

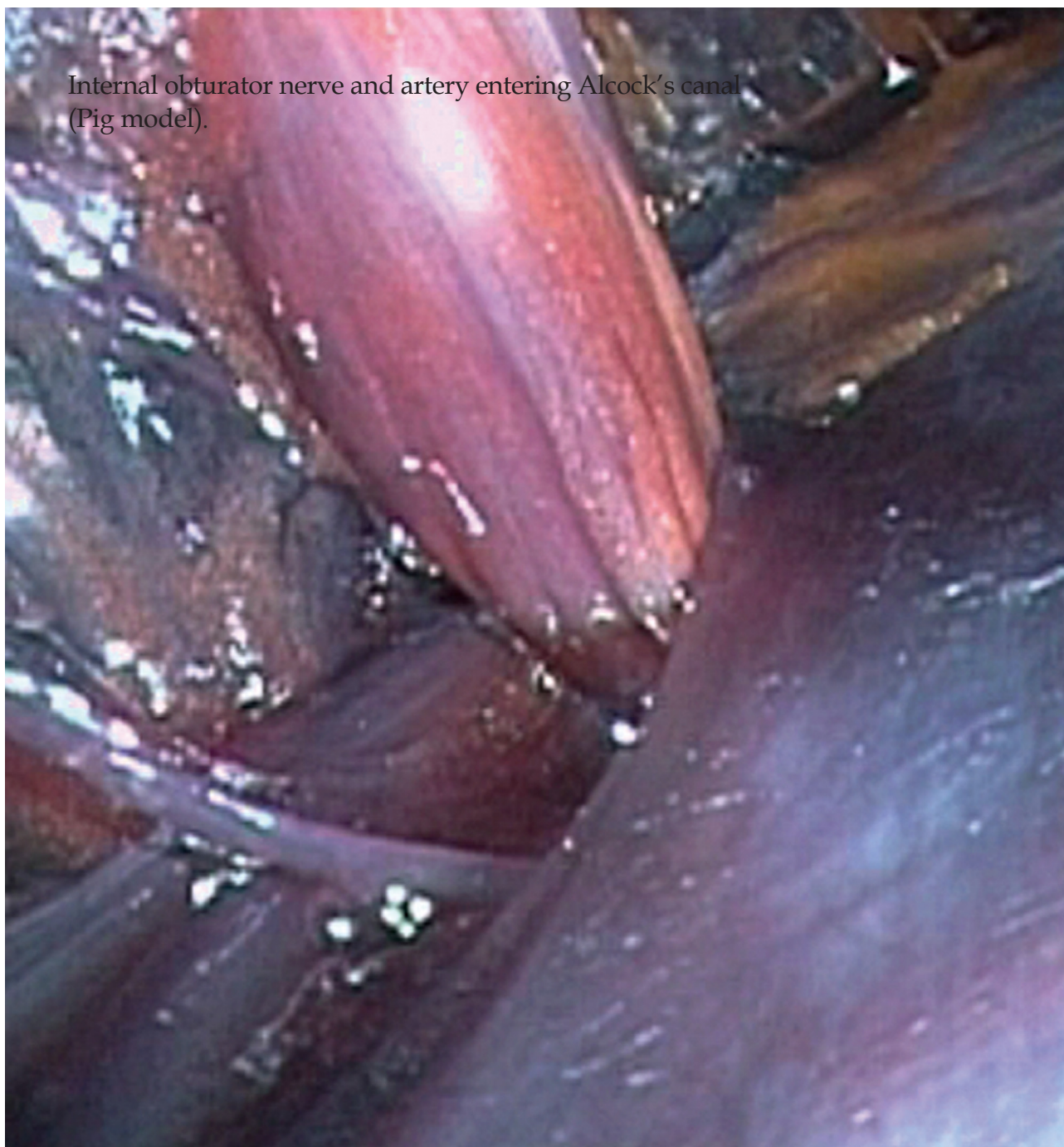


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World J Gastrointest Surg 2010 May 27; 2(5): 153-176

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Internal obturator nerve and artery entering Alcock's canal
(Pig model).





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Treatment of colorectal carcinoids: A new paradigm

Tsuyoshi Konishi, Toshiaki Watanabe, Hirokazu Nagawa, Masatoshi Oya, Masashi Ueno, Hiroya Kuroyanagi, Yoshiya Fujimoto, Takashi Akiyoshi, Toshiharu Yamaguchi, Tetsuichiro Muto

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invasion or tumor size larger than 1 cm carry the risk for metastasis equivalent to adenocarcinomas. Therefore, it should be emphasized that histological examination of lymphovascular invasion is mandatory in the specimens obtained by endoscopic resection or transanal local excision, as this would provide useful information for determining the need for additional radical surgery with regional lymph node dissection. Although the present guidelines or TNM staging system do not mention the impact of lymphovascular invasion, this would be among the next promising targets in order to establish better guidelines and staging systems, particularly in early-stage colorectal carcinoids.

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Key words: Lymphovascular invasion; Neuroendocrine tumor; Carcinoid; Colorectal cancer

Peer reviewer: Akira Tsunoda, MD, PhD, Professor, Department of Surgery, Kameda Medical Center, 929 Higashi-cho, Kamogawa City, Chiba 296-8602, Japan

Abstract

It is often difficult to evaluate the grade of malignancy and choose an appropriate treatment for colorectal carcinoids in clinical settings. Although tumor size and depth of invasion are evidently not enough to stratify the risk of this rare tumor, the present guidelines or staging systems do not mention other clinicopathological variables. Recent studies, however, have shed light on the impact of lymphovascular invasion on the outcome of colorectal carcinoids. It has been revealed that the presence of lymphovascular invasion was among the strongest risk factors for metastasis along with tumor size and depth of invasion. Furthermore, tumors smaller than 1 cm, within submucosal invasion and without lymphovascular invasion, carry minimal risk for metastasis with 100% 5-year survival in the studies from Japan as well as from the USA. This would suggest that these tumors could be curatively treated by endoscopic resection or transanal local excision. On the other hand, colorectal carcinoids with either lymphovascular

Konishi T, Watanabe T, Nagawa H, Oya M, Ueno M, Kuroyanagi H, Fujimoto Y, Akiyoshi T, Yamaguchi T, Muto T. Treatment of colorectal carcinoids: A new paradigm. *World J Gastrointest Surg* 2010; 2(5): 153-156 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v2/i5/153.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v2.i5.153>

ISSUES IN GRADING THE MALIGNANCY OF COLORECTAL CARCINOIDS

Carcinoid is synonymous with the term “well-differentiated neuroendocrine tumor” in the gastrointestinal tract (GI)^[1,2]. According to the classification of the World Health Organization (WHO), carcinoids of the colon and rectum are grouped together and are distinguished from those of the appendix or ileum^[3].

The biological behavior of colorectal carcinoids differs among tumors^[1,2,4-9]. The WHO classification defines

Table 1 TNM classification for endocrine tumors of colon and rectum^[20]

TNM	
T-primary tumor ¹	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa
	T1a size < 1 cm
	T1b size 1-2 cm
T2	Tumor invades muscularis propria or size > 2 cm
T3	Tumor invades subserosa/pericolic/perirectal fat
T4	Tumor directly invades other organs/structures and/or perforates visceral peritoneum
N-regional lymph nodes	
NX	Regional lymph node status cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-distant metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

¹For any T add (m) for multiple tumors.

colorectal carcinoids as benign if they are confined within submucosa, measure no larger than 20 mm and are without angioinvasion^[1,3]. However, there have been many reports critical of this definition. Soga^[10] examined 777 cases of rectal carcinoids with submucosal invasion, and found that metastatic rates of the tumors not larger than 5 mm and 5.1-10 mm were 3.7% and 13.2%, respectively. Heah *et al*^[11] and Seow-Cheon *et al*^[12] reported that even a 1-mm rectal carcinoid caused regional lymph node metastasis. In light of oncogenic development of carcinoids, intraglandular hyperplastic proliferation of argyrophil cells in the mucosal layer develops extraglandular budding and then invades to penetrate the muscularis mucosae, forming precursors of carcinoids (microcarcinoids) in the submucosal layer^[13,14]. Accordingly, GI carcinoids with submucosal invasion should be malignant if there is a submucosal invasion from a mucosal lesion.

Thus, it is often difficult to evaluate the grade of malignancy and choose appropriate treatment for this rare tumor in clinical settings. Numerous studies have reported various factors influencing survival and prognosis of colorectal carcinoids, including tumor size larger than 10 or 20 mm, invasion to the muscularis propria, older age, male gender, tumor site, histologic growth pattern and DNA ploidy^[2,5,15-23]. Among them, recent articles, including our study in 2007, have shed light on the importance of lymphovascular invasion in colorectal carcinoids^[6,15]. Although the prognostic importance of lymphovascular invasion has been well established in colorectal carcinomas, it has been scarcely investigated in a large series of colorectal carcinoids. This review highlights on the recent advance in grading the malignancy of colorectal carcinoids, particularly focusing on the importance of lymphovascular invasion.

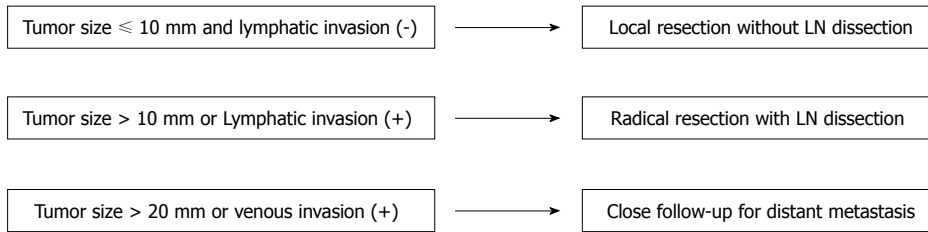
GUIDELINES AND TNM STAGING IN COLORECTAL CARCINOIDS

Tumor size is the most important indicator of metastasis

in colorectal carcinoids^[2,19]. It is generally accepted that tumors greater than 20 mm need radical resection for possible lymph node metastasis^[2,12,19,22]. On the other hand, the management of those smaller than 20 mm has been controversial. Recent guidelines from UKNET work for neuroendocrine tumours suggested that colorectal carcinoids smaller than 1 cm may be considered adequately treated by complete endoscopic removal^[19]. However, there has been opposition to these guidelines based on the fact that lymph node metastasis is found even in tumors smaller than 10 mm^[10-12,18]. In 2006, the Consensus Conference on the European Neuroendocrine Tumor Society Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumors, Part 2: Midgut and Hindgut Tumors was held in Francati (Rome Italy), and TNM staging and grading was proposed for colorectal carcinoids, based on this conference^[20]. In this staging system, the T factor consists of tumor size and tumor depth. Tumors within submucosa and less than 1 cm and 1-2 cm are defined as T1a and T1b, respectively, and those invading muscularis propria or size > 2 cm are defined as T2 (Table 1). Furthermore, this article proposed a grading system determined by mitotic count or Ki-67 index (Table 2). In this grading system, tumors are classified into G1, G2 and G3 according to the activity of mitosis. G3 indicates a poorly differentiated neuroendocrine carcinoma with high mitotic activity, so carcinoids (namely, well differentiated neuroendocrine tumors) are grouped as G1 or G2. Other studies have also confirmed the usefulness of the grading system by mitotic activity^[15,16,23,24].

IMPACT OF LYMPHOVASCULAR INVASION IN COLORECTAL CARCINOIDS

The impact of lymphovascular invasion on oncological outcomes has been scarcely investigated in colorectal carcinoids. However, recent studies have elucidated the

Figure 1 Treatment strategy of colorectal carcinoids^[7].Table 2 Grading proposal for neuroendocrine tumors of colon and rectum^[20]

Grade	Mitotic count (10HPF) ¹	Ki-67 index (%) ²
G1	< 2	≤ 2
G2	2-20	3-20
G3	> 20	> 20

¹10 HPF (High Power Field) = 2 mm², at least 40 fields (at 40 × magnification) evaluated in areas of highest mitotic density; ²MIB1 antibody; % of 2000 tumor cells in areas of highest nuclear labeling.

Table 3 CaRRS: carcinoid of the rectum risk stratification^[15,16]

Points	Size (cm)	Depth	Lymphovascular invasion	Mitotic rate (HPF)
0	< 1	Mucosa/submucosa	No	< 2/50
1	1-1.9	Muscularis or deeper	Yes	≥ 2/50
2	≥ 2			

CaRRS is obtained by adding points associated with each clinicopathological feature; Low risk: 0 points; Intermediate risk: 1-2 points; High risk: ≥ 3 points.

importance of lymphovascular invasion. Konishi *et al*^[6] have analyzed 247 colorectal carcinoids undergoing surgery among a total of 90057 colorectal cancers registered in the Japanese nationwide registry between 1984 to 1998. Multivariate analysis revealed that lymphatic invasion and tumor size over 10 mm were the two independent predictive factors for lymph node metastasis, while venous invasion and tumor size over 20 mm were the two independent predictive factors for distant metastasis. The present data indicated that lymphovascular invasion was more predictive of metastasis than the other evaluated variables in multivariate analysis, such as age, gender and muscular invasion. Furthermore, tumors without either of the two identified risk factors had no lymph node or distant metastasis, and this patient group had a 100% 5-year disease specific survival. Accordingly, Konishi *et al*^[6] proposed a treatment strategy as follows (Figure 1): Tumors not larger than 10 mm and without lymphatic invasion carry no risk for lymph node metastasis, and could be curatively treated by endoscopic resection or transanal local excision. Importantly, the resected specimen should undergo pathological assessment for lymphovascular invasion. If the tumors are larger than 10 mm or diagnosed as having lymphatic invasion, radical surgery should be considered for dissection of regional lymph nodes. Furthermore, tumors larger than 20 mm or with venous invasion carry a high risk for distant metastasis, and need close follow-up. Risk stratification with these risk factors could be simple and useful in determining the therapeutic approach for this rare tumors.

Another important finding in the present study was that the metastatic potential of colorectal carcinoids was not lower than well- and moderately-differentiated adenocarcinomas registered in the same period, if the tumors had either of the two identified risk factors for metastasis. Furthermore, colorectal carcinoids carry even higher risk for metastasis than adenocarcinomas if the tumors had

both of the two risk factors. Our data was compatible with Soga's report, in which the metastatic rates of early-stage rectal carcinoids were higher than carcinomas if the tumors were larger than 10 mm^[10].

Fahy *et al*^[15,16] also emphasized the impact of lymphovascular invasion in rectal carcinoids. The authors investigated the association between various clinicopathological variables and poor oncological outcomes in 70 rectal carcinoids that underwent surgical resection in a single institution. Their analysis revealed that the presence of lymphovascular invasion was strongly associated with metastasis, poor relapse free survival and disease specific survival. According to the results of their analysis, the authors proposed a novel scoring system called "carcinoid of the rectum risk stratification" (Table 3). In this simple scoring system, the total risk score was calculated by adding points assigned to the four variables identified as important in determining the behavior of rectal carcinoids: size, depth of invasion, lymphovascular invasion and mitotic rate. The risk was stratified into low, intermediate and high risk according to the total score. Survival analysis revealed that patients with low risk score exhibited a significantly higher 5-year relapse free survival than patients with either intermediate or high risk scores. Importantly, their results showed that patients in the low risk group, which was defined as tumor size smaller than 1cm, depth of invasion within submucosa, no lymphovascular invasion and less than 2/50 HPF mitotic rates, had essentially no risk of recurrence and a 100% 5-year disease specific survival. This result was completely compatible with the study by Konishi *et al*^[6] which also reported a 100% 5-year disease specific survival in the risk-free group. Regarding the methods for evaluation of lymphovascular invasion, there is no definite evidence at this point to conclude whether immunohistochemistry is better than HE stain to predict metastasis or prognosis in colorectal carcinoids. Future standardization is needed in the guidelines for better understanding of this rare disease.

Thus, the absence of lymphovascular invasion should be the key for confirming a good outcome of colorectal carcinoids. It should again be emphasized that histological examination of lymphovascular invasion is mandatory in the specimens obtained by endoscopic resection or transanal local excision, as this would provide useful information for determining the need for additional radical surgery with regional lymph node dissection. Although the size and depth of invasion are evidently not enough to stratify the risk of this rare tumor, the present guidelines or TNM staging system do not mention the impact of lymphovascular invasion. Lymphovascular invasion would be among the next promising targets to consider in order to establish better guidelines or staging systems, particularly in early-stage colorectal carcinoids.

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NOTES new frontier: Natural orifice approach to retroperitoneal disease

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cases without impairing the planned task. In the survival group, good clinical outcome was observed at a mean follow-up of 3 wk (range 2 to 6 wk). In the 3 cadavers, access was performed correctly. The mean time to fashion the access was 52 min (range 40 to 60 min). All the anatomical landmarks described in the pig model were clearly identified in the same sequence.

CONCLUSION: A retroperitoneal natural orifice transluminal surgical transvaginal approach is feasible in both animal and human models and allows performance of a large panel of interventions.

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Key words: Nephrectomy; Natural orifice; Natural orifice transluminal surgery; Pancreatectomy; Retroperitoneum; Adrenalectomy

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Abstract

AIM: To develop a pure transvaginal access to the retroperitoneum, that is simple, reproducible and uses endoscopic material available on the market.

METHODS: From February 2008 to April 2009, 31 pigs were operated on, with 17 as an acute experiment and 14 with a survival protocol. The animals were placed in a supine position and a 12-mm double-channel endoscope (Karl Storz™, Tuttlingen) was used for vision and dissection. During the same time period, the access experiment was reproduced on 3 human cadavers using material similar to that used in the animal model.

RESULTS: In the animal model, 37 interventions were done on the kidney, adrenal gland and pancreas. The mean time to fashion the access was 10 min (range 5 to 20 min). No intraoperative death was observed. Two major (5%) intraoperative complications occurred: one hemorrhage on the aorta and one tearing of the right renal vein. Peritoneal laceration was encountered in 5

INTRODUCTION

The retroperitoneal space contains many different organs that can be affected by a large variety of pathologies. For this reason, concern is shared by three surgical specialties: digestive surgery, urology and gynecology. Because these three disciplines evolved independently and relatively isol-

ated, they have developed many different approaches to this space, based on their specific working habits. Basically 3 different accesses have been described: anterior (trans-abdominal), posterior and trans-vaginal, each carrying specific complications and limitations.

During the 1980s, the onset of video assisted surgery has dramatically changed the surgical field. The development of new approaches has also been applied to retroperitoneal surgery in the early 1990s^[1-4], decreasing the invasiveness of interventions and improving the clinical outcome of patients^[5-22]. As in open surgery, laparoscopy was developed in a dichotomist fashion, where either the rigid endoscope was inserted through the abdominal cavity (conventional laparoscopy, LS in the following text)^[1,2,7-13] or through a posterior approach, a technique called retroperitoneoscopy (RPS)^[3,4,14-22], which was described many years previous as a diagnostic tool^[23]. If the advantage upon open surgery was obvious^[24-26], no differences were observed between these two approaches until now.

Specific complications during access were observed in large series^[21,27-29]. Because the two concepts are very different, they do not share the same problems, even if the rates of these difficulties are similar^[27-29]. Trocar site complications (hematoma, infections, cell seeding and hernia) are shared by both approaches, as are general complications of every endoscopic surgery, such as hemorrhage, gas loss and gas embolism. The laparoscopic approach is limited due to the risk of visceral damages (enhanced with previous open surgery) because of the trans-abdominal approach^[29], whereas pneumothorax and lesion of the 12th intercostals nerve are well-known complications of RPS^[27,28].

Another drawback proposed for LS (and for all anterior approaches) was opening of the peritoneum to reach an extra-peritoneal organ. Even if this concept is still debated, some authors advocated an immune role of the peritoneal barrier^[30-34], which could be misbalanced in the case of surgical trauma, which is a point particularly important in oncological surgery^[30,32]. Even though this concept seems interesting, there is still lack of clear evidence to scientifically support these assumptions.

After 20 years of experience, almost everything has been attempted using minimally invasive approaches in the retroperitoneum. However, in the literature, some specific situations are still considered limited for these technologies. One example is the highly technically demanding intervention, duodenopancreatectomy^[35-39], which is still strongly debated after 10 years of application. Another illustration, which may evolve in a few years, is the treatment of large adrenal tumors or primary malignant mass of the adrenal gland^[40-42]. Even though these two interventions were demonstrated as being feasible using laparoscopy/RPS, these works remain highly debated and the open approach is still considered as the gold standard in these two situations.

Another aspect that tends to disappear with time is the longer learning curve of RPS compared to LS. Described as a limitation of this technique in the first trials, this point seems not to be a real limitation, as experience is growing worldwide^[14].

After three decades, an alternative approach to laparoscopy has been proposed: the natural orifices transluminal endoscopic surgery[®] (NOTES). This emerging concept is at its dawn, but clinical experience is growing worldwide, offering to pass another step in minimally invasive concepts^[43-46]. This technique has been applied to retroperitoneal surgery in both animal models and human applications, mainly centered on renal and pancreatic interventions^[47-57]. All these attempts used trans-abdominal approaches through the stomach or the vagina. As we have seen, many complications can occur with such approaches^[43-46] and, because it is thought that the peritoneum should not be touched to access extra-peritoneal organs, we decided to develop a reproducible extra-peritoneal access using the potential that NOTES approaches could offer^[58-64].

The aim of the current experiment was to build a transvaginal retroperitoneal access to various organs. This approach was to be simple, reproducible and should use endoscopic material available on the market.

MATERIALS AND METHODS

Our research institute is officially authorized to conduct animal experimentation (No. B-67-482-16). Our animal models were managed according to the Directive of the European Community Council (86/609/EEC).

For all interventions, a dual channel 12 mm flexible endoscope (Karl StoryTM) was used for access, dissection and vision. A laparoscopic gas insufflator using CO₂ was employed to maintain constant gas pressure. Various endoscopic instruments (Karl StorzTM, OlympusTM and Boston ScientificTM) were used to dissect, cut, coagulate and clip the vessels.

Animal model

The interventions were accomplished under general anesthesia in 25-30 kg female pigs. Anesthesia was induced with propofol 10 mL/kg + 2 mL pancuronium. Endotracheal intubation was performed and sleep was maintained with isoflurane 2%.

On 17 pigs, the experiment was done based on an acute protocol. A lethal dose of propofol and potassium chloride were successively administrated at the end of the intervention.

The remaining animals were awake at the end of the procedure and kept alive for various periods of time (from 2 to 6 wk), depending on the outcome measured. Their social comportment, feeding patterns and weight gain were used as markers for a good clinical course.

From February 2008 to April 2009, 31 pigs were operated on. With the pig placed in a supine position, a 10 mm latero-posterior colpotomy was performed at mid length of the vagina. Blunt dissection with the finger was used to create a 3 cm-long postero-lateral tunnel into which the flexible endoscope was inserted through the vagina. A retroperitoneum of CO₂ was insufflated at a pressure of 12 mmHg *via* one channel. Dissection progressed cranially and posteriorly, using only the tip of the endoscope and

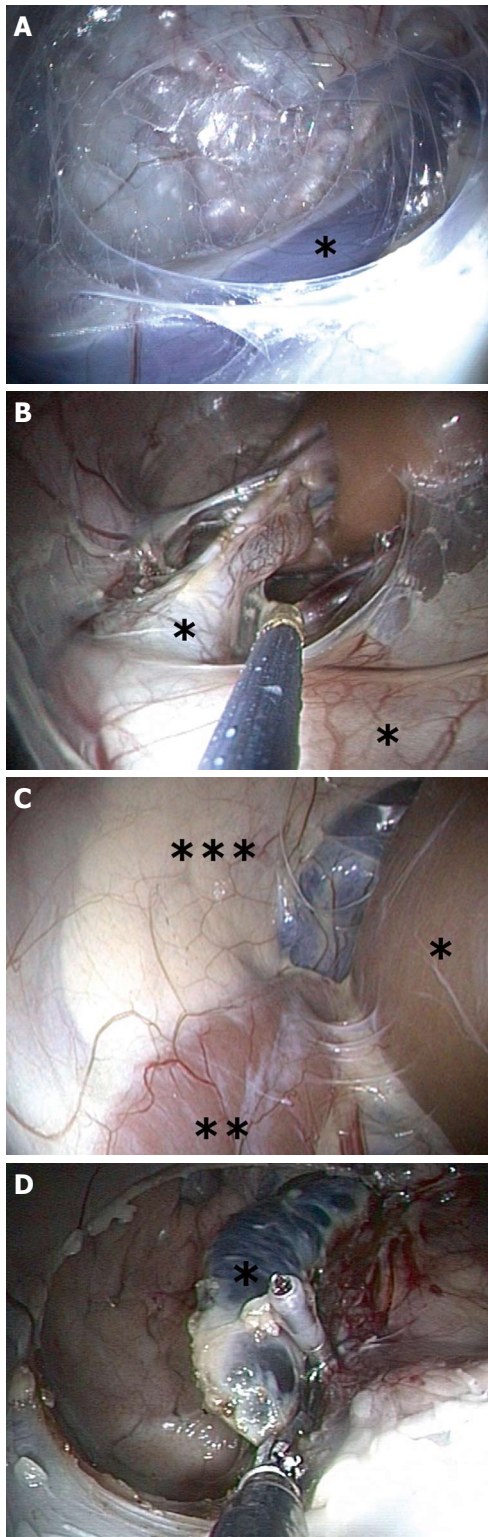


Figure 1 Animal model. A: Right side. *Right Iliac Vessels; B: Left side. *Ureter; C: Left side. *Kidney, upper pole; **Adrenal gland; ***Tail of the Pancreas; D: Left side. *Adrenal gland.

the pressure of the carbon dioxide. No extra instruments were employed. A complete and reproducible sequence of anatomical landmarks were visualized in the following sequence: the internal obturator muscle on the lateral side, the common iliac vessels (Figure 1A), the aorta or the IVC, de-

pending on the side, the Gerota's fascia (pre-renal fascia), the psoas muscle, the ureters (Figure 1B), the kidney (Figure 1B and C), the adrenal gland (Figure 1C and D) and the tail of the pancreas on the left side (Figure 1C).

Various procedures were attempted using a large panel of commercially available endoscopic devices. They were defined as following: (1) Total nephrectomy: dissection of the vessels, clipping and cutting, dissection of the ureters, clipping and cutting, dissection of the whole kidney, no retrieval due to limitation of the size of the vagina in our pig model; (2) Partial nephrectomy: dissection of the vessels, temporary clamping of one arterial branch, division of the parenchyma at the border of the ischemic tissue, hemostasis control, relies of the clamp, extraction of the specimen transvaginally; (3) Adrenalectomy: dissection of the lateral attachments, selective control of the vascular pedicles, complete dissection of the gland, extraction of the specimen transvaginally; and (4) Distal pancreatectomy: opening of the Gerota's fascia, dissection of the anterior aspect of the pancreas up to the body, dissection of the posterior side with separation of the splenic vein (spleen sparing technique), control of the parenchyma with non-absorbable endoloop and cutting of the specimen with an endoscopic monopolar snare, extraction of the specimen transvaginally.

Human cadaver model

Experiments were conducted on frozen human cadavers, warmed at ambient temperature for 12 h. From December 2008 to April 2009, the same access principles were applied on 3 human cadavers, using material similar to that used in the animal model.

The colpotomy was performed on the posterior wall of the vagina, approximately 3 cm proximal from the posterior fornix. A posterior and lateral tunnel (left side) was then created under direct vision, using standard and laparoscopic instruments. Once the para-rectal space was entered, a 12-mm dual channel endoscope was introduced and insufflation using 15 mmHg of CO₂ was applied through one of the channels.

The successive anatomical landmarks identified were: the internal obturator nerve and artery entering Alcock's canal (Figure 2A), the sacral nerves (running on the sacrum), the median rectal artery, emerging from the pelvic ring, the left external iliac vessel (Figure 2B) and the left inferior epigastric artery (Figure 2B). Progressing cranially, the lower pole of the kidney (Figure 2C) was dissected on its anterior aspect. The dissection was then prevented because of frozen tissues.

Various interventions were performed using the endoscope with a totally NOTES technique, without any percutaneous instruments. Surgical principles driving these interventions in standard surgery were preserved in all cases, but adapted with the endoscopic devices.

RESULTS

Animal model

Thirty-seven interventions were performed on the kidney,

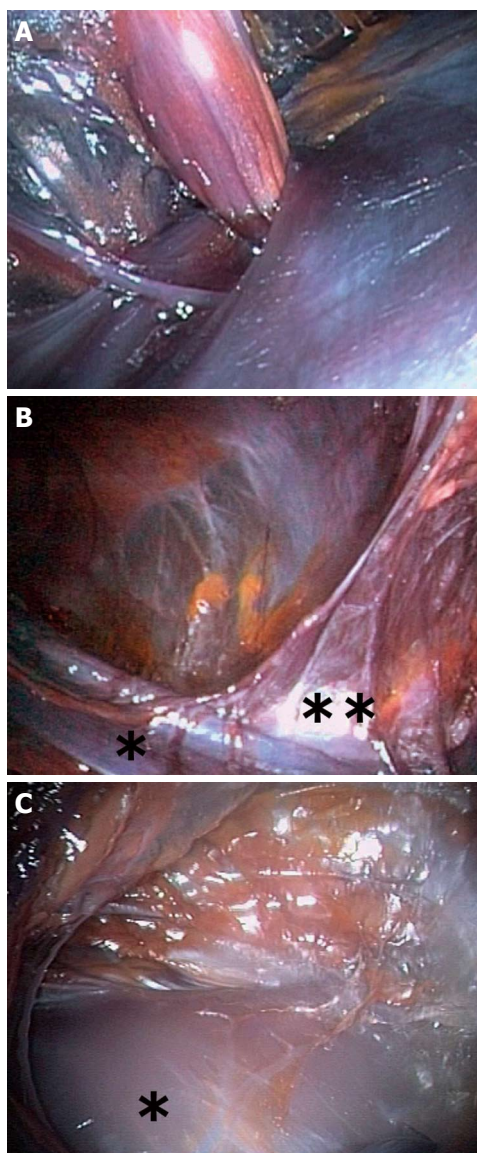


Figure 2 Cadaver model. A: Left side. Pudendal nerve entering the Alcock canal; B: Left side. *External Iliac Vein; **Inferior Epigastric Vein; C: Left side. *Kidney, lower pole.

the adrenal gland and the pancreas: 23 with an acute model and 14 with a survival model. A more detailed description of our lab experience is presented in Table 1.

All operative steps described previously for each intervention were successfully conducted. The mean time to fashion the access was 10 min (range 5 to 20 min).

No intraoperative death was observed. Two major (5%) intraoperative complications occurred: one hemorrhage on the aorta and one tearing of the right renal vein. These two complications were successfully managed with endoscopic clips. Peritoneal laceration was encountered in 5 cases, without impairing the task planned. They were all managed with the placement of an intraperitoneal Veress needle.

In the survival group, a satisfying clinical outcome was observed in all animals, with a mean follow-up of 3 wk (range 2 to 6 wk). Three occult postoperative complications were discovered at necropsy: one pancreatic fistula after distal pancreatectomy and two collections containing urine

Table 1 Detail of our animal experience

Intervention	Model (Number of intervention)
Lymphadenectomy	Acute ($n = 3$) Survival ($n = 6$)
Nephrectomy	Acute [$n = 5$ (left) +7 (right) +2 (partial)] Survival [$n = 1$ (right) +6 (partial)]
Adrenalectomy	Acute [$n = 2$ (left)+1 (right)]
Distal pancreatectomy	Acute ($n = 2$) Survival ($n = 1$)

Total 37 models, 23 with an acute model and 14 with a survival model.

after partial nephrectomies. No clinical signs were present in the animals concerned. Concerning the colpotomy, all accesses were found to be closed at 3 wk, without local complications such as abscesses or infection. The retroperitoneal space was found to be collapsed in all cases, without any objective infection.

Human cadaver model

The access was performed correctly in the 3 cadavers up to the iliac vessels. In the first case, frozen tissues prevented complete dissection up to the kidney. In the 2 remaining, the lower pole of the kidney was clearly visualized. The mean time to fashion the access was 52 min (range 40 to 60 min).

All the anatomical landmarks described in the pig model were clearly identified in the same sequence. Moreover, the sacral nerves and the middle rectal artery were identified in 2 of 3 cases.

DISCUSSION

We developed a model of transvaginal extra-peritoneal access to the retroperitoneum in both animal and human cadaver models^[58-64]. Using this access and simple endoscopic instruments, various procedures were performed^[59-64]. The mean time to fashion the access decreased dramatically with experience showing a quick learning curve and was strongly correlated with the introduction of a standardized anatomical landmarks-based dissection. As described previously for RPS^[14,21,22], the orientation is more difficult in the retroperitoneum due to the lack of a real space (compared to the abdominal cavity). In order to overcome this limitation, we developed a highly standardized technique in which every anatomical landmark observed allowed the operator to progress in the direction of the next structure^[58]. This is critical to guarantee reproducibility for other operators. This fact was clearly observed at the NOTES hands-on information session given at our institute during which our access was easily reproduced by endoscopic-naïve operators (data not published).

Pelvic lymph nodes

A complete mapping and extraction of all lymphatic stations of the pig was possible (up to renal pedicle lymph nodes) on both sides using the same vaginal incision^[60]. As the first structures encountered during our dissection are

the pelvic lymph nodes, this seems to represent a more practical intervention to be performed with such an approach and could be interesting for gynecology during the mapping of uterine cancer.

Nephrectomy

NOTES approaches have been widely used in urology for a few years with success^[47-55], but only through trans-abdominal accesses. Our approach seems to be a valuable option for such interventions, as the kidney was always dissected freely in all of our interventions, including in the human cadavers^[64]. Despite this easy access, important technical limitations have to be ruled-out (vascular control, cutting, and hemostasis) to allow more safe and practical interventions. In order to push the limits of our relatively simple instrumentation, we developed a survival model of partial nephrectomies (data not published). These interventions were possible, using advanced tactical tricks to perform temporary vascular control, but the need of suturing material was found to be a major limitation during the interventions. Attempts to close opened pyelocaliceal structures with endoscopic clips resulted in urine leak in two animals.

Adrenalectomy

Interventions on adrenal glands were found to be feasible in the pig model^[63], however, we encountered anatomical difficulties due to the firm attachments of the glands to vascular structures on both sides (the inferior vena cava and the aorta). This topographic distinction was responsible for two major intraoperative complications. No clinical repercussions were encountered as these two complications were managed quickly with compression and endoscopic control using clips. As in laparoscopy, the working space is closed and gas pressure greatly contributed to contain the hemorrhage, but measures to avoid massive gas embolism must also be quickly taken. In the two cases, the adrenal glands were situated deep into the wall of the vascular structure. In this context, we decided to limit our experiment on this model. These limits should not be extended to the human model, as the glands are well separated from these two major structures.

Pancreas

Even if laparoscopy remains a debated approach, it seemed interesting to try this approach for the distal part of the pancreas, due to its close proximity during the others interventions. Using simple and basic material, it was possible to perform resection of the distal part of this organ without touching the splenic vessels and the peritoneum^[62]. Due to the shape of the pelvis and the size of the vagina in the pig, it was not possible to insert a stapler for the transaction and this was done using endoscopic endoloop. This is probably the reason for the pancreatic stump leakage observed in one animal. Despite this technical drawback, this approach allows pushing our model to the limits. Posterior access to treat pancreatic pathologies has already been proposed for a long time, in open or endoscopic surgery, and

has shown many interesting benefits as a dissection of the pancreas without opening of the peritoneum^[16-20]. This was particularly important to prevent peritoneal seeding of aggressive pancreatic juice during acute pancreatitis.

Many advantages were discovered during this experiment. One of the leading was the use of the endoscope by itself. This provides an “all-in-one” flexible platform for vision, insufflation and access to deliver a large variety of endoscopic instruments without the need to retrieve the platform to clean the lens or change the instruments. Conceptually, the endoscope could be considered as a flexible long single port and allows us to save time and movements.

As this transvaginal approach could not be considered as a pure anterior or posterior access, it allows us to avoid all of the complications related to both LS and RPS. The risk of pneumothorax, intercostal nerve injury and abdominal viscera is *per se* almost impossible to occur. Moreover, through the same incision, it was possible to gain access to both sides from the pelvis to the diaphragm^[58]. This bilateral and full exploration of the retroperitoneum through one access is not possible in both RPS and LS (due to the interposition of abdominal organs).

This retroperitoneum-based access allows us to progress up to the targeted organ without opening the peritoneum in the vast majority of cases. In the few animals where this barrier was opened, it was limited to a small tear and a Veress needle was used to take the pneumoperitoneum out, which is a technique routinely used during extraperitoneal hernia repair (TEP)^[65]. Another advantage in not opening the peritoneum is that the space is perfectly dry, allowing the CO₂ to dissolve into the tissues and to enhance pneumo dissection. This effect, shared with RPS, is present during LS but to a lesser extent. Working in a closed space under pressure carries other advantages, such as a natural retraction coming from the areolar tissue surrounding the organs created by a selective and comprehensive dissection during the approach.

The orientation of the instruments and vision was found to be completely different compared to LS and RPS. Of particular interest was the direct access to the renal pedicle, allowing simple control of all the vessels, which is sometimes difficult during RPS nephrectomy for a large kidney.

As already pointed out, in all transvaginal access for NOTES, these techniques remain limited to women. If this point seems impossible to overcome, some other possibilities could be considered, such as transrectal access to the retroperitoneum, but close control of the infectious problems have to be studied first.

Another point concerning the access is the outcome of the colpotomy in terms of pain, fertility and local infections. If a transvaginal procedure is used many times in gynecology for intra-abdominal interventions (e.g. hysterectomy and fertility assessment), it may be an important issue for all transvaginal NOTES interventions, either transperitoneal or retroperitoneal.

Although complex interventions were feasible using simple endoscopic instruments, a revolution in terms of material is mandatory to transpose such technique to clinical

applications. If actual endoscopic clips are sufficient to control a 3 mm artery, such devices were not designed for larger structures. Moreover, if flexible stapling devices are available on the market, their miniaturization and handling should be improved.

One of the limitations of our pig model was the size of the vagina. This prevents retrieving the kidney in one piece after complete dissection or to insert another instrument alongside the endoscope. We believe that this limitation will not be encountered in a human model, as transvaginal retrieval of kidney was already performed and described^[47]. However, there could be a clear limit in the case of large tumors. Another detail concerning the extraction is the prevention of cell seeding. This point could be ruled out using plastic protectors, as in LS/RPS.

If this technique is going to be applied to regular practice, more research is needed to develop the same stepwise approach in a cadaver model. Indeed, this approach was designed to avoid the complications of existing techniques. This objective will only be reached with complete knowledge of surgical anatomy encountered during the endoscopic dissection.

In conclusion, the retroperitoneal NOTES transvaginal approach is feasible in both animal and human models and allows performing a large panel of interventions, even using basic instrumentation. This technique may contribute to a decrease in surgical trauma and the complications associated with current approaches.

COMMENTS

Background

Surgery of the organs situated in the retroperitoneum is shared by different operative specialties: general surgery, visceral surgery, urology and gynecology. This multidisciplinary approach comes from the different organs targeted. Technical evolutions have been applied in this field, particularly the arrival of video-assisted endoscopic surgery. This new approach has dramatically decreased the trauma induced by the surgical intervention and has been proved to have clear benefits for the patient's recovery. Basically two approaches have been developed: an anterior approach, through the abdominal cavity (laparoscopy) and a direct posterior approach (retroperitoneoscopy).

Research frontiers

Nowadays, new fields of research tend to lower again and again the invasiveness of this approach. Transluminal endoscopic surgery performed through natural orifices (NOTES) is one of these promising targets. Both laparoscopy and retroperitoneoscopy have some limitations and potential complications. NOTES approaches could eventually overcome some of the morbidity arising from the skin incisions. NOTES has been applied on a large panel of interventions in the retroperitoneum, in both animal and human models.

Innovations and breakthroughs

In the past experiments on retroperitoneal organs with NOTES, the access was always done through an anterior approach, via the peritoneal cavity, despite the targeted organs are situated behind the peritoneum. The main risk of such access is to damage intraperitoneal organs (bowel, liver, blood vessels). For this reason, the authors tried the purpose of this research was to study the potentialities of NOTES approach through a posterior approach, avoiding touching the abdominal cavity.

Applications

The results of this experiment demonstrate that a posterior approach of the retroperitoneum is feasible with NOTES technique in an animal model. Anatomical landmarks were essentials to provide a large reproducibility. Application to Human seems promising, but will require more advanced experiments.

Terminology

Retroperitoneum: anatomical space situated behind the peritoneal cavity. It con-

tains important organs such as the kidneys, the pancreas, the adrenal glands, the aorta, etc. NOTES: Endoscopic surgery performed through the natural orifices (the mouth, the vagina, the anus). Using these orifices avoids the need of the small incisions of the conventional endoscopic surgery, allowing surgery without visible scar.

Peer review

The author described retroperitoneal approach of NOTES technique for animal and human cadaver model. This experimental report may contribute for the surgeons who are going to perform NOTES in the retroperitoneum.

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Epidural anesthesia is effective for extracorporeal shock wave lithotripsy of pancreatic and biliary calculi

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RESULTS: Ninety eight percent of the 1509 patients underwent ESWL under TEA. The subjects selected were within American Society of Anesthesiologists grade I to III. ESWL using EA permitted successful elimination of bile duct or pancreatic calculi with minimal morbidity. The procedure time was shorter in patients with TEA than in those who underwent ESWL under total intravenous anesthesia.

CONCLUSION: Almost all patients undergoing ESWL with EA had effective blocks with a single catheter insertion and local anesthetic injection.

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Key words: Thoracic epidural anesthesia; Extracorporeal shock wave lithotripsy; Bile duct calculi; Pancreatic duct calculi

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Abstract

AIM: To evaluate the efficacy of thoracic epidural analgesia for extracorporeal shock wave lithotripsy (ESWL).

METHODS: ESWL is an effective, non-invasive technique for the treatment of difficult pancreatic and large bile duct calculi. The procedure is often painful and requires large doses of analgesics. Many different anesthetic techniques have been used. Patients with either large bile duct calculi or pancreatic duct calculi which could not be extracted by routine endoscopic methods were selected. Thoracic epidural anesthesia (TEA) was routinely used in all the subjects unless contraindicated. Bupivacaine 0.25% with or without clonidine was used to block the segments D6 to D12. The dose was calculated depending on the age, height and weight of the patient. It was usually 1-2 mL per segment blocked.

INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is an effective, non-invasive technique for the treatment of difficult pancreatic and large bile duct calculi^[1,2]. Millimetric fragmentation of pancreatic and bile duct stones by ESWL has improved the results of endoscopic therapy. The ESWL machine uses high pressure shock waves generated by an

ellipsoid cup with the aid of biplanar fluoroscopy. The treatment is often painful and requires large doses of analgesics. Many different anesthetic techniques have been used for ESWL. To date general anesthesia, epidural anesthesia (EA) with local anesthetic agents or opioids, intercostal nerve blocks with local infiltration, intravenous fentanyl, combinations of intravenous analgesics and sedatives have all been used^[3-12].

In our institution we routinely employ continuous thoracic epidural anesthesia (TEA) using Bupivacaine 0.25% with or without Clonidine to achieve a sensory block level in the region of T6-T12. This paper describes our vast experience of this regimen.

MATERIALS AND METHODS

The patient selection criterion for ESWL was the presence of large bile duct calculi which could not be extracted by routine endoscopic methods using a balloon or mechanical lithotripter^[11]. Old and frail patients with a high surgical risk or those with retained common bile duct stones after cholecystectomy were also considered^[13,14]. The subjects required nasobiliary drainage catheters or T-tubes to serve as conduits for injection of contrast media into the biliary tree to radiologically visualize the radiolucent stones before ESWL and to monitor stone position during ESWL^[2,3,14]. Subjects with pancreatic duct calculi not extractable by basket or balloon were included^[1]. Subjects with radiolucent pancreatic calculi needed a nasopancreatic tube for admitting radiographic contrast medium to localize the stone using fluoroscopy^[1]. The median diameter of the bile duct stones was 19 mm (range 6-40 mm) and 221 patients had more than one stone. The pancreatic calculi were of variable sizes and numbers. The patients were within American Society of Anesthesiologists (ASA) grade I to III. All the subjects underwent routine investigations including a complete blood picture, random blood sugar, blood urea, serum creatinine, ECG, coagulation profile, viral markers and X-Ray chest PA view. Informed consent was taken from all the patients. EA was avoided in pregnant women, patients in whom informed consent could not be obtained, ASA Class IV patients, subjects with neurological impairment, skin infections at the site of injection, disturbances of coagulation, pacemakers, uncontrolled dysrhythmias, severe scoliosis, vascular aneurysms and patients with known allergy to the drugs used^[15].

None of our patients received anti-emetic or anxiolytic injections prior to the insertion of the epidural catheter. All patients received prophylactic broad-spectrum antibiotics that were continued until the biliary system or the pancreatic duct were cleared of the stone debris^[14]. Thoracic epidural catheters were inserted in all subjects unless contraindicated. Detailed knowledge of the anatomy, technique and possible complications is important for correct placement of the epidural catheter. The catheter introduction approach was mostly midline or occasionally para median. An epidural catheter (Perifix 18 G B Braun) was inserted in the T 7-8, T 8-9 or T 9-10 thoracic intervertebral space. The insertion

site was covered with a sterile adhesive dressing (Tegaderm 3M). Bupivacaine 0.25 % (Sensorcaine Astra Zeneca India) in combination with or without Clonidine hydrochloride (Cloneon, Neon Laboratories Ltd. India) was injected incrementally in all the subjects to achieve a sensory analgesia level of T6 to T12. The dose of local anesthetic given was calculated depending on the age, weight and height of the patient and the segments to be blocked. Sensory analgesia was determined using pinprick testing^[16]. The procedure was initiated after adequate analgesia was achieved. The intensity of shocks used varied from 1 to 6, depending upon the density of the stone. A top-up dose of the local anesthetic was administered when breakthrough pain occurred. The number of sessions was a minimum of one to a maximum of four (rare). The epidural catheter was left in situ in patients who required multiple sessions of ESWL^[17]. The dose of local anesthetic had to be increased when more than one session was required due to tachyphylaxis [sensitization to the Local Anesthetic (L.A.) drug]^[18].

All the patients were moved to the post anesthesia care unit (PACU) after the procedure. PACU discharge criteria included: the patient being spontaneously awake and appropriately responsive to questioning and able to move all extremities; blood pressure and heart rate within 20% of baseline values; minimal or no pain; minimal or no nausea. The patients were allowed to go home when they could walk with a steady gait and void spontaneously without any difficulty^[19].

Statistical analysis

Descriptive statistics was analyzed by SPSS 13.0 version (Chicago, IL, USA).

Patient characteristics including age, height, weight, gender, ASA grade and insertion site of the epidural catheter were recorded (Table 1). The average procedure time per session was 55 min. Total dose of the anesthetic drugs given, the level of dermatomes blocked and the dermatome regression time were documented. Duration of stay in the PACU was recorded. Procedure starting time was defined as the beginning of ESWL. Patients rated their assessment of the adequacy of anesthesia in facilitating lithotripsy as excellent, good or fair. All medications administered during the procedure and recovery were noted. All intra operative complications like pain, patient movement, saturation of oxygen in arterial blood flow (Spo2) < 90% and hypotension were recorded. Postoperative complications recorded included nausea, emesis, and urinary retention. Nurses in the PACU assessed patients every 15 min until PACU discharge criteria were met.

RESULTS

The subjects selected for ESWL ranged from ASA- I to ASA-III [ASA- I 1103 (73%), ASA- II 358 (24%) and ASA-III 48 (3%)]. Out of a total of 1509 patients, 1490 (98.7%) underwent ESWL under TEA, 19 (1.3%) under general anesthesia and 8 under total intravenous anesthesia

Table 1 Patient characteristics

Characteristics	
Age (yr)	
Mean	34.64
Standard deviation	12.03
Range	7 to 79
Sex	
Male	984 (65%)
Female	525 (35%)
Total	1509
Height (cm)	
Mean	163.8
Standard deviation	61.3
Range	90.6 to 180.5
Weight (kg)	
Mean	55.8
Standard deviation	20.3
Range	21.5 to 83
ASA Classification	
ASA I	1103 (73%)
ASA II	358 (24%)
ASA III	48 (3%)
Inter vertebral space for epidural catheter	
D7-D8	1243 (82%)
D8-D9	198 (13%)
D9-D10	68 (5%)

ASA: American Society of Anesthesiologists.

(TIVA). The treatment plan was similar for both bile duct and pancreatic calculi. There was no correlation between age and recovery in any group^[10]. A difference in drug requirement was seen at extremes of age. Some anxious patients received midazolam at the time of epidural catheter insertion at a dose of 0.05 mg/kg body wt.

Thoracic epidural catheters were placed successfully on the first attempt in most of the patients. The volume of local anesthetic injected was 5 to 12 mL, and the maximal cephalad extent of sensory block was T5 (range T5-T6). The caudad spread was up to a maximum of L1 (T11 to L1). Some patients who had more than one ESWL session required a higher dose of epidural local anesthetic injection for the subsequent sessions^[18]. Subjects who underwent ESWL under TIVA were restless and registered a lot of disruptive movements due to pain. The procedure time was shorter in patients with TEA compared to those who underwent ESWL under TIVA. Transient hypotension during the procedure was observed in 91 (6%) patients and was treated with intravenous bolus injections of ephedrine (5-15 mg)^[16]. There was respiratory depression and hypoxemic episodes in some of these patients^[10,19,20]. Bradycardia was seen in some of our TEA subjects and was corrected by giving intravenous atropine injection. Ventricular premature complexes were observed in 53(3.5%) of our patients^[11,15]. They were controlled by a single dose of intravenous lignocaine at 1.0 mg/kg body wt. Most of our patients were pain free in the post procedure period. Some who underwent ESWL for pancreatic calculi had pain for which they were treated with NSAIDS or

Fentanyl at 1 mg/kg body wt. Patients were monitored in the PACU for 4 h and then moved out unless they required further monitoring for other co-morbid conditions. There were no airway related complications. One to three sessions were required for clearance of the calculi in either of the groups. Patients stone clearance was 448 (30%) in one session, 573 (38%) in two sessions and 475 (31%) in three sessions. There were very few who required a fourth session. The assessment of adequacy of EA was excellent in 1147 (76%), good in 302 (20%) and fair in 60 (4%) of our patients, including both groups i.e. pancreatic calculi and bile duct stones.

DISCUSSION

We chose EA because of its established effectiveness, continuous nature and low incidence of complications^[21]. The average recovery time after EA was 3 h. The patients were monitored in the PACU for about 4 h. The recovery time may not be as short as for general anesthesia, but the incidence of side effects observed is definitely low^[21]. The disadvantage of general anesthesia includes daily intubation of patients for 2 to 3 consecutive days depending upon the number of sessions required^[2]. An indwelling thoracic epidural catheter is a good neuraxial option. Midazolam anxiolysis (0.05 mg/kg body wt iv) was administered to patients who were sensitive to the sound generated by the Dornier Medtech Compact Delta machine^[22]. Pain is associated with increased levels of circulating catecholamines, which results in tachycardia, hypertension and increased cardiac work leading to increased myocardial oxygen consumption. Pain control due to EA can significantly decrease the incidence of pulmonary morbidity^[23]. TEA promotes faster recovery of bowel function (as it increases the microcirculation of the bowel) and earlier fulfillment of discharge criteria^[24]. Provision of good pain relief aids good targeting of the calculi (absence of tachypnea and tachycardia) and leads to reduction of morbidity and complications^[11,2]. This results in better patient satisfaction which is an important component of good quality care.

The premature ventricular beats observed in some patients were caused either by a triggering effect of the shock waves or by other factors in our elderly patients^[11]. There were no significant post-procedure complications. A very small number of patients who complained of nausea, were treated with antiemetics. TEA is an ideal mode of anesthesia for ESWL in the geriatric group of patients compared to general anesthesia. In TEA the drug volume requirement is significantly reduced and the degree of motor block is also minimal. Any hypotension, when it occurred, was very mild. Some patients who underwent ESWL for pancreatic calculi reported experiencing pain which required oral analgesics at the time of discharge. Patients with partial clearance of stones (pancreatic calculi) preferred to have EA again when they returned later for repeat ESWL. ESWL using EA permitted successful elimination of bile duct or pancreatic calculi with minimal rates of morbidity, and with no deaths among some high-risk

patients who were otherwise untreatable by conventional techniques. When used appropriately, regional anesthesia can provide good, prolonged analgesia and a safer alternative to general anesthesia.

Our experience suggests that continuous EA is ideal, safe and effective for outpatient procedures like ESWL^[3,25]. It comes with low morbidity, and high patient satisfaction

COMMENTS

Background

Extracorporeal shock wave lithotripsy (ESWL) is an effective, non-invasive technique for the treatment of difficult pancreatic and large bile duct calculi. The treatment is often painful and requires large doses of analgesics. Many different anesthetic techniques have been used. The aim was to evaluate the efficacy of thoracic epidural analgesia for ESWL

Research frontiers

Success for non-invasive techniques for the treatment of difficult pancreatic and large bile duct calculi lies in providing a quiet, co-operative and pain-free patient. Thoracic epidural anesthesia (TEA) is the ideal technique.

Innovations and breakthroughs

The authors aim to show that TEA which is not used in many centers is ideal, effective and safe for ESWL of difficult pancreatic and large bile duct calculi.

Applications

This methodology may represent a future strategy for therapeutic intervention in the treatment of patients with difficult pancreatic and large bile duct calculi.

Terminology

Millimetric fragmentation of pancreatic and bile duct stones by ESWL can be achieved by the safe introduction of epidural catheters in the D7 to D10 thoracic intervertebral space. 18G epidural catheters are ideal as they do not get blocked easily.

Peer review

As a surgeon, the manuscript tells interesting information about ESWL for stones in the hepato-pancreato-biliary area. It is kind of surprising to know so many patients undergo this treatment under EA with this disease.

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Intestinal perforation as an early complication in Wegener's granulomatosis

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Abstract

We present the case of a young man with involvement of the gastrointestinal tract in the early phase of Wegener's granulomatosis. The patient presented at the emergency department with sudden onset of abdominal pain, nausea and vomiting. Radiography work up was negative for free air although ultrasound examination showed extraluminal intra-abdominal fluid. Exploratory laparotomy showed perforation of the jejunum. The bowel was vital except for this small segment of jejunum. A 5-cm long segment of jejunum was resected which revealed ulcerative inflammation accompanied by occluded arteries of the small intestine. Although intestinal perforation in Wegener's granulomatosis is uncommon, several cases have been previously reported. Intestinal involvement in the early phase of the disease is even more uncommon. This case combined with previously reported cases emphasizes the possibility of gastrointestinal manifestation early in Wegener's disease.

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Key words: Wegener's granulomatosis; Intestinal tract; Perforation

INTRODUCTION

Wegener's granulomatosis (WG) is a necrotizing vasculitis of the small to medium-sized arteries characterized by involvement of the upper and lower respiratory tract and the kidneys, although other sites can also be involved^[1,2]. The etiology of WG remains elusive. However, previous studies have implicated interplay between genetic susceptibility and environmental triggers as possible risk factors^[3,4]. The gastrointestinal tract is rarely involved, occurring in 10%-24% of patients with WG^[1]. Only a few cases had histological confirmation of vasculitis at the site of perforation^[5-7]. In this case report, we describe a case of WG with intestinal perforation in the early course of the disease.

CASE REPORT

A previously healthy 35 years old Caucasian man with arthralgia of the knees, elbows and hands, skin rash, sinusitis, oral ulcers and renal impairment was admitted to our hospital in June 2009.

Laboratory findings showed: hemoglobin 7.7 mmol/L, C-reactive protein 13.5 mg/L, leucocytes 18000/mm³, serum creatinine 110 μmol/L and positive anti-neutrophil cytoplasmic antibodies proteinase 3. Urine sediment contained free red blood cells (142/h). Plain chest radiography was normal. Biopsy was performed on the skin lesions and

the microscopic findings showed leukocytoclastic vasculitis. Based on the laboratory and clinical findings, the patient was diagnosed with systemic vasculitis secondary to WG and intravenous prednisolone (60 mg/d, iv) combined with oral cyclophosphamide (200 mg/d) therapy was started.

Later in the disease course, the patient became respiratory insufficient and was intubated. A week after the diagnosis of WG, his clinical condition was determined by a persistent gastrointestinal hemorrhage for which he received a total of 150 units of packed cells. Gastrointestinal endoscopy was performed several times in order to treat the hemorrhage. However, except for ulcerative lesions in the gastrointestinal tract, no explanation for the hemorrhage was found. As the bleeding continued, angiography of the superior mesenteric artery was performed and arterial blood loss was seen in the proximal jejunum. Subsequently coils were successfully placed. In August 2009 the patient was discharged with continued oral medication.

In October 2009 the patient again presented with a sudden onset of severe abdominal pain, nausea and vomiting at the emergency department. On physical examination, his blood pressure was 138/80 mmHg with a pulse rate of 115 beats/min and temperature of 36.5°C. Abdominal examination revealed diminished bowel sounds with diffuse abdominal pain and signs of peritonitis. Laboratory analysis showed a C-reactive protein level of 16 mg/L, erythrocyte sedimentation rate of 17 mm/h and hemoglobin level of 7.0 mmol/L. X-ray analysis of the thorax was negative for abdominal free air although ultrasound examination of the abdomen revealed intra-abdominal extraluminal fluid. Exploratory laparotomy showed ischemia of the proximal jejunum and perforation at this site. Additionally, segmental resection of the jejunum was performed. The procedure could also have been performed laparoscopically.

Histopathological findings were central ulcerative inflammation and occluded small arteries in the intestinal wall. Giant cells were not found. Lamina elastica staining showed impaired arterial wall due to inflammatory processes. Immunohistochemical study for cytomegalovirus antigen was negative. The patient recovered without any additional adverse events and remains in remission on oral prednisolone and cyclophosphamide therapy.

DISCUSSION

WG is a necrotizing vasculitis defined by granulomatous changes of the upper and lower respiratory tract and is frequently associated with glomerulonephritis^[8].

Our case meets the diagnostic criteria of WG published by Fauci *et al.*^[1] which concludes that in order to establish the diagnosis there should be clinical evidence of disease in two of the three principle sites (upper airways, lung and kidney) with histological confirmation in at least one site^[1]. Our case shows severe intestinal involvement in an early phase of Wegener's disease. Whether the perforation of the jejunum was due to WG alone or the result

of intestinal ischemia due to coiling through angiography remains uncertain.

In our case gastrointestinal hemorrhage developed in the early course of the disease and an endoscopic maneuver was unable to precisely detect the cause of the hemorrhage. The bleeding was managed with coiling side-branches of the superior mesenteric artery through angiography examination. The coiling might have caused ischemia of the intestinal segment resulting in perforation of the intestinal wall. Since endoscopic examination a month after coiling did not show any anomalies of the intestinal wall, ischemia due to coiling through angiography examination seems unlikely. Moreover our patient did not have any clinical symptoms of colonic ischemia^[9] prior to the sudden onset of abdominal pain. In our patient, ischemia caused by vasculitis (characteristic for WG) seems to be the most logical explanation for the perforation of the intestinal wall.

Earlier case reports describe intestinal involvement of WG. Very few cases report perforation of the intestinal wall in the early course of the disease^[6,10-12].

Use of immunosuppressive therapy has been suggested as an etiological factor for intestinal involvement in WG^[6]. Intestinal involvement has however been described in a very early course of the disease in which no medical treatment was started. Also, in multiple cases, histological examination showed extensive vasculitis with fibrinoid necrosis resulting in intestinal perforation^[5-10]. Although immunosuppressive therapy is not proven as an etiological factor, it might exacerbate already existing areas of ulceration leading to perforation.

In conclusion, even though uncommon, intestinal involvement may be listed in the clinical symptoms of WG and can occur in the early course of the disease. The diagnosis should be suspected in patients presenting with sudden abdominal pain and symptoms of systemic vasculitis. An early diagnosis is vital and should not be missed since it could result in severe complications and death.

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Gallstone ileus: One-stage surgery in a patient with intermittent obstruction

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Abstract

Gallstone ileus, an uncommon complication of cholelithiasis, is described as a mechanical intestinal obstruction due to impaction of one or more large gallstones within the gastrointestinal tract. The clinical presentation is variable, depending on the site of obstruction, manifested as acute, intermittent or chronic episodes. A 51-year-old female patient was referred to our hospital with 3 events of intestinal obstruction during the previous 7 d. At admission, there were clinical signs of intestinal obstruction; abdominal film demonstrated dilated bowel loops, air-fluid levels and a vague image of a stone in the inferior left quadrant. Once stabilized, a laparotomy was performed. Surgical findings were distention of the jejunum and ileum proximal to a palpable stone in the

ileum as well as gallstones and a cholecystoduodenal fistula in the gallbladder. An enterolithotomy, repair of the cholecystoduodenal fistula and cholecystectomy were performed. The postoperative course was uneventful. There is no uniform surgical procedure for this disease. When the patient is too ill or when biliary surgery is not advisable, an enterolithotomy is the best option. The one-stage procedure should be offered to adequately stabilized patients when local and general conditions, such as good cardiorespiratory and metabolic reserve permit a more prolonged surgical procedure.

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Key words: Gallstone ileus; Cholecystoduodenal fistula; Intestinal obstruction

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INTRODUCTION

Gallstone ileus is an uncommon complication of cholelithiasis and is described as a mechanical intestinal obstruction due to impaction of one or more large gallstones within the gastrointestinal tract^[1]. Although it is a disease most commonly found in elderly patients, there is a wide range of age presentation^[2,3]. A biliary-enteric fistula allows the passage of a large gallstone, most commonly between

the gallbladder and the duodenum^[4]. A gallstone of at least 2 to 2.5 cm in diameter will result in its impaction in the terminal ileum or the ileocecal valve^[5].

The clinical presentation of a gallstone ileus is variable, depending on the site of obstruction, and may be manifested as acute, intermittent or chronic episodes^[2]. In 50% of cases, the diagnosis is only made at laparotomy^[3]. There is no uniform surgical procedure for this disease although enterolithotomy remains the most reported procedure. Nevertheless, the one-stage operative method of enterolithotomy, cholecystectomy and repair of the fistula may be indicated in selected cases^[6]. A mortality rate of between 7.5% and 15% has been reported, due to delayed diagnosis, concomitant conditions and advanced age.

CASE REPORT

A 51-year-old female patient was referred to our hospital with 3 events of abdominal pain and distension, postprandial vomiting and pain relief after vomits, absence of transit of feces and flatus, during the previous 7 d. There was no previous history of gallstone disease. At admission, physical examination revealed a temperature of 37.2°C, a pulse of 98 beats per minute, a respiratory rate of 18 per minute and blood pressure of 100/75 mmHg. Bowel sounds were hyperactive, her abdomen was mildly distended, with tenderness, but no guarding or rebound. White blood cell count was 9400 per cubic millimeter, with 86% neutrophils. Other tests were unremarkable. Plain abdominal film demonstrated dilated bowel loops, air-fluid levels and a vague image of a stone in the inferior left quadrant (Figure 1). On the second day after admission, the patient presented transit to feces and gases, and vital signs normalized; white blood cell count was 6400 per cubic millimeter, with 80% neutrophils. Once stabilized, with a diagnosis of intestinal obstruction and its intermittent presentation, probably due to a gallstone ileus, the decision was made to perform a laparotomy. Generalized distention of jejunum and ileum was found proximal to a palpable stone, impacted 70 cm from the ileocecal valve (Figures 2 and 3). The gallbladder presented gallstones and a firm adhesion to the first portion of the duodenum, suggestive of a cholecystoduodenal fistula. No other gallstones were palpated. Due to her stable condition, enterolithotomy and ileal suture repair, repair of the cholecystoduodenal fistula, duodenorrhaphy and cholecystectomy were performed. At histopathology, the gallbladder showed cholelithiasis, acute and chronic inflammation and a fistulous tract walled by fibrous and granulation tissue. Following an uneventful recovery, the patient was discharged 10 d later. After a 6 mo follow-up, she remains in good health.

DISCUSSION

Gallstone ileus is described as a mechanical intestinal obstruction due to impaction of one or more large gall-



Figure 1 Plain abdominal film suggestive of intestinal obstruction and a calcified stone (arrow).



Figure 2 Site of stone impaction in ileum.

tones within the gastrointestinal tract^[1]. It represents an unusual cause of intestinal obstruction, accounting for 1%-4% of all cases, but accounts for 25% of nonstrangulated small bowel obstructions in those over the age of 65^[3,7]. This condition is usually preceded by an event of acute cholecystitis, with its consequent adhesions and inflammation, facilitating the formation of a fistula with the small or large intestine, and allowing the passage of a gallstone^[1,4]. It has been suggested as part of the natural history of Mirizzi syndrome, where continuous inflammation may not only involve the biliary tract but the adjacent viscera as well^[8]. Cholecystoenteric fistulae complicate less than 1% of gallstone cases. Although it usually affects elderly patients, with a peak incidence between 65 and 75 years of age, the age range of reported cases has been from 13 to 91 years^[2,9].

The most common fistula is between the gallbladder and duodenum in 60%-86% of the cases. If the stone is large enough, usually greater than 2-2.5 cm in diameter, it will impact causing intestinal obstruction; the reported range is from 2 to 5 cm^[1,3,10-12]. Multiple stones are reported in 3%-40% of cases^[10].

The clinical presentation of gallstone ileus is that of intestinal obstruction, usually depends on the site of impaction, and may be manifested as acute, intermittent or chronic episodes^[2]. The vomiting of proximal intestinal

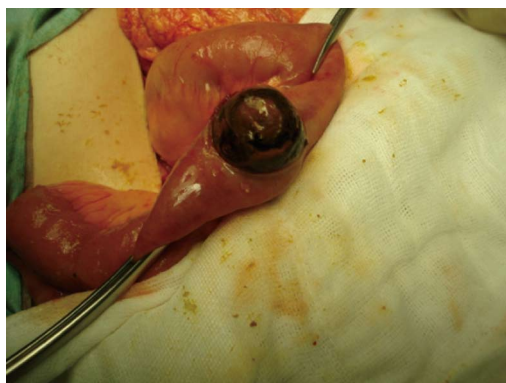


Figure 3 Enterostomy showing the obstructing gallstone.

material becoming dark and feculent is a process called “tumbling” obstruction to indicate the halting movement of the gallstone down the gastrointestinal tract^[11,13]. Most common sites of stone impaction are the terminal ileum and the ileocecal valve (50%-75%), while less common are the proximal ileum and jejunum (20%-40%), stomach, duodenum (less than 10%) and colon^[4,10].

The diagnosis of gallstone ileus is difficult, and is not made until laparotomy in 50% of cases. Plain abdominal films are diagnostic in about 50% of cases, although only 10% of gallstones may be visualized^[10]. Classical findings include: (1) pneumobilia; (2) intestinal obstruction; (3) aberrant gallstone location; and (4) change in location of a previously observed stone^[14]. The presence of two of the three first signs, or Rigler's triad, has been considered pathognomonic of gallstone ileus and is encountered in 40% to 50% of cases^[10]. Nevertheless, the reported rate of classic radiographic triad findings ranges from 0% to 87%^[15]. The finding of two air fluid levels in the right upper quadrant, secondary to air in the gallbladder, has been described as a fifth sign^[16].

Abdominal ultrasound is useful to confirm the presence of cholelithiasis, and may also identify the fistula^[17]. When compared to plain abdominal film and ultrasound, CT scan has proved to be the most valuable technique in the diagnosis of gallstone ileus cases, particularly to identify mechanical bowel obstruction, pneumobilia, and an ectopic gallstone within the bowel lumen^[18]. Helical single-detector and multi-detector computed tomography can also depict the biliary-enteric fistula, besides giving information on the exact number, size and location of ectopic stones as well as the site of intestinal obstruction and thereby improving diagnostic accuracy^[19,20].

The main goal of treatment is prompt relief of intestinal obstruction by removing the offending gallstone, with surgical intervention remaining the treatment of choice. Preoperative stabilization of the patient's condition is essential, with special attention being paid to fluid and electrolyte balance and management of comorbid conditions^[1].

There is no consensus on the choice of surgical pro-

cedure. The current approaches are: (1) enterolithotomy alone; (2) enterolithotomy with cholecystectomy performed later (two-stage surgery); and (3) enterolithotomy, cholecystectomy and fistula closure (one-stage surgery).

Enterolithotomy has been the most reported surgical procedure. The belief that the cholecystoenteric fistula will close spontaneously in the presence of a patent cystic duct has been reported. Nevertheless, the prevalence of recurrent cholecystitis has been highlighted as well as an increased incidence of gallbladder carcinoma in patients with fistulas^[21,22]. Although recurrence rates of gallstone ileus of less than 5% are reported with 10% of patients requiring reoperations for continued symptoms related to biliary tract, recurrence rates of 17% or even 33% have also occurred^[3,10,23,24]. A review of series reporting recurrences shows a recurrent gallstone ileus risk of 8.2% in patients who survive enterolithotomy alone; 52% of recurrences occur within the first month, while the remainder present within 2 years, with an associated 12%-20% mortality rate^[25]. With a one-stage procedure, further events of cholecystitis, cholangitis and recurrent gallstone ileus are prevented^[11].

On the other hand, in addition to the low recurrence rates of gallstone ileus and of further biliary-complications, simple enterolithotomy has been associated with an 11.7% mortality compared to 16.9% for the one-stage procedure^[3]. Moreover, in patients treated with enterolithotomy and subsequent cholecystectomy plus fistula repair, mortality as low as 0% has been reported, whereas a mortality rate of 19% has followed the one-stage procedure^[2]. Consideration should be taken of the fact that the severity of each case has influence on the outcome of any particular surgical procedure, and that mortality is not an absolute consequence of the surgical procedure itself. In a non-random study of three surgical groups comprising the one-stage procedure, two-stage procedure or enterolithotomy only, comparable in terms of patient age, associated concomitant diseases and APACHE II score, operative mortality and morbidity rates did not differ significantly among the three therapeutic groups^[10]. In a retrospective study, where 7 stable patients, classified as ASA I and II, underwent a one-stage surgery, while 6 out of 7 pre-operatively shocked patients with ASA III and IV underwent an enterolithotomy alone; no mortality occurred at 30 d after the surgery^[26]. In a recent retrospective study, all five patients in Group 1 were hypertensive and diabetic including two patients who had a history of ischemic heart disease, and all were hemodynamically unstable, with an ASA score of three or more, whereas the five patients in Group 2 were hemodynamically stable, with ASA score of two, and only two were hypertensive. Patients in Group 1 underwent enterolithotomy alone while patients in Group 2 underwent a one-stage procedure. There was no operative mortality in either group^[27].

Proponents of a one-stage procedure recommend palpation of the entire bowel as essential to prevent further

obstruction by a gallstone. It is also necessary to palpate the gallbladder and common bile duct, in order to exclude gallstones, evidence of leakage, abscess or necrosis^[1,10,11,28].

No randomized trial has compared these surgical options, probably due to the low rates of presentation and to possible ethical considerations.

Small bowel resection and anastomosis is a therapeutic option in patients with an impacted gallstone when irreversible ischemic bowel damage or perforation is found^[12].

The prognosis of gallstone ileus is usually poor, with mortality rates of up to 20%, due mainly to delayed diagnosis and comorbid conditions^[3,5]. The average period between the initial symptoms and the time of admission ranges from 1 to 8 d^[6,10,11,29], reflecting the intermittent gallstone movement until impaction occurs. Mechanical intestinal obstruction with abdominal pain and vomiting is seen in 80% of cases^[10]. Moreover, the range of time between admission and operation, (3 to 4.5 d)^[2,10] could be attributed to delays in establishing diagnosis and patient stabilization. A preoperative diagnosis in 43% to 73% of the patients has been reported, while more than 50% of the cases have been discovered only at laparotomy^[3,10]. The delay from initial symptoms to hospital admission, and to diagnosis and treatment, the presence of comorbid conditions such as cardiorespiratory and metabolic diseases, and the effect of postoperative complications, might be responsible for the high rate of mortality^[15].

The patient herein reported had a 7 d background of intermittent intestinal obstruction, with a vague calcified image suggestive of a gallstone in the abdominal film, although no clear pneumobilia was visualized. Stabilization was possible; passage of gases and feces were regained, due the presence of a gallstone “tumbling” obstruction, as already described^[11,13]. The patient’s general condition and the surgical findings justified a one-stage procedure.

Surgical management should be individualized. When the patient is too ill or dissection is of major risk and when biliary surgery is not advisable at the initial operation, an enterolithotomy is the best option. Cholecystectomy and fistula closure might be considered on an elective basis, and appears to be justifiable when there are biliary symptoms or residual cholelithiasis at ultrasonography. The one-stage procedure should be the offered to patients who have been adequately stabilized in the preoperative period, and when local and general conditions, such as good cardiorespiratory and metabolic reserve, permit a more prolonged surgical procedure. The exclusion of the presence of gallstones by palpation of the gallbladder, common bile duct and the entire bowel is of paramount importance when deciding on biliary surgery in either one-stage or two-stage surgery^[1,3,4,10-12,30].

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The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
<http://www.gilearn.org/clinical-congress>

January 27-31, 2010

Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
<http://www.alpshpbmeeting.soton.ac.uk>

February 25, 2010

Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, United Kingdom
<http://www.rsm.ac.uk/academ/pancreatitis10.php>

March 4-7, 2010

2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri, United States
<http://www.surgonc.org/>

March 25-28, 2010

20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
<http://www.apasl2010beijing.org/en/index.aspx>

April 14-18, 2010

The International Liver Congress™ 2010
Vienna, Austria

May 1-5, 2010

2010 American Transplant Congress
San Diego Convention Center, 111 West Harbor Drive, San Diego, United States
<http://www.atcmeeting.org/2010>

May 1-5, 2010

Digestive Disease Week 2010
Ernest N Morial Convention Center, 900 Convention Center Blvd, New Orleans, United States
<http://www.ddw.org/>

May 15-19, 2010

Annual Meeting of the American Society of Colon and Rectal Surgeons
Hilton Minneapolis Hotel & Convention Center, Minneapolis, Minnesota, United States
<http://www.fascrs.org/>

September 16-18, 2010

Prague Hepatology Meeting 2010
Prague, Czech Republic
<http://www.congressprague.cz/en/kongresy/phm2010.html>

September 23-25, 2010

2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, United States
<http://www.isgio.org/isgio2010/program.htm>

October 20-23, 2010

Australian Gastroenterology Week
Melbourne, Australia
<http://www.gesa.org.au/agw.cfm>

November 13-14, 2010

Case-Based Approach to the Management of Inflammatory Bowel Disease
San Francisco, United States

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Write as mean \pm SD or mean \pm SE.

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Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h, blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 $24.5 \mu\text{g/L}$; CO_2 volume fraction, 50 mL/L CO_2 , not 5% CO_2 ; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

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

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