾ 30				
< 30	0.669 (0.29-1.54)	0.344		
Total bilirubin				
< 3				
⩾ 3	0.468 (0.26-0.85)	0.013	1.455 (0.38-5.55)	0.583
Pancreatic duct diameter				
⩾ 5 mm				
< 5 mm	2.765 (1.47-5.18)	0.002	3.148 (0.81-12.27)	0.098
Operative time				
< 420 min				
⩾ 420 min	2.393 (1.26-4.55)	0.008	1.355 (0.59-3.07)	0.465
Blood loss				
< 1000				
⩾ 1000	0.616 (0.34-1.12)	0.11		
Gender				
Male				
Female	1.065 (0.59-1.92)	0.833		
DM				
No				
Yes	0.653 (0.33-1.29)	0.218		
Hx of cardiovascular disease				
No				
Yes	3.417 (1.48-7.86)	0.004	2.612 (0.96-7.08)	0.059
Preop biliary stent (no)				
No				
Yes	1.649 (0.88-3.08)	0.117		
Pancreatic texture				
Hard/firm				
Soft	4.682 (2.47-8.87)	< 0.001	3.598 (1.77-7.32)	< 0.001
Type of resection				
Pylorus-preserved pancreaticoduodenectomy				
Pancreaticoduodenectomy	0.518 (0.27-1.00)	0.051	0.807 (0.37-1.78)	0.597
Duct to mucosa				
Invagination	0.635 (0.34-1.19)	0.156		
Stent (no)				
No				
Yes	2.553 (1.31-4.99)	0.006	1.272 (0.52-3.09)	0.595
External				
Internal	0.500 (0.13-1.87)	0.303		
Malignant (no)				
No				
Yes	1.109 (0.52-2.34)	0.785		
Final diagnosis (CA ampulla)				
CA pancreas	0.324 (0.14-0.76)	0.01	0.439 (0.16-1.19)	0.105
CA duodenal	0.253 (0.06-1.05)	0.058	0.533 (0.11-2.59)	0.435
CA distal CBD	1.062 (0.36-3.11)	0.913	1.188 (0.33-4.29)	0.793
Other	0.650 (0.31-1.37)	0.258	0.543 (0.22-1.35)	0.189

Table 3 Relationships between patient characteristics, operative outcome and postoperative pancreatic fistula grade

Characteristic data	POPF (grading)		*P*-value	95%CI
	A (*n* = 58)	B + C (*n* = 30)		
Age, mean (SD)	59.2 (11.3)	58.8 (11.4)	0.874	56.67-61.46
Body mass index, median (IQR)	23.1 (20.4, 25.1)	23.1 (21.1, 26.5)	0.805	22.62-24.45
Albumin, median (IQR)	34.7 (32, 38)	35.4 (32, 37.9)	0.603	33.38-35.58
Total bilirubin, median (IQR)	0.9 (2, 5)	3.3 (1.2, 12)	0.01	3.44-6.66
Pancreatic duct diameter (mm), median (IQR)	3 (2, 5)	3 (2, 4)	0.175	3.07-3.79
Operative time, median (IQR)	480 (420, 600)	480 (360, 540)	0.49	462.22-511.75
Blood loss (mL), median (IQR)	800 (500, 1500)	900 (600, 1500)	0.071	985.10-1616.95
LOH day, median (IQR)	21 (14, 30)	42.5 (30, 60)	< 0.001	28.14-46.32
Gender, *n* (%)				
Male	34 (58.6)	12 (40.0)	0.097	
Female	24 (41.4)	18 (60.0)		
DM, *n* (%)				
No	45 (77.6)	24 (80.0)	0.794	
Yes	13 (22.4)	6 (20.0)		
Hx of cardiovascular disease, *n* (%)				
No	42 (72.4)	22 (73.3)	0.927	
Yes	16 (27.6)	8 (26.7)		
PBD, *n* (%)				
No	20 (34.5)	5 (16.7)	0.079	
Yes	38 (65.5)	25 (83.3)		
Pancreatic texture, *n* (%)				
Hard/Firm	20 (35.1)	7 (24.1)	0.301	
Soft	37 (64.9)	22 (75.9)		
Type of resection, *n* (%)				
PPPD	24 (41.4)	7 (23.3)	0.093	
PD	34 (58.6)	23 (76.7)		
Duct, *n* (%)				
Duct to mucosa	46 (79.3)	17 (56.7)	0.026	
Invagination	12 (20.7)	13 (43.3)		
Stent, *n* (%)				
No	32 (55.2)	22 (73.3)	0.097	
Yes	26 (44.8)	8 (26.7)		
External *vs* Internal, *n* (%)				
External	8 (32.0)	4 (50.0)	0.42	
Internal	14 (68.0)	4 (50.0)		
Malignant, *n* (%)				
No	12 (20.7)	4 (13.3)	0.396	
Yes	46 (79.3)	26 (86.7)		
Final diagnosis, *n* (%)				
CA ampulla	23 (39.6)	14 (46.7)	0.33	
CA pancreas	8 (13.8)	4 (13.3)		
CA duodenal	3 (5.2)	0		
CA distal CBD	5 (8.6)	6 (20.0)		
Other	19 (32.8)	6 (20.0)		
Age, *n* (%)				
< 70	47 (81.0)	26 (86.7)	0.505	
⩾ 70	11 (19.0)	4 (13.3)		
BMI, *n* (%)				
< 25	42 (71.4)	21 (70.0)	0.812	
⩾ 25	16 (27.6)	9 (30.0)		
Albumin, *n* (%)				
⩾ 30	50 (86.2)	27 (90.0)	0.743	
< 30	8 (13.8)	3 (10.0)		
Total bilirubin, *n* (%)				
< 3	43 (74.1)	13 (43.3)	0.004	
⩾ 3	15 (28.9)	17 (56.7)		
Pancreatic duct diameter, *n* (%)				
⩾ 5	12 (20.7)	11 (36.7)	0.106	
< 5	46 (79.3)	19 (63.3)		
Operative time, *n* (%)				
< 420	12 (20.7)	9 (30.0)	0.331	
⩾ 420	46 (79.3)	21 (70.0)		
Blood loss, *n* (%)				
< 1000	37 (63.8)	17 (56.7)	0.515	
⩾ 1000	21 (36.2)	13 (43.3)		

POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

Table 4 Univariate and multivariate logistic regression analysis of risk factors for clinically relevant-postoperative pancreatic fistula

Variable	Univariate OR (95%CI)	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Age (yr)				
< 70				
⩾ 70	0.657 (0.19-2.27)	0.507		
BMI (kg/cm^2)				
< 25				
⩾ 25	1.125 (0.43-2.96)	0.812		
Albumin				
⩾ 30				
< 30	0.694 (0.17-2.84)	0.611		
Total bilirubin				
< 3				
⩾ 3	3.749 (1.48-9.51)	0.005	4.506 (1.54-13.15)	0.006
Pancreatic duct diameter (mm)				
⩾ 5				
< 5	0.451 (0.17-1.20)	0.11		
Operative time (min)				
< 420				
⩾ 420	0.609 (0.22-1.66)	0.334		
Blood loss				
< 1000				
⩾ 1000	1.347 (0.55-3.31)	0.516		
Gender				
Male				
Female	2.125 (0.86-5.22)	0.1		
DM				
No				
Yes	0.865 (0.29-2.56)	0.794		
Hx of cardiovascular disease				
No				
Yes	0.954 (0.35-2.58)	0.927		
Preop biliary stent (no)				
No				
Yes	2.631 (0.87-7.92)	0.085	2.24 (0.67-7.49)	0.191
Pancreatic texture				
Hard/firm				
Soft				
Type of resection				
PPPD				
PD	2.319 (0.86-6.27)		1.787 (0.54-5.92)	0.342
Duct to mucosa				
Invagination	2.931 (1.12-7.67)	0.028	2.837 (0.89-9.08)	0.079
Stent (no)				
No				
Yes	0.447 (0.17-1.17)	0.101		
External				
Internal	0.471 (0.09-2.38)	0.362		
Malignant (no)				
No				
Yes	1.695 (0.50-5.80)	0.4		
Final diagnosis (CA ampulla)				
CA pancreas	0.821 (0.21-3.24)	0.779		
CA duodenal	-	-	-	-
CA distal CBD	1.971 (0.51-7.68)	0.328		
Other	0.519 (0.17-1.61)	0.256		

POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality[1-3] and the LOH. Many risk factors for POPF have been reported previously[4-9]. In the present study, the incidence of POPF and the 30-d mortality rate were similar to previous studies. In addition, we identified soft pancreatic texture as a main risk factor for POPF[8-12].

Our multivariate analysis showed that a soft pancreas is the most independent predictive factor for POPF. This is in agreement with previous studies[5,9-12,27]. There are many reasons why soft pancreatic tissue increases the risk of POPF. First, a soft pancreas makes it more difficult to secure PEA because friable pancreatic tissue cannot

hold suture tension. As a result, suture materials cut through the pancreatic parenchyma and anastomosis fails. A soft pancreas is also prone to ischemia when manipulated, which disrupts anastomosis. Finally, a soft pancreas has enriched exocrine function and pancreatic enzymes are released when leakage occurs[9,11,27,28].

The assessment of pancreatic texture is controversial and subjective. Pancreatic texture is commonly assessed intraoperatively by palpation. Callery *et al*[11] reported the clinical risk score for POPF based on pancreatic texture, pancreatic duct diameter and intraoperative blood loss. They classified the pancreatic texture as firm or soft[11]. Some studies have classified pancreatic texture as hard, firm or soft, but the distinction between a hard and firm pancreas remains unclear[1,5].

Recently, Ansorge *et al*[29] reported similar risk factors for POPF. They classified the pancreatic texture into four grades, including very hard (severe chronic pancreatitis), hard (fibrotic or atrophic obstructed pancreatic gland), soft (unaffected compact gland), and very soft (unaffected fatty pancreas). They found that 44/100 patients had a hard pancreas. The rate of POPF in the very hard/hard groups was significantly different to that in the soft/very soft groups[29]. There is a newly developed tissue strain imaging technology reflecting tissue fibrosis or stiffness and is integrated into a conventional ultrasound system called acoustic radiation force impulse (ARFI). Lee *et al*[30] and Harada *et al*[30] reported the high accuracy of ARFI for prediction of the stiffness of pancreas preoperatively.

The relationship between soft and fatty pancreatic tissue has been well studied[28-29,32]. A fatty pancreas refers to the increasing infiltration of adipose tissue into the pancreas[28]. Ansorge *et al*[29] found that the softness of pancreatic tissue was strongly associated with fat levels in the tissue. This was supported by previous reports that a fatty pancreas is a risk factor for POPF[13,28,32]. Taken together, these findings suggest that the infiltration of adipose tissue into the pancreas is associated with soft pancreatic texture.

The assessment of pancreatic texture is difficult and subjective. Currently, there are no standard procedures for the intraoperative assessment of pancreatic texture. Pancreatic texture has commonly been assessed intraoperatively by palpation[5,11,29]. In the present study, we also assessed pancreatic texture by palpation. This subjective assessment of pancreatic texture could have differed from surgeon to surgeon.

Unfortunately, it was not possible to assess pancreatic texture during the preoperative evaluation. Tranchart *et al*[33] used computed tomography to predict the occurrence of severe pancreatic fistula following PD. They found that a visceral fat area of more than 84 cm^3 was associated with a fatty pancreas (58.4% *vs* 48.1%, $P = 0.005$) and was a risk factor for CR-POPF (OR 8.16 95%CI: 2.2-3, $P = 0.002$). They suggested preoperative assessment of body fat distribution as a means of evaluating fat levels in the pancreas and predicting the occurrence of CR-POPF[33]. In our study, the incidence of CR-POPF is high when compared to previous studies[5,6,11,12]. This could be explained by the lower population of pancreatic cancer in this study that the pancreatic cancer is more likely to obstruct the pancreatic duct and therefore increase fibrosis of the pancreas[11].

Obstructive jaundice was previously regarded as the main factor increasing perioperative morbidity and mortality. The pathophysiology of obstructive jaundice includes increasing endotoxin concentrations in the portal circulation, altered Kupffer cell function affecting the reticuloendothelial system in the liver, over-activation of inflammatory cascades, decreased cellular immunity and renal dysfunction. These manifestations influence the nutritional status of patients. PBD decreased postoperative septic complications in mice by improving liver function, nutritional status, cell-mediated immune function, systemic endotoxemia, cytokine release and the overall immune response[34]. Regarding periampullary obstruction, endoscopic drainage approach today represents the procedure of choice with high succession rate[35,36].

In this study, a preoperative serum bilirubin level of more than 3 mg/dL was a risk factor for CR-POPF. Kimura *et al*[3] reported that serum bilirubin of more than 2.0 mg/dL was a significant preoperative risk factor for higher 30-d and in-hospital mortality rates following PD[3]. Gebauer *et al*[37] found that patients with POPF who underwent repeated surgery had higher in-hospital mortality (0.6 *vs* 0.7, $P = 0.002$) and total serum bilirubin levels (0.7 *vs* 1.1, $P = 0.003$) than POPF patients that did not undergo reoperation). In a previous study, multivariate binary logistic regression model analysis revealed that a serum bilirubin level of > 2.0 mg/dL is an independent risk factor for reoperation (OR 25.053, 95%CI: 3.486-180.069)[37]. Some previous studies have identified higher serum bilirubin levels in CR-POPF patients, but these differences were not statistically significant. For example, El Nakeeb *et al*[12] reported a preoperative bilirubin level of 4.6 mg/dL in patients with grade A POPF and 9.7 mg/dL in patients with CR-POPF, but this difference was not significant. This was supported by Braga *et al*[38], who detected higher total serum bilirubin in patients with grade Ⅲ-Ⅳ complications than patients with grade 0-Ⅱ complications (3.5 mg/dL *vs* 1.6 mg/dL). Again, this difference was not statistically significant. Fujii *et al*[39] found that endoscopic internal drainage posed a higher risk for POPF than endoscopic nasobiliary drainage.

In a recent systematic review, Scheufele *et al*[40] reported that POPF rates do not differ between PBD and no drainage groups. However, a higher infectious complications rate was detected in the PBD group. Most of the studies included in this review were retrospective studies, and the most frequent complications were wound-related[40]. A few randomized control trial studies have now been performed by a Dutch group. In these studies, the POPF rate did not differ between PBD and surgery first groups following PD. However, the population in the POPF group was only 16%, which may

not have been high enough to obtain sufficient statistical power[31]. Current evidence does not recommend routine PBD because the rate of infectious (usually wound-related) complications is higher. However, a randomized control trial of a large population is needed to clarify this in the case of CR-POPF.

In this study, 66.8% of patients underwent PBD, which is higher than previous reports[39-41]. This could be explained by the fact that Thailand is a low to mid-income country, therefore patients with periampullary tumor and pancreatic cancer usually present with severe obstructive jaundice and have poor nutritional status. Serum bilirubin levels were higher than 15 mg/dL and serum albumin levels were less than 30 mg/dL in most patients. In addition, high-volume centers have patient congestion, limited resources and long waiting lists for operations.

This study was limited by the small study population. A larger population study might have revealed more significant risk factors of POPF.

In conclusion, we have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

ARTICLE HIGHLIGHTS

Research background

Many risk factors have been reported for postoperative pancreatic fistula (POPF), including obesity, soft pancreatic texture, small pancreatic duct and low volume center. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct, pancreatogastrostomy, omental roll-up around pancreaticoenteric (PE) anastomosis, application of fibrin sealants around PE anastomosis and prophylaxis with somatostatin analogs. However, the outcomes of these different methods remain controversial. Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

Research motivation

The most common perioperative complication of pancreaticoduodenectomy is POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality and the LOH. Many risk factors for POPF have been reported previously.

Research objectives

The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

Research methods

The retrospective study design were required by reviewed data from January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand.

Research results

This is the study from tertiary care center from Thailand. To the best of the authors knowledge, this is the largest study from Thailand. The authors found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Research conclusions

The authors have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT is a potential method for predicting a soft pancreas preoperatively. Recently, the newly developed technology of ultrasonography have high accuracy to prediction of the stiffness of pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

Research perspectives

Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. which needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

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CASE REPORT

Surgically treated diaphragmatic perforation after radiofrequency ablation for hepatocellular carcinoma

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Informed consent statement: This is a retrospective study, as we are taking personal information measures, there is no possibility of suffering disadvantages.

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Abstract

We review 6 cases of diaphragmatic perforation, with and without herniation, treated in our institution. All patients with diaphragmatic perforation underwent radiofrequency ablation (RFA) treatments for hepatocellular carcinoma (HCC) performed at Kurume University Hospital and Tobata Kyoritsu Hospital. We investigated the clinical profiles of the 6 patients between January 2003 and December 2013. We further describe the clinical presentation, diagnosis, and treatment of diaphragmatic perforation. The change in the volume of liver and the change in the Child-Pugh score from just after the RFA to the onset of perforation was evaluated using a paired *t*-test. At the time of perforation, 4 patients had herniation of the viscera, while the other 2 patients had no herniation. The majority of ablated tumors were located adjacent to the diaphragm, in segments 4, 6, and 8. The average interval from RFA to the onset of perforation was 12.8 mo (range, 6-21 mo). The median Child-Pugh score at the onset of perforation (8.2) was significantly higher compared to the median Child-Pugh score just after RFA (6.5) (P = 0.031). All patients underwent laparotomy and direct suture of the diaphragm defect, with uneventful post-surgical recovery. Diaphragmatic perforation after RFA is not a matter that can be ignored. Clinicians should

carefully address this complication by performing RFA for HCC adjacent to diaphragm.

Key words: Diaphragmatic perforation; Diaphragmatic hernia; Radiofrequency ablation; Hepatocellular carcinoma

Core tip: Diaphragmatic perforation after radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) has been rarely described in the literature; however, it is one of the most serious complications. We conducted a retrospective analysis of 6 cases of diaphragmatic perforation after RFA, and considered the following 3 causative factors for this complication: Location, thermal damage, and liver cirrhosis. Moreover, we found that this complication tends to develop late after RFA. We propose that diaphragmatic perforation after RFA is a rare complication. Clinicians should take steps to prevent thermal injury to the diaphragm by performing RFA for HCC adjacent to the diaphragm and carefully follow up after RFA.

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INTRODUCTION

Radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) is a minimally invasive treatment commonly used for unresectable primary and metastatic hepatic tumors. Although studies have provided evidence of the safety of RFA, including a low rate of mortality and of major complication[1-4]. Numerous studies have reported complications associated with RFA. Mulier *et al*[1] calculated a complication rate of 8.9% and a mortality rate of 0.5%, with only 5 cases (0.1%) of injury to the diaphragm described. Curley *et al*[2] classified complications after hepatic RFA into early complications (within 30 d), including death, abscess at the RFA lesion, and hemorrhage, as well as late complications (more than 30 d after operation), including biliary fistula, hepatic insufficiency, and pleural effusion. They reported a rate of early complications of 7.1% and of late complications of 2.4%. However, they did not describe any occurrence of injury to the diaphragm. In the previous literature only 12 cases of diaphragm perforation with herniation and 3 cases of without herniation after hepatic RFA have been reported[5-19]. Yet, over the last decade, we have encountered 6 cases of late-onset perforation of the diaphragm, with and without herniation, after hepatic RFA, requiring surgical treatment. The etiology of the perforation of the diaphragm might be collateral thermal damage to the diaphragm during RFA. However, the clinical course of diaphragm perforation and herniation has not been sufficiently clarified. Therefore, the aims of our case report were to describe the clinical presentation, diagnosis, and treatment of our 6 cases of diaphragm perforation, with and without herniation, after RFA.

CASE REPORT

Patients

The study protocol was approved by the Institutional Review Board of Kurume University, Japan (No. 14113). All participants provided informed, written consent. Six patients were diagnosed with a perforation of the diaphragm after RFA for HCC, with a concomitant diaphragm herniation identified in 4 of the 6 patients. All patients underwent surgical treatment of the perforation, and herniation when present, at the division of Hepatobiliary Pancreatic Surgery of the Department of Surgery, Kurume University Hospital. All patients treated with RFA for HCC from January 2003 and December 2013 were evaluated for this study to define complications that happened within 6 mo after RFA (late-onset). Initial RFA treatments were performed at two different institutions: the Department of Gastrointestinal Medicine, Kurume University Hospital, and the Department of Surgery, Tobata Kyoritsu Hospital.

Procedure of RFA

The total number of the patients who underwent RFA during this period was 1427 patients, who carried 2134 tumors. In 1 of our 6 cases, RFA was performed using a cluster cool tip electrode for ablation (Cool-Tip Radiofrequency System, Radionics2, Cosman Medical; RF 3000, Boston Scientific), with return electrodes applied to the patient's legs. For the other 5 cases, RFA was performed using monopolar internally cooled electrodes, (Radionics, Cosman Medical). Expandable needles (LeVeen needle, Boston Scientific) were used to position the electrode on the target tissue in 5 of the 6 cases.

Under local anesthesia, the needle electrode was inserted percutaneously in 5 cases, and placed at the target tissue under ultrasonography guidance. In the remaining case, the needle electrode was inserted with the patient under general anesthesia and placed at the target tissue using a transthoracic approach *via* an artificial pneumothorax, under computed tomography (CT) guidance. No evidence of excessive bleeding at the needle insertion site was observed in any of the cases.

Follow up schedules of after RFA

Follow-up CT was performed one week after RFA ("just after RFA"), with subsequent CT follow-up conducted every 6-12 mo. Blood tests, including assessment of tumor markers, were performed every 3 mo.

Volumetry of the liver

A dynamic CT was performed in all cases at the onset of

Table 1 Clinical characteristics of patients

Case	Age/sex	Tumor location/size (mm)	Time from RFA to DP/DH (mo)	Underlying liver disease/CP sore	Previous intractable pleural effusion	Herniation viscera	Symptom	Treatment for DP/DH	Prognosis after DP/DH treatment
1	49/M	S4/17	17	Alcoholic-LC Child A	Absent	Absent	Absent	Surgical repair (laparotomy)	2 yr alive
2	79/F	S8/19	9	HCV-LC Child B	Present	Present (small intestine)	Abdominal pain	Surgical repair (laparotomy)	3 yr alive
3	68/M	S8/26	21	HCV-LC Child C	Present	Present (mesenteric fat)	Abdominal pain	Surgical repair (laparotomy)	6 mo died by LF
4	70/F	S6/23	8	HCV-LC Child C	Present	Present (large intestine)	Dyspnea	Surgical repair and colectomy (laparotomy)	4 yr died by LF
5	65/M	S8/21	16	HCV-LC Child B	Absent	Present (Large intestine)	Abdominal pain	Surgical repair (laparotomy)	2 yr died by LF
6	76/F	S8/20	6	HCV-LC Child A	Absent	Absent	Absent	Surgical repair (laparotomy)	4 yr alive

LC: Liver cirrhosis; LF: Liver failure; CP score: Child-Pugh score; DP: Diaphragmatic perforation; DH: Diaphragmatic hernia.

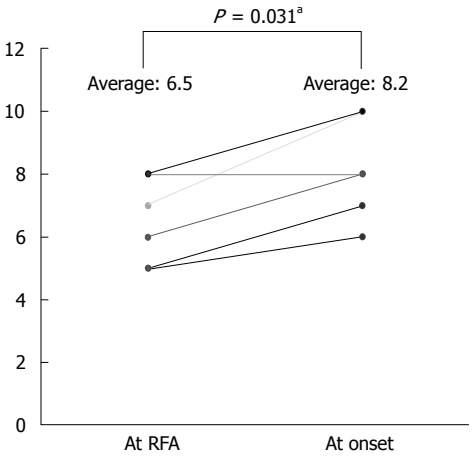

Figure 1 Child-Pugh score significantly increased between "just after radiofrequency ablation" to at the onset of perforation (P = 0.031). [a]Indicates values that are statistically significant (P < 0.05). RFA: Radiofrequency ablation.

perforation, using a 256 slice multi-detector computed tomography scanners (Brilliance iCT, PHILIPS/Aquilion, TOSHIBA) according to a standard protocol. Oyparomin or Iopaque (Fujiyakuhin Co., Saitama) was used as the contrast medium for CT imaging. The contrast medium was injected *via* peripheral intravenous administration using a power injector at a rate of 3 to 4 mL/s, with a total dosage of 1.5 mL/kg calculated from the patient's body weight. The change in the volume of the liver was measured from the dynamic CT images using a commercially available workstation (Synaps Vincent, Fujifilm Co. Kanagawa).

Statistical analyses

The change in the volume of liver and in the Child-Pugh score from just after the RFA to the onset of perforation was evaluated using a paired *t*-test analysis. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using JMP 11.0.0 (SAS: Roppongi, Minatoku, Tokyo, Japan).

Clinical data

The clinical profiles of all patients are summarized in Table 1 (Table 1). A perforation of the diaphragm developed in 6 patients, 3 men and 3 women, 49 to 79 years old. All patients had underlying liver cirrhosis, with two cases belonging to each of the cirrhosis Child-Pugh classes A, B, or C. The median Child-Pugh score just after RFA was 6.5, with a significant increase to 8.2 at the onset of perforation (P = 0.031; Figure 1). The tumors treated by RFA were single lesions; 21 to 31 mm in diameter; located in liver segments 4, 6, or 8; and adjacent to the diaphragm (Figure 2 A-B: Case 4). At the time of perforation, 4 patients had a perforation with herniated viscera, with the other 2 patients having a perforation without herniation. The interval between RFA and onset of perforation ranged from 6 mo to 21 mo. Three patients had a history of long standing refractory pleural effusion prior to the perforation.

Symptoms

Four cases with the herniation had symptoms, such as upper abdominal pain and dyspnea, but the case without herniation did not have symptoms. Symptom onset in cases with symptoms was sudden, which did not prevent progress. Meanwhile, 2 cases (Cases 1 and 6) were asymptomatic and were diagnosed at that time of operation of recurrent HCC incidentally.

Findings of CT

In 4 cases presenting with clinical symptoms, a right diaphragm defect, with and without herniated viscera in the right pleural cavity, was identified on coronal dynamic CT image (Figure 3: Case 4). The herniated viscera included the small intestine in 3 cases and the large intestine in 1 case. All cases were diagnosed with liver cirrhosis based on serum chemistry and CT findings of the morphological features of the liver and spleen. Table 2 shows findings of CT at just after RFA and at the onset (Table 2). At the onset of perforation,

Table 2 Findings of dynamic modified discrete cosine transform

Case	Just after RFA				At onset			
	Disintegration of diaphragm	Thickening of diaphragm	Ascites	Pleural effusion	Disintegration of diaphragm	Thickening of diaphragm	Ascites	Pleural effusion
1	No	No	No	No	No	No	No	No
2	No	No	No	Yes	Yes	Yes	Yes	Yes
3	No	No	No	Yes	Yes	No	Yes	Yes
4	No	No	No	Yes	Yes	No	Yes	Yes
5	No	No	No	No	Yes	No	No	Yes
6	No	No	No	No	No	No	Yes	Yes

RFA: Radiofrequency ablation.

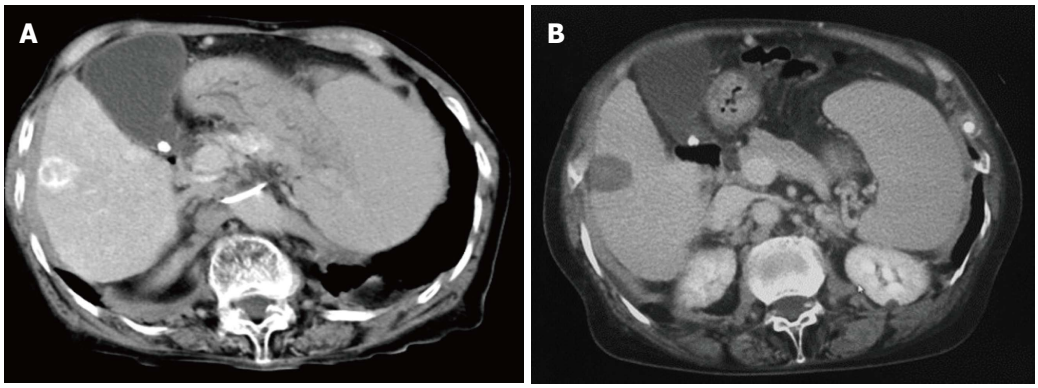

Figure 2 Tumors treated by radiofrequency ablation. A: Contrast-enhanced computed tomography (CT) shows hepatocellular carcinoma in segment 6 of the liver (Case 4); B: Abdominal CT image at just radiofrequency ablation shows a lesion of ablation (Case 4).

Figure 3 Coronal computed tomography image at onset of diaphragm perforation, showing a right diaphragm hernia. The right colon is deviated into the thoracic cavity through the diaphragm defect (white arrow) (Case 4).

disintegration of the diaphragm (4 of 6 cases) and pleural effusion (5 of 6 cases) were visible on CT imaging. However, characteristic findings of diaphragm injury were not visible on CT images obtained just after RFA. Liver volume at the onset of perforation was decreased from at just after RFA volume in 5 of the 6 cases, although this difference was not statistically significant (P = 0.138; Table 3).

RFA procedure

Relevant parameters of RFA procedures are summarized in Table 4. All cases underwent RFA with the electrode inserted *via* an intercostal approach. The peak power attained was 80 W, and the temperature of the ablated tissue was increased to 68℃-95℃. Total irradiation time ranged between 10 and 28 min. Dynamic CT performed just after RFA identified viability of a part of the HCC in 3 cases. Among these 3 patients, 2 underwent additional RFA using the same technique on the viable part of the tumor, with the other patient undergoing real-time CT guided RFA under pneumothorax.

Treatment of diaphragmatic perforation

All cases of diaphragm rupture were treated by surgical laparotomy and simple suture of the diaphragm defect (Figure 4 A-B: Case 2). In case 4, resection of the incarcerated large intestine was also performed. All cases had an uneventful postoperative course. Three patients died of hepatic deterioration due to advanced cirrhosis at 6, 24, and 48 mo postoperatively, respectively.

DISCUSSION

The mechanism of diaphragm perforation after RFA has not been clarified. In our cases, the RFA needle electrode did not penetrate the diaphragm directly except in one case in which RFA was performed under CT guidance using a transthoracic approach *via* an artificial pneumothorax. Therefore, mechanical damage caused by the needle itself may not completely explain

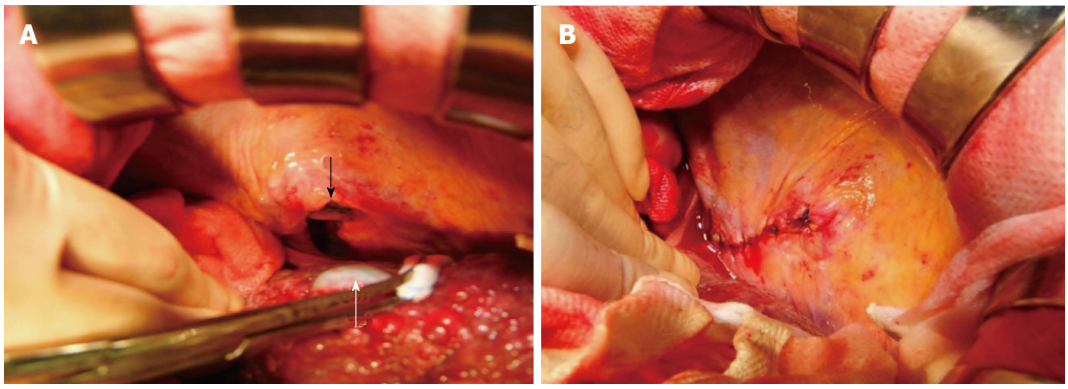

Figure 4 All cases of diaphragm rupture were treated by surgical laparotomy and simple suture of the diaphragm defect. A: A 5 cm defect of diaphragm is visible (black arrow), with evidence of post-ablation scarring (white arrow) (Case 2); B: The defect was repaired with interrupted sutures (Case 2).

Table 3 Changes of liver volume between radiofrequency ablation and onset

Case	Just after RFA (mL)	At onset (mL)
1	1005	1055
2		
3	653-	539
4	1130	893
5	971	946
6	987	866
Median	987	893

RFA: Radiofrequency ablation.

diaphragmatic injury. Considering the clinical profiles of our cases, there are 3 causative factors of diaphragm perforation after RFA: The location of the targeted lesions, collateral thermal injury during RFA, and the advanced cirrhosis status.

Collateral thermal damage to the diaphragm during RFA to these target areas adjacent to the diaphragm is common. In previous clinical case series, the targeted tumor was usually located adjacent to the diaphragm, in liver segments 7, 8, or 5[13]. Head *et al*[20] reported injury to the diaphragm in 5 of 29 patients (17%) who underwent ablation of hepatic tumors adjacent to the diaphragm. In our cases, all tumors that were treated by RFA were located adjacent to the diaphragm.

The thermal damage to the diaphragm may result in an inflammatory response, leading to fibrosis that could ultimately weaken the muscle fibers of the diaphragm and cause a late-onset defect[10,17]. Poor liver function might prevent the injured tissue from healing adequately, with complications, such as ascites and pleural effusion, thereby further contributing to tissue damage[5].

In this study, we found that the median Child-Pugh score at the onset was significantly higher than at just after RFA. As liver function gradually turns worse, the restoration for the diaphragmatic inflammatory change delays, and it is thought that it leads to diaphragmatic perforation.

Furthermore, one of the complications of aggravated liver function is Chilaiditi's syndrome. Moaven *et al*[21] reported that the incidence of Chilaiditi's syndrome inevitably increases in patients with cirrhosis due to atrophy of the right lobe of the liver, which creates space between the diaphragm and the liver. In our study, progressive atrophy of the liver was identified, on sequential dynamic CT after RFA, in 4 of 5 cases. Therefore, it is plausible that this atrophy of the liver was one of the factors contributing to the development of perforation and herniation of the diaphragm.

In the absence of characteristic symptoms of injury to the diaphragm and the relatively long interval between RFA and the onset of the perforation, it is difficult to predict and diagnose a late-onset diaphragm perforation caused by RFA. In this study, we experienced sudden symptom onset after more than 6 mo. Head *et al*[20] indicated that thickening of the diaphragm and localized fluid collection on post-ablation (just before perforation) CT scan were the most common imaging findings related to diaphragm damage. However, as in our cases, there may not be symptoms and CT findings specialized in diaphragm perforation at just RFA.

Development of intractable pleural effusion during the follow up period after RFA is another possible sign of diaphragm perforation[16,22]. In our cases, intractable plural effusion before the onset of diaphragmatic herniation was present in 3 of our 6 cases. Ascites following liver cirrhosis might have collected in the plural cavity through a defect in the diaphragm. In cases of intractable pleural effusion in which no defect of the diaphragm is detected by CT and ultrasonography, it would be helpful to perform a dual scope thoracoscopy or peritoneoscopy[22].

Diaphragm perforation and herniation, particularly with symptoms, must be surgically repaired as much as possible. In our experience, when there is not ileus, intestinal necrosis and breathing disorder, it is not necessary to hurry. Although the majority of our patients had advanced liver cirrhosis, prompt and appropriate surgical treatment was safe and effective, with patients recovering rapidly and uneventfully after surgery.

In summary, diaphragmatic herniation consequent

Table 4 Radiofrequency ablation procedure

Case	Anesthesia	Guidance	Approach	Electrode	Number of session	Max power (W)	Max Temperature (°C)	Additional RFA	Irradiation duration (min)
1	Local	US	Intercostal	Single cool-tip	1	50	76	Yes	10
2	Local	US	Intercostal	Single cool-tip	1	60	84	Yes	11
3	General	CT	Intercostal	Expansion-type	8	80		No	28
4	Local	US	Intercostal	Single cool-tip	2	80	86	No	16
5	Local	US	Intercostal	Single cool-tip	1	50	87	No	11
6	Local	US	Intercostal	Single cool-tip	2	80	95	Yes	21

RFA: Radiofrequency ablation.

to thermal injury of RFA is a rare complication, but it is not a matter that can be ignored in the management of HCC. In performing RFA for liver tumors located adjacent to the diaphragm, clinicians must devise methods for avoiding thermal injury of the diaphragm and regularly monitor the integrity of the diaphragm to achieve early diagnosis of defects over a long-term postoperative follow up.

ARTICLE HIGHLIGHTS

Case characteristics

In the case of diaphragmatic perforation with herniation after radiofrequency ablation (RFA), symptoms, such as upper abdominal pain or dyspnea, develop suddenly, while in the case of perforation without herniation, there may be no symptoms.

Clinical diagnosis

Diaphragmatic perforation with or without herniation after radiofrequency ablation for hepatocellular carcinoma.

Differential diagnosis

In case of acute onset, it is necessary to distinguish from acute abdomen and respiratory failure and the history of RFA for hepatocellular carcinoma located adjacent to the diaphragm and computed tomography (CT) findings would be helpful to diagnose.

Laboratory diagnosis

In the case of diaphragmatic perforation with and without herniation after RFA, liver function, such as Child-Pugh score, may decline in many cases.

Imaging diagnosis

In the case of diaphragmatic perforation with herniation after RFA, a right diaphragm defect and herniated viscera in the right pleural cavity is identified on coronal dynamic CT image.

Pathological diagnosis

There were no pathological findings as all cases may undergo direct discontinued sutures without trimming in this study.

Treatment

Diaphragm perforation and herniation, particularly with symptoms, must be surgically repaired as much as possible, but when there is not ileus, intestinal necrosis and breathing disorder, it is not necessary to hurry.

Experiences and lessons

In performing RFA for liver tumors located adjacent to the diaphragm, clinicians must devise methods for avoiding thermal injury of the diaphragm and regularly monitor the integrity of the diaphragm to achieve early diagnosis of defects over a long-term postoperative follow up.

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CASE REPORT

Ectopic gastrointestinal variceal bleeding with portal hypertension

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Author contributions: Minowa K, Komatsu S, Takashina K, Tanaka S, Kumano T, Imura K, Shimomura K, Ikeda J, Taniguchi F, Ueshima Y, Lee T, Ikeda E, Otsuji E and Shioaki Y performed research and analyzed the data; Minowa K and Komatsu S wrote the paper and contributed equally to this work.

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Abstract

Massive gastrointestinal bleeding from gastrointestinal varices is one of the most serious complications in patients with portal hypertension. However, if no bleeding point can be detected by endoscopy in the predilection sites of gastrointestinal varices, such as the esophagus and stomach, ectopic gastrointestinal variceal bleeding should be considered as a differential diagnosis. Herein, we report a case of ectopic ileal variceal bleeding in a 57-year-old woman, which was successfully diagnosed by multi-detector row CT (MDCT) and angiography and treated by segmental ileum resection. To date, there have been no consensus for the treatment of ectopic ileal variceal bleeding. This review was designed to clarify the clinical characteristics of patients with ectopic

ileal variceal and discuss possible treatment strategies. From the PubMed database and our own database, we reviewed 21 consecutive cases of ileal variceal bleeding diagnosed from 1982 to 2017. MDCT and angiography is useful for the rapid examination and surgical resection of an affected lesion and is a safe and effective treatment strategy to avoid further bleeding.

Key words: Ectopic gastrointestinal bleeding; Ileal varix; Portal hypertension

Core tip: Massive gastrointestinal bleeding from gastrointestinal varices is one of the most serious complications in patients with portal hypertension. If no bleeding point can be detected by endoscopy in the predilection sites of gastrointestinal varices, ectopic gastrointestinal variceal bleeding should be considered as a differential diagnosis. We report here a 57-year-old female case of ectopic ileal variceal bleeding, which were diagnosed by multidetector row CT (MDCT) and its angiography and treated by segmental ileum resection. From the review results of previous reports, MDCT and its angiography is a rapid and useful examination. Moreover, surgical resection of responsible lesion is safe and effective treatment strategy to avoid further bleeding.

Minowa K, Komatsu S, Takashina K, Tanaka S, Kumano T, Imura K, Shimomura K, Ikeda J, Taniguchi F, Ueshima Y, Lee T, Ikeda E, Otsuji E, Shioaki Y. Ectopic gastrointestinal variceal bleeding with portal hypertension. *World J Gastrointest Surg* 2017; 9(12): 288-292 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i12/288.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i12.288

INTRODUCTION

Massive gastrointestinal bleeding from a gastrointestinal varix is one of the most serious complications in patients with portal hypertension. However, if the point of continuous bleeding in the predilection sites of a gastrointestinal varix, such as the esophagus and stomach, is not found and no further strategy for the accurate diagnosis and effective treatment of the bleeding point exists, the condition may become life threatening.

Lebrec *et al*[1] classified the gastrointestinal varices other than those of the esophagus and stomach as ectopic varices. Ectopic gastrointestinal varices were reported in the sites of the duodenum, small intestine, colon, rectum, peristomal, biliary, peritoneal, umbilical, and other locations. Ectopic gastrointestinal varices cause an unusual hemorrhage and account for 5% of all variceal bleeding. In particular, ectopic ileal variceal bleeding is the major type of ectopic gastrointestinal variceal bleeding[2]. Herein, we report a case of ectopic ileal variceal bleeding, which was diagnosed by MDCT and angiography and was surgically treated. Moreover, we reviewed previous case reports regarding the clinical behaviors, diagnosis, and treatment strategies of ectopic ileal variceal bleeding, including our cases diagnosed between 1982 and 2017 from the PubMed database.

CASE REPORT

A 57-year-old Asian woman with autoimmune portal hypertension due to polymyositis was admitted to our hospital with a 2-d history of hematochezia. She had a history of esophageal variceal rupture, which had been treated by endoscopy 3 years before. At admission, she had a blood pressure of 92/58 mmHg, heart rate of 85/min, respiratory rate of 16/min, and body temperature of 35.2 ℃. Although she was pale and showed conjunctival pallor, and there was no jaundice, abdominal pain, or shifting dullness. Laboratory data were as follows: hemoglobin 7.3 g/dL, hematocrit 23.4%, platelets 112000/mm^3, prothrombin time 98%, serum albumin 3.5 g/dL, total bilirubin 1.1 mg/dL, aspartate aminotransferase/alanine aminotransferase 35/51 IU/L. Hepatitis B surface antigen was positive and hepatitis C virus antibody was negative. There was no encephalopathy. Her Child-Pugh score was 6 (class A).

We performed an emergent upper gastrointestinal endoscopy, which showed a mild esophageal varix without bleeding. However, lower gastrointestinal endoscopy revealed a large blood clot at the ileocecum, but there was no active bleeding lesion during the endoscopy. MDCT showed no definitive liver cirrhosis, but dilation of the hepatic portal vein and umbilical vein and splenomegaly and portosystemic collaterals indicated portal hypertension. In addition, enhanced MDCT and MDCT and angiography revealed the presence of an ileal varix, which showed no active bleeding into the abdominal cavity. In particular, the ileal varix had a portosystemic shunt *via* the superior mesenteric vein into the right ovarian vein.

She was treated conservatively for 2 d with a blood transfusion. On the 3rd day after admission, she had massive hematochezia. We performed a second MDCT and angiography and diagnosed the patient as hematochezia due to massive ileal varix bleeding because there was a massive coagula at the distal ileal lumen of the ileal varix. We performed emergent segmental ileal resection, which included the ileal varix, *via* a small laparotomy (Figure 1). The varix was located at the 20-cm proximal portion of the ileocecal valve. Her postoperative condition was uneventful. She had no further bleeding and was discharged on the 8th day after surgery.

DISCUSSION

Portal hypertensive enteropathy is present in 5%-11% of patients with portal hypertension and often gives rise to gastrointestinal varices in the esophagus and stomach, which cause active bleeding[3]. Gastrointestinal varices other than those of the esophagogastric area

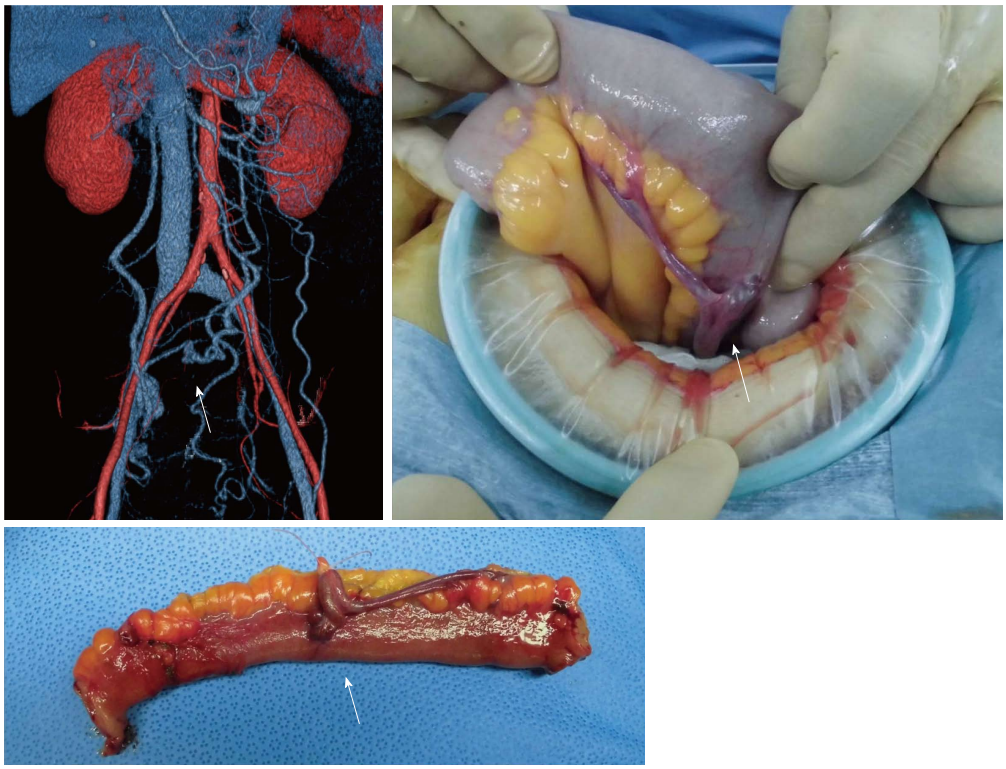

Figure 1 Ileal varices (arrow) were detected using multi-detector row CT and angiography and were resected by laparotomy.

are rare and are classified as ectopic gastrointestinal varices. Ectopic gastrointestinal varices occur at sites such as the duodenum, small intestine, colon, rectum, peristomal, biliary, peritoneal, umbilical, and other locations. Various related factors of an ectopic gastrointestinal varix such as portal hypertension due to cirrhosis, portal vein thrombosis, a history of abdominal surgery, chronic intraperitoneal inflammation, and hematochezia have been reported[4,5].

An ileal varix is the major type of ectopic gastrointestinal varix. In a review 169 cases of ectopic gastrointestinal variceal bleeding, 17% was the highest rate of bleeding among all sites and was derived from jejunal and ileal varices[2]. Ileal varices are associated with a history of abdominal surgery and adhesions[6]. Presumably, abdominal surgery and intraperitoneal inflammation may cause adhesion of the intestinal tract. Then, collateral vessels within the adhesion may give rise to ectopic intestinal varices, particularly, in the jejunum and ileum[7]. Ectopic ileal varices most commonly flow into systemic circulation through the gonadal veins and less commonly through branches of the internal iliac veins[7]. In our case, there were various compatible features such as autoimmune portal hypertension and previous surgeries for appendicitis and hematochezia. Moreover, a portosystemic shunt, which flowed from the superior mesenteric vein into the right ovarian vein, was detected.

From the PubMed database including our own, we reviewed 21 consecutive cases of ileal variceal bleeding diagnosed from 1982 to 2017. The clinical features of 21 patients are shown in Table 1. Patients with ileal variceal bleeding consisted of 5 male and 16 female patients with a median age of 57 years (range 33-80 years). From the medical history, 71.4% (15/21) of patients were associated with portal hypertension due to liver cirrhosis. Previous abdominal surgery was noted in 57.1% (12/21) of patients. Regarding the diagnosis, 61.9% (13/21) of patients were diagnosed by SMA angiography. Capsule endoscopy was used in two cases. However, recent cases were mainly diagnosed by MDCT or MDCT and angiography and treated by surgical resection with no further bleeding. Surgical resection was performed in 76.1% (16/21) of all patients. Some recent patients underwent interventional radiology (IVR) treatment methods such as transjugular intrahepatic portosystemic shunt (TIPS)[8-10] and balloon-occluded retrograde transvenous obliteration (BRTO)[11,12].

There were no patients with re-bleeding in previous reports of ileal variceal bleeding. However, re-bleeding rates of 23%-39% have been reported in TIPS and 5%-16.6% in BRTO in all reports of ectopic gastrointestinal variceal bleeding[13-16]. Although non-invasive treatment such as IVR may be desirable for ectopic gastrointestinal variceal bleeding in high-risk patients with co-morbidities, surgical resection of an affected intestine is currently a safe and effective treatment strategy to avoid further re-bleeding. Moreover, laparoscopic surgical resection of an affected intestine could be possible effective strategy as a minimally invasive procedure (Figure 2).

Ectopic gastrointestinal varices bleeding, especially ileal variceal bleeding, in patients with portal hypertension

Table 1 Summary of the reported ileal variceal bleeding

Case	Year		Age	Sex	Past history	Previous abdominal surgery	Diagnosis	Treatment	Outcome
1	1982	Falchuk	52	F	liver cirrhosis	Cholecystectomy	SMA angiography	Partial enterectomy	Dead
2	1984	Shimada	49	M	liver cirrhosis	Ruputured esophageal varix	SMA angiography	Partial enterectomy	Alive
3	1986	Hojhus	80	F	Periappendicular abscess	(-)	SMA angiography	Partial enterectomy	Dead
4	1986	Arst	56	F	Liver cirrhosis	(-)	Laparotomy	Ileocolectomy	Dead
5	1990	Lewis	72	F	Liver cirrhosis	Hysterectomy	SMA angiography	Ileocolectomy	Alive
6	1994	Kurihara	43	M	(-)	(-)	SMA angiography	Partial enterectomy	Alive
7	1997	Ahn	54	M	Liver cirrhosis	(-)	SMA angiography	ileocolEctomy	Dead
8	1999	Ohtani	66	F	Liver cirrhosis	Ectopic pregnancy	SMA angiography	Partial enterectomy	Alive
9	2001	Kobayashi	62	F	Hepatocellular carcinoma	Hysterectomy	SMA angiography	Ligation of ileocecal and ovarian vein	Alive
10	2006	Ueda	72	F	Liver cirrhosis	Abdominal aortic aneurysm	MDCT	Partial enterectomy	Alive
11	2007	Lopez	56	F	Liver cirrhosis	Pelvic surgery	SMA angiography	TIPS	Alive
12	2007	Mashimo	33	F	Liver cirrhosis	Endometriosis	SMA angiography	Partial enterectomy	Alive
13	2009	Suzuki	74	F	Liver cirrhosis	Acute appendicitis	MDCT	Partial enterectomy	Alive
14	2009	Traina	58	F	Liver cirrhosis	(-)	ES	Sclerotherapy + TIPS	Alive
15	2009	Sato	55	M	Liver cirrhosis	Laparotomy for colonic tumor	Retrograde transvenous venography	BRTO	Alive
16	2010	Konishi	54	F	(-)	(-)	CE	Partial enterectomy	Alive
17	2011	Ambiru	62	F	Liver cirrhosis	Ectopic pregnancy	MDCT	Partial enterectomy	Alive
18	2011	Castagna	70	M	Liver cirrhosis	(-)	CE	TIPS	Alive
19	2013	Vamadevan	48	F	Liver cirrhosis	(-)	MDCT	TIPS	Alive
20	2015	Garcia	74	F	Venous thromboembolism	(-)	MDCT	Partial enterectomy	Alive
21	2017	Our case	57	F	Portal hypertension	Acute appendicitis	MDCT	Partial enterectomy	Alive

CE: Capsule endoscopy; MDCT: Multi-detector raw computed tomography; ES: Enteroscopy; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Balloon occluded retrograde transvenous obliteration.

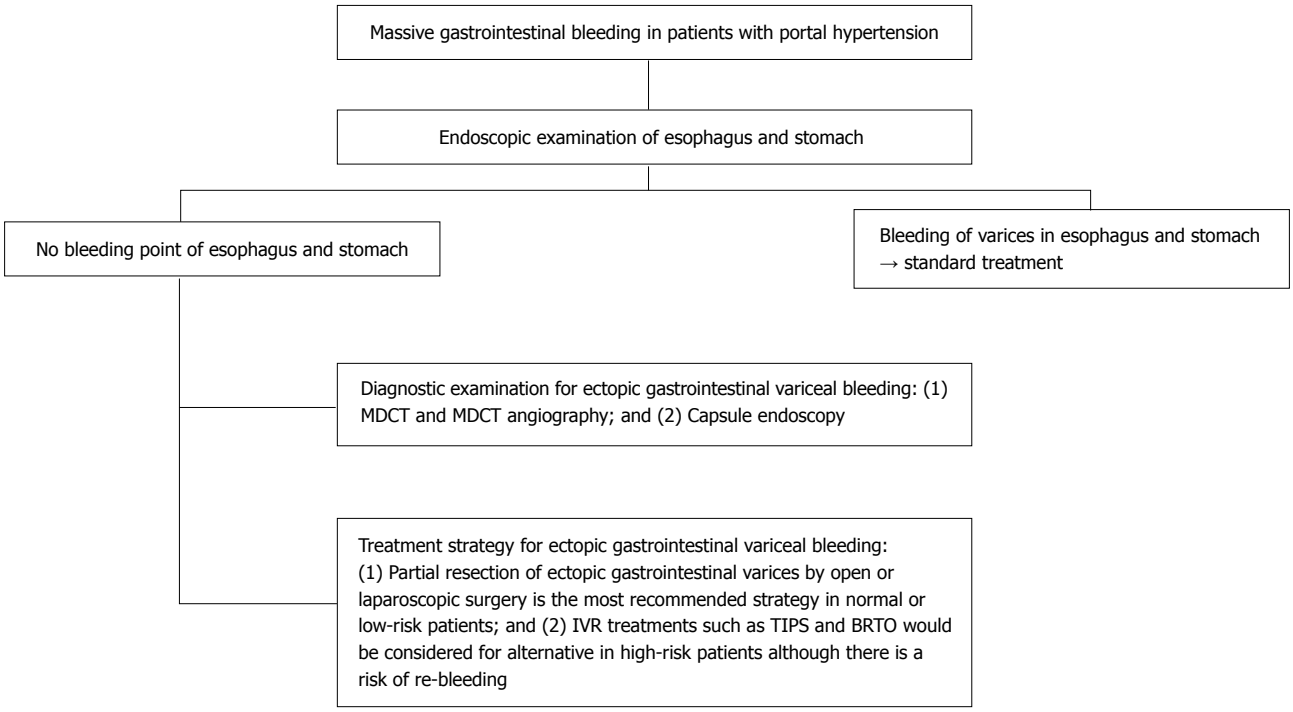

Figure 2 The management algorythm for massive gastrointestinal bleeding in patients with portal hypertension. MDCT: Multi-detector raw computed tomography; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Baloon occluded retrograde transvenous obliteration.

might be considered as a differential diagnosis if upper or lower endoscopy cannot detect a bleeding point such as in the esophagus or stomach. MDCT or MDCT angiography is useful for the rapid examination and surgical resection of an affected ileum and is a safe and effective treatment strategy to avoid further bleeding.

ARTICLE HIGHLIGHTS

Case characteristics

A 57-year-old Asian woman with autoimmune portal hypertension due to polymyositis was admitted to our hospital with a 2-d history of hematochezia. She had a history of esophageal variceal rupture, which had been treated by endoscopy 3 years before.

Clinical diagnosis

On the 3rd day after admission, she had massive hematochezia. The authors performed a second multi-detector row CT (MDCT) and angiography and diagnosed as massive ileal varix bleeding because there was a massive coagula at the distal ileal lumen of the ileal varix.

Differential diagnosis

There was no differential diagnosis because upper and lower endoscopic examinations could not detect the responsible lesion.

Laboratory diagnosis

Laboratory diagnosis was a severe anemia with hemoglobin 7.3 g/dL and hematocrit 23.4% because other data showed no apparent disorder.

Imaging diagnosis

Imaging diagnosis by MDCT and its angiography was massive ileal varix bleeding because there was a massive coagula at the distal ileal lumen of the ileal varix.

Pathological diagnosis

Pathological diagnosis was the leal varix.

Treatment

The authors performed emergent segmental ileal resection, which included the ileal varix, *via* a small laparotomy. The varix was located at the 20-cm proximal portion of the ileocecal valve.

Related reports

Jejunal varices as a cause of massive gastrointestinal bleeding. *Am J Gastroenterol* 1992; **87**: 514-517.

Term explanation

The authors used common terms, which were used in previous reports.

Experiences and lessons

Ectopic gastrointestinal variceal bleeding might be considered as a differential diagnosis if upper or lower endoscopy could not detect bleeding point. From the review results of previous reports including our case, MDCT and its angiography is a rapid and useful examination. Moreover, surgical resection of responsible lesion is safe and effective treatment strategy to avoid further bleeding.

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