J Gastrointest Surg (2010) 14:587–593
DOI 10.1007/s11605-009-1135-9

ORIGINAL ARTICLE

Significance of Limited Hiatal Dissection in Surgery for Achalasia

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Received: 15 October 2009 / Accepted: 4 December 2009 / Published online: 22 December 2009

Abstract
Introduction It is speculated that postoperative pathologic gastroesophageal reflux after Heller's myotomy can be diminished if the lateral and posterior phrenoesophageal attachments are left intact. The aim of this study was to evaluate the effectiveness of limited hiatal dissection in patients operated due to achalasia.
Methods Prospective, randomized, 3 years follow-up of 84 patients operated due to achalasia. In 26 patients, Heller–Dor with complete hiatal dissection was done (G1), limited hiatal dissection combined with myotomy and Dor's procedure was performed in 36 patients (G2), and with Heller's myotomy alone in 22 (G3). Stationary manometry and 24 h pH study were performed in regular postoperative intervals.
Results Postoperatively, higher median values of lower esophageal sphincter resting pressures were marked in G2 and G3, while patients in G1 were presented with higher median values of pH acid score ($p<0.001$). Abnormal DeMeester score 3 years after surgery was present in 23.1% of patients in G1 and 8.5% and 9.1% in G2 and G3 accordingly. There was no statistical difference between the groups concerning postoperative dysphagia recurrence.
Conclusion Indicating further long-term studies, 3 years after the operation limited hiatal dissection compared to complete obtains better reflux control in achalasia patients, regardless of Dor's fundoplication.

Keywords Achalasia · Esophageal manometry · Myotomy · Limited hiatal dissection

Presented at 11th World Congress of the International Society for Diseases of the Esophagus. Free papers session/motor disorders: diagnosis and treatment. Budapest, September 10th–13th, 2008

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Introduction

Secondary to GERD, the most common functional disorder of the foregut that requires surgical intervention is achalasia. The goal of treatment in patients with achalasia is to relieve the functional outflow obstruction secondary to the loss of relaxation and compliance of the lower esophageal high pressure zone (LEHPZ). Although the relief of dysphagia is the ultimate clinical objective, it should not be the only one.[1]

The most common surgical procedure performed worldwide for achalasia is Heller's myotomy after dissection of the phrenoesophageal membrane (PM) and complete encroachment of the abdominal esophagus, followed by Dor's fundoplication.[2,3] Although with this procedure more than 90% of satisfactory results have been reported in a long-term follow-up (up to 5 years), one of the main causes of surgical failure remains postoperative gastroesophageal

reflux (GER).[4–6] In objective follow-ups of this procedure, the incidence of GER ranges from 5% to 17%.[7,8] Taking this into the account, among other things, controversy continues regarding the addition of antireflux procedures to prevent reflux after myotomy and the necessity for complete distal esophageal mobilization.[9–11]

The proponents of an antireflux procedure indicate a relatively high rate of subsequent gastroesophageal reflux following myotomy alone, as well as the protective effect against esophageal leaks.[12,13] Lyass et al. published a meta-analysis concerning this problem and concluded that there is no clear demonstration concerning the efficiency of partial fundoplication in preventing reflux; therefore, there are no arguments to recommend it.[14] On the other hand, in a randomized double-blind clinical trial, Richards et al. demonstrated that Heller myotomy with Dor fundoplication was superior to Heller myotomy alone with regard to the incidence of postoperative gastroesophageal reflux evaluated with 24-h pH monitoring after surgery.[15]

In most of the aforementioned publications, the surgical procedure is usually performed with complete destruction of natural antireflux components. By performing a limited hiatal dissection (LHD), the dissection itself is limited mostly to the anterior attachments of the phrenoesophageal membrane, allowing enough space to perform an adequate myotomy. In studies published by Bonavina et al. and Braghetto et al., it has been concluded that performing this type of dissection provides better functional postoperative outcome regarding the reflux control.[1,16] It has also been stressed out that only when an associated hiatal hernia exists, distal esophagus has to be encircled and a posterior crural repair performed.[17]

The aim of this prospective, board approved study was to objectively analyze, through a 3-year follow-up, results obtained from employing limited hiatal dissection in surgery for different types of achalasia.

Material and Methods

Study Population

The study population consisted of 102 consecutive previously untreated patients with achalasia that underwent surgical treatment at our department between May 2002 and May 2005. Follow-up was completed in 84 patients (82.35%); two patients died of unrelated causes, and the other 16 skipped two or more regular controls and, therefore, were excluded from the statistical evaluation. A prospective database (Microsoft Excel) was established for all patients and included: clinical features, endoscopic and radiological findings, stationary manometric and esophageal pH studies, and also surgical details and complications. Informed consent was obtained from each patient, and Hospital Ethics Committee approved the study.

All patients reported functional dysphagia of 8 months to 12 years duration, with a mean weight loss of 8 kg (range 0 to 30 kg). Upper GI endoscopic studies demonstrated normal findings of the esophageal body in 22, but enlargement of esophageal lumen and food retention were visualized in 62 patients. Radiology with barium swallow confirmed type I achalasia in 39, type II in 32, and type III in 13 patients. The types of achalasia were categorized according to the classification previously reported by Pinotti et al.[18] All patients included in the study met manometric criteria for achalasia.

Surgical Procedure

Randomization of the patients included in the study was based on the type of the surgical treatment. Randomization between the groups was performed in the manner that simple computer generated random numbers were used (simple randomization). Random Allocation Software edition 1.0 was used.

In the first group of patients (G1) full esophageal mobilization was done, meaning that complete disruption of the phrenoesophageal membrane was accomplished. After removing the fat pad, extramucosal myotomy was performed by incising the distal 6 to 8 cm of the esophagus, followed by 2 to 3 cm incision bellow the esophagogastric junction onto the gastric wall. Anterior fundoplication was performed by suturing the gastric wall to the left and right borders of the myotomy and to the diaphragmatic pillars according to Dor, without employing bougie or endoscope during the procedure.

Group two (G2) consisted of patients in whom only the anterior attachment of the phrenoesophageal membrane was divided for identification of the anterior surface of the esophageal muscle, therefore, preserving the lateral and posterior periesophageal anatomic structures, the procedure entitled as limited hiatal dissection. The anterior fat pad was removed for identification of the anterior vagus nerve and esophagogastric junction, exposing this area for the myotomy, which was performed in described manner, followed by addition of the anterior partial fundoplication. In the third group of patients (G3), myotomy with described limited hiatal dissection was performed, whereas no fundoplication was added.

Postoperative Diagnostics and Follow-Up

After signed informed consent the follow-up procedure was started. Objective follow-up data were collected prospectively and stored in our computer database. Postoperative dysphagia was graded from 0 to 3; grade 0 representing no symptoms, grade 1 occasional transient sensation of food sticking, grade 2 episodes of dysphagia requiring liquids to

clear, and grade 3 severe dysphagia requiring medical attention or dilatation. Upper GI endoscopy was performed on regular basis, on 6 months, 1, 2, and 3 years after the surgery. Endoscopy was performed to exclude or to confirm the presence of hiatal hernia and erosive esophagitis, as well as to evaluate the position of Dor's fundoplication if present.

Stationary esophageal manometry was performed to evaluate the postoperative changes of the LEHPZ and esophageal body motility on 6 months, 1, 2, and 3 years after the surgery. Stationary pull-trough perfused manometry (Medtronic® 98 Poligraf ID) was carried out using a 4-lumen catheter with side holes at 5 cm apart and orientated 90° from each other. The catheter was passed per nares and positioned in the stomach. It was then withdrawn in 1 cm increments to document the LEHPZ, which was measured in end-expiratory pressure at the point of respiratory reversal. Sensors were then placed in the manner that the most distal one was positioned 3 cm above LEHPZ. Esophageal body pressure was assessed by presence of peristalsis in the esophageal body in response to 5 ml boluses of water, in minimum of 10 wet swallows. A commercial software program (Polygram 98 Esophageal Manometry Application) was used for the interpretation of manometric traces and for data analysis.

In all patients, 24-h ambulatory esophageal pH metry was performed 1, 2, and 3 years after the surgery. It was carried out by positioning pH electrode (Medtronic® Multi-use Slimline Catheter) 5 cm above LEHPZ, which was previously defined by esophageal manometry. The data were recorded by a portable data-logger (Medtronic® Digitrapper 400 pH II) for 24 h. The DeMeester composite acid score was computed using Medtronic® Polygram 98 pH Testing Application, and abnormal intraesophageal pH was defined as a score higher than 14.7.

Statistical Analysis

All data were presented as mean values with standard deviations and percentages. A two-tailed unpaired Student's *t* test was used to compare all continuous variables of LEHPZ and DeMeester 24-h pH metry acid scores. Different groups were compared by using one-way ANOVA and Man–Whitney test. *P* values of less than 0.05 were considered statistically significant. The statistic software program SPSS for Windows, release 10 (SPSS, Inc., Chicago, IL) was used.

Results

Based on the operative technique all 84 patients, in which the follow-up was completed, were divided into three groups. There were 26 patients (30.9%) in the group one (G1), in whom full esophageal dissection, with esophageal encroachment was performed followed by Heller myotomy and Dor's fundoplication. Group two (G2) consisted of 36 patients (42.9%) in whom LHD was followed with myotomy and Dor's fundoplication. Third group (G3) consisted of 22 (26.1%) patients in whom Heller myotomy and LHD without Dor's fundoplication was performed.

There were 36 male and 48 female patients, with the median age of 49.6±29.2 years (ranging from 21 to 82). Average preoperative duration of achalasia symptoms was 4.25±2.1 years (ranging from 8 months to 12 years). No concomitant hiatal hernia was diagnosed during preoperative evaluation. Mean hospital stay after the surgery was 5.2 days. Mucosal perforation, intraopeartively recognized, occurred in two, and splenectomy had to be performed in three patients. Two patients, who were treated due to postoperative pneumonia, left the hospital on the 14th and 19th postoperative day. There was no intrahospital mortality.

Preoperative LEHPZ manometric findings were similar in all three groups. Mean value of LEHPZ resting pressure in G1 was 36.9±5.3 mmHg, in G2 38.7±5.4, and in G3 34.2±5.1 mmHg (mean LEHPZ resting pressure was 36.7±5.2 mmHg). First postoperative stationary manometric testing showed significant decrease in LEHPZ mean values in all three groups. Mean values of LEHPZ resting pressure 6 months after the operation in G1 were 12.5±2.3 mmHg, in G2 13.9±3.1 mmHg, and in G3 10.7±3.4 mmHg, to some extent indicating the contribution of partial fundoplication in overall LEHPZ resting pressure. One year after the surgery, these values remained statistically unchanged but kept a decreased trend after 2 years. Three years after the operation, mean values of LEHPZ resting pressure were 6.4 mmHg in G1, 9.6 and 8.9 mmHg in G2 and G3 accordingly. Highest decrease in LEHPZ resting pressure during a 3-year follow-up was observed in G1, with statistically significant difference opposed to LEHPZ values in G2 and G3 of patients ($p<0.05$; Fig. 1).

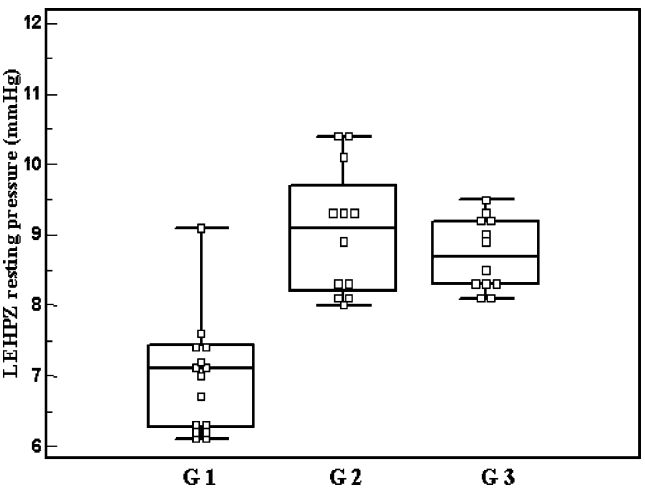

Figure 1 Comparative analysis of LEHPZ resting pressures between the groups 3 years after the operation.

Mean values of DeMeester acid score 1 year after the surgery were 20.1 in G1, 11.7 and 13.2 in G2 and G3 accordingly, with a statistically significant difference ($p<0.001$) between the groups (G2 and G3 opposed to G1). Increased trend of these values occurred in all three groups 2 and 3 years after the surgery. Mean values of DeMeester acid score 3 years after the surgery were 22.4 in G1, 12.6 and 13.5 in G2 and G3 accordingly (Fig. 2). Statistically significant higher values ($p<0.001$) were marked in G1 opposed to G2 and G3. Mean values in all three groups did not reach statistical difference 3 years after the surgery opposed to first measurements ($p>0.05$). Three years after the surgery, six patients (23.1%) were pH metry positive in G1, three (8.5%) in G2, and two (9.1%) in G3, and in all these patients, PPIs were introduced. Overall, 13.1% of patients enrolled in this study had positive pH metry findings.

Prevalence of postoperative reflux esophagitis marked endoscopically was 11.5% in G1, 5.5% in G2, and 9.1% in G3, with no statistical difference among the groups and with predominant grade A according to the LA classification. Upper GI endoscopy revealed presence of postoperative hiatal hernia in five (19.1%) patients operated with complete disruption of the phrenoesophageal attachments (G1). Postoperative hiatal hernia emerged in only one patient in G3, whereas there were none in G2.

In all three groups of patients, nadir amplitude of esophageal body contractions statistically improved 3 years after the operation ($p<0.05$), with subsequent decrease of simultaneous waves frequency. The average nadir amplitude of esophageal body contractions 3 years after the operation was 37.62 mmHg in G 1, 41.21 and 33.12 mmHg in G2 and G3 accordingly. There was no statistical difference in nadir contraction values between the groups during the follow-up and 3 years after the surgery (Fig. 3).

We also evaluated nadir amplitude of esophageal body contractions with regard to preoperative radiological type of achalasia. Patients with types I and II showed dramatic benefit on 3 years after the operation (nadir amplitude contraction 44.3 and 41.2 mmHg accordingly), but no statistical improvement occurred in patients with type III achalasia (nadir amplitude contraction 12.3 mmHg).

There was no statistical difference ($p>0.05$) between the groups concerning the incidence of postoperative dysphagia recurrence (Table 1). One patient out of G1 and two of G2 required pneumatic dilatation and were treated successfully after just one session. Overall postoperative dysphagia incidence in LHD groups of patients was 11.2%, with two (3.8%) patients requiring further treatment.

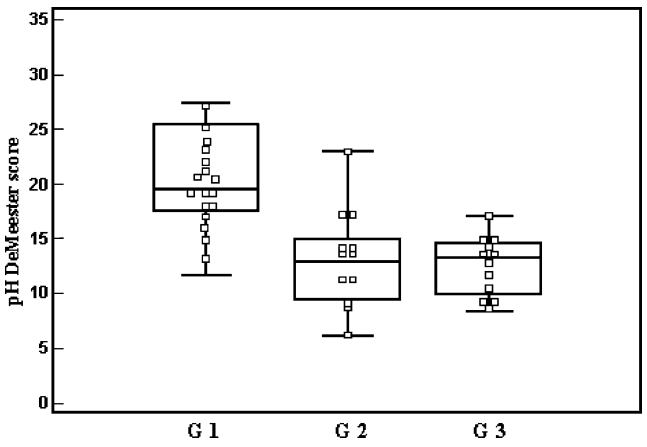

Figure 2 Comparative analysis of pH DeMeester scores between the groups 3 years after the operation.

Discussion

All contemporary treatments of achalasia aim to alleviate symptoms, although none of them reverses the underlying neuropathological changes or possibly associated impaired relaxation of the lower esophageal high pressure zone. Disruption of the LEHPZ either by balloon or surgery usually provides effective symptom relief for patients with achalasia, although surgery shown to be superior procedure in several published studies.[19,20]

Surgical treatment involves a very delicate balance between the relief of outflow obstruction and destruction of the natural antireflux barrier. The ideal operation should result is palliation of dysphagia by facilitating gravity-aided esophageal emptying, achieved through permanent interruption of the LEHPZ muscle fibers, and at the same time diminishing the possibility of postoperative GER. However, these purposes seem incompatible and, therefore, could be impossible to achieve simultaneously.

The main surgical strategy in preventing the postoperative GER over the decades has been the addition of fundoplication that followed myotomy. Currently, laparoscopic esophagocardiomyotomy with Dor's fundoplication remains the mainstay in achalasia surgery,[1,4,6] although some authors favor other antireflux procedures combined with myotomy.[21,22] The reasons for the high popularity of Dor's fundoplication could be several possible advantages other than antireflux protection: a serosal patch over the myotomy that perhaps reduces postoperative leak, stitching the edges of a fundoplication to the edges of a myotomy that "holds" the myotomy open, and providing a buttress to the myotomized esophagus, therefore, preventing formation of a pseudodiverticula.

Some complications of Heller–Dor procedure in the long-term follow-up can appear, most commonly hiatal hernia, gastroesophageal reflux, reflux induced esophagitis, or recurrent dysphagia, whose overall frequency ranges from 10% to 25%.[14–17] Postoperative hiatal hernias can be caused mainly by an excessive dissection of the distal

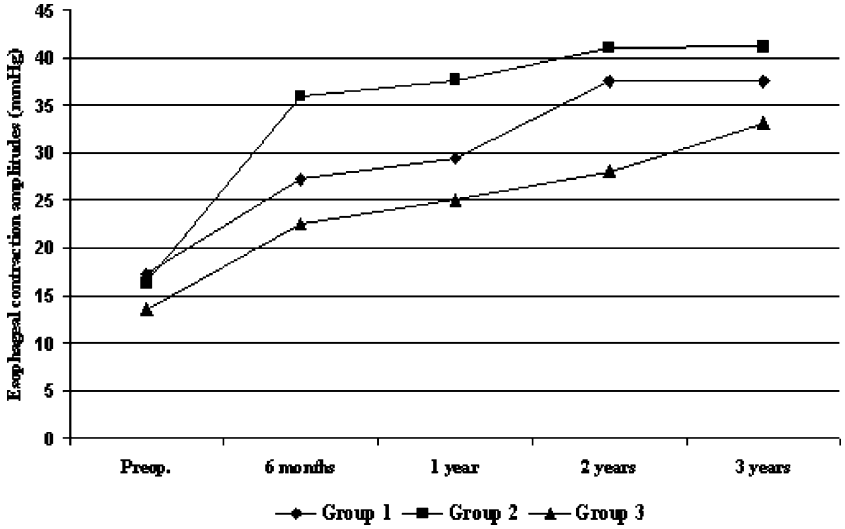

Figure 3 Comparative analysis of nadir distal esophageal contraction amplitudes through the follow-up period.

esophagus. In presence of diminished clearance capacity of the esophageal body, GER can also be directly related to integrity alterations of the periesophageal anatomic structures, especially the length of the intra-abdominal esophagus, as well as the function of PM. Possible mitigation of the benefits of myotomy and fundoplication could be the reduction of esophageal emptying, indicating that addition of Dor fundoplication reduces the adequacy of myotomy.[23] Contrarily, concerning postoperative dysphagia, other authors concluded that anterior hemifundoplication does not improve or worsen clinical results.[24] Therefore, complications resulting from Heller–Dor's procedure not only could be the result of the procedure itself but also can be caused by the severe alterations of normal anatomic relations.

It is well documented that the LEHPZ, crural diaphragm, and a PM all contribute independently to the stiffness of the esophagogastric junction (EGJ).[25] The main component of the PM is its posterior attachment, which represents the continuum of the dorsal mesentery. Adequacy of posterior PM allows stable fixation of the EGJ, therefore, maintaining efficient antireflux barrier and bolus transport through the esophagus.[26] Maintaining anatomical structures of the PM, as much as it is possible, most likely contribute to a better outcome in the terms of GER prevention.

Several authors published papers in which they described technique which partially preserves EGJ anatomy in surgery for achalasia, showing excellent early and long-term results regarding not only dysphagia relief but also a low postoperative incidence of GER. Castrini et al. indicated that complete division of PM could facilitate the appearance of pathologic GER. To avoid a disruption of anatomical antireflux barriers, they reported a very meticulous transthoracic technique to prevent this complication.[27] A decade later, Bonavina et al. were the first who reported similar technique performed by transabdominal aproach, and they postulated importance of preserving PM in obtaining satisfactory durable results.[1] Applying this technique, Ackroyd et al. reported significant reduction of symptoms with more than 90% of patients highly satisfied after surgery.[28] An article describing the similar technique published by Braghetto and al. proved it very satisfactory in GER prevention, while at the same time, there were no postoperative hiatal herniations, and the dysphagia rates remained low. They also stated that by adopting this procedure, one can overcome the posterior vagal nerve and esophageal wall injuries, while at the same time, intraabdominal esophageal length remains intact.[16]

Table 1 Incidence and Severity of Postoperative Dysphagia Among the Groups of Operated Patients

	No. of patients	Grade 0	Grade 1	Grade 2	Grade 3
G1	26	22	2	1	1
G2	36	32	2	0	2
G3	22	20	1	1	0

The results of our study pointed out that the effects of LHD are equal if not superior to Heller–Dor's operation proceeded by complete hiatal dissection in the terms of postoperative reflux prevention. There were several reasons contributing to this statement. On a 3-year follow-up, patients with complete esophageal dissection proved to have statistically lower mean values of the LEHPZ basal pressure, even compared to patients with LHD and no fundoplication added. Further, 24-h pH metry marked higher incidence of patients with pathologic GER and statistically higher mean values of DeMeester acid score in patients in whom complete disruption of the PM had been done compared to both LHD groups. In the addition to these findings, there was no statistical difference between the LHD groups, regardless of fundoplication, on a subject of LEHPZ manometric values or pH metry measurements 3 years after the operation. Overall

incidence of pH metry positive patients in LHD groups was 8.6% and is comparable to the worldwide high volume center studies reporting LHD in achalasia surgery, with the incidence of pH metry positive findings ranging from 9.7% to 17%.[16,17,28] On the other hand, no specific conclusions regarding the role of Dor's fundoplication can be based on this study, because it is limited to a follow-up period of 3 years. Durability of Dor's fundoplication has long been on test, and very long-term follow-up studies are needed to undeniably enlighten its roll. But, if we can make a parallel with GERD surgery where even the Toupet fundoplication showed not to be durable through the years, another doubt relating to Dor's role in surgery for achalasia is set.[29,30]

Concerning the occurrence of postoperative hiatal hernia in our study, there was an overall of six (7.1%) patients with endocopically recognized postoperative herniation. All but one of the cases emerged among the patients with complete phrenoesophageal dissection, which proves LHD also to be superior regarding this matter. Although the hiatal dissection was limited, it definitively provided sufficient space for an adequate myotomy. In present study, this fact was demonstrated by low postoperative dysphagia rates (3.8% grade III). These results were in conjunction with other authors employing LHD during achalasia surgery, regarding the dysphagia incidence requiring additional treatment.[13,16,28,31]

What also came up from our follow-up, as a rather questionable phenomenon, were the postoperative increase in the esophageal body amplitude values and the reduction in simultaneous aperistaltic waves. This peristaltic improvement occurred in all three groups of patients, regardless of the surgical technique. On the other hand, it did not take place in patients with type III achalasia, probably because of the irreversible transmural esophageal wall degeneration. Even if not comparable, these findings partially concurred to a Pandolfino et al. recent publication concerning the use of high-resolution manometry in patients with achalasia.[32] In this paper, three patterns of aperistalsis have been recognized that are distinct in terms of their responsiveness to therapy. Utilizing these subclassifications in surgical treatment would likely strengthen future prospective studies of treatment efficacy in achalasia. The observation that esophageal peristalsis can return in patients with classic achalasia after myotomy supports the possibility that the primary abnormality may be the outflow resistance posed by a noncompliant, incompletely relaxing LEHPZ.[33] Bending of an LEHPZ in animals, pseudoachalasia caused by tumor infiltration, or a fundoplication that is too tight have all been reported to produce motility changes of the esophageal body characteristic of achalasia.[34,35] Finally, the partial or even complete return of peristaltic activity observed after surgical myotomy in our study would further support the fact that reduced compliance of the LEHPZ is the primary abnormality. Deterioration of esophageal peristaltic function with time, and the fact that peristalsis can reoccur after surgical myotomy, suggest that the motor abnormalities secondary to esophageal outflow resistance may be reversible and that early definitive treatment of achalasia is essential to preserve esophageal function.[33]

Conclusion

We can conclude that esophagocardiomyotomy with limited hiatal dissection avoids disruption of the intraadbominal esophageal anatomic structures, therefore, avoiding the possible additional factors associated with the appearance of hiatal hernia and/or postoperative pathologic GER. By performing limited hiatal dissection of the distal esophagus in patients with achalasia, the goals of the surgery are completely met, and the risk of postoperative gastroesophageal reflux is diminished. Therefore, limited hiatal dissection certainly needs to be employed in achalasia surgery, raising the necessity for further, longer, and more objective assessment as has recently been shown.[36]

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J Gastrointest Surg (2010) 14:594–600
DOI 10.1007/s11605-010-1158-2

ORIGINAL ARTICLE

Laparoscopic Cardiomyotomy for Achalasia: Clinical Outcomes Beyond 5 Years

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Received: 13 November 2009 / Accepted: 4 January 2010 / Published online: 5 February 2010

Abstract
Background Laparoscopic cardiomyotomy is the most common surgical procedure for the treatment of achalasia, although few reports describe long-term surgical outcomes.
Methods The outcomes for 155 patients who underwent a laparoscopic cardiomyotomy with anterior partial fundoplication more than 5 years ago (July 1992 to May 2004) were determined. Patients were followed prospectively at yearly time points using a structured questionnaire which evaluated symptoms of dysphagia, reflux, side-effects, and overall satisfaction with the clinical outcome.
Results Clinical data were available for 125 patients. Thirteen patients died within 5 years of surgery, four were unable to complete the questionnaire, and one developed esophageal squamous cell carcinoma. Nine patients were lost to follow-up, and three would not answer the questionnaire (92.2% late follow-up). Postoperative dysphagia, odynophagia, chest pain, and heartburn was significantly improved at 1 year, 5 years, and late (5+years) follow-up, with outcomes stable beyond 12 months. Seventy-seven percent of patients reported a good or excellent result (minimal or no symptoms) at 5 years and 73% at late follow-up. At late follow-up, 90% considered they had made the correct decision to undergo surgery.
Conclusions At minimum 5 years follow-up, laparoscopic cardiomyotomy for achalasia achieves effective and durable relief of symptoms, and most patients are satisfied with the outcome.

Keywords Achalasia · Laparoscopy · Cardiomyotomy · Long-term follow-up · Esophagus · Dysphagia

Introduction

Achalasia is an uncommon esophageal motility disorder characterized by the absence of esophageal peristalsis, a high resting lower esophageal sphincter (LES) pressure, and the inability of the LES to relax. Treatment focuses on lowering the resistance of the LES, and over the last decade laparoscopic cardiomyotomy has become the standard of care. Short-term follow-up suggests that laparoscopic cardiomyotomy achieves excellent symptom relief.[1–3] Most series report only short-term results, with few reporting extended follow-up over a period of greater than 5 years. However, knowing the long-term outcome for this operation is important, as this ultimately determines its place in the treatment armamentarium for achalasia. In this study, we evaluated longer term outcomes following laparoscopic cardiomyotomy and anterior partial fundoplication in a large group of patients who were followed prospectively for at least 5 years.

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Methods

Clinical outcomes of five or more years after a primary laparoscopic cardiomyotomy with anterior partial fundoplication for achalasia were sought for all patients undergoing surgery in hospitals in Adelaide, SA, Australia. The diagnosis of primary achalasia was based on clinical

history, barium swallow, endoscopy, and esophageal manometry. During the study period, all cardiomyotomies were attempted using a laparoscopic technique. Twenty-three patients had undergone previous failed pneumatic dilatation, whereas 132 had not undergone any prior endoscopic therapy. No patient in this experience had been treated with Botulinum toxin injection before surgery.

Surgery Technique

Surgery was carried out by one of six upper gastrointestinal surgeons or by a surgical trainee under their direct supervision. The surgical technique has been standardized since 1992, and it has been described elsewhere.[4] Briefly, all procedures were initiated laparoscopically, with anterior and lateral division of the phrenoesophageal ligament to mobilize the anterior and anterolateral aspects of the lower esophagus, and the fat pad overlying the gastroesophageal junction was removed to ensure that the gastroesophageal junction was accurately identified. The aim of surgery was to divide the circular muscle of the lower 5–6 cm of the esophagus and to extend the myotomy onto the cardia of the stomach. Intraoperative endoscopy was routinely used to assess the completeness of myotomy and to identify any inadvertent intraoperative mucosal perforation. Posterior hiatal repair was only undertaken when a hiatus hernia was present. An anterior partial fundoplication was constructed in all but one patient. Postoperatively, patients were usually discharged from day 2 onwards, when able to tolerate a vitamized diet.

Follow-up and Outcome

Information about the preoperative assessment, surgical procedure, and postoperative outcome for each patient was collected prospectively and stored on a computerized database. Postoperative clinical follow-up was obtained using a standardized questionnaire, which was administered by a research nurse at 3 and 12 months following surgery, and then annually thereafter. The questionnaire was initially mailed to each patient, but if it was not returned and the patient could be located, data was collected by telephone interview using the same structured questionnaire. Effort was made to obtain follow-up information for every patient at the 5-year follow-up point. The questionnaire assessed symptoms of dysphagia and reflux as well as overall satisfaction with the outcome of surgery. Visual analog scales (0–10) were used to determine dysphagia for solids and dysphagia for liquids (0=no dysphagia; 10=severe dysphagia). The scores on this scale were clustered into four groups for further data analysis (0=none; 1–3=mild; 4–6=moderate; 7–10=severe). The frequency of dysphagia, odynophagia, chest pain, and heartburn was assessed separately on a categorical scoring scale similar to that described by DeMeester (absence, occasional episodes, frequent episodes, and daily symptoms).[5] Patients were also asked to indicate whether they could eat a normal diet without restrictions.

A Visick score was used to assess overall outcome: Visick grade I represented no symptoms; Visick grade II, mild symptoms easily controlled; Visick grade III, moderate symptoms not controlled by simple methods; Visick grade IV, moderate symptoms which interfered with quality of life; and Visick grade V, symptoms worse than before the operation. The overall outcome was also determined using a 0–10 analog satisfaction score (0=unsatisfied, 10=very satisfied), and this was recategorized into three groups (0–3=bad outcome; 4–6=intermediate; 7–10=good outcome). On a categorical scale, patients also graded their overall outcome as excellent, good, fair, poor, and worse than before surgery. Patients were also asked whether they thought their original decision to undergo an operation had been correct. Twenty-four-hour pH studies, esophageal manometry, and endoscopy were not routinely scheduled during follow-up but were performed when clinically indicated.

Statistical Analysis

Follow-up data at five or more years after surgery (late follow-up) were gathered and compared with preoperative data, follow-up at 1-year, and follow-up at 5-years. Statistical evaluation was undertaken using the SPSS statistical package (SPSS, Inc), with the Wilcoxon matched-pairs signed-ranks test used to test for significance between paired continuous variables. Cross-tabulated comparisons between groups of categorical variables were achieved by chi-square test, or if sample sizes were small the two-sided Fisher's exact test was applied. A difference was regarded as significant if $p<0.05$.

Results

Demographics

Between July 1992 and April 2004, 155 patients underwent a primary laparoscopic cardiomyotomy with anterior partial fundoplication. They included 80 men and 75 women, with a median age of 48 years (range 15 to 88 years). The median operating time was 80 min (range 30–210). Postoperative hospital stay ranged from 1 to 40 days (median 3), and 89% of patients were able to be discharged within 4 days of surgery. Postoperative complications were: bleeding from a splenic injury requiring open splenectomy ($n=1$), subphrenic abscess requiring percutaneous drainage ($n=1$), and a leak from a myotomy requiring open surgery

Table 1 Analog Liquid and Solid Dysphagia Scores Preoperatively and at Various Follow-Up Time Points

	Liquid score	Solid score	*n*
Preoperative	6.5±3.3	8.9±1.8	125
Postoperative 1 year	1.3±2.4	3.2±2.8	104
5 years	2.0±2.7	3.7±3.0	105
Late follow-up (5+years)	2.1±2.8	4.1±3.0	125

Mean ± standard deviation (SD); $p<0.0001$ for three time points postoperative vs preoperative for scores for liquids and solids

for repair and drainage ($n=1$). One patient died on the tenth postoperative day following a subdural bleed, secondary to recommencement of warfarin therapy.

The operation was converted to an open procedure in seven (4.5%) patients. The reasons for conversion were: upper abdominal adhesions ($n=2$), obesity ($n=2$), and repair of mucosal perforation ($n=3$). Five of these seven patients were in the first 20 patients in our experience with laparoscopic cardiomyotomy. Intraoperative mucosal perforation occurred in a further 12 patients, and all of these perforations were repaired laparoscopically at the primary procedure with sutures.

Follow-up and Outcome

Clinical outcomes were available for 143 (92.3%) patients. Actual outcome scores were available for 125 out of 155 patients at late follow-up (5 years follow-up or later). For these patients, follow-up ranged from 60 to 202 months (median, 116 months). Thirteen patients died within 5 years of the primary operation, all from causes unrelated to esophageal achalasia or the operation. One patient developed squamous cell carcinoma of the esophagus 7 years after laparoscopic myotomy, and then refused esophagectomy, dying the next year. Three refused any follow-up, and four were unable to complete the questionnaire due to intellectual disability or inability to speak adequate English. Nine patients were lost to follow-up.

Table 1 shows the analog dysphagia scores for liquids and solids at various follow-up intervals. Scores were significantly improved at all postoperative time points, compared with preoperative scores. There were no significant differences in dysphagia scores at the 1 year, 5 years, and late follow-up points.

The frequency of dysphagia, odynophagia, and chest pain was significantly reduced at the follow-up time points, compared with preoperative symptoms, and there were no significant differences seen across all follow-up time points (Tables 2, 3, and 4). Table 5 shows a significant reduction in the frequency of heartburn at follow-up. Seventy-nine (63.2%) patients were able to eat an unrestricted diet at late follow-up.

Table 6 shows the postoperative Visick scores. Most patients had a sustained improvement following cardiomyotomy. One hundred thirteen (90.4%) were satisfied with their decision to undergo myotomy at late follow-up, and

Table 2 Frequency of Preoperative and Postoperative Dysphagia

	Preoperative	Postoperative (1year)	Postoperative (5years)	Late follow-up (5+years)
Never	0	37	21	20
Rarely	0	0	3	3
Once/month	0	17	27	30
Few times/ week	12	27	28	32
Daily	110	23	25	26
Few times/ week and daily (%)	100%	48%	51%	52%

$p<0.0001$ for all three postoperative time points vs preoperative

Table 3 Frequency of Preoperative and Postoperative Odynophagia

	Preoperative	Postoperative (1year)	Postoperative (5years)	Late follow-up (5+years)
Never	20	68	52	56
Rarely	0	0	3	0
Once/month	5	13	20	29
Few times/ week	16	19	24	24
Daily	83	3	6	11
Few times/ week and daily (%)	80%	21%	29%	29%

$p<0.0001$ for all three postoperative time points vs preoperative

Table 4 Frequency of Preoperative and Postoperative Chest Pain

	Preoperative	Postoperative (1year)	Postoperative (5years)	Late follow-up (5+years)
Never	33	65	51	55
Rarely	0	0	4	0
Once/month	8	19	31	42
Few times/week	42	19	16	19
Daily	41	1	3	6
Few times/ week and daily (%)	68%	19%	18%	20%

$p<0.0001$ for all three postoperative time points vs preoperative

Table 5 Frequency of Preoperative and Postoperative Heartburn

	Preoperative	Postoperative (1year)	Postoperative (5years)	Late follow-up (5+years)
Never	42	61	35	43
Rarely	0	0	4	0
Once/month	8	24	39*	47**
Few times/ week	33	17	20	28
Daily	39	3	6	6
Few times/ week and daily (%)	59%	19%	24%	27%

$p<0.0001$ for all three postoperative time points vs preoperative

*$p=0.0218$ (5 years vs 1 year); **$p=0.0052$ (late follow-up vs 1 year)

the rate of satisfaction was similar across all follow-up time points. A good or excellent result was achieved in 73–77% of patients at 5 years and late follow-up (Table 7). Likewise, postoperative analog satisfaction scores were similar across all follow-up time points.

At late follow-up, the subjective outcome of dysphagia for solid food in patients who had had an intraoperative mucosal perforation was worse than for the other patients (mean dysphagia score 5.5 vs 3.8, $p=0.035$), and the number of patients reporting a good or excellent outcome was less (55% vs 75%).

Twenty (12.9%) patients underwent either pneumatic dilatation or reoperation or both for recurrent or persistent dysphagia. Pneumatic dilation was used to treat 11 patients, and this was effective for six of these. The remaining five subsequently underwent a revision operation. Overall, 14 patients underwent a revision operation. The findings at revision indicated scar tissue at the gastroesophageal junction in three patients, an incomplete primary myotomy in eight, and an esophageal diverticulum in one. In addition, two patients underwent esophagectomy for end stage achalasia. There were six other patients with symptoms of recurrent dysphagia who refused either further investigations or treatment. Figure 1 shows the number of patients developing recurrent dysphagia vs the length of follow-up. Most problems presented in the first 3 years of follow-up. Overall, symptoms improved following treatment in 95% of patients with achalasia, allowing for treatment with primary laparoscopic cardiomyotomy and any additional pneumatic dilatation or further surgery as needed. At late follow-up, the patients who required reintervention (dilatation or surgical revision) for dysphagia had higher dysphagia scores for liquids (mean 3.2 vs 1.8, $p=0.030$), and the proportion reporting a good or excellent late term outcome was less than for the patients not requiring reintervention (50% vs 77%).

Eight (6.4%) patients reported heartburn or acid regurgitation symptoms which required proton pump inhibitor medication. No revision surgery was required for gastroesophageal reflux.

Discussion

The development of minimally invasive surgery over recent decades has heralded significant changes in the management of achalasia. Both thoracoscopic and laparoscopic approaches are feasible, although we and others believe that the laparoscopic approach offers advantages in the primary treatment of achalasia, including superior visualization of the gastroesophageal junction, single lumen endotracheal intubation, and the ability to add an antireflux procedure.[3,6]

In our current study, we have evaluated the long-term clinical outcome following laparoscopic cardiomyotomy with anterior partial fundoplication for achalasia in a large group of patients. In general, our results confirm a good outcome for most patients, with generally stable clinical outcomes beyond 1-year follow-up. The frequency of symptoms of dysphagia for liquids, odynophagia, and chest pain were similar at early and late follow-up, although dysphagia for solids and heartburn did become somewhat more frequent at later follow-up, with satisfaction scores deteriorating slightly with time. Nevertheless, 73% patients were highly satisfied with their situation five or more years after laparoscopic cardiomyotomy, and 90% of patients considered that the original operation had been worthwhile.

In most other published reports of outcomes following surgical treatment of achalasia, the length of the follow-up has been relatively short, and most papers have described median or mean follow-up of less than a year.[2,7–11] Only four previous papers have reported longer term outcomes, two following open surgical approaches and two after laparoscopic surgery. Ortiz et al. reported 1–27 years follow-up in a series of 149 patients, with median follow-up of 6 years following open cardiomyotomy.[12] Fifty-three

Table 6 Visick Scores at and at Various Follow-Up Time Points

postoperative	I	II	III	IV	V	*n*	I+II+III (%)
1 year	21	49	15	8	1	104	88%
5 years	17	55	15	13	5	105	83%
Late follow-up (5+ years)	19	61	22	16	7	125	82%

Table 7 Postoperative Outcome Scores

Postoperative	Excellent	Good	Fair	Poor	*n*	Excellent or good (%)
1 year	41	40	18	5	104	78%
5 years	29	52	19	5	105	77%
Late follow-up (5+ years)	32	59	24	10	125	73%

of these patients were followed for 10 years. Their results suggested that the outcome gradually deteriorated from an initial 90% success rate at early follow-up to 75% at longer term follow-up. Csendes et al. reported similar outcomes in a series of 67 patients who were followed for 6 to 30 years (mean 16).[13]

More recently, Cowgill et al. reported follow-up for 33 of 47 patients who underwent laparoscopic myotomy more than 10 years earlier, with good results in the majority of patients.[14] In a larger laparoscopic series, Zaninotto et al. [11] reported 407 laparoscopic cardiomyotomies, with 97% follow-up. Median follow-up was 30 months, and 177 patients were followed for more than 5 years. An 87% 5 year actuarial success rate was reported. In our study, we obtained minimum 5 years clinical follow-up from 92% of 155 patients, and median follow-up in our series was nearly 10 years.

As with other reports,[11–13,15] we identified some deterioration in outcome at later follow-up, although most symptomatic failures occurred early. Of the 26 patients who developed recurrent dysphagia, 12 (46%) developed symptoms within 1 year of surgery, and 20 (77%) of the recurrences were within 3 years. Correspondingly, most pneumatic dilations and reoperations for dysphagia were undertaken early in the follow-up period. Possible explanations for recurrent dysphagia include: incomplete myotomy at the original operation, periesophageal inflammation, excessive scar tissue formation in the region of the previous myotomy, esophageal dilatation with sigmoid deformity, and mechanical obstruction by a fundoplication, paraesophageal hernia, or diaphragmatic hiatal repair, as well as late occurrence of carcinoma.

Extending the myotomy below the gastroesophageal junction and onto the cardia remains a crucial part of the procedure. Mattioli et al.,[16] suggested that it is necessary to extend the myotomy for approximately 2 cm onto the stomach, and Oelschlager et al. have advocated extending the myotomy to 3 cm on the gastric side.[17] We assessed the adequacy of the myotomy with intraoperative endoscopy, and adequate opening of the gastroesophageal junction usually only required extension of the myotomy for 5 to 10 mm, and never beyond 2 cm.

It is generally accepted that achalasia is a precancerous condition, and the assumption is that retained food and saliva in the gullet can cause bacterial overgrowth and increased production of nitrosamine, leading to mucosal inflammation, dysplasia and eventually, squamous cell cancer.[18–22] A recent study of 2,869 patients by Zendehdel and colleagues showed that men with achalasia have a standardized incidence ratio of 8.4 and 13.1 for adenocarcinoma and squamous cell cancer, respectively, compared with the general population.[23] Only one patient developed esophageal squamous cell carcinoma in our series, and our data suggests that cancer development in achalasia patients remains uncommon.

Although myotomy lowers esophageal outflow resistance and improves esophageal emptying, it also increases the propensity for the development of gastroesophageal reflux. The importance of adding a fundoplication to the myotomy has, until recently, been debated, with many

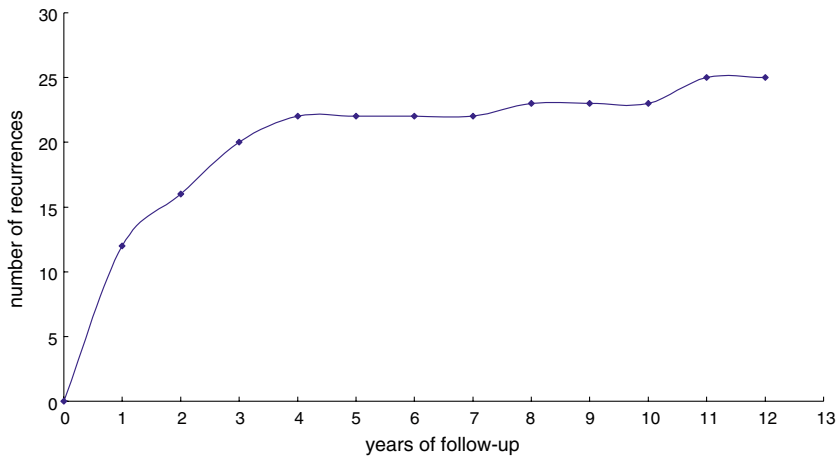

Figure 1 Cumulative number of patients with recurrent dysphagia vs length of follow-up.

opposing views advanced over the years.[24,25] A recent meta-analysis of 7,855 patients from 105 published papers[26] showed that postmyotomy reflux was less likely when a fundoplication was added (31.5% without a fundoplication vs 8.8% with; $p=0.003$). In the presence of an aperistaltic, and at times dilated and tortuous esophagus, most surgeons now agree that a complete fundoplication should be avoided, and a partial fundoplication of some type is preferred.[27] However, the actual extent (180^0 vs 270^0) and location (anterior vs posterior) is debated. Current data suggests little difference between posterior and anterior partial fundoplications. We have routinely added an anterior partial fundoplication. Apart from its antireflux effect, it might also buttress the myotomized esophageal segment. In addition, anterior fundoplication allows preservation of natural posterior attachments at the gastroesophageal junction, and only anterior hiatal dissection is required.

We have previously described a learning curve for laparoscopic cardiomyotomy for achalasia.[28] In this study, the duration of surgery and the risk of conversion to open surgery were influenced by the experience of the operating surgeon and the overall experience of the unit. However, the learning curve did not impact on any of the subjective clinical outcomes reported in our current study, specifically dysphagia, satisfaction with the overall surgical outcome, and the risk of subsequent surgical reintervention. For this reason, it is unlikely that the results of our current study have been influenced by a learning curve for laparoscopic cardiomyotomy.

Our current study only evaluated clinical outcomes at late follow-up. Objective evaluation, with barium swallow, esophageal manometry, pH monitoring, or endoscopy, was not routinely performed. However, resolution of clinical symptoms is the outcome patients seek, and for this reason late clinical follow-up data is still valuable. Our study has confirmed that laparoscopic cardiomyotomy with anterior partial fundoplication is a safe, effective, and durable treatment for achalasia at minimum 5 years follow-up.

Acknowledgments The authors are grateful for the contributions of surgeons from the Royal Adelaide Hospital who contributed patients to the database. We are also acknowledge the assistance of Ms. Lorelle Smith, Ms. Nicky Ascott, and Ms. Carolyn Lally who coordinated collection and entry of clinical outcome data into the database.

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J Gastrointest Surg (2010) 14:601–606
DOI 10.1007/s11605-009-1127-9

ORIGINAL ARTICLE

Clinicopathologic Features of Gastric Carcinoma with Signet Ring Cell Histology

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Received: 24 October 2009 / Accepted: 30 November 2009 / Published online: 22 December 2009

Abstract
Background Reports of clinicopathological features and prognosis in patients with signet ring cell carcinoma of the stomach (SRC) are conflicting. The aim was to describe the clinicopathological features and prognosis of patients with SRC in comparison with non-signet ring cell carcinoma of the stomach (NSRC).
Methods In this retrospective study, we reviewed the records of 1,439 consecutive patients diagnosed with gastric carcinoma who were resected surgically from 1993 to 2003. Among them, 218 patients (15.1%) with SRC were compared with 1,221 patients with NSRC.
Results There were significant differences in tumor size, tumor location, macroscopic type, depth on invasion, lymph node metastasis, lymphatic invasion, tumor stage, chemotherapy, and curability between the patients with SRC histology and NSRC. The overall 5-year survival of patients with SRC was 44.9% as compared with 36.0% for patients with NSRC (P= 0.013). Multivariate analysis showed that lymph node metastasis and curative resection were significant factors affecting survival. A significant survival benefit for curative resection was observed, with a 5-year survival rate of 58.5% compared with non-curatively resected cases (8.4%).
Conclusions When stage matched, SRC patients had a similar survival to NSRC patients. Curative resection is recommended to improve the prognosis of patients with SRC.

Keywords Curative resection · Gastric cancer · Prognosis · Signet ring cell carcinoma · Survival

Introduction

Gastric signet ring cell carcinoma (SRC) is a histological based only on the microscopic characteristics of the tumor as described by the World Health Organization (WHO),[1] but not on the biological behavior. SRC is characterized by its poor prognosis and potential to infiltrate the stomach wall.[2,3] SRC has been variously designated as 'undifferentiated type' by the Japanese Research Society of Gastric Cancer,[4] 'diffuse type' by Lauren,[2] 'infiltrative type' by Ming[5] and 'high grade' by the WHO and the International Union Against Cancer.[6] The incidence of SRC has been reported variously from 3.4% to 39%.[7–11] SRC is reported to occur more frequent among women and young patients.[9]

Although there have been studies of the clinicopathological features and prognosis of SRC, the results were inconsistent. In some reports,[8,12–14] SRC was associated with a better prognosis, although other studies found no difference in a 5-year survival between patients with SRC and those with non-signet ring cell carcinoma of the stomach (NSRC).[7,15]

In the present study, we retrospectively analyzed the records of patients with gastric carcinoma and described the biological behavior of SRC by comparing clinicopathological features and prognosis with NSRC.

Patients and Methods

Patients

Between 1993 and 2003, 1,439 patients with histologically proven gastric carcinoma underwent gastrectomy at the

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Table 1 Clinicopathological Features of Gastric Signet Ring Cell Carcinoma Versus Other Types of Gastric Carcinoma

Variables	SRC (n=218; %)	NSRC (n=1221; %)	P value
Age (mean, years)	56.2±12.4	57.9±11.3	0.173
Sex			
Male	145 (66.5)	884 (72.4)	
Female	73 (33.5)	337 (27.6)	0.076
Tumor size (mean, cm)	6.1±2.9	6.7±3.2	0.009
Tumor location			
Upper	21 (9.6)	204 (16.7)	
Middle	51 (23.4)	192 (15.7)	
Lower	124 (56.9)	709 (59.1)	
Whole	22 (10.1)	116 (9.5)	0.006
Macroscopic type			
Early gastric carcinoma	49 (22.5)	89 (7.3)	
Borrmann I	8 (3.7)	106 (8.7)	
Borrmann II	23 (10.6)	329 (26.9)	
Borrmann III	113 (51.8)	589 (48.2)	
Borrmann IV	25 (11.5)	108 (8.8)	<0.001
Depth on invasion			
T1	49 (22.5)	89 (7.3)	
T2	40 (18.3)	269 (22.0)	
T3	98 (45.0)	527 (43.2)	
T4	31 (14.2)	336 (27.5)	<0.001
Lymph node metastasis			
N0	52 (23.9)	251 (20.6)	
N1	75 (34.4)	334 (27.4)	
N2	47 (21.6)	372 (30.5)	
N3	44 (20.2)	264 (21.6)	0.024
Stage			
Ia	36 (16.5)	61 (5.0)	
Ib	38 (17.4)	203 (16.6)	
II	43 (19.7)	220 (18.0)	
IIIa	38 (17.4)	197 (16.1)	
IIIb	27 (12.4)	175 (14.3)	
IV	36 (16.5)	365 (29.9)	<0.001
Liver metastasis			
Absent	211 (96.8)	1178 (96.5)	
Present	7 (3.2)	43 (3.5)	0.818
Peritoneal dissemination			
Absent	198 (90.8)	1124 (92.1)	
Present	20 (9.2)	97 (7.9)	0.540
Lymphatic invasion			
Absent	75 (34.4)	304 (24.9)	
Present	143 (65.6)	917 (75.1)	0.007
Vascular invasion			
Absent	201 (92.2)	1153 (94.4)	
Present	17 (7.8)	68 (5.6)	0.198
Curability			
R0	158 (72.5)	749 (61.3)	
R1	35 (16.1)	261 (21.4)	
R2	25 (11.5)	211 (17.3)	0.007
Chemotherapy			
Yes	107 (49.1)	712 (58.3)	
No	111 (50.9)	509 (41.7)	0.011

SRC gastric signet ring cell carcinoma, *NSRC* non-signet ring cell carcinoma of the stomach

Department of Gastroenterologic Surgery, Affiliated Tumor Hospital of Harbin Medical University, Harbin, China. Of these, 218 patients (15.1%) had a histological diagnosis of SRC. Of the patients with SRC, 49 (22.5%) cases had early gastric carcinomas and 169 (77.5%) cases had advanced gastric carcinomas.

We followed the criteria of the WHO classification for histological typing of gastric carcinomas: a diagnosis of SRC was made when an adenocarcinoma with a predominant component (more than 50% of the tumor) of isolated carcinoma cells containing mucin was observed. The pathological criterion of SRC has not been changed during the period of our study. All of the tissues were examined by experienced gastrointestinal pathologists. The operative procedures were performed according to the rules of the Japanese Research Society for Gastric Cancer.[4] Patients with a pathological diagnosis of SRC were compared with the NSRC group.

Information on the patient's age, sex, tumor size, tumor location, macroscopic type, depth on invasion, lymph node metastasis, lymphatic invasion, vascular invasion, liver metastasis, peritoneal dissemination, stage of disease, chemotherapy, and curability of operation were obtained from the hospital records. These findings were assessed according to the Japanese General Rules for Gastric Cancer Study in Surgery and Pathology.[4] The American Joint Committee on Cancer tumor–node–metastasis staging system was used for pathologic staging.[16] Curative resection (R0) was determined as there being no tumor left macroscopically or microscopically after the operation. R1 indicates microscopic residual cancer (positive margins); and R2 indicates gross (macroscopic) residual cancer (positive margins) but not distant disease. Of 218 patients with SRC, 158 (72.5%) underwent R0, 35 (16.1%) underwent R1, and 25 (11.5%) underwent R2. In 1,221 patients with NSRC, 749 (61.3%) underwent R0, 261 (21.4%) underwent R1, and 211 (17.3%) underwent R2. Informed consent had been obtained, and the Ethics Committee of Harbin Medical University approved this study.

A follow-up of all patients was carried out according to our standard protocol (every 3 months for the first year, every 6 months for the next 2 years, and after 3 years every 12 months for life). Patient follow-up lasted until death or

Table 2 Comparison by Stage of 5-year Survival Rates between Gastric Signet Ring Cell Carcinoma and Other Types of Gastric Carcinoma

Stage	SRC		NSRC		*P* value
	Number of patients (%)	5-year survival rate (%)	Number of patients (%)	5-year survival rate (%)	
Ia	36 (16.5)	80.6	61 (5.0)	78.7	0.826
Ib	38 (17.4)	71.1	203 (16.6)	69.3	0.798
II	43 (19.7)	55.8	220 (18.0)	56.8	0.903
IIIa	38 (17.4)	36.8	197 (16.1)	37.1	0.980
IIIb	27 (12.4)	11.1	175 (14.3)	19.1	0.425
IV	36 (16.5)	0.0	365 (29.9)	5.7	0.239

SRC gastric signet ring cell carcinoma, *NSRC* non-signet ring cell carcinoma of the stomach

the cut-off date of December 31, 2008. At the time of the last follow-up, 56 patients (3.9%) had been lost to follow-up. The median follow-up period was 49 months (range, 1–157 months).

Statistical Analysis

The intergroup comparisons of clinicopathologic variables were performed with the chi-square test for discrete variables and Student's *t* test for continuous variables. The Kaplan–Meier method was used for calculating cumulative survival rate, and the difference between groups was assessed by using the log-rank test. Covariates that remained significant through the univariate analysis were selected for multivariate analysis. Cox regression was used for multivariate analysis, with backward stepwise elimination model. The accepted level of significance was $P<0.05$. All data analysis was performed using the SPSS for Windows, Version 10.0 software package.

Results

Clinicopathologic Findings

The clinicopathological features of 218 patients with SRC and 1,221 patients with NSRC were compared (Table 1). There were significant differences in the distribution of tumor size, tumor location, macroscopic type, depth on invasion, lymph node metastasis, lymphatic invasion, stage of disease,

Table 3 Clinicopathologic Factors and Survival of Patients with Gastric Signet Ring Cell Carcinoma

Variable	Number of patients	5-year survival rate (%)	*P* value
Tumor size (cm)			
<8	146	49.6	
≥8	72	35.1	0.039
Depth on invasion			
T1	49	77.8	
T2	40	55.2	
T3	98	32.7	
T4	31	16.1	<0.001
Lymph node metastasis			
N0	52	78.8	
N1	75	56.0	
N2	47	29.8	
N3	44	0.0	<0.001
Peritoneal dissemination			
Absent	198	49.4	
Present	20	0.0	<0.001
Lymphatic invasion			
Absent	75	66.9	
Present	143	33.1	<0.001
Curability			
Curative	158	58.5	
Noncurative	60	8.4	<0.001

Table 4 Multivariate Analysis of Prognostic Factors for Survival in Patients with Gastric Signet Ring Cell Carcinoma Using the Cox Proportional Hazard Model

Variables	Risk ratio	95% confidence interval	*P* value
Lymph node metastasis (present vs. absent)	1.990	1.102–3.615	0.002
Curative resection (no vs. yes)	2.878	1.865–4.440	<0.001

chemotherapy, and curability of operation between the patients with SRC histology and NSRC. The size of SRC was smaller than that of NSRC, and 10.1% of SRC occupied the whole stomach. Serosal invasion was less prominent; lymph node metastasis and lymphatic invasion were less likely to be present in SRC. More early gastric carcinoma was noted in SRC than NSRC. SRC was detected at the lower stage than stage II in 53.7% of patients. The rate of operative curability was higher in SRC group.

Survival and Prognostic Factors

The overall 5-year survival of patients with SRC was 44.9% as compared with 36.0% for patients with NSRC carcinoma (P=0.013). Furthermore, we compared the 5-year survival rate by stage. For the patients with the same stage, there was no significant difference between the two groups (Table 2).

With respect to patients with SRC, the 5-year survival rate was influenced by tumor size, depth on invasion, lymph node metastasis, peritoneal dissemination, lymphatic invasion, and curability of operation (Table 3). A significant survival benefit for curative resection was observed, with a 5-year survival rate of 58.5% compared with non-curatively resected cases (8.4%). Six factors significant in the univariate analysis were included in the multivariate analysis, which indicated that the length of the survival period was independently influenced by lymph node metastasis and curative resection (Table 4). With respect to the overall patients with gastric carcinoma, the Cox proportional hazards model showed that tumor size, serosal invasion, lymph node metastasis and surgical curability were significant factors affecting survival. SRC histology was not an independent prognostic factor (Table 5).

There were significant differences in recurrence rates and patterns between the patients with SRC histology and NSRC (Table 6). Recurrence occurred more frequently in the NSRC group than in the SRC group (P=0.001). Of the 799 patients that experienced recurrence, peritoneal recurrence occurred more frequently in the SRC group than the NSRC group (52.0% vs. 33.0%, P<0.001).

Discussion

This multivariate prognostic study on SRC examined the 14 clinicopathologic parameters and identified factors associated with the survival after gastrectomy; the two findings were: lymph node metastasis and curative resection.

The incidence of SRC has been reported variously from 3.4% to 39%.[7–11] In the present study, SRC was diagnosed in 15.1% of gastrectomy specimens. In this study, SRC occurred more frequently in the middle third of the stomach. The result is similar to that of Ostuji et al. [12]. In contrast, another study showed there was no significant difference in tumor location between SRC and NSRC carcinomas.[14]

Kim et al.[14] reported that mean tumor size tended to be smaller in SRC than in NSRC, However Li et al.[11] showed that mean tumor size tended to be larger in SRC than in NSRC. In our study, mean tumor size tended to be smaller in SRC than in NSRC (6.1 vs. 6.7 cm; p=0.009).

Several authors reported that the percentage of early gastric carcinoma for each histological type was higher in SRC than NSRC.[8,14] In this study, 22.5% of the patients with early gastric carcinoma had SRC histology. However, only 7.3% of the patients with early gastric carcinoma had NSRC histology.

SRC is a histological type with unclear prognosis, although many survival studies compare carcinomas with and without SRC features. We found that the overall 5-year survival of patients with SRC histology were better than that of patients with NSRC carcinoma (44.9% vs. 36.0%; P=0.013). Because survival after gastrectomy for gastric carcinoma is known to be significantly influenced by disease stage at the time of operation, we evaluated outcomes with respect to histologic type at same stages. For the patients with the same stage, there

Table 5 Multivariate Analysis of Prognostic Factors for Survival in Patients with Gastric Carcinoma Using the Cox Proportional Hazard Model

SRC gastric signet ring cell carcinoma, *NSRC* non-signet ring cell carcinoma of the stomach

Variables	Risk ratio	95% confidence interval	*P* value
Tumor size (≥8cm vs. <8cm)	1.538	1.216–1.937	0.028
Serosal invasion (present vs. absent)	1.875	1.052–3.313	<0.001
Lymph node metastasis (present vs. absent)	1.993	1.532–2.580	<0.001
Curative resection (no vs. yes)	1.592	1.237–2.041	0.004
Histology (NSRC vs. SRC)	1.263	0.983–1.621	0.068

Table 6 Patterns of Gastric Cancer Recurrence of Gastric Signet Ring Cell Carcinoma Versus Other Types of Gastric Carcinoma

Variables	SRC (n=218)	NSRC (n=1221)	P value
Number of patients who had recurrence/ number of recurrence	98/124	701/857	
Recurrence rate	45.0%	57.4%	0.001
Pattern of recurrence			
Peritoneal	51 (52.0%)	231 (33.0%)	<0.001
Hematogenous	31 (31.6%)	264 (37.7%)	0.247
Local	33 (33.7%)	265 (37.8%)	0.428
Distant lymph nodes	9 (9.2%)	97 (13.8%)	0.203

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was no significant difference between SRC and NSRC. We also compared the 5-year survival rate by stage (early and advanced gastric carcinoma). There was no significant difference in survival rate as a function of patient stage (early and advanced gastric carcinoma). In contrast, Hyung et al.[13] reported that the cumulative survival rate of patients with early SRC was significantly higher than that of patients with early NSRC. Kim et al.[15] reported a worse prognosis for patients with advanced SRC, especially for stage III. Our result was similar to that of Kim et al.[14]. In their study, the overall 5-year survival of patients with SRC was 60.2% as compared with 48.9% for patients with NSRC carcinoma ($P<$ 0.01). One explanation is that SRC is less likely to lymph node metastasis, and it had a higher proportion in the early stage of gastric carcinoma than did NSRC. It has been reported that SRC tumors show tendencies to be larger and to spread superficially to mucosal and submucosal layers.[17] For this reason, SRC can be diagnosed at an earlier stage.

Lymph node metastasis was reported to be one of the important prognostic factors of gastric carcinoma.[18–21] In patients with SRC, we found that lymph node metastasis was an independent prognostic factor. With regard to SRC, Kim et al.[14] reported that curative resection was an independent prognostic factor according to multivariate survival analysis. In the research, a significant survival benefit for curative resection was observed, with a 5-year survival rate of 58.5% compared with non-curatively resected cases (8.4%).

Differentiated cancers are known to be characterized by hematogenous metastasis, whereas undifferentiated cancers are characterized by peritoneal dissemination.[22] In the present study, it was found that more peritoneal dissemination occurred in the SRC group.

Conclusion

In patients with SRC, lymph node metastasis and curative resection were two independent prognostic factors for long-term survival. When stage matched, SRC patients had a similar survival to NSRC patients. Curative resection is recommended to improve the prognosis of patients with SRC.

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J Gastrointest Surg (2010) 14:607–613
DOI 10.1007/s11605-009-1083-4

ORIGINAL ARTICLE

Outcome After Curative Resection of Large (≥10 cm) Gastric Gastrointestinal Stromal Tumors: How Frequent is Adjacent Organ Involvement and is Concomitant Distal Pancreatectomy Necessary?

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Received: 21 May 2009 / Accepted: 26 October 2009 / Published online: 12 January 2010

Abstract
Introduction Complete tumor resection with clear margins including adjacent organs is the treatment of choice for gastrointestinal stromal tumors (GISTs). However, true tumor invasion of adjacent organs has been reported to be rare. Concomitant distal pancreatectomy (DP) for suspected tumor infiltration is not infrequently performed during resection of large gastric GISTs. This study aims to determine the true frequency of adjacent organ involvement by large gastric GISTs with particular attention to the pancreas and compares the outcome after curative resection with and without a concomitant DP in order to determine if DP is truly necessary.
Methods A retrospective review of 37 patients who underwent curative resection of large (≥10 cm) gastric GISTs was conducted.
Results Wedge resections were performed in 22, partial gastectomies in nine, and total gastrectomies in six patients. The median operative time was 180 min (range, 60–330 min), and the patients had a median postoperative stay of 8 days (range, 4–29 days). Overall, there were eight (22%) morbidities including two (5%) mortalities. Nineteen (51%) had concomitant adjacent organ resection, and these included 15 (41%) DPs with splenectomies. Direct organ invasion was demonstrated in 5/19 patients (26%) and 7/30 organs (23%) resected. Only 1/15 (6.7%) DP specimens demonstrated tumor infiltration. Comparison between the patients with and without a concomitant DP demonstrated that performance of a DP was associated with a longer operation time [225 min (range, 105–305 min) vs 158 min (60–330 min), P=.002)], increased postoperative stay [9 days (range, 7–29 days) vs 7.5 days (4–19 days), P=.042], and increased postoperative morbidity [6 (40%) vs 2 (9%), P=.025]. The DP cohort also had a statistically significant poorer 5-year recurrence free survival (22% vs 60%, P=.017).
Conclusion Although adjacent organ involvement is not uncommon with large gastric GISTs, concomitant DP is usually unnecessary as direct pancreatic invasion is rare. Furthermore, concomitant DP with splenectomy is associated with an increase in postoperative morbidity.

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Keywords Gastrointestinal stromal tumor · GIST · Gastric · Pancreatectomy · Surgery · Large

Introduction

Gastrointestinal tumors (GISTs) are the most common mesenchymal tumors arising within the gastrointestinal tract.[1] Currently, there is uniform agreement that the surgical treatment of choice for GISTs is resection of the tumor with clear surgical margins including adjacent organs if necessary.[1,2] As regional lymph node involvement and

submucosal spread is infrequent in GIST, routine lymph node dissection is not advocated and limited resections are frequently performed.[1,3,4] GISTs frequently grow locally to extremely large sizes without distant spread, and complete resection often entails removal of adjacent organs. The stomach is the most common site of origin of GISTs,[5,6] and when these tumors grow to large sizes, surgical resection often involves removal of adjacent organs such as the pancreas, transverse colon, left liver lobe, and spleen. However, although every effort should be made to achieve complete resection of all gross disease,[5] the status of microscopic margins does not seem to influence survival especially for large GISTs,[5,7] and several authors have proposed that adjacent vital structures should not be sacrificed if gross tumor clearance has been achieved.[5] Nonetheless, it is often difficult at the time of surgery to determine if there is true infiltration of adjacent structures.

True invasion of GISTs into adjacent organs have been reported to be rare,[8,9] although there is a paucity of data in the literature documenting the actual frequency and type of adjacent organ infiltration confirmed histologically. The largest study on gastric GISTs to date from the Armed Forces Institute of Pathology (AFIP) on 1,765 cases (381, ≥10 cm) reported that only 80 cases (5.4%) had peritoneal or adjacent organ involvement.[8] However, no information was available on the frequency of adjacent organ resection and the actual organs involved.

In recent times, performance of a distal pancreatectomy (DP) has been reported to be associated with a low mortality rate.[10,11] However, morbidity rates remain high often in excess of 30% to 40%.[10,11] This is especially so when DP is performed as part of a multi-organ resection.[10,11] Large gastric GISTs often appear to involve the pancreas, and performance of a concomitant DP is not uncommon. In a recent study of 232 consecutive DPs,[10] gastric adenocarcinomas (15%) and gastric GISTs (6%) were the two main diseases of extrapancreatic origin for which a DP was indicated.

Based on information in the literature that true adjacent organ involvement is rare *with GISTs*,[8,9] we hypothesize that similarly, the pancreas is infrequently involved by gastric GISTs. Hence, performance of a concomitant pancreatic resection may not be necessary to achieve complete tumor clearance. Furthermore, we postulate that performance of a concomitant DP may increase the morbidity of surgery without contributing any benefit to the long-term outcome of these patients. In order to test this hypothesis, we conducted a retrospective review of 37 consecutive patients who underwent complete resection of a large (≥10 cm) primary gastric GIST at our institution. The pathology reports were reviewed to determine true tumor invasion of the adjacent organs. Subsequently, we also compared the outcomes between patients who had a concomitant DP with those who did not.

Methods

Between 1990 and 2008, all patients who underwent surgery at Singapore General Hospital for an intra-abdominal or retroperitoneal mesenchymal tumor were identified from a prospectively maintained surgical database. This study was approved by the Singapore General Hospital Institutional Review Board. All patient data were subsequently obtained retrospectively from the clinical, radiological, and pathological records. Pathological specimens of tumors resected before 2002 (when CD117 staining was not routinely performed) were retrieved and reviewed by either one of two pathologists with a special interest in GIST as described in our previous study.[6] These tumors were subsequently reclassified as GISTs after immunohistochemical staining according to current diagnostic criteria.[12] Thirty-seven patients who underwent complete resection (R0/R1) of a large (≥10 cm) primary gastric GIST were identified and were the focus of the present study. During the time period, the treatment philosophy towards GIST adopted at our institution was complete resection preferably with clear margins. En bloc resection of adjacent organs was performed if these were thought to be involved by tumor intraoperatively.

Pancreatic fistula was defined and graded as that proposed by the International Study Group of Pancreatic Fistula.[10,13] Although grade A fistulas (clinically asymptomatic, biochemical fistulas) were reported, these were not included as a postoperative morbidity in this study so as not to unfairly bias the complication rate in favor of the group without a concomitant DP.

All statistical analyses were conducted using the computer program Statistical Package for Social Sciences for Windows, version 10.0 (SPSS Inc, Chicago, IL, USA). Univariate analyses were performed using Mann–Whitney U tests and Chi-squared tests as appropriate. Survival analyses on recurrence-free survival (RFS) were performed using the Kaplan–Meier method. Univariate and multivariate analyses of prognostic factors were performed using the log-rank test and Cox regression model, respectively. All tests were two-sided, and $P<.05$ was considered statistically significant.

Results

Clinicopathological Features

Thirty-seven consecutive patients underwent complete resection of a large (≥10 cm) gastric GIST during the time period. Their median age was 56 years (range, 34–85 years), and there were 19 males. The median tumor size was 16.0 cm (range, 10.0–30.0 cm). Twenty-nine (78%) patients were symptomatic at presentation. Some of the common

clinical features at presentation include abdominal pain or discomfort (n=23), occult or gross upper gastrointestinal bleed (n=10), and an abdominal mass (n=29). The tumors were most commonly detected via gastroscopy (n=20) and computed tomographic scan (n=35).

Of the 37 patients, 22 underwent wedge resections, nine underwent partial gastectomies, and six underwent total gastrectomies. Nineteen patients (51%) underwent adjacent organ resection including 15 (41%) who had a concomitant DP with splenectomy. Four patients had a R1 resection (microscopic margins involved). The median operative time was 180 min (range, 60–330 min), and the patients had a median postoperative stay of 8 days (range, 4–29 days). Overall, there were eight (22%) postoperative morbidities including two (5%) mortalities. The postoperative deaths occurred in a patient who developed an esophagojejunostomy leak after a total gastrectomy and another patient who developed severe nosocomial pneumonia and succumbed to multi-organ failure. The postoperative complications included a postoperative hemorrhage requiring relaparotomy for hemostasis, postoperative cardiac arrhythmia, bile leak post-liver resection, severe atelectasis, and a superficial wound infection. Seven patients (47%) with a DP developed a postoperative pancreatic fistula of which five were grade A and two were grade B fistulas (grade A asymptomatic pancreatic fistulas were not considered a morbidity in this study). None of the patients had neoadjuvant imatinib and one had adjuvant imatinib treatment after surgery.

Pathological examination revealed that mucosal ulceration was found in 18 patients (49%), tumor necrosis in 32 (87%), serosal involvement in 25 (68%), nuclear pleomorphism in 15 (41%), and lymph node involvement in two (5%). Nineteen tumors (51%) had a mitotic count of >10 per 50 HPF, five (14%) had a count of 6–10 per 50 HPF, and 13 (35%) had a count of <5 per 50 HPF. Twenty-four tumors were classified as spindle cell type, six were of epitheloid cell type, and seven were mixed cell type.

Adjacent Organ Involvement

Nineteen patients had concomitant adjacent organ resection for suspected tumor invasion, and these included DP with splenectomy (n=15), colectomy (n=6), diaphragmatic resection (n=3), small bowel resection (n=1), splenectomy only (n=1), liver resection (n=1), nephrectomy (n=1), adrenalectomy (n=1), and cholecystectomy (n=1). Of the 19 patients who had concomitant adjacent organ resection, final histology confirmed direct tumor invasion into the adjacent organ in five patients (26%). Three of six colectomy specimens (50%) demonstrated tumor invasion (all microscopic) into the colon or mesocolon, one of three diaphragmatic specimens (33%) demonstrated tumor infiltration (microscopic), and only one of 15 (6.7%) pancreatectomy specimens demonstrated tumor invasion (gross) into the pancreatic parenchyma. Gross tumor involvement of both the small bowel and adrenal gland was confirmed on histology. The remaining specimens only demonstrated tumor adherent to or abutting the organ frequently from a benign desmoplastic reaction but no direct infiltration. Overall, only seven of 30 organs (23%) resected for suspected tumor involvement demonstrated true tumor infiltration of which three were gross tumor invasion. However, six of 15 (40%) organs excluding the pancreas had tumor involvement.

Follow-Up and Survival

Follow-up data were available for all patients although six were lost during the course of follow-up. At a median follow-up time of 32 months (range, 1–168 months), 19 patients were alive without disease, 10 patients were alive with disease, six patients died of disease, and two patients died of other causes. Sixteen patients (43%) developed recurrences. These were distant in 11, local in two, and both distant and local in three patients. The median time to first recurrence was 6.5 months (range, 3–43 months). The 5-year actuarial recurrence-free survival was 45%, and the 5-year actuarial disease-specific survival was 65%.

All four patients who underwent R1 resection developed recurrences with a median time to first recurrence of 5 months (range, 3–7 months). Three of the recurrences were distant, and one occurred at both local and distant sites.

Prognostic Factors

Mitotic count, tumor perforation, serosal involvement, and R1 resection were statistically significant predictive factors of RFS on univariate analyses (Table 1). On multivariate analysis, only mitotic count and serosal involvement were independent predictors of RFS (Table 2). Figure 1a, b demonstrates the RFS curves of large gastric GISTs stratified by mitotic count.

Comparison Between Patients Who Underwent Concomitant Distal DP Versus Those Without

There was no difference between the baseline characteristics of patients who underwent a concomitant DP compared to those who did not (Table 3). Comparison between the outcomes of the two groups demonstrated that patients who underwent a concomitant DP had a statistically significant longer operation time, longer postoperative stay, and increased postoperative morbidity (Table 4). The DP group also had a statistically significant poorer

Table 1 Univariate Analyses of Prognostic Factors of Recurrence-Free Survival in 37 Patients with Large (≥10 cm) GISTs Who Underwent Curative Resection

Factor		Mean RFS, m (95% C.I.)	*P* value
Age, years	>50	69 (34–105)	0.249
	≤50	80 (46–114)	
Sex	M	72 (44–101)	0.453
	F	74 (34–114)	
Symptoms	Y	85 (52–119)	0.988
	N	45 (19–70)	
Pre or intra-op perforation	Y	8 (2–13)	**0.003**
	N	94 (63–125)	
Postoperative morbidity	Y	26 (11–40)	0.808
	N	86 (54–118)	
Mitotic count, per 50 h.p.f.	>5	44 (13–74)	**0.001**
	≤5	115 (97–132)	
Epitheloid cell component	Y	55 (25–84)	0.667
	N	81 (45–118)	
Necrosis	Y	76 (45–108)	0.226
	N	86 (53–120)	
Nuclear pleomorphism	Y	68 (25–111)	0.286
	N	69 (42–97)	
Mucosal ulceration	Y	64 (33–95)	0.998
	N	81 (42–119)	
Serosal involvement	Y	44 (20–67)	**0.006**
	N	131 (85–177)	
Adjacent organ involved	Y	17 (0–38)	0.061
	N	91 (60–122)	
R1 resection	Y	5 (3–7)	**<0.001**
	N	95 (63–126)	

Significance is when *P* value < .05

prognosis with a 5-year RFS of 22% versus 60%. The majority of recurrences in both groups occurred at distant sites.

Discussion

The treatment of choice for GISTs is complete surgical resection of the tumor with clear surgical margins including adjacent organs as necessary.[1] The stomach is the most common organ involved by GIST, and these often grow to sizes of more than 10 cm.[8] Curative resection of large gastric GISTs often involve resection of adjacent organs such as the colon, pancreas, and spleen in order to obtain clear margins although actual adjacent organ involvement is reported to be rare.[8,9] Presently, to our knowledge, there is no study in the literature specifically correlating the frequency of adjacent organ resection for GIST and the actual incidence of organ involvement as proven on histology.

Two recent large studies on gastric GISTs from the AFIP[8] and the National Cancer Center, Tokyo[9] on 1,765

Table 2 Multivariate Analysis of Prognostic Factors of Recurrence-Free Survival in 37 Patients with Large (≥10 cm) Gastric GISTs Who Underwent Curative Resection

Multivariate analyses of factors associated with recurrence-free survival			
Variable	Hazard ratio	95% C. I.	*P* value
Perforation	1.64	0.47–5.72	0.437
Mitosis >5/50 HPF	19.1	1.94–187	**0.011**
Serosal involvement	8.55	1.47–49.5	**0.017**
R1 resection	3.00	0.78–11.3	0.111

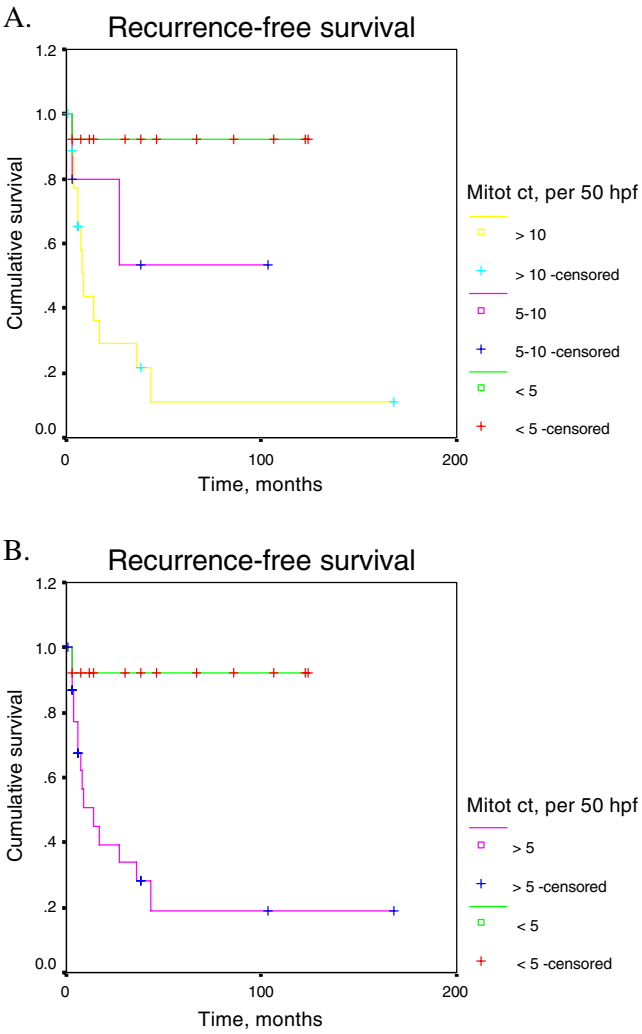

Figure 1 Recurrence-free survival of large gastric GISTs stratified by mitotic count. **a** Mitotic count, <5 vs 5–10 vs >5 per 50 HPF, P=0.002; **b** mitotic count, ≤5 vs >5 per 40 HPF, P=0.001.

and 140 cases, respectively, reported an incidence of adjacent organ involvement of 5.4% (80/1765) and 3% (4/140). The number of large (≥10 cm) tumors in these two studies were 381 and 22, respectively. The study from Japan reported tumor involvement of the diaphragm (n=2), spleen, and pancreas. In our present experience of 37 large (≥10 cm) gastric GISTs, 19 (51%) underwent concomitant adjacent organ resection for suspected tumor involvement of which five (26%) had true tumor infiltration as confirmed on pathology. Of these, 15 had a distal pancreatectomy of which only one (6.7%) demonstrated true tumor infiltration. On the other hand, six of 15 (40%) non-pancreatic organs resected were involved by tumor.

Our present results show that adjacent organ invasion is not uncommon with large gastric GISTs. However, direct involvement into the pancreas is very rare. These findings suggest that every attempt should be made to avoid a pancreatic resection even when aiming for a R0 resection for large gastric GISTs. An attempt should be made to "shave" these tumors adherent superficially to the pancreas as these are usually due to a desmoplastic reaction rather that direct tumor invasion. This is unlike gastric adenocarcinoma whereby pancreatic invasion is not uncommon. Nonetheless, we acknowledge that this decision may be extremely difficult as it is frequently impossible to differentiate desmoplastic reaction from true tumor invasion. DP should always be performed if the tumor is found to involve the pancreatic parenchyma; more deeply "shaving" these will result in an increased risk of pancreatic leak. The increased morbidity when performing radical resection with concomitant DP and splenectomy and poorer long-term outcome as demonstrated in this study provides further support that every effort should be made to avoid performing a concomitant DP. This dismal outcome in the DP group is likely a reflection of the aggressive biological nature of the tumors in this group and suggests that aggressive radical surgery is unlikely to alter the prognosis of these patients. The high morbidity rate associated with DP reported in this study is not surprising as it has been well-documented recently in the literature that DP especially when performed together with concomitant multi-organ resection is associated with an increase in postoperative morbidity.[10,11] The most common postoperative complication after DP is the occurrence of a pancreatic fistula which occurred after 7/15 DPs (47%) in this study of which two (13%) were clinically significant (grade B fistula). In this study, all the DPs were performed with splenectomy as it is almost technically impossible to preserve the spleen when resecting tumors of these proportions. This need for a concomitant splenectomy may also have contributed to the increased morbidity in the DP group as it has previously been shown that performance of a splenectomy is associated with an increase in infectious complications which has been attributed to the important immunological function of the spleen.[10,14]

There is further evidence available in the literature which also seems to indirectly support the role of pancreatic preservation during resection of large GISTs. It has been shown that the status of microscopic margins does not seem to be an important prognostic factor especially for large GISTs.[5,7,15] This has been attributed to the direct seeding of tumor cells into the peritoneal cavity resulting in recurrent disease at distant sites when GISTs grow to a considerable size.[15,16] Hence, the need for radical surgery has been questioned by some, and these authors have proposed that adjacent organs should be preserved as much as possible as long as all gross diseases can be removed (R0/R1 resection).[5,7] The results of the present study seemed to support this view as a R1 resection was not an independent prognostic factor of RFS on multivariate analysis. Further-

Table 3 Comparison Between the Baseline Characteristics of Patients Who Underwent Curative Resection of a Large (≥10 cm) Gastric GIST with Versus Without a Concomitant Distal Pancreatectomy

		Resection with distal pancreatectomy (n=15)	Resection without distal pancreatectomy (n=22)	P value
Median age, years		56 (42–85)	55 (34–81)	0.676
Sex, male		9 (60%)	10 (46%)	0.385
Symptomatic		13 (87%)	16 (73%)	0.312
ASA score	1	2 (13%)	8 (36%)	0.301
	2	12 (80%)	13 (59%)	
	3	1 (7%)	1 (5%)	
Median size, cm		15.0 (10.0–26.0)	17.0 (11.0–30.0)	0.556
Mitotic count, per 50 HPF	≤5	3 (20%)	10 (46%)	0.247
	6–10	3 (20%)	2 (9%)	
	>10	9 (60%)	10 (46%)	
Perforation		1 (7%)	4 (18%)	0.314
Necrosis		13 (87%)	19 (86%)	0.979
Mucosal involvement		8 (53%)	10 (46%)	0.638
Serosal involvement		12 (80%)	13 (59%)	0.127
Pleomorphism		8 (53%)	7 (32%)	0.191
Epitheloid component		6 (40%)	7 (32%)	0.609
Microscopic margins involved		0	1 (5%)	0.403
Gastric resection	Wedge	9 (60%)	13 (59%)	0.811
	Partial	3 (20%)	6 (27%)	
	Total	3 (20%)	3 (14%)	
Other organ resected[a]		6 (40%)	4 (18%)	0.142
R1 resection		2 (13%)	2 (9.1%)	0.683

[a] Concomitant distal pancreatectomy and splenectomy was not considered an additional organ resection

more, three of the four recurrences after a R1 resection were distant, and the other occurred at both local and distant sites. However, one must remain cautious when interpreting these data which are from relatively small retrospective studies. Presently, we and most investigators would still recommend aiming for a R0 resection whenever possible, although this should be balanced against the morbidity of performing a radical multi-organ resection. The role of

Table 4 Comparison Between the Outcomes of Patients who Underwent Curative Resection of a Large (≥10 cm) Gastric GIST with Versus Without a Concomitant Distal Pancreatectomy

		Resection with distal pancreatectomy (n=15)	Resection without distal pancreatectomy (n=22)	P value
Operation time, min		225 (105–305)	158 (60–330)	0.002
Postoperative morbidity[a]		6 (40%)	2 (9%)	0.025
Postoperative mortality		1 (7%)	1 (5%)	0.779
Postoperative stay, days		9 (7–29)	7.5 (4–19)	0.042
Median follow-up time, months		32 (6–49)	20 (6–120)	0.070
Recurrences		9 (60%)	7 (32%)	0.089
Site of first recurrence	Distant	7 (78%)	4 (57%)	0.633
	Local	1 (11%)	1 (14%)	
	Both	1 (11%)	2 (29%)	
Median time to first recurrence, months		6 (3–27)	5.5 (3–43)	0.749
Actuarial mean recurrence-free survival (95% C.I.), months		17 (9–24)	109 (74–144)	0.017
Actuarial 5-year recurrence-free survival, months		22%	60%	

[a] Only grade B/C pancreatic fistulas were considered a morbidity

imatinib as neoadjuvant treatment for GIST is also presently increasing as it has been shown to be able to downstage large tumors.[17] Its use will potentially allow curative resection of large GISTs with organ preservation. With the positive results from the recent American College of Surgeons Oncology Group trial,[18] we would also advocate the use of adjuvant imatinib in patients with large gastric GIST, although it is not known if the use of adjuvant imatinib is superior to the administration of imatinib only after the recurrence.

Several factors have been identified as important prognostic indicators after complete resection of GIST. These include tumor size, mitotic count, disease extent, tumor perforation, mucosal involvement, epitheloid subtype, serosal involvement, and nuclear pleomorphism.[6] Of these, tumor location, size, and mitotic count have been consistently shown as the most important factors and are presently used in the risk stratification of GISTs.[6] In the present cohort of large (≥10 cm) gastric GISTs, mitotic count and serosal involvement were the two independent predictors of RFS of which mitotic count was the most important prognostic factor (Table 2, Fig. 1). Even for large tumors, a low mitotic count ≤5 per 50 HPF was associated with an actuarial 5-year RFS of 92% whereas tumors with a mitotic count >10 per 50 HPF had an actuarial 5-year RFS of 11% (Fig. 1b). Our results were consistent with the largest study to date on gastric GISTs from the AFIP which reported the outcomes of 1,765 gastric GISTs of which 381 were ≥10 cm.[8] In the AFIP study, mitotic count was a highly important prognostic indicator for large gastric GISTs, and the authors classified large gastric GISTs with a mitotic count ≤5 per 50 HPF as intermediate risk and those with a mitotic count >5 per 50 HPF as high risk.[8,19]

Conclusion

Large gastric GISTs not infrequently invade directly into adjacent organs. However, direct tumor involvement of the pancreas is rare, and concomitant DP is frequently unnecessary for complete surgical resection. Furthermore, concomitant DP with splenectomy is associated with an increase in postoperative morbidity.

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J Gastrointest Surg (2010) 14:614–619
DOI 10.1007/s11605-009-1142-x

ORIGINAL ARTICLE

The Node Ratio as Prognostic Factor after Curative Resection for Gastric Cancer

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Received: 12 May 2009 / Accepted: 14 December 2009 / Published online: 26 January 2010

Abstract
Introduction The depth of the tumor invasion and nodal involvement are the two main prognostic factors in gastric cancer. Staging systems differ among countries and new tools are needed to interpret and compare results and to reduce stage migration. The node ratio (NR) has been proposed as a new prognostic factor.
Materials and Methods We retrospectively reviewed 282 patients who underwent curative resection for gastric cancer at Parma University Hospital between 2000 and 2007. TNM stage, NR, overall survival, survival according to nodal status, and survival according to the total number of nodes retrieved were calculated.
Results At univariate analysis, the TNM stage, number of metastatic nodes, NR, and depth of tumor invasion, but not the number of nodes retrieved, were significant prognosis factors. Patients with more than 15 nodes retrieved in the specimen survived significantly longer ($p<0.04$). This was confirmed for all N or NR classes within N groups. There was a correlation between the number of nodes retrieved and N but not with the NR category. NR was an independent prognostic factor at Cox regression.
Conclusion NR is a reliable and sensitive tool to differentiate patients with similar characteristics, probably more so than the TNM system. NR is not strictly related to the number of nodes retrieved and this may potentially decrease the stage migration phenomenon. More trials are needed to validate this factor.

Keywords Gastric cancer · Gastric surgery · Gastrectomy · Node ratio · TNM · Prognostic factor

Introduction

The depth of tumor invasion and nodal involvement are the main prognostic factors in gastric cancer.[1–5] A longstanding controversy exists regarding which nodal staging method most accurately identifies categories of patients with similar characteristics and prognosis.

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Previously, the anatomic location of the metastatic lymph nodes was considered to be the main determinant for nodal staging, according to the guidelines of the Japanese Research Society for Gastric Cancer (JRSGC). However, after 1997, the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) reviewed the staging system and stated that the number of nodes involved had a more profound influence on survival and established that 15 was the minimum number of nodes to be retrieved during surgery to allow for reliable staging.[6]

However, in most Japanese centers, the most widely used nodal classification remains the one proposed by the JRSGC. The latter, in addition to differences in surgical approaches (D1 vs D2 or extended lymphadenectomies) and methodological issues from a pathological perspective (mapping of the different nodal stations, pathologist's accuracy in retrieving nodes from the specimen), compli-

cates the identification of international guidelines for the treatment and prognosis of gastric cancer.

The new TNM classification simplified matters, but a new resource is needed to minimize the phenomenon of stage migration, which occurs in 10% to 30% of cases and becomes more relevant when patients with a limited lymphadenectomy are downstaged.[7–13] The node ratio (NR), defined as the ratio between metastatic and examined lymph nodes, has been proposed as a useful and reliable tool that may overcome these issues. It has proven to be an independent prognostic factor regardless of the type of lymphadenectomy performed and of the number of nodes retrieved during the surgical procedure.[2,9,13–18] Our study is a preliminary report validating the importance of the NR in the staging of gastric cancer.

Patients and Methods

We retrospectively report on 282 patients who underwent curative gastric surgery for biopsy-proven gastric adenocarcinoma between January 2000 and December 2007.

Exclusion criteria included: distant metastasis (including macroscopically evident nodal metastasis to lymph nodes of the superior mesenteric vein and middle colic vein and paraaortic lymph nodes), previous gastric surgery, postoperative death (within 30 days post surgery), and palliative surgery (R1 or R2). Of the 282 patients, 104 were included in our study while 178 were excluded for the following reasons: 51 lost at follow-up, 50 incomplete pathology reports, five tumors of the gastric stump, 17 deaths within 30 days after surgery, and 56 were inoperable or underwent palliative surgery.

A D1 lymphadenectomy was performed, according to the JRSGC, in all patients.[19] Nodal status was classified according to the UICC/AJCC 1997: N0 no metastasis, N1 one to seven metastatic nodes, N2 eight to 15 metastatic nodes, N3 16 or more metastatic nodes. The NR intervals were determined as described elsewhere[1] and were as follows: NR0=0%, NR1=1–10%, NR2=11–25%, NR3=>25%

Overall survival, survival stratified by number of nodes retrieved (group A = less than 15, and group B = more than 15), and survival by N group (N status of the TNM classification) and NR group were calculated using the Kaplan–Meier method, and the log rank test was used to determine statistically significant differences.

For each N and NR category, 5-year survival was calculated in groups A and B and the differences were evaluated using the log rank test. In the N1 class (according to the TNM classification), patients were divided according to their NR group and survival curves were compared. It was impossible to apply the same statistical tests to the N2 group due to the small number of cases.

The mean follow-up was 824.4 days (range 47–2,557 days). Events different from disease-specific related death were considered to be censored. Statistical analysis was performed with SPSS 11.0 for Windows 2001 (SPSS Inc., Chicago, IL, USA). Values of $p<0.05$ were considered significant. Variables examined for statistical analysis were: age (<70 or >70 years old); sex (male vs female); type of procedure performed (resection vs total gastrectomy); location of the primary tumor (cardia, upper third, middle third, lower third); T stage of the TNM; number of nodes retrieved; and number of metastatic nodes and NR (i.e.,

Table 1 Patients Characteristics and Univariate Analysis

Sex	$p<0.05$	Males, 67
		Females, 37
Age	NS	Mean, 71.1±10.6 years
		>70, 68; <70, 36
Surgical procedure	NS	Total gastrectomy, 57
		Subtotal gastric resection, 47
Anatomic location of primary tumor	NS	Upper third, 44 (42.3%)
		Middle third, 27 (25.9%)
		Lower third, 13 (12.5%)
		Cardias, 19 (18.2%)
		Diffuse, 1 (0.96%)
Number of lymph nodes retrieved	NS	Mean, 23±12
		<15, 31 (29.8%)
		>15, 73 (70.1%)
T (local extension)*	$p<0.0001$	1, 12 (11.5%)
		2, 35 (33.6%)
		3, 27 (25.9%)
		4, 30 (28.8%)
N (nodal involvement)*	$p<0.0001$	0, 27 (25.9%)
		1, 38 (36.5%)
		2, 21 (20.1%)
		3, 18 (17.3%)
Number of metastatic nodes	$p<0.0004$	
NR	$p<0.0001$	0, 27 (25.9%)
		1 (1–10%), 13 (12.5%)
		2 (11–25%), 14 (13.4%)
		3 (>25%), 50 (48%)
TNM stage	$p<0.0001$	IA, 8
		IB, 17
		II, 14
		IIIA, 19
		IIIB, 7
		IV, 39
Pathology	NS	Anaplastic, 1 (0.96%)
		Diffuse, 32 (30.7%)
		Intestinal, 43 (41.3%)
		Diffuse + intestinal, 6 (5.7%)

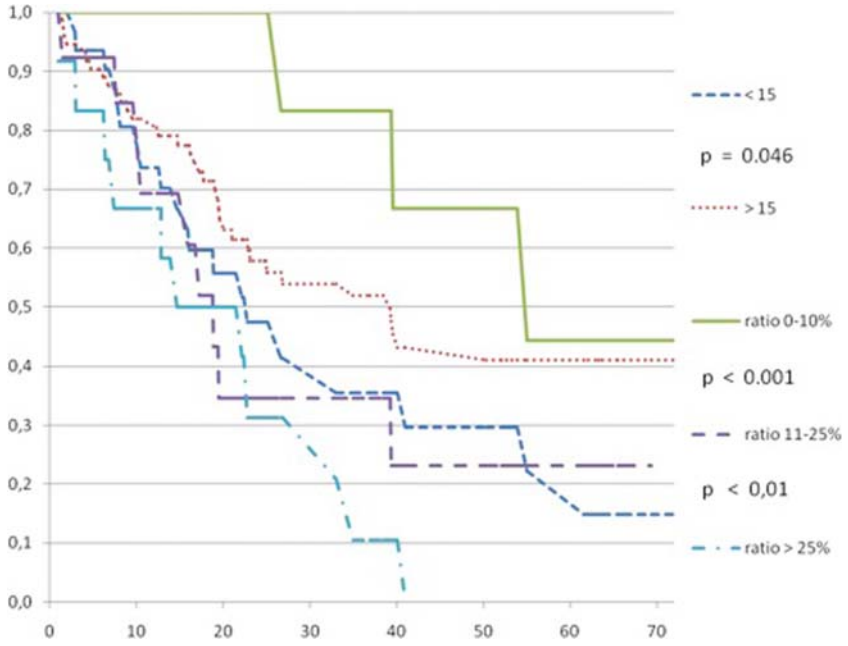

Figure 1 Survival in groups A and B and within N1 class by NR class.

number of metastatic nodes/number of total nodes retrieved). Relationships between the number of metastatic nodes, total number of nodes, and NR were evaluated with the Pearson correlation test.

Results

The patients' characteristics and analysis of variance for the total population are shown in Table 1.

At univariate analysis, statistically significant prognostic factors were: sex, T and N of the TNM staging system, number of metastatic lymph nodes, NR, TNM stage, and extension of gastric wall infiltration. The number of retrieved nodes was insignificant. Univariate analysis was then performed separately on group A and group B and the number of nodes retrieved was not identified as a prognostic factor in any of the groups.

Overall 5-year survival was 38% and group B survived significantly longer than group A (41% vs 15%, p=0.04; Fig. 1).

Survival was calculated for both groups inside each N and NR class and the results are summarized in Table 2.

If we consider the stratification by N class, in the N1 class, patients in group B survived statistically longer than group A (p<0.03); within the N2 class, group A consisted of one patient, therefore, no significant difference in survival could be calculated due to the paucity of data. If we observe the results obtained when the patients were divided according to their NR category, the p value was never significant for any class, indicating that NR may be less sensitive to the number of nodes retrieved when compared to N (Table 2).

In Table 2, it is evident that patients in group A, with less than 15 nodes retrieved, survived less than 5 years in every N/NR class but N/NR0, confirming that 15, which is the minimum number of nodes to be retrieved according to the most recent UICC/AJCC guidelines, is also significant in terms of survival benefit.

A total of 2,383 nodes were examined from 104 patients (mean 23±12, median 22, range 2–74). In 73 patients

Table 2 Survival According to Nodal Class (N and NR) in Groups A and B

N	Number of patients and 5-year survival	p value	NR	Number of patients and 5-year survival	p value
N0	<15, 11, 77% >15, 17, 92%	NS	0	<15, 11, 77% >15, 17, 92%	NS
N1	<15, 20, 0% >15, 18, 47%	0.001	1	<15, 4, 0% >15, 9, 75%	NS
N2	<15, 1, 0% >15, 20, 8%	NS	2	<15, 6, 0% >15, 8, 0%	NS
N3	>15, 18, 22%		3	<15, 11, 0% >15, 39, 16%	NS

Table 3 NR in Different N Classes

	NR				
N	NR0, 0%	NR1, 1–10%	NR2, 11–25%	NR3, >25%	Total
N0 (0)	27 (100%)	0	0	0	27
N1 (1–6)	0	14 (37.8%)	11 (29.7%)	12 (32.4%)	37
N2 (7–15)	0	0	1 (4.7%)	20 (95.2%)	21
N3 (>15)	0	0	0	18 (100%)	18

(70.1%), 15 or more nodes were retrieved, while in 31 (30%), less than 15 lymph nodes were examined. A total of 793 nodes were metastatic (mean 8, median 4, range 0–39).

Patients were classified according to their N and NR category and the results are the following: 27=N0 (25.9%), 38=N1 (36.5%), 21=N2 (20.1%), 18=N3 (17.3%); NR0= 27 (25.9%), NR1=13 (12.5%), NR2=14 (13.4%), NR3=50 (48%). In Table 3, patients were divided according to their NR category for each N class. In the groups N0 and N3, patients belonged to the same NR category, respectively (NR0 and NR3). However, inside the N1 and N2 categories, different NR groups were present and survival of some of these subpopulations proved to be statistically different at log rank test ($p<0.01$; Fig. 1). This may indicate that NR is more sensitive than N to discriminate subgroups of patients with similar characteristics and prognosis. Analysis within the N2 group was not feasible due to the lack of data in the group.

Survival curves were calculated for each class of the two main nodal staging systems (N and NR), as shown in Fig. 2. N0 patients survived longer than N1 patients ($p<0.0002$) but there were no other significant differences in survival between the other classes (N1 vs N2, N2 vs N3), while in the NR curve, there was no difference between NR0 and NR1 patients but NR1 survived longer than NR >1 ($p<0.02$). These results were not expected and are likely to be the effect of the small number of patients in each category rather than a true nonsignificant difference between the N0 and N1 group, but this cannot be clearly ascertained.

The Pearson correlation test showed that the number of retrieved nodes was related to the number of metastatic lymph nodes ($p<0.0001$) but it was not related to the NR (p=NS). When the same test was applied within the two groups, in group A, the number of metastatic nodes was not related to the total number of nodes retrieved, while in group B, the same relationships were maintained. Moreover, Cox regression proved that NR is an independent prognostic factor on multivariate analysis ($p<0.0001$).

Conclusions

In this present retrospective study, we analyzed the role of the NR in a series of patients affected by gastric carcinoma who underwent curative surgery.

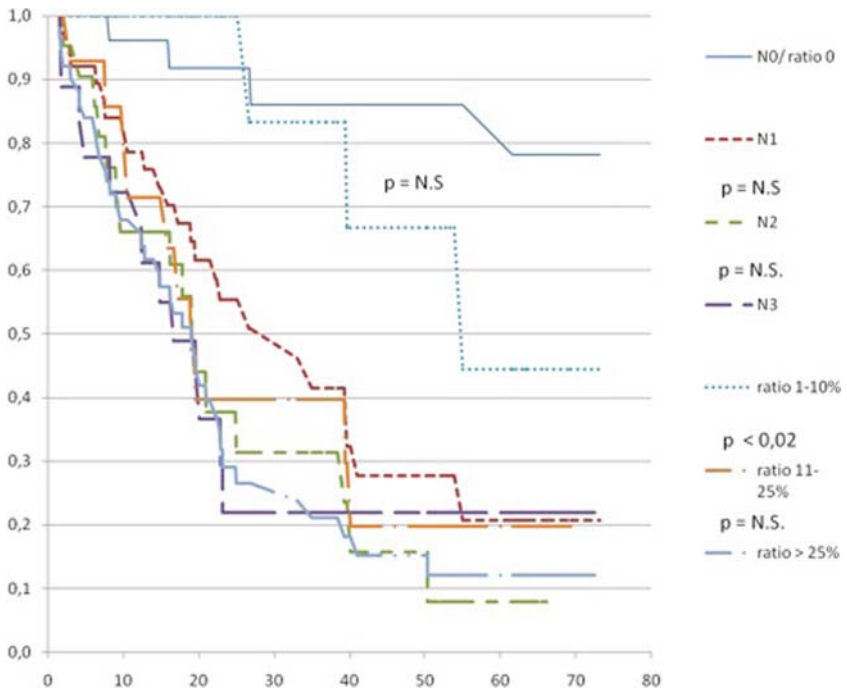

Figure 2 Survival in different N and NR classes.

In the last decade, the scientific community has gone to great lengths to create uniform guidelines regarding the staging and the treatment of patients with gastric cancer. Nevertheless, differences in surgical techniques (in particular regarding lymphadenectomy), stage migration, and staging systems have yet to be resolved.

This study is not to imply which nodal dissection is more appropriate but rather to point out two major considerations.

Firstly, a limited nodal dissection may not allow an appropriate staging as suggested by the latest UICC/AJCC guidelines that state the cut-off for an accurate staging at 15 nodes.[6,20–24] A quantity which can also be achieved for D1 procedures, as in our series, but in this case the number of nodes would be more susceptible to the pathologist's accuracy in isolating and identifying nodes and nodal metastasis and to the individual anatomical variability.[11,25–29]

Secondly, patients with limited lymphadenectomy (less than D2),[7,26] especially when the number of nodes retrieved is less than 15,[9,30–32] may experience stage migration. In fact, De Manzoni et al.[7] observed that the number of positive nodes increased along with the extension of nodal dissection, which is an expression of the disease progression.

Western centers perform mostly a D1 lymphadenectomy, while in Japan, D2 or above is the treatment of choice. To date, there are no randomized or nonrandomized studies or any meta-analysis conclusive on the longstanding debate on which type of lymphadenectomy is most appropriate (D1 vs D2 or above) for a patient undergoing curative gastric resection for carcinoma. The abovementioned findings may encourage surgeons to perform more extensive procedures. However, this change is ill-advised without more solid evidence that extended lymphadenectomies are clearly the gold standard.[25,26,33–36]

NR has been proposed as a tool to stage gastric cancer patients in order to minimize these confounding factors.

Nitti et al. were the first to suggest that NR is of greater prognostic value than the TNM/UICC and JRSGC staging systems after D2 resection and that it may reduce the influence of confounding factors such as the number of nodes retrieved and individual differences in the number of gastric nodes.[1] It offers clear advantages compared to the other nodal prognostic factor, named nodal extension, expressed as number of metastatic nodes (N of the TNM classification): it is minimally influenced by the extent of the lymphadenectomy, as confirmed by Hyung et al. and in our series, or by the pathologist's accuracy in looking for an adequate number of nodes.[11,26–29]

Therefore, it has been proposed as a valuable and independent prognostic tool in patients affected by gastric cancer after D2 and also D1 dissection, suggesting that this parameter should be included in a future comprehensive staging system for its potential to overcome the main drawback of the TNM system, namely, stage migration.[1,6–9,18,30,37–39]

The results of the present nonrandomized retrospective single center study, although with a limited value because of the small size of the cohort and because all patients had undergone a D1 lymphadenectomy, seem to confirm the promising role of the NR as a prognostic factor for patients with gastric cancer undergoing curative surgery at univariate and regression analysis. Our results suggest that NR may be more sensitive than the total number of metastatic nodes in identifying classes of patients with similar behavior and life expectancy, as is shown by the survival curves according to NR within N classes.

However, a NR-based staging system needs some fundamental improvements. NR intervals that correlated more strictly with prognosis have not been universally established yet and many cut-offs have been proposed.[7,30,32] The minimum number of nodes, if it exists, below which the NR maintains its value and correlation with prognosis, has yet to be defined. Due to the paucity of data in this study, we were unable to perform such an analysis.

In conclusion, multicentric randomized trials are needed in the future to confirm these preliminary results. Possibly including the NR in a more complete and accurate staging system, thereby reducing the methodological differences among groups, helping to identify the best treatment option and the correct prognosis for patients affected by gastric cancer.

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J Gastrointest Surg (2010) 14:620–627
DOI 10.1007/s11605-009-1139-5

ORIGINAL ARTICLE

Fast-track Surgery Improves Postoperative Recovery in Patients with Gastric Cancer: A Randomized Comparison with Conventional Postoperative Care

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Received: 9 September 2009 / Accepted: 14 December 2009 / Published online: 28 January 2010

Abstract
Background Fast-track surgery is a new, promising comprehensive program for surgical patients and is beneficial to recovery. Prospective randomized, controlled clinical trials involving fast-track surgery for gastric cancer are lacking.
Patient and methods Ninety-two patients with gastric cancer were randomly divided into a fast-track surgery group (n=45) and conventional surgery group (n=47). We compared outcomes (duration of postoperative stay in hospital, fever, and flatus, complications, and medical costs); postoperative serum levels of tumor necrosis factor-α, interleukin-6, and C-reactive protein; and resting energy expenditure between two groups.
Results Compared with the conventional surgery group, the fast-track surgery group had no more complications (P>0.05) with a significantly shorter duration of fever, flatus, and hospital stay, and less medical costs as well as a higher quality of life score on hospital discharge (all P<0.05). With a significantly lower resting energy expenditure (days 1 and 3) postoperatively (P<0.05), the fast-track surgery group showed a lower serum level of tumor necrosis factor-α (days 1 and 3), interleukin-6 (days 1 and 3), and C-reactive protein (days 1, 3, and 7) than the conventional surgery group (all P<0.05).
Conclusions Fast-track surgery can lessen postoperative stress reactions and accelerate rehabilitation for patients with gastric cancer.

Keywords Fast-track surgery · Gastric cancer · Stress reaction · Conventional surgery

Abbreviation

CRP	C reaction protein
FTS	fast-track surgery
GC	Gastric cancer
IL-6	interleukin-6
REE	resting energy expenditure
TNF-α	tumor necrosis factor-α

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Introduction

In recent years, fast-track surgery (FTS) or enhanced recovery after surgery has frequently appeared in the literature. FTS was initiated by Kehlet,[1, 2] and has been applied in patients undergoing colorectal resection,[3–5] repair of aortic aneurysms,[6] and hip replacement.[7] In Europe, this has led to a significant reduction in postoperative stay in hospital, lower complications rates, and a reduction in hospital costs. FTS has been developed by combining several techniques with evidence-based adjustments, including the use of nasogastric tubes, drains, and urinary catheters; preoperative bowel preparation; and early initiation of oral feeding and mobilization. The combination of these approaches reduces the stress response and organ dysfunction, and therefore greatly shortens the time required for full recovery.[1]

Studies have shown that fast-track muti-modal rehabilitation programs result in a significant reduction in postoperative stay in hospital and hospital costs.[3, 8–10] However, the results of recent multi-center studies indicate that implementation of

the evidence-based elements of fast-track perioperative care into clinical practice has not been widely accepted owing to the primary concern about safety.[11] Surgeons therefore need to increase their understanding of perioperative pathophysiology and major multicenter randomized trials are needed to confirm positive results regarding FTS.

Gastric cancer (GC) is common. Each year, approximately one million cases are diagnosed worldwide, 400,000 of which are diagnosed in China.[12, 13] China, Japan, South America, Eastern Europe, and parts of the Middle East are reported to have the highest incidence of GC.[14] For the surgical treatment of GC, conventional elective gastric resection is associated with a complication rate of 10–45% and a postoperative hospital stay of 8–13 days.[15–18] It has been established that a higher rate of serious postoperative complications is associated with an excessive response to surgical stress,[2, 19, 20] and that C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and resting energy expenditure (REE) may act as markers for the severity of the surgical stress response.[21–26] FTS is based on the reduction of surgical stress by various surgical and anesthetic approaches to aid faster recovery. Reports on fast-track rehabilitation in GC are very rare, and the feasibility and safety of fast-track rehabilitation programs in patients with GC requires further evaluation. Some studies have demonstrated that routine nasogastric decompression, intra-abdominal drainage, and fasting after gastrectomy are unnecessary and are not beneficial to recovery.[17, 18, 27–29]

We integrated some perioperative evidence-based programs into a fast-track protocol for GC patients. We evaluated the feasibility and safety of FTS in patients with GC during the perioperative period by designing a prospective, randomized comparative study.

Patients and Methods

Clinical studies were carried out according to the Declaration of Helsinki. The Research Ethics Committee of Qingdao University Medical College (Qingdao, China) approved the study protocol. Written informed consent was obtained from patients and their families.

The study was conducted in the Department of General Surgery, Affiliated Hospital of Qingdao University Medical College from January to August 2008. Patients eligible for the study were first seen in the outpatient clinic. Cardiovascular risk assessment was undertaken by anesthesiologists. Patients were clinically diagnosed as having GC. The diagnosis was confirmed preoperatively by gastroscopic evaluation and intraoperative macroscopic assessment. Inclusion criteria were patients younger than 80 years of age who were not receiving preoperative chemotherapy and radiotherapy. Exclusion criteria were: primary diabetes mellitus or impaired glucose tolerance; primary hepatonephric diseases; primary cardio-cerebral diseases; severe obesity or body mass index (BMI) >30 kg/m^2; severe malnutrition (BMI<15 kg/m^2), and hyperthyroidism or hypothyroidism.

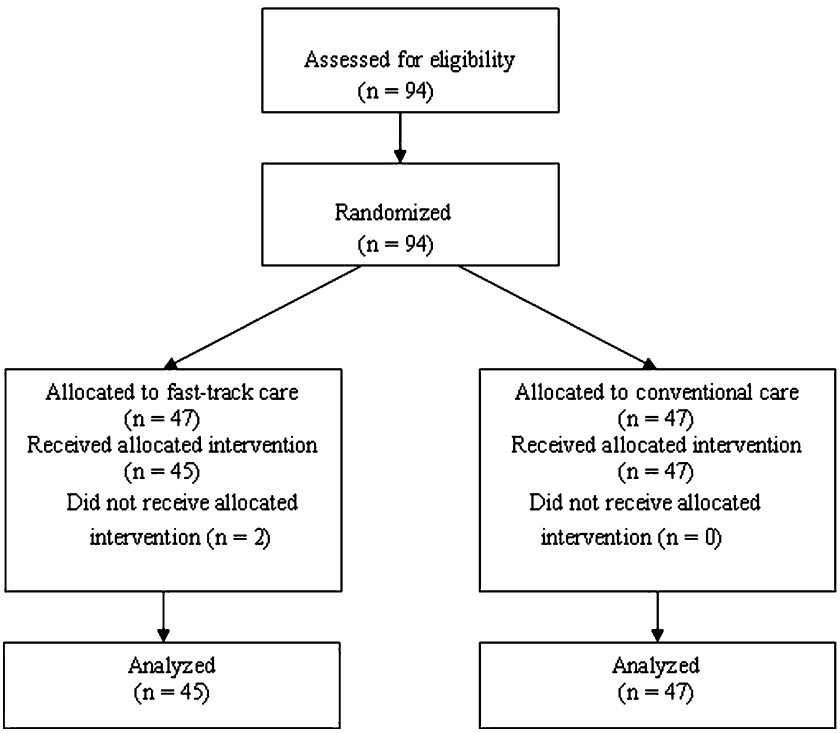

Figure 1 Flow diagram of the randomized control trial designed to compare the safety and efficacy between the fast-track surgery group and the conventional surgery group. Two participants were lost to follow-up and were excluded from the analysis.

Table 1 Comparison of Fast-track and Conventional Postoperative Care Protocols

	Fast-track	Conventional
Day before surgery	Preoperative information about FTS education	Normal meal until midnight
		No intake of oral carbohydrate drink on the day of surgery
	Normal meal until 6 h before surgery	Pre-anesthetic medication
	Normal carbohydrate drink until 2 h before surgery	Routine bowel preparation
	No pre-anesthetic medication	
	No bowel preparation	
Day of surgery	Mid-thoracic epidural anesthesia and analgesia (T7–10, depending on resection)	Tracheal intubation and general anesthesia
	Combined tracheal intubation and general anesthesia	Routine nasogastric tube drainage
	No routine nasogastric tube drainage; if used, remove as early as possible after surgery	Standard fluid regimen during surgery (Ringer's lactate 20 mL/kg in the first hour, followed by 10–12 mL/kg/h)
	Restricted fluid regimen during surgery (Ringer's lactate 20 mL/kg in the first hour, followed by 6 mL/kg/h)	Additional fluid infusion as the first choice for management if the mean arterial pressure is <60 mmHg or urine output is <0.5 mL/kg/h
	Vasopressor drugs as the first choice for management if the mean arterial pressure is <60 mmHg or urine output is <0.5 mL/kg/h	Standard laparotomy approach
	Minimally invasive incision	No infiltration of surgical wounds with bupivacaine
	Infiltration of surgical wounds with bupivacaine	Standard use of abdominal drains
	No routine use of abdominal drains	Patients transferred to anesthesia recovery room
	Patients transferred to anesthesia recovery room	Fasting until normal bowelsounds are heard
	Oral intake of a little clear water as soon as effects of anesthesia disappear+i.v. infusion of Ringers lactate 2.0 L (avoid excessive i.v. fluids)	I.v. infusion of about 2.5–3.0 L of Ringer's lactate by the attending surgeon
	Mobilization on bed in the evening	Bed rest
Postoperative day−1	Continue epidural analgesia with local anesthetic + 1,000 mg paracetamol every 6 h	Continuous i.v. infusion of morphine or PCA-morphine
	Patients drink at least 0.5 L liquid (follow a stepwise plan from water to other liquids to semi-fluids to normal food; adhere to the premise of eating little and often)+i.v. infusion of Ringer's lactate (appropriate level of i.v. fluid intake based on the volumes of liquid intake and output, and physiological need by the attending surgeon)	Oral intake is initiated if normal bowel sounds are heard (follow a stepwise plan from water to other liquids to semi-fluids to normal food; adhere to the premise of eating little and often)+i.v. infusion of about 2.5–3.0 L of Ringer's lactate by the attending surgeon until adequate oral intake
	Remove urine catheter as early as possible	Encourage patients to mobilize out of bed
	Patients mobilize out of bed at least four times per day	
Postoperative day−2	Patients drink at least 1 L liquid+others as above (patients gradually resume eating a normal diet; the daily increase in oral intake after surgery is managed by the attending surgeon)	As above + patients gradually resume eating a normal diet
Postoperative day−3	Stop epidural analgesia	As above until discharge criteria are fulfilled
	Continue mobilization	
	Others as above	
Postoperative day−4	Continue as above	As above until discharge criteria are fulfilled
	Check discharge criteria	

Ninety-four patients were assigned randomly to two groups comprising 47 patients each: FTS and conventional surgery (Fig. 1). Two patients who withdrew their consent in the FTS group were excluded from the study. The sample size was calculated to have a power of 80%.

Patients were admitted to the hospital 2-3 days before surgery. A slightly modified fast-track protocol proposed by Kehlet and Wilmore[2] was used in the FTS group. Patients in the conventional surgery group received conventional postoperative care. Details of the two care protocols are given in Table 1. Gastrectomies were carried out in accordance with standardized procedures using a midline epigastric laparotomy by the same group of experienced surgeons.

Table 2 Clinical Characteristics of Patients in the Fast-track Group and Conventional Surgery Group

	Conventional	Fast-track	t/χ^2	p
Age (years)	56.87±9.16	58.76±9.66	−0.960	0.340
Sex (M/F)	29/18	32/13	0.911	0.340
Height (m)	1.67±0.07	1.68±0.08	−0.842	0.402
BMI (kg/m^2)	23.25±2.79	23.85±2.40	−1.116	0.267
Type of surgery			0.525	0.769
Distal subtotal resection D_2	36	32		
Proximal subtotal resection D_2	6	6		
Gastectomy D_2	5	7		

Parameters of the Clinical Study and Follow-up

Using indirect MedGraphic calorimetry,[30] REE was measured on the day before surgery (day−0) and on days 1, 3, and 7 after surgery. Pain was evaluated from day−0 to day−5 after surgery using the visual analog system (VAS). Fever duration, flatus time, hospital stay, and complications were recorded postoperatively. The quality of life (QOL) score was determined upon hospital discharge using questionnaires.[31]

The duration of hospital stay was the primary clinical endpoint and expressed as hospitalization days after surgery. Hospital discharge was suggested if the patient was fully mobile and felt comfortable with controlled pain only by oral analgesics and established tolerance of oral food. Oral food intake was considered sufficient if the patient could eat more than two-thirds of the daily meal.

The telephone number of the operating surgeon was available to patients for direct communication. Within 24 h after discharge, patients were contacted by a specially trained doctor to aid in better convalescence. Thereafter, patients were followed up once a week for 4 weeks. The telephone questionnaire consisted mainly of open questions. It was designed to collect detailed information that surgeons could use to describe delayed recovery. The symptoms associated with delayed recovery would prompt them to consider intervention. Patients were followed up to determine the next treatment program at the outpatient clinic about 2 weeks after surgery.

Measurement of Serum Stress Cytokines

Blood samples were collected before surgery and on days1, 3, and 7 after surgery. Serum samples were aliquoted, frozen at −20°C, and then stored at −80°C for analysis. The serum concentration of interleukin IL-6, CRP and TNF-α were measured using a commercially available enzyme-linked immunosassay kit (Beifang Biotechnology Institute, Beijing, China) according to manufacturer's instructions.

Statistical Analysis

Numerical variables are expressed as mean ± standard deviation or median (quartile range) [M (Q)]. Categorical variables were expressed by a constituent ratio or rate. Differences between the two groups were tested using a two-tailed Student's t test for normally distributed data and a Mann–Whitney U test for non-continuous variables. The chi-square test and Fisher's exact test were used to compare discrete variables. The level of significance was set at $P<0.05$. Data analysis was undertaken with SPSS® version 13.0 (SPSS, Chicago, IL, USA).

Results

Clinical Characteristics

Table 2 shows the clinical characteristics of enrolled patients. There was no loss in the number of patients available for follow-up. The mean age of the FTS group was 58.76±9.66 years, and did not differ significantly from that of the conventional surgery group (56.87±9.16 years; $P>0.05$). There were no significant differences in sex, body weight, BMI, and types of surgery between the two groups (all $P>0.05$).

Outcome

Patients in the FTS group stayed in hospital for 6 (six to seven)days after surgery, which was significantly shorter than that in the conventional surgery group [8 (seven to eight)days] ($P<0.001$; Table 3). The duration of postoperative fever [2 (two to three)days] and flatus time [three (2–4 days)] in the FTS group were significantly shorter than those in the conventional surgery group [4 (three to four)

Table 3 Summary of Outcome in the Fats-track and Conventional Surgery Groups

	Conventional	Fast-track	*t/u*	*p*
Duration of fever (days)	4 (3–4)	2 (2–3)	609.00	<0.001
Duration of flatus (days)	4 (4–5)	3 (2–4)	509.00	<0.001
Hospital stay (days)	8 (7–8)	6 (6–7)	302.00	<0.001
QOL score	14.72±1.30	15.71±1.83	2.98	<0.05
Medical cost (RMB)	31,124.57± 3,608.94	26,992.98±3,629.22	−5.47	<0.001

days, 4 (four to five)days] (both $P<0.001$; Table 3). The medical cost (26,992.98±3,629.22) Chinese renminbi (RMB) in the FTS group was significantly less than that in the conventional surgery group (31,124.57±3,608.94) RMB ($P<0.001$; Table 3). The mean QOL score upon discharge (15.71±1.83) in the FTS group was significantly higher than that in the conventional surgery group (14.72±1.30; $P<0.05$; Table 3). VAS analysis illustrated that patients receiving FTS experienced significantly less pain than those in the conventional surgery group from day−1 to day−5 after surgery (all $P<0.05$; Fig. 2).

Stress-associated Cytokine Profiles

Levels of serum TNF-α, IL-6, and CRP were used as markers for the surgical stress response. As shown in Table 4, on days 1 and 3 after surgery, the mean serum levels of TNF-α [(12.54±2.57) fmmol/L, (13.29±2.68) fmmol/L] and IL-6 [(112.21±24.91) pg/mL, (129.11±23.00) pg/mL] in the FTS group were significantly lower than those in the conventional surgery group [(14.81±3.19) fmmol/L, (15.41±3.13) fmmol/L] [(123.95±22.28) pg/mL, (142.25±20.27) pg/mL] (all $P<0.05$; Table 4). On days 1, 3, and 7 after surgery, the mean serum levels of CRP [(56.20±11.20) mg/mL, (136.41±19.88) mg/mL, (48.52±13.10) mg/mL] in the FTS group were significantly lower than those in the conventional surgery group [(70.75±12.27) mg/mL, (157.01±28.37) mg/mL, (64.38±19.65) mg/mL] (all $P<0.05$; Table 4). The mean REE level [(1,370.16±146.54) Kcal/d, (1,263.82±153.55) Kcal/d] in the FTS group on days 1 and 3 after surgery also were significantly lower than those in the conventional surgery group [(1,469.47±152.22) Kcal/d, (1,345.87±155.34) Kcal/d] (both $P<0.05$; Table 4).

Complications with 4-week Follow-up

No death and no anastomotic leakage occurred in either group (Table 5). The prevalence of complications was 20% in the FTS group and 14.9% in the conventional surgery group ($P>0.05$; Table 5). In the FTS group, one patient suffered from incision infection on day−5 after surgery and stayed in hospital for 10 days; one subject experienced *superficial wound infection*; four had nausea and vomiting after eating (one of whom had a full recovery after fasting for 2 days and the other three patients all fully recovered after receiving a gastric tube catheter for 3 days); and two with acute urinary retention after early removal of a urinary catheter fully recovered after insertion of a urinary catheter for 3 days. The conventional surgery group contained two cases of *antibiotic associated diarrhea* and one case each of incision infection, urinary tract infection, and deep vein thrombosis. One patient was considered to have a pulmonary infection based on the symptoms of coughing, fever, and yellow sputum. All patients were cured by conservative treatment.

One patient in the FTS group was readmitted for conservative treatment on the twentieth day after surgery due to severe nausea and vomiting. After a series of examinations including CT, gastroscopy and upper gastrointestinal radiography, this patient was diagnosed as having gastroparesis. Subsequently, the patient was cured by fasting, nasogastric decompression, supportive care, and other measures. One patient in the conventional surgery group was readmitted on the 16th day after surgery because of nausea, vomiting, abdominal pain and abdominal distention. Based on the symptoms of vomiting bile and computerized tomography, this case was diagnosed as

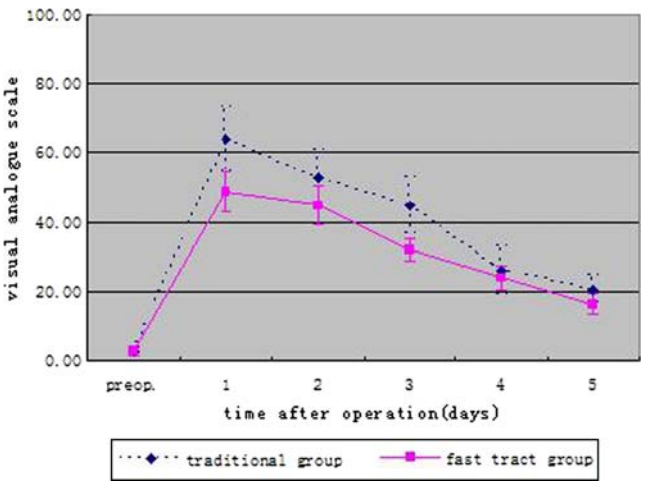

Figure 2 Comparison of preoperative and postoperative VAS of patients in the fast-track and conventional surgery groups.

Table 4 Comparison of Serum Level of IL-6, TNF-α and CRP in the Fast-track and Conventional Surgery Groups

	Conventional	Fast-track	*p*
IL-6 (pg/mL)			
Preoperative	100.83±31.45	97.17±28.31	0.559
Postoperative day−1	123.95±22.28	112.21±24.91	<0.05
Postoperative day−3	142.25±20.27	129.11±23.00	<0.05
Postoperative day−7	114.21±29.25	106.67±25.55	0.192
TNF-α (fmmol/L)			
Preoperative	11.64±2.49	12.05±2.89	0.466
Postoperative day −1	14.81±3.19	12.54±2.57	<0.05
Postoperative day −3	15.41±3.13	13.29±2.68	<0.05
Postoperative day −7	12.90±1.97	12.18±2.69	0.146
CRP (mg/mL)			
Preoperative	4.26±1.27	4.43±1.27	0.529
Postoperative day−1	70.75±12.27	56.20±11.20	<0.001
Postoperative day−3	157.01±28.37	136.41±19.88	<0.001
Postoperative day−7	64.38±19.65	48.52±13.10	<0.001
REE (Kcal/d)			
Preoperative	1,196.02±118.41	1,181.49±131.57	0.579
Postoperative day−1	1,469.47±152.22	1,370.16±146.54	<0.05
Postoperative day−3	1,345.87±155.34	1,263.82±153.55	<0.05
Postoperative day−7	1,209.02±124.86	1,198.73±110.23	0.677

afferent loop obstruction. The patient recovered fully after conservative treatment.

Discussion

The objective of this study was to evaluate the safety and outcome of a FTS protocol employed in the treatment of GC in comparison with conventional postoperative care. We found fast-track muti-modal rehabilitation programs were feasible for the perioperative care of GC patients. Compared with patients in the conventional surgery group, patients in the FTS group had a faster recovery, including shorter postoperative stay in hospital, shorter duration of fever, and shorter flatus time without an increase in the prevalence of complications. It was encouraging that the medical cost in the FTS group was significantly less than that in the conventional surgery group, and patients had a higher QOL score upon hospital discharge.

Conventional treatment of GC dictates that preoperative placement of a stomach tube and fasting until the bowels open are essential for the recovery of the patient after

Table 5 Comparison of Postoperative Complications with 4-week Follow-up in the Fast-track and Conventional Surgery Groups

	Fast-track	Conventional	χ^2	*p*
Total cases (%)	9 (20.0)	7 (14.9)	0.417	0.518
Anastomotic leakage	0	0	-	-
Pulmonary embolism	0	0	-	-
Lung infection	0	1	-	1.000
Myocardial ischemia	0	0	-	-
Nausea/vomiting	4	0	-	0.053
Deep-vein thrombosis	0	1	-	1.000
Intestinal obstruction	0	0	-	-
Incision infection	2	1	-	0.613
Urinary tract infection	0	1	-	1.000
Acute urinary retention	2	0	-	0.237
Diarrhea	0	2	-	0.495
Re-admission to hospital	1	1	-	1.000
Death	0	0	-	-

gastrectomy. This is based on the rationale that eating too soon after surgery can increase the risk of intestinal obstruction and more severe anastomotic tension. Recent studies have demonstrated that a gastric tube is not essential, and that it may induce pulmonary complications after GC surgery.[17, 18, 32] Some reports also indicate that early intake of liquid and food after surgery can facilitate postoperative restoration without increasing the incidence of fistulas.[27, 33] Patients in the FTS group resumed oral intake as early as possible under the principle that "eating little and often, a stepwise plan from water to other liquids to semi-fluids to normal food" after surgery, and there were no more complications in the FTS group. Some recent studies have demonstrated a restricted fluid infusion regimen during the perioperative period may reduce the occurrence of delayed gastrointestinal function.[34, 35] We therefore strictly limited the perioperative intake of fluid in the FTS group.

Our results also indicated that FTS without routine surgical drainage in combination with removing urinary catheter as early as possible after surgery enabled patients to have better physical movement without an increase in the risk of postoperative complications compared with conventional surgery. Increasing evidence supports the notion that surgical drainage does not reduce the prevalence of complications, but does increase intra-abdominal fluid collection, infection, and risk of fistulas, leading to a delay in discharge from the hospital.[29, 36]

In the FTS group, patients benefited from the use of epidural analgesia, oral analgesics, minimal invasive incisions, and infiltration of surgical wounds with bupivacaine which allowed patients to get out of bed faster after surgery. VAS in the FTS group was significantly lower than that in the conventional surgery group. Early mobility or activity is recognized as a critical step in fast-track care because it promotes patient recovery by reducing bed rest-induced loss of muscle strength, preventing problems with pulmonary function, and improving the supply of oxygen to tissues.[37]

Several cytokines such as IL-6, TNF-α, and CRP have been demonstrated to be involved in the response to surgical stress and are therefore useful serum markers for evaluating the severity of surgery-induced stress.[21–24] The postoperative profile of IL-6, TNF-α and CRP in patients with GC supported the notion that FTS generated significantly less stress in patients. Surgical trauma causes marked metabolic changes, and REE also acts as the marker for surgical stress.[25, 26] The REE rate of patients from the FTS group was lower than that in the conventional surgery group, particularly on postoperative days 1 and 3. Compared with patients in the conventional surgery group, patients in the FTS group experienced milder stress, less damage to immune function, faster recovery, and a better QOL.

Advances in surgical and anesthetic techniques have enabled the development of FTS.[38] It has been clearly established that an excessive surgical stress response is responsible for many postoperative complications such as systematic inflammatory response syndrome, wound infection, and cardiopulmonary insufficiency.[39, 40] The core elements of FTS include: fully understanding the pathophysiology of patients during the perioperative period, trying to reduce unnecessary stress and tissue damage, helping patients have faster rehabilitation with a shorter time of staying in bed, ensuring patients are satisfied, and maintaining surgical safety. We speculate that the faster rehabilitation of patients in the FTS group could be attributed to the milder traumatic manipulation during surgery compared with conventional surgery. Other factors contributing to better outcomes could be intraoperative application of epidural anesthesia, postoperative use of epidural analgesia, blocking of sympathetic introduction to outside stimulation, and inhibition of hormone secretions of the hypothalamic-pituitary-adrenal axis, all of which may be beneficial in attenuating responses to stresses.[41]

Conclusion

The present study indicates that FTS can lessen the stress reaction of patients, decrease REE during the perioperative period, and accelerate the rehabilitation of patients with GC. Some studies[8] have shown that FTS may lead to higher rates of readmission to hospital, which were not found in the present study. Large, multicenter, randomized, controlled clinical trials are therefore needed to demonstrate the safety and efficacy of FTS in the surgical treatment of GC.

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J Gastrointest Surg (2010) 14:628–635
DOI 10.1007/s11605-009-1130-1

ORIGINAL ARTICLE

Epidemiology and Prognostic Factors in Acute Superior Mesenteric Artery Occlusion

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Received: 7 November 2009 / Accepted: 30 November 2009 / Published online: 5 January 2010

Abstract
Background Reports on trends in incidence and mortality of acute superior mesenteric artery (SMA) occlusion and evaluation of prognostic factors in recent years are lacking.
Methods Patients with acute SMA occlusion were identified through the in-patient and autopsy registry between 1970 and 1982 (n=270), 1987 to 1996 (n=135), and 2000 and 2006 (n=100) in Malmö, Sweden.
Results The overall incidence rate decreased from 8.6 to 5.4/100,000 person years and the autopsy rate from 87% to 25% over time. A higher serum creatinine level was associated with a lower probability of undergoing multi-detector row computed tomography with intravenous contrast (MDCTiv) (p=0.006). Not performing a MDCTiv (odds ratio 4.0; 95% confidence interval [1.0–16.0]) remained as independent prognostic factor for in-hospital mortality. General and vascular surgeons collaborated in 25 out of 61 patients that underwent an intervention, of which 21 (84%) (p<0.001) survived.
Conclusions A close collaboration between radiologists and general and vascular surgeons seems to be most important to lower the mortality in patients with acute SMA occlusion.

Keywords Thrombo-embolic occlusion · Superior mesenteric artery · Incidence · Mortality · CT · Prognostic factors

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Introduction

Based on retrospective studies of clinical series, it has been claimed that acute superior mesenteric artery (SMA) occlusion is an uncommon disease,[1] maybe due to unawareness and difficulties to establish the diagnosis in time on clinical grounds. Robust estimates of the overall, age- and gender-specific incidence of acute SMA occlusion owing to the lower diagnostic and therapeutic activity, and the high autopsy rate of 87% have been published in one previous report from Malmö between 1970 and 1982,[2] and the disease proved to be more common than ruptured abdominal aortic aneurysm.[3] The mortality of acute SMA occlusion varies, which likely reflects a heterogenicity of the studied populations[4–8] in terms of study period, frequency of acute SMA occlusion, frequency of chronic mesenteric ischemia, operation frequency, and autopsy rate. It can be assumed that the reported mortality in these clinical series are underestimated and that the true overall mortality rate only can be assessed in population-based studies with a reasonably high autopsy rate. The substantial reduction in autopsy rate that followed changes in Swedish

legislation[9] in 1992 might affect the assessment of contemporary incidence and mortality.

Mortality of acute SMA occlusion has been exclusively related to the extent of intestinal infarction.[6,10,11] Patients with a thrombotic occlusion seem to have a poorer prognosis than those with an embolic occlusion,[12] maybe due to a more extensive intestinal infarction.[10] Comparative series on outcome from the same population is rare, but there was a failure in improving outcome in the series from Glasgow.[13] The aims of the present population-based study were to assess the incidence and mortality rates in view of previous reports from Malmö[2,14] and to evaluate prognostic factors for mortality in a recent series of patients with acute SMA occlusion.

Materials and Methods

Study Population and Setting

The population of Malmö, Sweden was studied between 2000 and 2006, and the population in 2003 with 267,000 inhabitants was used as reference population (Swedish Central Bureau of Statistics, SCB, www.scb.se). The city has one hospital for acute diseases, the Malmö University Hospital. The Department of Pathology is the sole referral unit for post-mortem examinations in Malmö. During the period, 20,784 deaths occurred in the Malmö population. In all, 3,576 clinical autopsies and 1,520 forensic autopsies were performed on patients from Malmö, resulting in an average autopsy rate of 25%.

An analysis of trends of incidence and mortality was compared to previous population-based studies between 1970 and 1982,[2] and 1987 and 1996.[14]

Retrieval of Patients with Acute SMA Occlusion

The identification of all in-hospital patients with the diagnosis of acute mesenteric ischemia managed operatively or non-operatively during the 7-year study period (1 January 2000 to 31 December 2006) was based on the International Classification of Disease, ICD, 10th edition, code I74.8 and K55 and collected in a computerized registry. Medical records were analyzed. The computerized registry at the Department of Pathology, Malmö University Hospital, were used to identify the protocols of patients either undergoing bowel resection with subsequent pathological anatomical diagnosis of acute mesenteric ischemia or deceased patients with acute mesenteric ischemia: The software database system *SymPathy* and the specific topographic and diagnostic codes for duodenal infarction, duodenal ischemia, duodenal bleeding, small bowel infarction, small bowel ischemia, small bowel bleeding, colon infarction, colon ischemia, colon bleeding, rectal infarction, rectal ischemia, rectal bleeding, blood vessel and embolus, blood vessel and thrombosis were used in the search. The data-based registry at the Institution of Forensic Medicine in Lund, Lund University Hospital, was used to identify deaths from acute mesenteric ischemia. Patients with porto-mesenteric venous thrombosis with or without intestinal infarction (n=51) and non-occlusive mesenteric ischemia (NOMI; n=8), as well as acute SMA occlusions referred for vascular intervention from hospitals outside of Malmö (n=12) were excluded.

In the overall epidemiological evaluation of acute mesenteric ischemia, data from 1970 to 1982 were retrieved from both autopsy registries and a 3-year clinical sample,[2] and data from 1987 to 1996 were retrieved from a consecutive clinical series of acute mesenteric ischemia.[14]

Definitions

Classification of the SMA occlusions into embolus or thrombosis was based on radiological, operation, autopsy, or clinical findings. Computed tomography (CT) was performed between 2000 and 2003, and multi-detector row CT (MDCT) was performed from 2004 and onward. A person that either lives together under marriage-like circumstances or is under supervision around the clock was defined as a cohabitant. Ischemic heart disease was defined as previous myocardial infarction, angina pectoris, history of coronary artery by-pass grafting, or percutaneous coronary angioplasty. Renal insufficiency was defined as serum creatinine higher than 105 μmol/L (1.2 mg/dL) in men and 90 μmol/L (1.0 mg/dL) in women. Anemia was considered if hemoglobin was lower than 134 g/L in men and 117 g/L in women. New pathological changes on electrocardiogram (ECG) were defined as occurrence of new changes such as ST elevation or depression, rhythm, or atrio-ventricular block at admission. Bloody stools were denoted if there was macroscopic or microscopic blood, measured with available test kits, in the stools. Oliguria was based on documentation of poor or no urinary output at admission. The clinical triad was present if the patient suffered from severe abdominal pain but minimal abdominal findings, vomitus/diarrhea/bloody stools, and a source for arterial embolus. Abnormal bowel sounds were defined as silent abdomen or aggravated bowel sounds.

Ethics

This study was approved by the Research Ethics Committee of the University of Lund.

Statistical Methods

Data management and statistical analysis were performed using the SPSS for Windows program package (SPSS Inc., Chicago, IL, USA). Cause-specific mortality ratios were expressed as number of deaths from acute SMA occlusion per thousand deaths. Overall incidence rates were based on the number of cases with acute SMA occlusion/acute mesenteric ischemia and were expressed as number of cases per 100,000 person years. Confidence intervals were calculated assuming a Poisson distribution of events, using the exact method for $N<15$ and the normal approximation for larger numbers. Differences in proportions were evaluated using the chi-square or the Fisher's exact test. Age and laboratory values were expressed as median and interquartile range, and comparisons between groups were made with the Mann–Whitney *U* test. Variables associated with in-hospital mortality ($p\leq0.05$) were further tested in a stepwise multivariate binary logistic regression model and expressed in terms of odds ratio (OR) with 95% confidence interval (CI). $p\leq0.05$ was considered significant.

Results

Distribution of Etiologies in Patients with Fatal Acute Mesenteric Ischemia

The overall incidence rate of fatal acute mesenteric ischemia between 1970 and 1982, diagnosed at either autopsy or operation, in the population of Malmö was estimated to 12.9 (95% CI 11.6–14.1)/100,000 person years. The autopsy rate was 87%. In all, 402 patients were diagnosed: 270 (67.2%) with acute SMA occlusion, 63 (15.7%) with mesenteric venous thrombosis, 62 (15.4%) with NOMI, and seven (1.7%) with indeterminate etiology.

Trends in Incidence of Acute SMA Occlusion

The overall incidence of acute SMA occlusion in Malmö between 1970 and 1982 was estimated to 8.6/100,000 person years. Most patients (65%) were diagnosed at autopsy, and the autopsy rate was 87%. The incidence and autopsy rates in the population have decreased significantly over the two following time periods, whereas the percentage of octogenarians has doubled (Table 1). The mode of diagnosis has shifted from autopsy or laparotomy in the former time period to laparotomy (42%) or CT (27%) in the latest time period. From 2004 to end of study, 55 patients were diagnosed, mainly with MDCT with intravenous contrast enhancement (MDCTiv) ($n=25$; 46%) or laparotomy ($n=19$; 34%).

Trends in Mortality of Acute SMA Occlusion

The overall cause-specific mortality was 6.0/1,000 deaths in 1970–1982, and the in-hospital mortality rate was 93%. These mortality estimates has decreased since then (Table 1) as has the autopsy rates. From 2004 to end of study, in-hospital mortality rate was 58% (32/55). The subset of patients undergoing a MDCTiv had an in-hospital mortality rate of 36% (9/25) ($p=0.002$).

Evaluation of Patients with Acute SMA Occlusion During 2000–2006

One hundred patients were found to have acute SMA occlusion during this time span, with a median age of 82 years (range 40–95), of which 75 were women. Forty-four out of 95 patients with known civil status were living as cohabitants, of which 28 (64%) were women. Data on patient characteristics and co-morbidity are found in Table 2 and symptoms and physical examination in Table 3.

Laboratory Investigations

The following biomarkers at admission were elevated: creatinine kinase MB (>10 μg/L) in four of 27 patients, lactate (>2.2 mmol/L) in six of 10, metabolic acidosis (base excess <−3) in seven of 12, and D-dimer≥0.2 mg/L in three of three. Troponin I was not elevated (>0.5 μg/L) in any of the seven measured patients. Clear elevation of white cell blood count ($\geq20\times10^9$/L) and C-reactive protein (CRP) (≥100 mg/L) was found in 15 of 48 and in 25 of 76 patients, respectively. New pathological changes on ECG were found in 49 of 78 patients at admission. According to reference values from the local laboratory, 67 of 95 (72%) patients had renal insufficiency at admission. Serum creatinine ≥150 and ≥200 μmol/L were found in 38 (40%) and 18 (19%) patients, respectively. Previously known renal failure was found in three of 75 (4%) of the patients prior to admission.

Computed Tomography

In all, CT of the abdomen was performed in 52 of 100 patients and MDCTiv in 25 patients from 2004 and onward. The MDCTiv's were performed with imaging in the arterial ($n=11$), venous ($n=10$), and both arterial and venous phase ($n=4$). Patients undergoing MDCTiv had a significantly lower serum creatinine level at admission, compared to those who did not ($p=0.006$), whereas there were no differences between the two groups in terms of age ($p=0.63$), medication with diuretics ($p=0.41$), or CRP levels at admission ($p=0.067$).

Table 1 Time Trends in Epidemiological Characteristics in Studies of Acute SMA Occlusion in the Population of Malmö, Sweden

Study	1970–1982[2]	1987–1996[14]	2000–2006
Studied entity of acute mesenteric ischemia	Acute SMA occlusion	Acute mesenteric ischemia	Acute SMA occlusion
Demographic data			
Malmö population	240,000 (1976)	237,000 (1992)	267,000 (2003)
Percentage ≥80 years	3.0%	5.5%	6.0%
Autopsy frequency	87%	42%[15]	25%
Overall incidence rate[b]	8.6 (7.6–9.7)	5.7 (4.7–6.7)	5.4 (4.3–6.4)
Median age (years)	80	79	82
Mode of diagnosis (%) cases			
All	270	135	100
Autopsy only	176 (65%)	43 (34%)	18 (18%)
Surgery	94 (35%)	55 (41%)	42 (42%)
CT	0 (0%)	20[a] (15%)	27 (27%)
Angiography	0 (0%)	0 (0%)	2 (2%)
Clinical diagnosis	0 (0%)	17 (13%)	11 (11%)
Overall cause-specific mortality[c]	6.0 (5.2–6.8)	3.3 (2.7–4.0)	3.0 (2.3–3.8)
In-hospital mortality (%)	93%	76%	63%

[a] All radiological (CT, plain abdominal X-ray, and ultrasound) or endoscopical investigations together

[b] The population of 1976, 1992, and 2003 were defined as the average population in the analysis, respectively, and expressed as number of cases per 100,000 person years (95% CI)

[c] per 1,000 deaths (95% CI)

The SMA occlusions were classified as embolic (n=37), thrombotic (n=35), or indeterminate (n=28).

Prognostic Preoperative Factors for In-hospital Mortality

The in-hospital mortality for the 100 patients diagnosed in the Malmö population between 2000 and 2006 was 63%. Patient characterized as *cohabitant* (p=0.026) or with co-morbidities such as *renal insufficiency* (p=0.019) or *medication with diuretics* (p=0.010) were associated with increased in-hospital mortality (Table 2). There was an association between renal insufficiency and medication with diuretics (p=0.028) and also between lower *serum creatinine* levels and performing a *MDCTiv* (p=0.006). A

Table 2 Patient Characteristics and Co-morbidities in Relation to In-hospital Mortality in Patients with Acute SMA Occlusion

	Patients (%)	In-hospital mortality (%)	p
All	100	63 (63)	
Age ≥80 years	58 (58)	41 (71)	0.061
Women (%)	75 (75)	49 (65)	0.40
Cohabitant	44/95 (46)	33 (75)	0.026
Co-morbidities			
Ischemic heart disease	32/97 (33)	20 (62)	0.93
Heart failure	28/97 (29)	19 (68)	0.44
Atrial fibrillation	35/97 (36)	20 (57)	0.47
Stroke	11/96 (11)	8 (73)	0.46
Diabetes mellitus	12/97 (12)	7 (58)	0.79
Anemia at admission	29/90 (32)	18 (62)	0.90
Renal insufficiency at admission	67/95 (72)	46 (69)	0.019
Previous vascular surgery	20/96 (21)	11 (55)	0.44
Medications			
Diuretics	51/96 (53)	38 (75)	0.010
Digitalis	19/96 (20)	11 (58)	0.64
Beta blockers	37/96 (39)	25 (68)	0.42

Table 3 Clinical Findings at Admission in Relation to In-hospital Mortality in Patients with Acute SMA Occlusion

	Patients (%)	In-hospital mortality (%)	*p*
All	100	63 (63)	
Symptoms at admission			
Acute onset of abdominal pain	31/82 (38)	15 (48)	0.15
Vomitus	51/87 (59)	29 (57)	0.69
Hematemesis	7/86 (8)	6 (86)	0.23
Diarrhea	35/87 (40)	21 (60)	0.83
Obstipation	9/87 (10)	5 (56)	0.84
Bloody stools	12/86 (14)	8 (67)	0.58
Clinical triad	14/88 (16)	8 (57)	0.80
Oliguria	11/86 (13)	11 (100)	0.003
Confusion	11/88 (12)	8 (73)	0.32
Physical examination at admission			
Abnormal bowel sounds	42/76 (55)	25 (60)	0.41
Tenderness at abdominal palpation	75/83 (90)	42 (56)	0.30
Peritonitis	20/83 (24)	12 (60)	0.82

lower serum creatinine level was also associated with an increased survival rate (p=0.006). Symptoms coherent with (oliguria p=0.003) (Table 3) and laboratory findings of *CRP≥100 mg/L* (p=0.037) were associated with increased in-hospital mortality. Performance of a MDCTiv (p=0.037) was associated with a superior in-hospital survival rate. When entering the variables cohabitant, medication with diuretics, renal insufficiency, CRP≥100 mg/L, and MDCTiv as covariates in a multivariate binary logistic regression model, medication with diuretics (OR 4.3; 95% CI [1.4–13.8], p=0.014) and not performing a MDCTiv (OR 4.0; 95% CI [1.0–16.0], p=0.050) remained as independent prognostic factors for in-hospital mortality, whereas there was a trend for CRP≥100 mg/L (OR 3.1; 95% CI [0.88–10.8], p=0.077).

The Operations

In all, 61 patients were operated with either laparotomy, bowel resection, open vascular surgery, endovascular surgery, or a combination (Fig. 1). Two out of 39 patients managed non-operatively survived: One 92-year-old female with transient abdominal pain, diarrhea, and a SMA embolus were managed conservatively and given low molecular weight heparin (LMWH). The second, 87-year-old female patient was found to have an asymptomatic synchronous SMA embolus and a symptomatic femoral artery embolus at angiography. The SMA embolus was identified at re-evaluation of the images of the abdominal aorta and the visceral arteries 1 h after the angiography procedure was completed. The patient was first given LMWH and then an anti-platelet agent at discharge and she remained asymptomatic. Laparotomy was performed in 55 patients. Bowel resection was performed in 35 patients; small bowel (n=25) and colon resection (n=20) at primary operation. Additional small bowel resections were performed in three and one patient at second and third looks, respectively. Fourteen second looks and one third look were performed.

Vascular Surgery

Eighteen out of 20 (90%) patients underwent their vascular procedures from 2004 and onward. The following 15 endovascular procedures were performed in 14 patients: stent placement (n=7), aspiration embolectomy (n=5), thrombolysis (n=2), and aspiration thrombectomy (n=1). Open vascular surgery was performed in eight patients: embolectomy (n=6) and SMA exposure for retrograde endovascular recanalization and stenting (n=2). Hence, two patients underwent hybrid vascular intervention. Bowel resection was performed in six patients. MDCTiv was performed prior to vascular operation in 16 (80%) out of these 20 patients.

Prognostic Factors for Survival After Operation

General and vascular surgeons collaborated in 25 out of 61 patients that underwent an operation. Twenty-one of these 25 patients (84%) survived, whereas 14 of 36 (39%) patients survived among those managed by general surgeons only (p<0.001). In-hospital survival rate was 90% (18/20) of those who underwent an intestinal revascularization procedure (Fig. 1). Performance of endovascular intestinal revascularization (n=14) was associated with increased survival rate (p<0.001), whereas open vascular surgery (n=8) was not (p=0.45). Bowel resection (n=35) was not associated with any survival benefit (p=0.63).

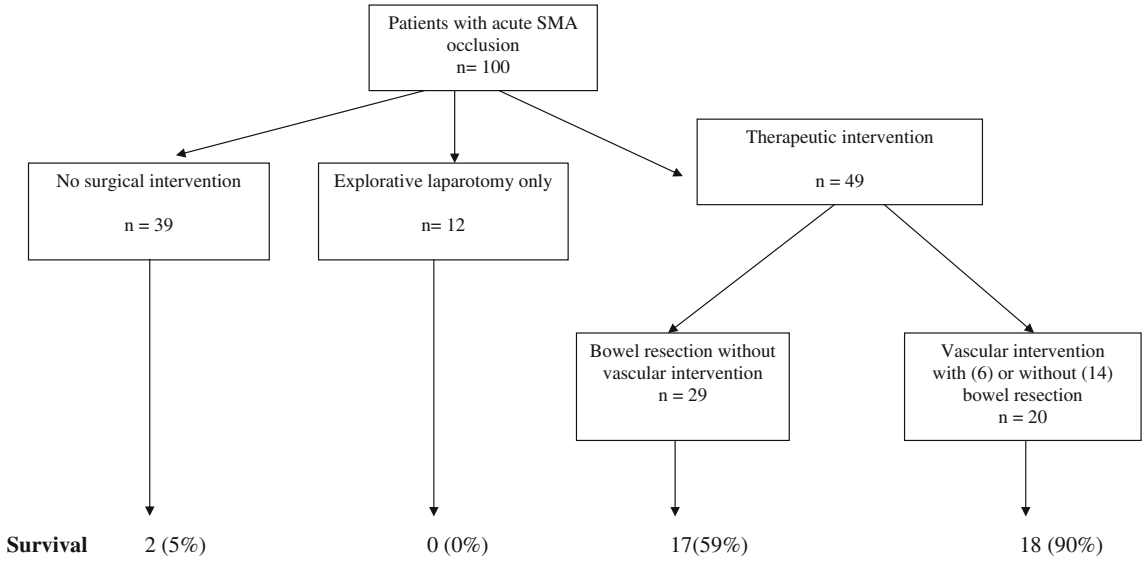

Figure 1 Management and survival of patients with acute SMA occlusion in Malmö 2000–2006.

Discussion

The overall estimated incidence of acute SMA occlusion in the Malmö population appeared to decrease over the past three decades. Even though there is a much greater preventive activity against arterial thrombosis and embolism, it is unlikely that this factor can explain the decline in incidence. On the contrary, the incidence should have increased as for the patients with ruptured abdominal aortic aneurysm,[16] since the higher proportion of octogenarians in the latter time period should have yielded higher incidence rates.[2] Instead, it is very likely that the much lower autopsy rate, especially among the elderly,[17] explains the failure of showing the expected increase in incidence. The encouraging and favorable results after diagnostic MDCTiv of the abdomen indicates that this is the key tool nowadays for early diagnosis, vascular management, and high survival rate after operation. However, a high autopsy rate in the population is still needed to be able to study the overall incidence and mortality.

A high creatinine level at admission seemed to have influenced the clinicians, maybe after consulting the radiologists in some cases, not to perform a MDCTiv, which consequently led to a high mortality rate in this group. Consequently, factors associated with renal insufficiency in the present study such as medication with diuretics was, not unexpectedly, a negative prognostic factor. However, very few of the patients deemed to have renal insufficiency based on a single creatinine level at admission had a previous known renal failure according to the case records, The acute deterioration of renal function found at admission may have been caused by various factors such as dehydration, renal hypoperfusion caused by lowered cardiac output due to worsening of cardiac failure and/or atrial fibrillation,[18] synchronous renal artery embolism,[19] or late stage of disease with multiple organ failure. Somewhat similar, a high proportion of patients with ruptured adominal aortic aneurysm often present themselves with renal insufficiency. However, careful perioperative fluid resuscitation among survivors may result in renal function preservation and even lower creatinine levels at discharge, despite the state of hypovolemia at admission and the exposure of accumulated doses of iodinated contrast media after both preoperative CT and peroperative angiography series performed during the endovascular repair.[20] It is therefore suggested that clinicians should support the radiologist in the decision to carry on with contrast injection to obtain proper MDCTiv images in cases with a strong suspicion of acute SMA occlusion and concurrent high creatinine level. If not, there is a high risk that a MDCT without contrast injection will be non-diagnostic, leading to a fatal delay in the handling of the patient. Simultaneously, periprocedural hydration with isotonic saline should be administered to prevent radiocontrast nephrotoxicity.[21,22] The finding that cohabitant was a factor associated with mortality was surprising, since it is thought that elderly people living alone may not be capable of getting adequate help in time. A qualitative analysis has however shown that the spouses' conceptions of an acute event may actually sometimes lead to a pre-hospital delay to hospital admission.[23] Cohabitee or not, a high proportion of deceased octogenarians die in their ordinary homes without any in-hospital care during the last year prior to death,[24] and in view of the contemporary low autopsy rate,

many patients die without a clear diagnosis. Hence, it is most likely that some patients with acute SMA occlusion, especially in the contemporary series, may have died at home.

The finding that all patients with oliguria died may be a sign of the advanced stage of intestinal infarction, subsequent systemic hypoperfusion, and multiple organ failure. At this late stage, intestinal infarction has led to impairment of the bacterial barrier, translocation of bacteria, out-flow of endotoxins into the bloodstream, release of inflammatory cytokines, and CRP. Even though clinicians are alerted by a high CRP level in a patient with acute abdomen, it is important to identify patients with a suspicion of acute SMA occlusion at an earlier stage, preferably when the CRP is normal, since high CRP typically is raised late in the course[25] and was associated with a high mortality in the present study.

Severe acute abdominal pain together with minimal signs at abdominal evaluation, vomitus, and atrial fibrillation are typical findings early in the course in an elderly patient with acute SMA occlusion. Patients are evaluated at different stages of the disease at their admission, which may be one of the reasons why these typical findings were inconsistent in the present study. In addition, clinical presentation in the very old might be further obscured by lack of abdominal symptoms and confusional conditions.[14] However, the clinicians need to be aware of that the diagnosis is not uncommon, and in fact more common than ruptured abdominal aortic aneurysm.[3] A prompt MDCTiv is needed whenever either of these conditions are called upon.

The overwhelming majority of acute SMA occlusions are located in the main stem,[19] and it is very likely that high-quality MDCTiv will diagnose these central SMA occlusions. Even though the MDCT in the present study often was performed in the venous phase and not in the arterial phase, they allowed assessment also of the presence of occlusion of the SMA. Prompt invasive angiography of the visceral arteries has been advocated[7] in patients with suspicion of acute SMA occlusion, but clinicians may simply find the symptoms too unspecific to go ahead directly with an angiography. In addition, angiographic services around the clock are probably not possible in most hospitals. Instead, MDCTiv seems to be the most appropriate diagnostic investigation, since other abdominal conditions can be ruled out and that the time delay related to the MDCT procedure is not that crucial in comparison with the information gathered from the investigation. Indeed, non-diagnostic MDCT without intravenous contrast enhancement and/or explorative laparotomy by the general surgeons late in the clinical course contributed to the higher mortality figures for patients managed by the general surgeons only, whereas the present study identified that the collaboration between general and vascular surgeons at our center is most important for the survival of patients that are diagnosed in time for an attempt of intestinal revascularization. The diagnostic MDCTiv was a prerequisite for acute planning of the vascular intervention. The need for laparotomy prior or after the intestinal revascularization and evaluation of bowel viability is another key step in the management and should be discussed across specialities. The results after vascular surgery in the present study, especially endovascular therapy, were favorable with a high survival rate and low frequency of bowel morbidity.

Conclusion

The overall mortality rate in patients with acute SMA occlusion remains high. A close collaboration between radiologists and general and vascular surgeons seem to be most important to lower the mortality. It is suggested that MDCTiv should be considered in patients with high creatinine when there is a high suspicion of acute SMA occlusion.

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J Gastrointest Surg (2010) 14:636–644
DOI 10.1007/s11605-009-1122-1

ORIGINAL ARTICLE

Sacral Nerve Stimulation Induces Changes in the Pelvic Floor and Rectum that Improve Continence and Quality of Life

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Received: 27 May 2009 / Accepted: 25 November 2009 / Published online: 8 January 2010

Abstract
Purpose Sacral nerve stimulation (SNS) can improve fecal incontinence, though the exact mechanism is not known. This study examines the following hypotheses: SNS leads to contraction of the pelvic floor, influences rectal perception, and improves continence and quality of life.
Methods Fourteen patients with sacral nerve stimulators implanted for fecal incontinence were examined prospectively. Morphological and functional assessment was done by endosonography, manometry, and volumetry with the stimulator turned on and off in direct succession. Questionnaires were used to determine incontinence and quality of life.
Results With the stimulator turned on, rectal filling conditions were perceived only at higher volumes; in particular, the defecation urge was sensed only at higher volumes. There was also a reduction in the diameters of the external and internal anal sphincters and a decrease in the distance between the anal mucosa and the symphysis as a sign of pelvic floor elevation. Six months after surgery, continence and quality of life were markedly better than before the operation.
Conclusions We were able to confirm the hypotheses given above. The improvements of pelvic floor contraction and rectal perception are rapid adjustment processes in response to stimulation of sacral nerves S3/S4 when turning on the stimulator.

Keywords Sacral nerve stimulation · Pelvic floor · Rectal perception · Quality of life · Fecal incontinence

Introduction

In industrial countries, 2% of the total population and 15% of the elderly suffer from fecal incontinence.[1–3] Involuntary loss of stool or gas leads to social isolation and depression.[3,4] Conservative treatment measures like diet, physiotherapy, biofeedback, and constipating drugs fail to achieve lasting improvement of the symptoms in about 50% of those affected.[5–7] Surgical measures such as sphincter repair or creation of a neosphincter also have a high failure rate, especially in patients with no morphological sphincter defect. Particularly, the neosphincter procedures have a high complication rate.[8–15]

Sacral nerve stimulation (SNS), originally developed in 1989 to treat urinary incontinence,[16] is a promising new approach for patients with failed conservative therapy. Matzel et al. published the first results for treatment of fecal incontinence in 1995.[17] This minimally invasive method can markedly improve continence in patients who have no morphological sphincter defect and would normally not benefit from the above-mentioned surgical reconstructions.[18–26]

However, the exact mechanism of action for the effect of SNS on fecal incontinence has not yet been clarified. Fecal continence is a complex interaction of the puborectal muscle, anal sphincter, colon motility, and anorectal sensitivity. There are various hypotheses relating to an effect of SNS on sensory, motor, and autonomic nerves or to a connection with the central nervous system. However,

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Presented at the meeting of the German Congress of Surgery, 22–25 April 2008.

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it has not yet been possible to obtain clear results here or to definitively clarify the exact sphincter and bowel changes induced by stimulation.

This prospective study assesses SNS for short-term morphological and functional effects on the anal sphincter, pelvic floor, and rectum by examining patients 6 months after implantation with the stimulator turned on and off in direct succession for all investigations. To our knowledge, such a direct short-term comparison has not been performed thus far; most studies demonstrate long-term changes in the postoperative course. Continence and quality of life were also evaluated.

The aim of this study is to verify the following hypotheses:

1. SNS leads to contraction of the pelvic floor.
2. SNS influences rectal perception.
3. SNS improves continence and quality of life.

Materials and Methods

This prospective unicenter study examines SNS for its morphological and functional effects on the anal sphincter, pelvic floor, and rectum as well as for its influence on continence and quality of life. The investigation was performed in 14 patients consecutively implanted with a permanent sacral nerve stimulator for treatment of fecal incontinence. The examinations were part of the routine follow-up. Informed consent was obtained.

Morphological and Functional Examinations

All examinations were performed in direct succession with the sacral nerve stimulator turned on and off. Patients were blinded to the stimulator setting. The stimulator was set at a subsensory level of intensity so that the patient did not perceive the stimulation and was thus unaware of the setting.

Endosonography

Endosonography was done to assess the diameter of the external anal sphincter (12 o'clock and 3 o'clock lithotomy position [LP], mid sphincter), the diameter of the internal anal sphincters (9 o'clock LP, mid sphincter), and the distance between the anal canal mucosa and the symphysis with relaxed and tensed pelvic floor (12 o'clock LP). The examination was performed using a rigid probe with a 360° multifrequency transducer rotating in water and the B&K Medical Ultrasound Diagnostic System 3535. The rotation frequency was 7 MHz for visualizing the anal sphincters and 5 MHz for measuring the distance between symphysis and anal canal mucosa.[27–30] All examinations were performed by the same ultrasonographer.

Stationary anal Perfusion Manometry

Perfusion manometry was performed to determine the resting and squeeze pressures. The examination was done using a 75-cm long, 5-mm thick flexible catheter with eight lateral exit orifices for perfusion channels (perfusion rate 4 ml/min). Intraluminal pressures were measured at the exit orifices. Assessment was done using the Medtronic Polygram software. The site of maximum resting pressure was determined by slow withdrawal of the catheter and corresponded to the zone of highest anal canal pressure via all eight channels. The maximum squeeze pressure was then measured at the same site by pelvic floor contraction.[28–30]

Vector Volume Perfusion Manometry

Vector volume perfusion manometry was used to determine the vector volume, the sphincter length, and the radial asymmetry of the sphincter with the pelvic floor relaxed and tensed. For this examination, the above-described catheter was pulled through the anal canal (1 cm/s). The Medtronic Polygram software was used to analyze the pressures during pull-through. The vector volume reflects sphincter pressure related to the total length of the pressure zone. Radial asymmetry is determined by three-dimensional assessment of the values in the entire anal canal and comparison with the mean pressure of all channels.[28,29]

Volumetry

Volumetry was used for the assessment of the rectal reservoir function: rectal compliance, rectoanal inhibitory reflex, and rectal filling volumes and pressures. Measurements were performed using a catheter similar to the above-described but with a 4-cm elastic balloon at the tip. A channel attached to the balloon was used to measure its pressure. The catheter was placed with the balloon positioned in the rectum, while the sphincter pressure and thus the correct catheter position were monitored via two exit orifices. This was followed by slow air insufflation into the balloon. The patient was asked to indicate the subjective "perception threshold" (first sensation of rectal expansion), the "defecation urge," and the "maximum tolerated volume." The respective balloon filling volumes were recorded together with the corresponding pressures in the balloon and thus also in the rectum. The no-load curve of the balloon was determined separately and subtracted. The rectoanal inhibitory reflex was tested by rapid insufflation of a 50-ml air bolus into the balloon and was considered to be present if the volume administration led to a rapid decrease of sphincter pressure followed by a return to the initial level.[29]

Continence and Quality of Life

Patients were also questioned with regard to their continence and quality of life preoperatively and 6 months after stimulator implantation by the following questionnaires. Continence was determined according to three established incontinence scores: CACP score, Cleveland Clinic score, and Kelly–Holschneider score (Table 1).

Health-related quality of life was assessed by using the validated SF-36 questionnaire with a total of 36 questions in two categories: "physical health" and "mental health."[31]

Patients

A total of 14 patients, consecutively implanted with a permanent sacral nerve stimulator (stimulation level S3/S4), were examined from 2005 to 2007: five men and nine women with a mean age of 61 years (range, 37–86 years). All patients suffered from severe fecal incontinence with regular involuntary excretion of solid stool and an average of eight bowel movements a day. All patients had previously failed at least 6 months of conservative therapy and eight patients had not derived any benefit from other surgical measures (Table 2). SNS for 2 weeks by a temporarily implanted test electrode was found to improve continence in all patients. No surgical complications occurred. At the time of the examination 6 months after implantation, the stimulators were set at a subsensory level so that patients could not consciously perceive the stimulation. There was no alteration of the stimulation level at least 1 month prior to the examination.

Statistics

Statistical significance was assessed using the binominal test (alpha=0.05). The standard deviation (SD) was given for mean values.

Results

Morphological and Functional Changes

The endosonographic examination of sphincter and pelvic floor morphology revealed a decrease in all examined parameters as an indication of generalized contraction enhancement when the sacral nerve stimulator was turned on: decrease in the diameter of the external anal sphincter from 8.3 to 7.0 mm, respectively, from 8.7 to 7.0 mm; in the diameter of the internal anal sphincter from 3.3 to 2.7 mm; and in the distance between the anal mucosa and the symphysis from 51.4 to 48.8 mm, respectively, from 46.5 to 43.4 mm (Table 3).

A change was also found in the patient's subjective perception of rectal filling volumes. The same sensations

Table 1 Incontinence Scores[46–48]

Score with point scale	Assessment criteria	Points for each assessment criterion
CACP (0 points=complete incontinence, 17 points=normal)	Defecation rate Stool consistency Defecation urge Discrimination Warning period Incontinence episodes Fecal smearing Drug intake	0 (poor) to 1 or 2 or 4 points (normal)
Cleveland Clinic (0 points=normal, 20 points=complete incontinence)	Incontinence for solid stool Incontinence for liquid stool Incontinence for gas Wears pad Alteration of lifestyle	0 (never) to 4 points (always)
Kelly–Holschneider (0 points=complete incontinence, 14 points=normal)	Defecation rate Stool consistency Fecal smearing Defecation urge Warning period Discrimination Need for additional care	0 (poor) to 2 points (normal)

Table 2 Patient Characteristics (Total Number of Patients=14)

Gender, men/women		5/9
Age (years)		61 (range 37–86)
Conservative therapy before implantation (no. of patients)	Constipating drugs	7
	Biofeedback	14
Surgical measures before implantation (no. of patients)	Resection rectopexy	3
	Sphincter repair	3
	Gracilis neosphincter	2
Symptoms before implantation	Incontinence for solid stool (no. of patients)	14
	Defecation rate (per day, mean)	8
Patient history (no. of patients)	Perineal tear	4
	Intussusception	3
	Colectomy (colitis ulcerosa)	3
	Stroke	2
	Anal cancer	1
Additional diagnoses (no. of patients)	Hypertension	4
	Coronary heart disease	3
	Obesity	2
	Diabetes	1
	Parkinson's disease	1
	Urinary incontinence	1

were only triggered by higher volumes with the stimulator turned on: The perception threshold increased from 62.1 to 86.4 ml, the volume evoking the defecation urge increased from 108.2 to 145.7 ml, and the maximum tolerated volume increased from 148.9 to 188.2 ml. On the other hand, the intrarectal pressures measured together with the corresponding volumes did not differ when the stimulator was on or off: 34.9 and 33.6 mmHg for the perception threshold, 47.6 and 49.1 mmHg for the defecation urge, and 53.3 and 60.5 mmHg for the maximal tolerated volume (Table 4).

The resting and squeeze pressures showed a tendency toward higher values with the stimulator turned on: The resting pressure was 33.8 mmHg (SD=18.6) and the squeeze pressure was 86.5 mmHg (SD=67.0) with the stimulator turned off and 39.7 mmHg (SD=25.6) and 101.3 mmHg (SD=62.9) with the stimulator turned on. However, these differences are not significant (p=0.211 and p=0.246). Other parameters examined also showed no difference: With the stimulator turned off, the vector volume was 216.1 cm^3Hg (SD=404.7) with a relaxed pelvic floor and 464.5 cm^3Hg (SD=686.4) with a tensed pelvic floor. With the stimulator turned on, the vector volume was 223.6 cm^3Hg (SD=374.3) with a relaxed pelvic floor and 542.0 cm^3Hg (SD=625.4) with a tensed pelvic floor (p=0.897 and p=0.252). With the stimulator turned off, the radial asymmetry was 29.3% (SD=12.3) with a relaxed pelvic floor and 22.0% (SD=11.4) with a tensed pelvic floor. With the stimulator turned on, the radial asymmetry reached 34.4% (SD=18.3) with a relaxed pelvic floor and 20.9% (SD=11.6) with a tensed pelvic floor (p=0.136 and p=0.759). Rectal compliance was 0.23 ml/mmHg (SD=0.23)

Table 3 Diameter of the External and Internal Anal Sphincter and Distance Between the Anal Mucosa and Symphysis with a Relaxed and Tensed Pelvic Floor

	SNS off (mm)	SNS on (mm)	p value
External anal sphincter (12 o'clock LP)	8.3 (2.9)	7.0 (2.2)	0.007*
External anal sphincter (3 o'clock LP)	8.7 (3.3)	7.0 (2.9)	<0.001*
Internal anal sphincter (9 o'clock LP)	3.3 (1.5)	2.7 (1.4)	<0.001*
Symphysis, relaxed	51.4 (13.5)	48.8 (14.0)	0.01*
Symphysis, tensed	46.5 (13.3)	43.4 (12.5)	0.036*

Mean values (SD), number of patients=14

LP lithotomy position

*p<0.05, statistically significant

Table 4 Intrarectal Volumes and Pressures at which Patients Perceive the Following Sensations: Volume/Pressure I—Perception Threshold, Volume/Pressure II—Defecation Urge, Volume/Pressure III—Maximum Tolerated Volume

	SNS off	SNS on	*p* value
Volume I (ml)	62.1 (43.3)	86.4 (50.6)	0.021*
Volume II (ml)	108.2 (68.1)	145.7 (74.5)	<0.001*
Volume III (ml)	148.9 (83.5)	188.2 (81.1)	<0.001*
Pressure I (mmHg)	34.9 (26.8)	33.6 (18.9)	0.835
Pressure II (mmHg)	47.6 (30.2)	49.1 (30.6)	0.778
Pressure III (mmHg)	53.3 (29.1)	60.5 (33.8)	0.198

Mean values and SD, number of patients=14

*$p<0.05$, statistically significant

with the stimulator turned off and 0.29 ml/mmHg (SD=0.21) with the stimulator turned on ($p=0.325$). All the above are mean values obtained from the 14 patients examined. The rectoanal inhibitory reflex was triggered in 13 of 14 patients with the stimulator turned off and in 14 of 14 patients with the stimulator turned on ($p=0.051$).

Continence and Quality of Life

Questioning the patients prior to implantation of the sacral nerve stimulator and 6 months after the intervention revealed marked improvement in both continence and quality of life. Regarding continence, patients showed a decrease in the defecation rate and incontinence episodes for solid and liquid stool and for gas 6 months after surgery (Tables 5 and 6). Patients also reported a more solid stool consistency, less fecal smearing, a longer warning period before defecation, improvement of discrimination, less need for additional care, less frequent use of pads, and fewer alteration of lifestyle due to fecal incontinence (Table 7). In accordance with these findings, the three incontinence scores used also showed a marked improvement of continence 6 month postoperatively (Table 8).

We were also able to detect a definite increase in quality of life 6 months after surgery by using the SF-36 questionnaire for health-related quality of life: patients showed improvement in physical functioning, vitality, and social functioning. The overall score disclosed an increase in the mental health-related quality of life. Assessment of the overall physical health-related quality of life revealed a tendency toward better results, but they were not statistically significant (Table 9).

Table 6 Improvement of Continence for Solid and Liquid Stool as Well as for Gas by Use of the Sacral Nerve Stimulator

		Number of patients with accordant finding (total number of patients=14)		*p* value
		Before Implantation	After Implantation	
Incontinence for solid stool	Never	5	11	0.016*
	Rarely	0	1	
	Sometimes	4	0	
	Weekly	1	0	
	Daily	4	2	
Incontinence for liquid stool	Never	0	3	<0.001*
	Rarely	0	3	
	Sometimes	3	6	
	Weekly	0	1	
	Daily	11	1	
Incontinence for gas	Never	2	6	0.002*
	Rarely	1	4	
	Sometimes	1	1	
	Weekly	1	1	
	Daily	9	2	

Never 0, *Rarely* <1/month, *Sometimes* <1/week, ≥1/month, *Weekly* <1/day, ≥1/week, *Daily* ≥1/day

*$p<0.05$, statistically significant

Discussion

We were able to verify that short-term SNS leads to contraction of the pelvic floor and influences rectal perception. The patients also showed a marked improvement in continence and quality of life and an uneventful course.

Regarding hypothesis 1 "SNS leads to contraction of the pelvic floor," we were able to show that turning on the stimulator decreases the diameters of the external and internal anal sphincters, thus causing them to approximate the normal values (external anal sphincter 5–10 mm and internal anal sphincter 1–3 mm, values in healthy subjects

Table 5 Reduction of Daily Defecation Rate

	Before implantation	After implantation	*p* value
Defecation rate (bowel movements per day)	7.9 (4.6)	4.1 (3.1)	0.001*

Mean values (SD), number of patients=14

*$p<0.05$, statistically significant

Table 7 Change in Continence Parameters by Use of the Sacral Nerve Stimulator (Total Number of Patients=14)

		Number of patients with accordant finding		*p* value
		Before implantation	After implantation	
Stool consistency	Normal/solid	0	5	0.012*
	Pasty	8	8	
	Liquid	6	1	
Fecal smearing	Never	1	2	0.008*
	During stress	1	8	
	Always	12	4	
Defecation urge	Normal	2	6	0.063
	Insecure	8	8	
	Missing	4	0	
Warning period	Normal	0	7	<0.001*
	Shortened	2	6	
	Missing	12	1	
Discrimination	Normal	2	8	0.016*
	Inadequate	6	4	
	Missing	6	2	
Need for additional care	Never	1	6	0.004*
	Sometimes	3	4	
	Always	10	4	
Wears pad	Never	0	2	0.031*
	Rarely	0	1	
	Sometimes	0	3	
	Daily	14	8	
Alteration of lifestyle	Never	0	1	0.008*
	Rarely	0	4	
	Sometimes	1	2	
	Weekly	0	1	
	Daily	13	6	
Drug intake	Yes	7	9	0.5
	No	7	5	

Never 0, *Rarely* <1/month, *Sometimes* <1/week, ≥1/month, *Weekly* <1/day, ≥1/week, *Daily* ≥1/day

*$p<0.05$, statistically significant

already published by our department).[27] There was also a decrease in the distance between the anal mucosa and the symphysis as a sign of pelvic floor elevation. These results are attributable to contraction or an increase in tension of the pelvic floor. In keeping with this is also the observed tendency toward higher resting and squeeze pressures with the stimulator turned on, but the difference is not statistically significant. This may be due to the small study size. Other studies support this result: Holzer et al. and Kenefick et al. found higher squeeze and resting pressures in the postoperative course than in the preoperative phase.[22,32]

Table 8 Improvement of Continence by Use of the Sacral Nerve Stimulator, as Demonstrated by the Three Incontinence Scores—CACP, Cleveland Clinic, and Kelly–Holschneider

	Before implantation	After implantation	*p* value
CACP score	3.0 (2.6)	10.0 (3.0)	<0.001*
Cleveland Clinic score	16.3 (3.1)	9.6 (5.9)	0.002*
Kelly–Holschneider score	3.1 (2.1)	8.9 (2.7)	<0.001*

Results of incontinence scores derived from the values in Tables 5 to 7; see Table 1 for assessment. Mean values (SD), number of patients=14

*$p<0.05$, statistically significant

Table 9 Change in Quality of Life Through SNS, as Determined by Using the SF-36 Questionnaire

	Before implantation	After implantation	*p* value
Physical functioning	42.9 (28.7)	57.1 (24.4)	0.009*
Role physical	26.8 (44.4)	42.9 (43.2)	0.108
Bodily pain	43.0 (30.3)	53.4 (25.7)	0.134
General health	39.2 (20.8)	48.9 (17.8)	0.116
Vitality	41.1 (14.7)	51.1 (18.2)	0.043*
Social functioning	41.1 (24.7)	61.6 (24.3)	0.008*
Role emotional	33.3 (47.1)	54.8 (46.4)	0.069
Mental health	49.7 (20.5)	62.3 (19.7)	0.072
Physical health (summary)	33.9 (12.7)	38.1 (9.6)	0.07
Mental health (summary)	37.3 (10.6)	44.6 (11.6)	0.042*

Mean values (SD), number of patients=14

*$p<0.05$, statistically significant

The fact that the described changes affect the internal anal sphincter (autonomically innervated) as well as the external anal sphincter and the pelvic floor (somatically innervated by the pudendal nerve) points to an involvement of both the autonomic and somatic nervous system. Stimulation at S3/S4 can affect efferent somatic nerves (pudendal nerve) and efferent parasympathetic nerves, but not efferent sympathetic nerves. Based on animal experiments,[33–35] however, stimulation of the parasympathetic nervous system would be expected to cause relaxation of the internal anal sphincter. This is not the case in our investigations. These results support the hypothesis of the so-called neuromodulation: The positive effect on continence achieved may be explained by a complex adaptive neural response to the stimulation. Apart from efferent components acting directly on motor neurons, the effect is also largely attributed to afferent signals that are triggered by stimulation of tension receptors in the pelvic floor and transmitted to higher centers in the spinal cord and brain. This in turn leads to modulation of all efferent impulses to the organ of continence.[22,26,36–39]

Regarding hypothesis 2 "SNS influences rectal perception," our study shows that, with the stimulator turned on, defined sensations (perception threshold, defecation urge, and maximum tolerated volume) are triggered only by higher volumes. On the other hand, there is no change in the concomitantly determined rectal pressure and rectal compliance. This suggests that SNS evokes rectal relaxation with a consecutively increased rectal volume without influencing rectal elasticity. The enhanced rectal capacity can help to improve continence during SNS. This may be attributed to the activation of afferent autonomic nerves of the rectum.[40,41] Attention should be called particularly to the defecation urge and the maximum tolerated volume being sensed only at higher filling volumes as the expression of a better rectal storage function during SNS.

These two verified hypotheses and the above results describe short-term changes achieved by turning the stimulator off and on in direct succession. This supplements hitherto published studies demonstrating long-term postoperative changes in the continence organ: increase of resting and/or squeeze pressure;[22,32,36,42] constant resting and squeeze pressures;[25,43] enhancement of rectal sensitivity;[32] higher volumes for the perception threshold, defecation urge, and maximum tolerated volume; and an increased rectal capacity.[36] All these results relate to the postoperative course. There have only been two studies thus far that directly compare patients with the stimulator turned on and off, but the intervals were markedly longer in each case (1 month on/off, $n=34$; 2 weeks on/off, $n=2$).[19,44] In addition, Leroi et al. describe long-term functional changes even after the actual stimulation period and attribute them to permanent neuromodulatory alterations.[19] We have now found that, even 6 months after surgery, marked morphological and functional changes occurred as soon as the stimulator was turned on, although it was set at a subsensory level of intensity.

The third hypothesis, "SNS improves continence and quality of life," is also confirmed by our study results. Our study includes a large number of incontinence parameters and three incontinence scores. The detected improvement involves nearly all parameters recorded as well as all three scores. Apart from the markedly reduced incontinence episodes, other functional changes we detected are also important factors associated with improving continence, particularly the longer warning period before defecation and the reduced number of daily bowel movements. Thus, our results also demonstrate a quality of life improvement, particularly a marked improvement of mental health, which underscores the psychosocial components of incontinence. These results coincide with those of other studies. In 2004, Matzel et al. published a study in Lancet that examined 35 patients with an implanted stimulator for fecal incontinence. Here too, the postoperative course was characterized by a reduction of incontinence episodes and an improvement in the ability to delay bowel movements. The quality of life was also improved.[20] More recent studies have also confirmed the reduction of incontinence episodes[18,19,21–24]

and the quality of life improvement[21–24] achieved by SNS. In a controlled randomized study published by Tjandra et al. in 2008, SNS reduced incontinence episodes and enhanced the quality of life, while conservative therapy failed to achieve any improvement at all.[25]

Apart from improving continence and quality of life, as demonstrated in our study, SNS is characterized by low-invasive implantation and an uneventful course such as the one seen in our patients. SNS is also financially favorable in comparison to other surgical methods.[45] We, therefore, advocate implantation of a permanent stimulator after successful test stimulation, particularly in view of the social stigma attached to fecal incontinence.

Conclusion

Our study demonstrates that short-term SNS improves pelvic floor contraction as well as rectal perception. These results support the hypothesis of neuromodulation in response to the stimulation of the sacral nerves S3/S4. Our patients also showed a marked improvement in continence and quality of life and an uneventful course. We, therefore, recommend SNS for the treatment of fecal incontinence in selected patients.

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J Gastrointest Surg (2010) 14:645–650
DOI 10.1007/s11605-009-1150-x

ORIGINAL ARTICLE

Safety and Feasibility of Laparoscopic Intersphincteric Resection for Very Low Rectal Cancer

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Received: 10 September 2009 / Accepted: 16 December 2009 / Published online: 22 January 2010

Abstract
Background Laparoscopic surgery has been reported to be one of the approaches for total mesorectal excision (TME) in rectal cancer surgery. Intersphincteric resection (ISR) has been reported as a promising method for sphincter-preserving operation in selected patients with very low rectal cancer.
Methods From July 2005 to December 2008, 35 patients with very low rectal cancer underwent laparoscopic TME with ISR. The results were compared retrospectively with those of previous open TME with ISR.
Results Conversion to open surgery was necessary in one (3%) patient. The median operation time was 293 min and median estimated blood loss was 40 ml. The pelvic plexus was completely preserved in 32 patients. There was no mortality. Postoperative complications occurred in three (9%) patients. The median length of postoperative hospital stay was 17 days. Macroscopic complete mesorectal excision was achieved in all cases. Complete resection (R0) was achieved in 34 patients. Clinical lymph node stage, operation time, and blood loss were significantly different between the laparoscopic group and open group, but the differences of other factors were not statistically significant.
Conclusions Laparoscopic TME with ISR is technically feasible and a safe alternative to laparotomy with favorable short-term postoperative outcomes.

Keywords Laparoscopic surgery · Total mesorectal excision · Intersphincteric resection · Low rectal cancer

Introduction

Laparoscopic approach offers some potential benefits over open surgery, including earlier return of bowel function, reduced postoperative pain, shorter hospital stay, and better cosmesis.[1] Laparoscopic surgery for rectal cancer is more complicated than laparoscopic colectomy, owing to its technical difficulty in the pelvis. Despite the procedural complexity, some studies have reported laparoscopic approach for total mesorectal excision (TME) with sphincter preservation for rectal cancer.[2–4] Our previous report also showed that laparoscopic surgery for rectal cancer is technically feasible.[5] We consider that laparoscopic surgery provides definite advantages both to patients in quick postoperative recovery and to surgeons in good view of the pelvic floor.

Abdominoperineal resection (APR) is the standard surgery for rectal cancer located 5 cm below the anal verge or 2 cm below the dentate line. However, quality of life after APR is unsatisfactory because a permanent stoma results in social limitations. Intersphincteric resection (ISR) has been reported as a promising method for sphincter-preserving operation in selected patients with very low rectal cancer to avoid a permanent stoma.[6–9] Recently, several studies have reported the long-term results after ISR in patients with low rectal cancer.[10–13]

Although laparoscopic rectal resection involves some procedural complexities and technical difficulties, ISR combined with laparoscopic approach could be achieved

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with high quality. Moreover, when ISR is carried out laparoscopically, it can be performed unwounded, except for covering ileostomy, by removing the resected rectum through the anus. However, there have been few reports on laparoscopic ISR.[14–16] The present study reports on 35 patients who were treated by a combination of laparoscopic TME and ISR. The results were compared retrospectively with those of previous ISR by laparotomy.

Methods

Patient Selection

From July 2005 to December 2008, 35 patients with very low rectal cancer underwent laparoscopic TME with ISR followed by hand-sewn coloanal anastomosis and diverting ileostomy. Preoperative staging was done by physical examination, colonoscopy with biopsy, abdominal and pelvic computed tomography (sometimes pelvic magnetic resonance imaging), chest radiography, and digital examination to evaluate fixation and location of tumor from the anal verge. This allowed us to determine which patients were candidate for laparoscopic procedure. In our institute, preoperative chemoradiotherapy (CRT) is given to patients with tumors staged T3/T4 and/or N1 according to the International Union Against Cancer (UICC) classification. A total dose of 45 Gy in 25 fractions over 5 weeks (1.8 Gy/day) is delivered to all pelvic fields with concurrent administration of oral 5′-DFUR at a dose of 800 mg/day for 5 weeks. In the present study, some patients could undergo sphincter-preserving operation because preoperative CRT achieved tumor downstage. Operation was performed 6–8 weeks after preoperative CRT. The clinical records and postoperative courses were collected for review.

Surgical Procedure

The surgical technique was standardized for both open and laparoscopic approaches. For the open procedure, a midline laparotomy was performed from the pubis to at least 5 cm above the umbilicus. For the laparoscopic approach, a five-port technique was employed, as we described previously.[5] Medial-to-lateral retroperitoneal dissection of the mesocolon and early division of the inferior mesenteric vessels were performed, which preserved the inferior mesenteric plexus and superior hypogastric plexus. We used an electronic cautery for precise dissection. The dorsal dissection was performed in the avascular plane between the mesorectum and the parietal pelvic fascia, with preservation of the hypogastric nerve, sufficiently down to the floor of pelvis. Next, lateral dissection was completed by recognizing and preserving the hypogastric nerve and inferior hypogastric (pelvic) plexus. Great care was taken to preserve the neurovascular bundle in the anterolateral dissection. The dissection was progressed to the endopelvic fascia and levator ani muscle. With transanal dissection, as the mucosa and internal anal sphincter were circumferentially incised, transanal intersphincteric dissection allowed connection with the laparoscopic dissection. The specimen was extracted through the anus. Reconstruction consisted of a hand-sewn coloanal straight anastomosis without creating colonic pouch. A diverting ileostomy was created in all cases. We evaluated the preservation of pelvic innervation by assessing the remaining autonomic pelvic nerves in intraoperative views after resection.

Statistical Analysis

We retrospectively compared clinical records and postoperative courses between the laparoscopic group and open group. The Mann–Whitney *U* test and Fisher's exact test or the chi-squared test was used to analyze the statistical differences between the groups. Statistical analysis was performed with the SPSS Statistical Software Package (version 11.0J, SPSS-Japan Inc., Tokyo, Japan). Differences were considered significant if the P value was <0.05.

Results

During the study period, 41 patients with very low rectal cancer underwent ISR. Six of the 41 patients underwent open TME with ISR because of the patients' preference in three cases and the necessity of lateral lymphadenectomy due to suspected lateral lymph node metastasis in three cases. Thus, the present study included 35 patients who underwent laparoscopic TME with ISR followed by hand-sewn coloanal anastomosis and diverting ileostomy. Of the patients, 21 were men and 14 were women. The median age of the patients was 61 years (range, 33–82 years). The median tumor size was 27 mm (range, 10–90 mm) and the distance from the dentate line was 1 cm (range, 0–3 cm). Eleven patients had clinical T1 tumors, 11 had clinical T2 tumors, 13 had clinical T3 tumors, and no patient had T4 tumors. Lymph node metastases were suspected in 17 patients. Preoperative CRT was performed in 11 patients.

Conversion to open surgery was necessary in one (3%) patient due to bleeding from the internal iliac vein. The remaining 34 patients completely underwent laparoscopic approach. The median operation time was 293 min (range, 195–456 min) and the median estimated blood loss was 40 ml (range, 0–740 ml). No patients required blood transfusion. The pelvic plexus was completely preserved in 32 patients. There was no mortality. Postoperative

complications occurred in three (9%) patients, including one with wound infection and two with obstructions, and they recovered with conservative therapy. There was no anastomotic leakage. Short-term urinary retention occurred in one patient. The median length of postoperative hospital stay was 17 days (range, 11–121 days). An ileostomy was closed in 31 patients after a median period of 123 days (range, 42–169 days), although it had not been closed in two patients with recurrent disease and in two patients undergoing postoperative chemotherapy.

The resected specimen after laparoscopic TME with ISR was submitted to histopathological evaluation. Macroscopic complete mesorectal excision was achieved in all cases. The median macroscopic distal resection margin was 15 mm (range, 5–45 mm). However, microscopic distal resection margin was 12 mm (range, 0–40 mm) and was positive in a single case. The median microscopic circumferential resection margin was 3 mm (range, 0.2–10 mm) and was positive (<1 mm) in a single case. The distal resection margin and lateral resection margin were microscopically positive in one patient. The location of positive resection margin was an area resected by transanal dissection, not by the technique of laparoscopic TME. Complete resection (R0) was thus achieved in 34 of 35 patients. The median number of lymph nodes harvested was 13 (range, 8–52). Lymph node metastases were present in 14 patients. According to the UICC classification, histopathologically complete response after neoadjuvant CRT (ypT0) was observed in two patients. There were 13 pathological T1 tumors, 12 T2 tumors, and eight T3 tumors. Pathological stage I was confirmed in 17 cases, stage II in two, stage III in 13, stage IV in one (T1N1M1: the patient had regional and lateral lymph node metastasis), and no cancer (histopathological findings showed complete response) in two.

Out of 14 patients with stage III or IV, 11 received postoperative chemotherapy, but two did not receive chemotherapy because of higher age. One patient with stage III underwent postoperative radiation therapy and chemotherapy due to positive resection margin (R1: microscopically both distal and lateral resection margin was positive) and died of recurrent disease (liver and bone metastasis). The median follow-up period was 19 months (range, 5–42 months), and no local recurrence was found. Two patients developed lung metastasis. One underwent lung resection, and the other received chemotherapy. The remaining 32 patients were still alive without recurrence.

On the other hand, 13 patients with very low rectal cancer underwent open TME with ISR between July 2004 and June 2005. From July 2005 to December 2008, six patients underwent open TME with ISR. A total of the 19 patients who underwent open ISR were compared with 35 patients who underwent laparoscopic ISR. Comparisons between the groups are shown in Table 1. Clinical lymph node stage, operation time, and blood loss were significantly different between the two groups, but the differences of other factors were not statistically significant.

Discussion

Laparoscopic surgery has been performed more often for the treatment of rectal cancer based on the advancement of laparoscopic surgical techniques. Laparoscopic TME is now performed in some institutions since it has been shown to be technically feasible and safe with successful oncologic resection and good short-term results.[2–4] However, there have been only a few reports on laparoscopic ISR,[14–16] and technical and oncological feasibility of this treatment was only reported by a single institution.[14,15] The current study aimed to show that laparoscopic TME with ISR is technically feasible and a safe alternative to laparotomy with favorable short-term postoperative outcomes.

Rectal cancer surgery presents major technical difficulties, especially in men, obese patients, and patients with large tumors. However, a magnified view obtained by laparoscopy provides more precise image of dissection plane covering the mesorectum and makes the preservation of the pelvic autonomic nerves easier even in a narrow pelvis. Laparoscopic surgery is also advantageous in sufficiently mobilizing the lower rectum from the lateral ligaments, pelvic floor, and vagina/prostate with good view, and even the dissection of the intersphincteric groove between the internal and external sphincter muscle can be performed exactly. When the rectal dissection is laparoscopically performed until the level of intersphincteric groove, the transanal intersphincteric dissection communicates easily with the dissection layer from above. Moreover, intracorporeal rectal transection and anastomosis within a narrow pelvis, which is one of the most difficult procedures of the laparoscopic TME, is not necessary in laparoscopic TME with ISR. Thus, laparoscopic TME with ISR would be beneficial to patients concerning the oncological quality of operation and the preservation of urinary and sexual function.

The quality of laparoscopic surgery for rectal cancer was enhanced by a standardized surgical procedure.[5] In the present study, a standardized technique of laparoscopic TME as well as careful patient selection by excluding large or fixed tumors by preoperative examination contributed to the low conversion rate. Tumor size was smaller in the laparoscopy group than in the open group, although the difference was not significant (P=0.098). There was no T4 tumor in both groups. No difference was found in clinical

Table 1 Comparison of Laparoscopy and Laparotomy

	Laparoscopy (n=35)	Laparotomy (n=19)	P value
Age (years)[a]	61 (33–82)	58 (28–67)	0.147
M/F	21/14	12/7	1.000
Tumor size (mm)[a]	27 (10–90)	35 (12–70)	0.098
Distance from the dentate line (cm)[a]	1 (0–3)	1 (0–3)	0.191
Clinical tumor stage[b]			0.197
Tis	0	1 (5%)	
T1	11 (31%)	3 (16%)	
T2	11 (31%)	4 (21%)	
T3	13 (37%)	11 (58%)	
T4	0	0	
Clinical lymph node stage[b]			0.001
N0	18 (51%)	10 (53%)	
N1	16 (46%)	2 (10%)	
N2	0	0	
Lateral lymph nodes	1 (3%)	7 (37%)	
Preoperative CRT	11	6	1.000
Operation time (min)[a]	293 (195–456)	360 (225–920)	0.002
Blood loss (ml)[a]	40 (0–740)	380 (90–3,500)	<0.001
Pelvic nerve preservation	32	16	0.425
Distal resection margin (mm)[a]	15 (5–45)	15 (5–30)	0.826
Lymph node harvest[a]	13 (8–52)	18 (8–64)	0.051
Complications	3	4	0.226
Wound infection	1	2	
Obstructions	2	1	
Anastomotic leakage	0	1	
Postoperative stay (days)[a]	17 (11–121)	17 (11–31)	0.656
R0 resection[c]	34	18	1.000
Distal margin (mm)[a]	12 (0–40)	13 (4–28)	0.627
Circumferential margin (mm)[a]	3 (0.2–10)	3 (0–10)	0.912
Pathological stage[b]			0.081
I	17 (48%)	9 (47%)	
II	2 (6%)	5 (26%)	
III	13 (37%)	3 (16%)	
IV	1 (3%)	2 (11%)	
Complete response	2 (6%)	0	
Anastomotic stricture	2	2	0.523
Recurrence	3	5	0.113

CRT chemoradiotherapy

[a] Values are median (range)

[b] UICC classification

[c] Complete microscopic resection

tumor stage, but clinical lymph node stage was more advanced in the open group than in the laparoscopy group. This is because we routinely perform lateral lymphadenectomy by open approach, when preoperative examinations show suspected lateral lymph node metastasis. Operation time was longer and estimated blood loss was higher in the open group than in the laparoscopy group in the present study. Operation time is generally longer in laparoscopic TME than in open TME,[14] but the opposite result was shown in the present study. This may be explained by the fact that the open group included nine (47%) patients who underwent lateral lymph node dissection, which is a time-consuming procedure. In contrast, the laparoscopic group underwent TME only, except for four patients (11%). Of the four patients, one patient requiring conversion to laparotomy due to bleeding from the internal iliac vein underwent lateral lymph node dissection, and pathological finding showed metastasis in the lateral lymph node. The other three patients underwent pick-up dissection of the lateral lymph node. Since no difference was observed in the quality of excision such as

distal tumor margin or circumferential resection margin between the two groups, laparoscopic ISR is considered technically and oncologically feasible. Furthermore, since the complication rate and postoperative hospital stay were similar between both groups, laparoscopic ISR is a safe alternative to laparotomy with favorable short-term postoperative outcome.

In the present study, postoperative bladder function was satisfactory because short-term urinary retention occurred only in one patient despite that a urinary catheter was usually removed on postoperative day 2 or 3. However, this study was not estimated exactly because the International Prostatic Symptom Score was not used to estimate bladder function and the laparoscopic group was not compared with the open group. Sexual function was not evaluated due to lack of research.

ISR was introduced as an ultimate surgical treatment for sphincter preservation and excision for extremely low rectal cancer.[6] While there is a potential risk of increasing local recurrence, some studies have reported that early results and local recurrence rates after ISR are satisfactory in patients with low rectal cancer.[6–9] There have been only four studies on long-term oncologic outcomes after ISR in large series in which local recurrence and 5-year overall survival rates after ISR were reported as 2–6.6% and 81–91%, respectively.[10–13] Akasu et al.[13] reported that T3 tumors and positive resection margin were significantly associated with local recurrence after open ISR. No local recurrence has occurred in the present study, but a longer follow-up is necessary as the median follow-up period was still short (19 months), despite that local recurrence develops within 2–3 years in most cases.[9–12] In the present study, 77% (10 out of 13) of patients with T3 tumor received preoperative CRT. For T3 tumors, preoperative CRT could reduce the risk of local recurrence.[10] Furthermore, we consider that preoperative CRT is expected to increase the chance of sphincter-preserving surgery following tumor downstaging. Rullier et al.[17] reported that sphincter-saving resection after preoperative chemoradiation led to good local control and good functional results in patients with T3 low rectal cancers that, otherwise, would have been treated with APR. We have also reported previously that laparoscopic TME with preoperative CRT is a safe and feasible procedure.[18,19]

There are important limitations of this study to be noted. First, this is not a randomized study; a prospective randomized study is needed to demonstrate that laparoscopic TME with ISR is truly a feasible procedure for very low rectal cancer. In addition, a longer follow-up is required to assess the incidence of local recurrence, cancer-free survival, and functional outcome. Second, simple comparison between open and laparoscopic ISR is difficult, particularly because of the different rate of lateral lymphadenectomy between both groups. However, we believe that our study suggests that, with careful case selection and expertise, laparoscopic TME with ISR for very low rectal cancer is a safe and feasible procedure with favorable short-term postoperative outcome.

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J Gastrointest Surg (2010) 14:651–657
DOI 10.1007/s11605-010-1155-5

ORIGINAL ARTICLE

Avoiding or Reversing Hartmann's Procedure Provides Improved Quality of Life After Perforated Diverticulitis

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Received: 25 September 2009 / Accepted: 4 January 2010 / Published online: 2 February 2010

Abstract
Introduction The existing literature regarding acute perforated diverticulitis only reports about short-term outcome; long-term following outcomes have not been assessed before. The aim of this study was to assess long-term quality of life (QOL) after emergency surgery for perforated diverticulitis.
Patients and Methods Validated QOL questionnaires (EQ-VAS, EQ-5D index, QLQ-C30, and QLQ-CR38) were sent to all eligible patients who had undergone emergency surgery for perforated diverticulitis in five teaching hospitals between 1990 and 2005. Differences were compared between patients that had undergone Hartmann's procedure (HP) or resection with primary anastomosis (PA) and also compared to a sex- and age-matched sample of healthy subjects.
Results Of a total of 340 patients, only 150 patients (44%) were found still alive in July 2007 (median follow-up 71 months). The response rate was 87%. In patients with PA, QOL was similar to the general population, whereas QOL after HP was significantly lower. The presence of a stoma was found to be an independent factor related to worse QOL. The deterioration in QOL was mainly due to problems in physical function and body image.
Conclusions Survivors after perforated diverticulitis had a worse QOL than the general population, which was mainly due to the presence of an end colostomy. QOL may improve if these stomas are reversed or not be performed in the first place.

Keywords Perforated diverticulitis · Quality of life · Hartmann's procedure · Primary anastomosis

Meeting presentation Annual Meeting of the Dutch Society of Surgery. Long-term quality of life after emergency surgery for perforated diverticulitis. 15th May 2009, Veldhoven, The Netherlands

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Introduction

Diverticulitis is one of the most common diseases related to the gastrointestinal tract in western countries. In The Netherlands, 14,000 new cases have been estimated for 2006, which equals an incidence of 80/100,000 patients each year.[1] In spite of this, only 2% of these patients who present for urgent evaluation have acute perforation due to diverticulitis.[2]

Emergency surgery for perforated diverticulitis is associated with substantial morbidity and mortality, regardless of selected strategy.[3] For many surgeons, Hartmann's procedure (HP) still remains the favored option, but it leaves the patient with an end colostomy. It is well known that patients with stomas may face both physical and psychological difficulties.[4] Reversal of HP is also associated with substantial morbidity and even mortality.[5] This is one of the main reasons why HP is never reversed in about half of patients.

Improvements in surgical and radiological intervention techniques and progress in the management of peritoneal

sepsis have led to an increasing interest in colonic resection with primary anastomosis (PA). Although not proven in randomized controlled trials, PA seems not to be inferior to HP in terms of postoperative complications and mortality.[3, 6–8] In these patients, a stoma can be withheld or, in case of a defunctioning loop ileostomy, reversed easily and quickly.[5]

The existing literature regarding perforated diverticulitis only reports on short-term outcome such as mortality and postoperative complications. Patient-orientated outcomes, such as quality of life (QOL), have never been assessed previously in patients needing emergency surgery for acute perforated diverticulitis. Quality of life is increasingly recognized as a crucial factor when assessing clinical outcomes after surgical interventions as it presents a patient's perspective, which is obviously a key outcome in clinical decision-making. To provide more data from a patient's perspective, the present study evaluates the long-term functional and health-related QOL outcomes of patients after emergency surgery for acute perforated diverticulitis. QOL will be examined in relation to surgical technique (HP or PA), surgeon's experience in colorectal surgery, severity of the primary disease, and patients' characteristics.

Patients and Methods

A cohort of 340 consecutive patients had undergone emergency surgery for perforated diverticulitis between January 1990 and December 2005 at the surgical departments of the academic and the four major teaching hospitals of Rotterdam, The Netherlands (Erasmus University Medical Centre, Ikazia Hospital, Medical Centre Rijnmond-Zuid (formerly St. Clara Hospital and Zuider Hospital), and St. Franciscus Gasthuis Hospital). Patients were selected from computerized surgery registration databases using the search codes: exploratory laparotomy, diverticulitis, perforated hollow viscus, Hartmann's procedure, left hemicolectomy, sigmoid resection, low anterior resection. Using this searching strategy, a complete overview of all patients presenting at the surgical units of the hospitals mentioned above was obtained, as all patients with acute perforated diverticulitis undergo emergency surgery. The indications for surgery were clinical signs of diffuse peritonitis or presence of septic status with acute abdominal pain, free gas on plain abdominal radiography, or specific findings for perforated diverticulitis at ultrasonography or computerized tomography (CT). The type of surgical procedure (HP $n = 238$; PA $n = 93$; suture repair $n = 9$) was left to the discretion of the surgeon on call. There were no laparoscopic emergency operations performed during the study period.

Follow-up of all patients was conducted until July 2007. Data regarding the patients' course after initial hospital discharge was gathered from the hospitals' medical reports and by telephone inquiry from the patients themselves or when necessary, the patient's direct relatives and general practitioner. At 1 July 2007, 150 patients were still alive (HP $n = 90$; PA $n = 58$; suture repair $n = 3$). Ten patients were lost in follow-up as they moved abroad ($n = 3$) or their home addresses were not available ($n = 7$). Validated questionnaires were sent by post to all 150 eligible patients after they were asked by phone to participate. The response rate was 87% (131 patients).

In order to assess long-term QOL, the patients filled in the EuroQol EQ-VAS, the EQ-5D index, and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR38 questionnaires. The EQ-VAS is a single-item visual analog scale (VAS), ranging from 0 "worse imaginable health state" to 100 "best imaginable health state." The EQ-VAS represents the "value" of the current health state from a patient perspective. Next to the EQ-VAS, the patients classify their current health state using the five items of the EuroQol EQ-5D. This classification can be transformed to a so-called index score representing "the societal value" of the health state. Such societal value represents the value the general public attaches to current health state of the patient.[9]

Disease-specific QOL was measured according to the official scoring procedures for the EORTC QLQ-C30 and EORTC QLQ-CR38 questionnaires. Both were originally developed to assess the QOL of cancer patients from a patient's perspective.[11] Other than the EuroQol, the outcomes of the EQRTC questionnaires are multidimensional. EORTC QLQ-C30 contains 30 items that can be computed in five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales, and six single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties).[12]

The EORTC QLQ-CR38 is subdivided into two functional scales (i.e., body image and sexual functioning), seven symptom scales (micturition problems, gastrointestinal tract symptoms, chemotherapy side effects, defecation problems, stoma-related problems, and male and female sexual problems), and three single-item measures (sexual enjoyment, weight loss, and future perspective).

The validity and reliability of both the EORTC QLQ C30 and QLQ-CR38 have been established in Dutch patients with colorectal cancer.[11] In both questionnaires, scores are summed within scales and rescaled from 0 to 100. A higher score indicates better functioning, future perspective, and a lower level of symptomatology.

Differences in QOL were determined and compared between patients that underwent HP or PA. Both groups were also compared to a sex- and age-matched community-based sample of healthy people in The Netherlands.[10]

Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney test. Differences in QOL between the two surgical groups were determined with multivariate logistic regression analysis, adjusting for age, gender, American Society of Anesthesiologist (ASA) classification, Hinchey score, and the presence of a stoma. These variables were a priori hypothesized as potential confounders based on literature and/or significant clinical variables in univariate analysis. Differences were considered statistically significant at a two-tailed p value of <0.05.

Results

Patient characteristics regarding type of procedure and clinical data are listed in Table 1. Responders were similar to the nonresponders regarding gender, age, and surgical procedure. Patients that had undergone HP had significant higher ASA and Hinchey scores during primary surgery compared to patients that underwent PA ($p < 0.01$ and $p = 0.04$, respectively). PA was more frequently performed by specialist colorectal surgeons ($p = 0.03$). At time of the questionnaire, 30 HP patients (39%) still had an end colostomy. Two PA patients still had a loop ileostomy (4%). The median duration of time interval between the operation and the questionnaire was 71 months (range 23–205 months).

The mean scores and ranges of the EQ-VAS and EQ-5D index are presented in Table 2. From the patient perspective, the mean general QOL score (EQ-VAS) was better after PA compared to HP. Also from the social perspective, the mean EQ-5D index score was better in patients after PA. In patients who had undergone PA, the EQ-VAS and EQ-5D index score was similar to that of the general population. The patients who had undergone HP had a significantly lower EQ-VAS and EQ-5D scores compared to the sex–age-matched general population (EQ-VAS $p < 0.01$; EQ-5D $p = 0.02$).

The presence of a stoma was found to be an independent factor related to the QOL, with patients without a stoma having a better QOL (EQ-VAS $p = 0.03$; EQ-5D $p = 0.04$). When assessing a subgroup containing patients after HP who had undergone restoration of bowel continuity ($n = 46$), differences in QOL from the patients perspective and the social perspective were no longer significant compared to the general population and the patients after PA.

No difference in QOL was found between patients who were operated by an experienced colorectal surgeon or a general surgeon. There was no correlation between Hinchey scores and QOL scores. Higher ASA classifications were associated with a lower QOL (EQ-VAS $p = 0.04$; EQ-5D $p = 0.01$). ASA classification and type of surgery were significantly related to QOL in bivariate analyses but were not found to be significant in multivariate analysis. Only the presence of a colostomy was found to be an independent predictor for lower QOL (EQ-VAS odds ratio 2.4; 95% CI 1.2 to 4.8; $p = 0.03$) after multivariate logistic regression analysis.

Scores of the EORTC QLQ-CR30 and the QLQ-CR38 for the patient groups are presented in Tables 3 and 4. Differences between HP and PA were found on five scales. PA patients had significantly higher scores with regard to global health status, physical function, fatigue, dyspnea,

Table 1 Baseline Characteristics of the Responders

	Primary Surgery		
	HP	PA	Suture repair
Numbers of patients	76	53	2
Age	62	59	56
Length of follow-up (months)	72	69	134
Male/female (%)	52/48	40/60	50/50
Patients with stoma[a]	30 (39%)	2 (4%)	0 (0%)
ASA I/II/III/IV (%)[a]	25/28/33/14	41/34/17/8	100/0/0/0
Hinchey I/II/III/IV (%)[a]	24/12/52/12	23/43/26/8	50/0/50/0
MPI < 26/MPI = 26	93/7	86/14	100/0
Reintervention (%)[b]	19	13	100
Specialist colorectal surgeon[a]	41%	62%	50/50

Data are median numbers with percentages in parentheses, unless otherwise specified. HP=Hartmann procedure, *P*=primary anastomosis., ASA= American Society of Anaesthesiologist classification, MPI=Mannheim peritonitis index.

a=PA vs. HP: P < 0.05; b=Reinterventions were defined as radiological-assisted percutaneous drainage of abdominal or pelvic abscess, open abdominal wound management or reoperation for ongoing sepsis, abdominal abscess, evisceration, anastomotic leakage or stoma-related complications.

Table 2 General Quality of Life Scores

	HP	PA	Population
EQ-VAS	65 (20-100)	74 (10-100) [a]	79 (68-87) [b]
EQ-5D index	67 (-18-100)	77 (67-93) [a]	77 (67-92) [b]

Data are mean scores with ranges in parentheses. EQ-VAS=Quality of life from the patient perspective, EQ-5D index=Quality of life from the social perspective. HP=Hartmann procedure, PA=primary anastomosis. Population=a sex- and age-matched community-based sample of healthy Dutch persons.

a=PA vs HP: $p < 0.05$; b=Population vs. HP: $p < 0.05$.

and body image compared to HP patients. The QOL from the patient perspective (EQ-VAS) was affected by the presence of physical function problems and body image problems ($p < 0.01$ and $p = 0.04$, respectively). Global health status, physical function, fatigue, and body image were predictors of QOL in social perspective (EQ-5D) (global health status, physical function, and fatigue, all $p < 0.01$; body image $p = 0.04$). Again, after assessing the patients who had undergone HP followed by restoration of bowel continuity, the EORTC QLQ-CR30 and QLQ-CR38 scores were not significantly different compared to those of patients that had undergone PA.

Discussion

The present study compared long-term QOL among patients that underwent HP and PA for acute perforated diverticulitis. The QOL outcomes were also compared to the general Dutch population. Survivors from acute perforated diverticulitis reported worse QOL compared to the Dutch population. QOL in patients who had undergone HP was lower compared to patients who underwent PA, both from the patient's and a social perspective. After reversal of HP, this difference disappeared, but HP reversal was performed in only 61% of the patients. QOL in patients after perforated diverticulitis was mainly influenced by the presence of a stoma postoperatively.

Functional aspects and QOL of survivors have become increasingly important for patients with perforated diverticulitis because survival after emergency surgery for perforated diverticulitis is poor, both in the short and long terms.[13] Previously, we described the long-term survival after perforated diverticulitis.[13] The 5-year mortality after perforated diverticulitis was approximately 50%. The main reason for this observation was the poor general condition of the patients. Almost half of the patients that presented with acute perforated diverticulitis were classified ASA III or IV, and one third was older than 75 years of age.[13] It is stated before that the incidence of perforated diverticulitis is highest in elderly patients, suffering from multiple comorbidities as indicated by a higher ASA classification.[14] These factors are known to be correlated with mortality. Direct postoperative mortality after perforated diverticulitis can increase to 40% in patients of older age.[15] It is therefore not surprising that this group of patients have a poor prognosis in the short and long term.

QOL of patients is also important for surgeons when making a decision about the strategy of primary surgery. The optimal surgical treatment of perforated diverticulitis is still a matter of debate; neither PA nor HP has been proven the superior surgical strategy in terms of mortality and

Table 3 Disease Specific Quality of Life Scores (EORTC QLQ-C30)

	HP		PA	
	Mean	Median (range)	Mean	Median (range)
Physical function [a]	66	67 (0-100)	79	87 (13-100)
Role function	70	92 (0-100)	76	100 (17-100)
Emotional function	77	92 (0-100)	81	92 (0-100)
Cognitive function	78	83 (17-100)	85	100 (17-100)
Social function	75	83 (0-100)	76	89 (0-100)
Global health status [a]	69	71 (14-100)	79	86 (14-100)
Fatigue [a]	64	67 (0-100)	76	89 (0-100)
Nausea/vomiting	92	100 (33-100)	94	100 (50-100)
Pain	74	100 (0-100)	79	100 (0-100)
Dyspnoea [a]	65	67 (0-100)	80	100 (0-100)
Sleep disturbance	70	100 (0-100)	67	67 (0-100)
Appetite loss	85	100 (0-100)	85	100 (0-100)
Constipation	86	100 (0-100)	77	100 (0-100)
Diarrhea	87	100 (0-100)	87	100 (0-100)
Financial worries	85	100 (0-100)	91	100 (0-100)

A high subscale score indicates low distress and good functioning. HP=Hartmann procedure, PA=primary anastomosis.

a=PA vs HP: $p < 0.05$.

Table 4 Disease Specific Quality of Life Scores (EORTC QLQ-CR38)

	HP		PA	
	Mean	Median (range)	Mean	Median (range)
Micturition problems	75	78 (0-100)	78	78 (22-100)
Gastrointestinal problems	82	87 (13-100)	81	87 (13-100)
Weight loss	86	100 (33-100)	93	100 (33-100)
Body image [a]	72	85 (0-100)	80	89 (0-100)
Defaecation problems	86	90 (43-100)	89	95 (48-100)
Stoma problems	73	76 (0-100)	81	81 (81 – 81)
Chemo side effects	82	89 (33-100)	83	100 (33-100)
Sexual function	21	17 (0-67)	20	17 (0-67)
Sexual enjoyment	48	33 (0-100)	58	67 (0-100)
Male sex problems	61	67 (0-100)	69	100 (0-100)
Female sex problems	86	100 (17-100)	81	83 (33-100)
Future perspective	64	67 (0-100)	74	67 (0-100)

A high subscale score indicates low distress and good functioning. HP=Hartmann procedure, PA=primary anastomosis.

a=PA vs HP: $p < 0.05$.

morbidity. Because the impairment of function that may occur after different operations varies considerably, an assessment of QOL for each type of surgical procedure is becoming an essential principle to follow in a successful healthcare system.[16] A very small number of studies have evaluated QOL in patients with (complicated) diverticulitis, but the literature is diverse and frequently based on heterogeneous pathologies. The present study is the first to assess patient's long-term QOL after emergency surgery for acute perforated diverticulitis.

One study used questionnaires to examine whether diverticular disease has an impact on QOL. The authors suggested that the lower QOL scores found in diverticulitis patients compared to healthy controls could be useful in decision making and selection of patients for elective surgical treatment.[17] Two studies assessed long-term QOL after laparoscopic or open sigmoid resection for uncomplicated diverticulitis. Both found no significant differences between the two surgical techniques.[18, 19] A recent study comparing two surgical strategies for treatment of complicated diverticular disease showed no difference in QOL in patients after PA or HP.[20] Unfortunately, this study was performed in a heterogeneous group of patients varying from emergency surgery for diverticular peritonitis to elective laparoscopic surgery in patients failing conservative treatment of diverticulitis. A recent study of quality-adjusted life-years after surgery for diverticular peritonitis concluded that PA was superior to HP, unless the risk of postoperative complication was higher than 40%.[21] The conclusions were based on decision analysis techniques for a hypothetical 65-year old, with the use of so-called utilities (a measure of the patient's or surgeon's relative preference for each individual outcome) to calculate. Unfortunately, there are no available published utilities specifically for diverticular disease, and therefore, many of the used utilities arose from studies assessing other colorectal diseases, small or dated studies, expert judgment, and assumptions. Given the state of imperfect evidence and the high degree of uncertainty, the conclusion that PA was superior to HP in terms of quality-adjusted life expectancy is at least doubtful.

This study, however, included only patients with acute perforated diverticulitis and supports the conclusion that PA is superior to HP in terms of QOL. The indications for surgery were clinical signs of diffuse peritonitis or presence of septic status with acute abdominal pain or specific findings for perforated diverticulitis at radiographic investigations. The decision for surgical management was made by the surgeon on call, and not all patients had undergone preoperative CT-scanning. Therefore, some patients showed Hinchey I or II perforated diverticulitis at surgery. It is now recognized that patients with small, contained perforations, who are not systemically ill can be treated initially with antibiotics alone or by CT-guided percutaneous drainage.[22] In this study, all patients that underwent emergency surgery for acute perforated diverticulitis were examined. Patients underwent either HP or resection with PA.

QOL in patients who underwent HP and PA were compared after a median of 71 months after primary surgery using the EQ-VAS, EQ-5D, and QLQ-C30 and QLQ-CR38. These questionnaires have proven to be efficient and reliable tools for establishing the health status within the Dutch community.[12, 23] General QOL scores were significantly lower in patients that had undergone HP compared to patients after PA. HP patients were associated with lower physical performances mainly due to a lower physical function and more complains of fatigue. They also showed a diminished body image compared to PA patients.

QOL of patient after PA was comparable with the general population both from the patient's and societal

perspective. Although not significant, QOL from the patient's perspective (EQ-VAS, Table 2) in PA patients was lower than the general Dutch population. This might not be so much a difference in perspective as it is a difference in the methods: the societal perspective of the EQ-5D is based on "time trade off" (TTO), and the patient perspective is based on a VAS. TTO is a more conservative valuation of burden of disease than VAS.[24] Furthermore, the EQ-5D societal perspective is known to produce a ceiling effect.[25] This could explain why EQ-VAS remained significantly higher in PA patients than HP patients, whereas EQ-5D did not, after multivariate analysis.

Patients that had undergone HP and subsequent reversal of their end colostomy in a second operation showed comparable QOL outcomes to patients that had undergone PA and the general population. HP reversal was performed in only 61% of the patients, which is in reflective of the literature.[26] It has been stated previously that patients with a stoma may face many difficulties both physical and psychological.[4] It is known that patients with direct intestinal continuity after surgery for colon cancer showed better QOL scores than those who received an end colostomy.[27] Also, when having a stoma, reversal of it can result in significant improvements in global QOL and physical and social function.[28] In the present study, patients without an end colostomy (PA) and the HP patients who had their stoma reversed showed similar QOL scores from a social perspective to the general population, whereas patients with an end colostomy (HP without reversal) showed a worse QOL. QOL was independently related to body image problems, e.g., the presence of a stoma.

In the light of body image problems, the use of minimally invasive treatment strategies for perforated diverticulitis may be an interesting development. Although its exact role is still unclear, several studies have shown excellent results in treatment of patients with peritonitis due to perforated diverticulitis by laparoscopic peritoneal lavage and drainage.[29–31] Compared to HP or PA, laparoscopic lavage and drainage seems to have a lower morbidity and mortality rate. And in most patients a subsequent elective resection is probably unnecessary so a stoma can be avoided.[30, 31] As the presence of a stoma plays an important role in QOL in the patients after perforated diverticulitis, laparoscopic procedures might not only appear to be superior over HP and PA in the short term (postoperative morbidity and mortality) but also in the long-term (QOL). Future comparative studies must confirm these statements.

Although QOL was mainly affected by body image problems, it is also important when interpreting the QOL scores to consider that the outcomes are dependent on patient's preoperative expectations. Fear or ignorance of the long-term consequences of the operation is associated with lower QOL.[32] Optimistic and well-informed patients may be more resistant to the negative influence of limitations (caused by their stoma) on their QOL. Surgeons, with support from the stoma care therapist and the multidisciplinary team, can anticipate this by offering appropriate education regarding a colostomy. Ideally, education should start preoperatively so patients require less time and have fewer problems with their rehabilitation.[33] When a colostomy becomes necessary, modern stoma appliances are so effective that most patients with a colostomy can enjoy normal lives. Engel et al. who reported that patients after an abdominal perineal resection have a consistently lower quality of life stated that 60% of the patients in their sample were poorly informed about stoma irrigation techniques.[34] This underlines the importance of instruction and education by stoma care therapists on colostomy care and washout, enabling more bowel control. In patients with acute perforated diverticulitis, preoperative counseling is not possible, as these patients require immediate surgery. Postoperative counseling of the patient (and family) is therefore very important to obtain better control of their bowel function and hence improve long-term outcome.

General health prior to surgery is also associated with postoperative QOL. In general, patients with more than one comorbid condition report the poorest level of QOL.[35] It is known, for example, that neurological comorbidities, like cerebral vascular accident or multiple sclerosis, may be a reason for stoma care problems, causing lower quality of life.[36] Patients with higher ASA classifications (multiple comorbidities) experience more functional limitations and show a lower QOL life than ASA I patients.[32] In this study, patients who underwent HP had significant higher ASA classifications and Hinchey scores prior to initial surgery compared to patients after PA. Therefore, it seems that the more severely affected and high-risk patients underwent HP. These patients appeared to have lower postoperative QOL scores than patients after PA and the general Dutch population. To assess whether the lower QOL was caused by differences in patient's characteristics and severity of disease scores (selection bias), a multivariate analysis was performed. After adjusting for the differences between the groups, QOL remained worse after HP compared to PA.

In conclusion, survivors after perforated diverticulitis had a worse QOL compared to the general Dutch population, which is mainly related to the presence of an end colostomy. When such stoma can be avoided (PA) or reversed, the QOL in these patients may improve.

Acknowledgments We thank E. van der Harst and P.P.L.O. Coene of the Maasstad Hospital, W.F. Weidema of the Ikazia Hospital and G. H.H. Mannaerts of the St. Franciscus Gasthuis, all in Rotterdam, The Netherlands and J.C. Oliver of the Groote Schuur Hospital in Cape Town, South Africa for their contributions in the production of this manuscript.

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J Gastrointest Surg (2010) 14:658–663
DOI 10.1007/s11605-010-1157-3

ORIGINAL ARTICLE

Laparoscopic Colectomy for Crohn's Colitis. A Large Prospective Comparative Study

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Received: 28 October 2009 / Accepted: 4 January 2010 / Published online: 2 February 2010

Abstract
Introduction The purpose of this study was to compare short-term outcomes of laparoscopic (LC) vs open colectomy (OC) in patients with Crohn's colitis.
Materials and Methods We collected data on all patients undergoing colectomy for primary or recurrent Crohn's disease confined to the colon from July 2002 to August 2008. Patient and disease-specific characteristics and perioperative and short-term postoperative outcomes were prospectively collected and analyzed.
Results A total of 125 patients underwent colectomy during the study period, 55 (44%) LC. There were six conversions (10.9%). Median operative time was shorter in the LC group (212 min, interquartile range (IQR) 180–315 LC vs 286 min, IQR 231–387 OC, $p=0.032$). Estimated blood loss was less for the LC group (100 ml, IQR 90–250 LC vs 250 ml, IQR 100–400 OC, $p=0.002$). Earlier return of bowel function was noted in the LC group (3 days vs 4 days, OC). Length of post-op stay was shorter in the LC group (6 days, IQR 5–8 vs 8 days, IQR 6–10 OC, $p=0.001$). There was one death in the OC group. Postoperative complications occurred in eight (14.5%) LC patients vs 16 (22.9%) OC. Disease recurrence rate was 16%, 10.9% LC and 20% OC, respectively.
Conclusions Laparoscopic colectomy is a safe and effective technique in the hands of experienced surgeons. Benefits of laparoscopic colectomy in Crohn's disease include reduced operative blood loss, quicker return of bowel function, and shorter hospital length of stay.

Keywords Crohn's disease · Laparoscopic surgery · Surgical outcome

Introduction

Crohn's disease patients, especially with colonic involvement, are considered poor laparoscopic candidates due to the use of aggressive and often morbid medical management that increases the risk of postoperative complications and the presence of abscesses, phlegmon, adhesions, and a markedly inflamed and friable mesentery. Furthermore, a large percentage of patients with Crohn's disease has a history of previous laparoscopic or open abdominal operations making laparoscopy often complex and time consuming. With advances in laparoscopic colon and rectal surgery and growing experience with laparoscopic surgery for Crohn's disease, especially ileocolic resection, the indications for laparoscopic surgery in Crohn's disease have been steadily expanding over the past decade. While the indication for surgical intervention has not changed, the timing for colectomy in Crohn's colitis has been significantly affected by advances in medical management of Crohn's disease with the introduction of immunomodulators and biologic agents in the late 1990s.

A number of reports, including two prospective randomized clinical trials,[1,2] have been published describing the

Poster presented at the 50th Annual Meeting of the Society for Surgery of the Alimentary Tract during Digestive Disease Week. May 30–June 3, 2009
Chicago, IL

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advantages of laparoscopic surgery over traditional surgery in the treatment of Crohn's disease. There have been three meta-analyses[3–5] demonstrating the benefits of a laparoscopic approach in the context of decreased morbidity, shorter hospital stay, earlier return of bowel function, and decreased intraoperative blood loss. However, the majority of the studies included in these meta-analyses are based on disease located in ileocolic or ileal regions. There are very little data that address the role of laparoscopic surgery for Crohn's disease of the colon. Given the understanding that Crohn's disease at different anatomical sites may pose distinct anatomic, physiologic, and technical challenges, a thorough analysis of surgical outcomes of laparoscopic colectomy (LC) is needed.

The results of laparoscopic colectomy in Crohn's colitis as well as the risk of recurrence have been studied only in one single institution study reported in literature.[6] The aim of our study is to present our experience with the largest reported prospectively collected series of laparoscopic vs open colectomy (OC) cases in consecutive patients with Crohn's colitis refractory to medical management.

Materials and Methods

All patients undergoing laparoscopic or open colectomy for Crohn's colitis at our institution between July 2002 and August 2008 were prospectively entered into an IRB-approved Inflammatory Bowel Disease database. Information was drawn from the database and supplemented by direct chart review and operative notes as needed. Patients undergoing resection of all or any part of the colon and/or rectum were included in the study. Patients undergoing ileocolic resection and patients with a diagnosis of ulcerative colitis or indeterminate colitis were excluded.

Both cohorts were compared for age, gender, body mass index (BMI), duration of disease, corticosteroid-based therapy, comorbidities, prior abdominal surgery, indication for surgery, and type of surgery performed. Intraoperative and postoperative parameters included: operative time, estimated blood loss, return of bowel function (determined as passage of flatus or stool per anus or ostomy) and length of postoperative stay. Morbidity, mortality, and recurrence rates were analyzed as postoperative outcomes. Recurrence was defined as any endoscopic or radiological evidence of active Crohn's disease anywhere in the gastrointestinal tract. Recurrences requiring surgical intervention were recorded.

All procedures were performed by the two surgeons (RDH and AF) at the University of Chicago Medical Center. Discharge criteria were identical for both groups and included tolerance of solids, passage of flatus, adequate pain control, and independent ambulation. Data were analyzed using intent to treat analysis; cases initiated laparoscopically were analyzed in the LC group regardless of whether or not conversion was required.

Statistical Analysis

Comparisons of the LC and OC groups were performed using Chi-square or Fisher's exact tests with respect to categorical data and using the Wilcoxon rank-sum test with respect to continuous quantitative data. Parametric data were reported as means with standard deviation, and nonparametric data were reported as medians with interquartile range (IQR). A level of alpha <0.05 was used to establish statistical significance for p values. Rate of recurrence was analyzed using the Kaplan–Meier method and compared using the log-rank test.

Results

One hundred and twenty-five consecutive patients underwent colectomy between August 2002 and July 2008 and were included in the study. A total of 55 patients were in the LC group and 70 in the OC group. Groups were similar for age, gender, and duration of disease (Table 1). There was no statistical difference in the percentage of patients on corticosteroid-based therapy at the time of surgery (40% LC vs 32.9% OC, $p=0.456$). LC patients were less likely to have undergone a previous abdominal surgery (34.5% LC vs 65.7% OC, $p<0.001$) but had higher BMI (25.0±6.5 LC vs 22.9±5.1 OC, $p=0.028$).

The groups were also comparable in terms of comorbidities. Four patients in the LC group had obstructive airway disease vs two patients in the OC group. There were no patients with history of valvular heart disease in the LC group and three in the OC. Each group had one patient with coronary artery disease. Three patients in each group had type 2 diabetes, and two patients in the LC group vs four in the OC group had a history of deep vein thrombosis or pulmonary embolism. None of these differences were statistically significant.

Table 1 Patient Characteristics

	Laparoscopic	Open	p value
Total patients	55	70	
Mean age at surgery (SD)	40.0 (±13.8)	40.7 (±16.4)	
Number of males (%)	20 (36.4)	33 (46.5)	0.275
Months of disease (SD)	149.1 (±98.9)	166.5 (±125.5)	
Steroid use (%)	22 (40.0)	23 (32.9)	
BMI (SD)	25.0 (±6.5)	22.9 (±5.1)	0.028
Albumin (SD)	3.8 (0.7)	3.5 (0.7)	
Previous abdominal surgery (%)	19 (34.5)	46 (65.7)	0.001

Table 2 Type of Surgery

Type of Surgery	Laparoscopic	Open	*p* value
Right colectomy	8	2	
Left colectomy	2	4	
Transverse colectomy	0	1	
TAC with EI	10	11	
TAC with IRA	7	6	
TPC with EI	25	18	0.024
Restorative Proctocolectomy with IAA	0	1	
Segmental colectomy at 1 or more sites	2	4	
Proctectomy	1	17	<0.001
Completion colectomy with EI	0	5	0.066
LAR	0	1	

The types of operations performed are listed in Table 2. The most common procedure in each group was total proctocolectomy with end ileostomy. Proctectomies were mostly performed via open technique (one LC vs 17 OC, $p<0.001$). It should be noted that 12 of the 17 open proctectomies were completion proctectomies. The most common indication for surgery in either group was failure of medical management (Table 3). There was a tendency to treat patients with dysplasia (seven LC vs one OC, $p=0.021$) and bowel obstruction laparoscopically (nine LC vs one OC, $p=0.005$). Among the patients treated for obstruction by LC, seven had an active Crohn's disease, one mildly active disease, and one patient had a high grade dysplasia-associated lesion or mass (DALM) on the background of quiescent Crohn's colitis. In the OC group, the patient who required colectomy due to obstruction was found to have mildly active Crohn's disease without evidence of dysplasia. A standard oncologic technique for colonic resection was utilized in both LC and OC when evidence of dysplasia, cancer, or stricture-related malignancy was suspected. In our study population, the only patient who was found to have stricture due to DALM on the background of quiescent Crohn's colitis had a standard oncologic colon resection with recovery of 42 lymph nodes all of which were negative for malignancy.

Table 4 Intraoperative and Postoperative Findings

	Laparoscopic (median (interquartile))	Open (median (interquartile))	*p* value
Operative time (min)	212 (180–315)	286 (231–387)	0.032
Estimated blood Loss (mL)	100 (90–250)	250 (100–400)	0.002
Return of bowel function (days)	3 (2–5)	4 (3–5)	0.036
Overall postoperative length of stay	6 (5–8)	8 (6–10)	0.001

Using the two independent sample Wilcoxon rank-sum test

Median operative time was statistically shorter in the LC group (212 min, IQR 180–315 LC vs 286 min, IQR 231–387 OC, $p=0.032$, Table 4). Even with exclusion of all proctectomies (one LC, 17 OC), this trend is maintained (212 min, IQR 180–315 LC, vs 267 min, IQR 225–345 OC). Estimated blood loss was significantly less for the LC group (100 ml, IQR 90–250 LC vs 250 ml, IQR 100–400 OC, $p=0.002$). Despite the difference in EBL, transfusion requirement did not differ; five patients from each group received perioperative blood transfusions. Return of bowel function was defined as passage of flatus or stool via anus or ostomy. Earlier return of bowel function was noted in the LC group (3 days, IQR 2–5 LC vs 4 days, IQR 3–5 OC, $p=0.036$). Length of post-op stay was significantly shorter in the LC group (6 days, IQR 5–8 LC vs 8 days, IQR 6–10 OC, $p=0.001$). There were six conversions (10.9%).

Table 3 Indications for Surgery

Indications for surgery	Laparoscopic $N=55$	Open $N=70$	*p* value
Failure of medical management	25 (45.5%)	32 (45.7%)	
Dysplasia	7 (12.7%)	1 (1.4%)	0.021
Cancer	2	0	
Fistulas[a]	5	10	
Perineal disease[b]	8 (14.5%)	15 (21.4%)	
Pain	0	6	0.034
Stricture	5	7	
Colon obstruction	9 (16.4%)	1	0.005
SBO	2	2	
Intraabdominal abscesses/sepsis	1	6	
Lower GI bleed	0	1	
Resection of excluded bowel	1 (1.8%)	8 (11.4%)	0.076
Proctitis	1	1	

[a] Including enterovesicular, coloenteric, rectal stump to small bowel fistulas

[b] Including perineal fistulas and rectovaginal fistulas

Table 5 Postoperative Morbidity and Mortality

	Laparoscopic	Open
Death	0	1
Sepsis	0	1
Small bowel obstruction	1	0
Anastomotic leak	1	0
Post-op intraabdominal abscess	2	3
Intraabdominal bleeding	0	1
Wound infection	3	3
Thrombotic event	0	2
Post-op fistula	3	0
Pneumonia	0	1
Urinary retention	0	2
Refractory pain	0	1

Reasons for conversion included bleeding in one case, inability to mobilize ascending colon secondary to dense adhesions in one case, large inflammatory masses in two cases, an abdominal abscess in one case, and multiple strictures in one case.

Postoperative complications occurred in eight (14.5%) LC patients vs 16 (22.9%) OC (Table 5). There were no statistically appreciable differences in complications between the groups. There was one death in the OC group. The patient was a 79-year-old lady who had a complicated postoperative course involving septic shock and a prolonged stay in the intensive care unit. She eventually suffered a massive fatal myocardial infarction. With a mean follow-up of 20.7±18.6 months, the overall recurrence rate was 16%, 10.9% LC and 20% OC, respectively (Fig. 1). This

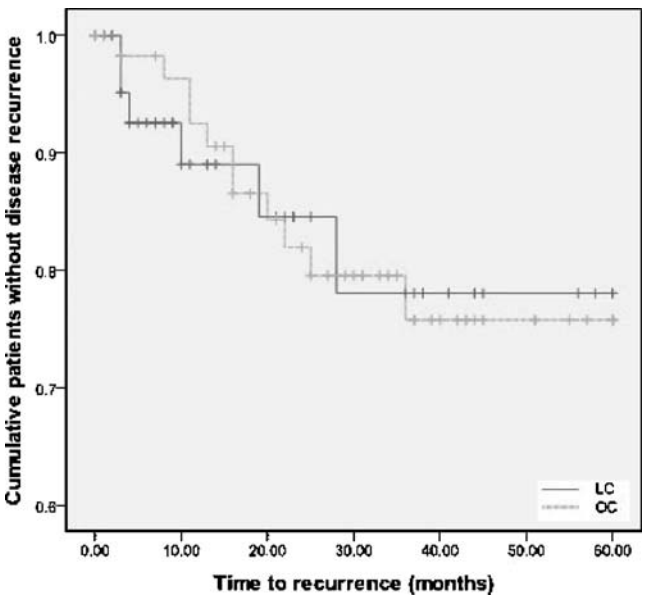

Figure 1 Recurrence of Crohn's disease following laparoscopic vs open colectomy.

Table 6 Long-Term Outcomes

	Laparoscopic $N=55$	Open $N=70$	p value
Mean months of follow-up (SD)	19.5 (20.7)	29.1 (21.9)	0.021
Months follow-up (interquartile)[a]	9 (2–34)	27 (5–43)	
Overall recurrence[b]	6 (10.91%)	14 (20.0%)	
Recurrence treated surgically[b]	0	2 (2.9%)	

[a] Median (interquartile)

[b] Number of patients (percent)

difference in overall recurrence rate between the two groups was not statistically significant as calculated by the log-rank test ($p=0.842$). Follow-up was significantly shorter after laparoscopic surgery, 9 months, IQR 2–34 vs 27 months, IQR 5–34, OC, $p<0.021$(Table 6). All recurrences in the LC group were treated medically whereas two of the recurrences in the OC group required surgical treatment.

Discussion

Our study represents the largest series to date comparing the outcomes of LC to OC in Crohn's colitis. We have demonstrated decreased operative time, decreased blood loss, quicker return of bowel function, and shorter length of hospital stay with the use of laparoscopic surgery while maintaining similar morbidity and comparable recurrence rates.

One of the most striking results of our study was significantly shorter operative times in LC group. Earlier reports on differences in operative time between laparoscopic and open surgery in Crohn's Disease have not been consistent.[1,7–9] In a previous report published by our group, we found no difference in operative time between patients undergoing laparoscopic vs open surgery for Crohn's Disease at the ileocolic region.[10] We attribute the statistically shorter operative times in this study for LC to the

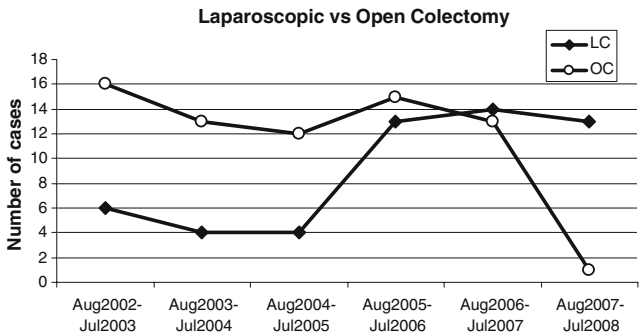

Figure 2 Trends in laparoscopic vs open colectomy for Crohn's disease.

considerable experience our group has accumulated with the laparoscopic technique. Similar to previous reports, blood loss was significantly less in the LC group compared to OC. We suggest that decreased blood loss in laparoscopic surgery is a result of an essential requirement for a dry surgical field in order to optimize visualization. Moreover, the introduction of hand-activated advanced bipolar laparoscopic vessel sealing devices that allow for safe control of blood vessels up to 7 mm in diameter has dramatically improved our ability to achieve perfect hemostasis even during division of the thickened friable mesentery.

Quicker return of bowel function and shorter duration of hospital stay was noted in our study and are consistent with previous reports in Crohn's disease as well as colon cancer.[11–13]

Our conversion rate of 10.9% is comparable to that reported by two previous randomized controlled trials describing laparoscopic ileocolic resection.[1,2] The conversion rate tends to remain constant as the laparoscopic experience accumulates since the surgeons feel more comfortable in attempting laparoscopic colectomy in more challenging cases that would have been deemed not suitable for laparoscopic surgery in the past.

Reports of recurrence rates available in literature have shown no difference between laparoscopic and open technique for Crohn's disease at the ileocolic region.[14,15] Our data showed a recurrence rate of 10.9% in the LC group and 20% in the OC group with a mean follow-up of 19.5±20.7 months and 29.1±21.9 months, respectively (p=0.014). While it is plausible that mild or quiescent Crohn's disease could have contributed to improved surgical outcomes, resulting in less need for postoperative medical maintenance therapy in turn contributing to higher recurrence of Crohn's disease, this notion has not been supported by our study. There were no correlation between Crohn's disease activity at the time of the colon resection and its recurrence in either OC or LC groups. The difference in length follow-up is explained by our progressive transition from predominantly OC to LC for Crohn's colitis as illustrated in Fig. 2. Given the difference in follow-up times between the groups, it is expected that the overall long-term recurrence rate will be similar between LC and OC groups.

Our study included all elective surgeries in patients with a diagnosis of Crohn's colitis. Patients were selected for laparoscopic or open colectomy based on the surgeon's preference, inevitably leading to selection bias. As a result, significant difference between the groups included a lower incidence of previous abdominal surgery in the LC group. Further disparity between the groups was in the rate of proctectomy. In fact, all but one proctectomy was done via the open approach. There are two reasons for this. First, 12 of the OC group proctectomies were completion procedures following an open colectomy. Second, laparoscopic proctectomy was an evolving technique during the study period. Because of the nature of the study, the cases were not randomly assigned to groups. Even though the groups were quite similar, they were not perfectly matched. A balance between the groups could be achieved only within confines of randomized trial. Because of relatively infrequent isolated colonic disease and proven benefits of laparoscopic colectomy, such a study is not likely to be accomplished.

Conclusion

Laparoscopic colectomy in Crohn's colitis is a safe and effective technique in the hands of experienced surgeons for appropriately selected cases. Our study suggests that the potential benefits of laparoscopic colectomy in Crohn's disease could include decreased operative blood loss, quicker return of bowel function, and shorter hospital length of stay with an obvious cosmetic advantage conferred by smaller incisions and without an observable difference in the complication rate. Longer follow-up is required to elucidate the differences in the rate of disease recurrence after LC and OC.

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J Gastrointest Surg (2010) 14:664–667
DOI 10.1007/s11605-009-1118-x

ORIGINAL ARTICLE

Myoglobinuria After Laparoscopic Radiofrequency Ablation of Liver Tumors

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Received: 17 July 2009 / Accepted: 22 November 2009 / Published online: 22 December 2009

Abstract
Background There are scant data in the literature about myoglobinuria after radiofrequency ablation (RFA) of liver tumors. The aim of this study is to analyze the incidence and identify the risk factors involved in this complication after RFA.
Patients and Methods An initial case of myoglobinuria and acute kidney injury (AKI) during laparoscopic liver RFA after 10 years of the liver ablation program led to the design of this study. Prospective data were collected on 41 consecutive patients undergoing laparoscopic RFA at our institution over a 9-month period. Urine myoglobin, serum creatinine kinase, and serum creatinine levels were obtained preablation and postablation. Variables were compared between patients to identify possible risk factors that might be related to this rare complication. Data are expressed as mean ± standard error of the mean.
Results Two patients were excluded from the study due to preoperative myoglobinuria of unknown etiology. Of the remaining 39 patients, three developed dark urine with significant myoglobinuria on postoperative day 1. Two of these patients had carcinoid liver metastases; the remaining patient had a metastatic colorectal lesion. The number of tumors ablated in these patients was 14, 11, and 3 vs. 2.4±0.4 in the rest of the patients. Cumulative tumor volume was larger in the group of patients that developed the complication vs. those who did not (127.9±59.5 vs. 48±3 cm^3). Two grounding pads were used in the three patients that had a complication vs. four pads in the rest of the patients. Dark urine was identified promptly intraoperatively and treated aggressively. All of these patients required intensive care unit (ICU) admission and had a prolonged hospital stay. Marked elevation of transaminases and creatinine kinase as well as a drop in hematocrit and platelet count was observed in patients with myoglobinuria. In our retrospective review of 706 patients that underwent liver RFA in the past 10 years, we detected 27 patients (3.8%) with ten or more lesions (11.9±0.4). None of these patients had significant elevation of serum creatinine postoperatively. In the whole series of 706 patients, 22 (3.2%) were found to have elevated creatinine after liver RFA, with return to baseline in all but seven patients in follow-up.
Conclusion Myoglobinuria after liver RFA is a rare but potentially devastating complication that may lead to AKI with significant morbidity and prolonged hospital stay. Patients with large tumor volumes requiring longer ablation times need to be monitored closely for the development of this complication. The fact that this was not observed in other patients with similar tumor characteristics suggests that individual patient-related factors might play an important role.

Presented at the AHPBA 2009 Meeting in Miami Beach, FL, USA on March 12–15, 2009

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Keywords Laparoscopic radiofrequency ablation · Liver tumor · Myoglobinuria

Introduction

Radiofrequency ablation has gained widespread acceptance for the treatment of liver tumors. Since its introduction in 1996,[1] an increasing number of procedures for the treatment of unresectable primary or metastatic liver tumors

are performed worldwide. In a recent review at our institution, we reported a 30-day mortality rate of 0.4% and a morbidity of 3.8%.[2]

Minor complications after the procedure have been described extensively and commonly include abdominal pain, fever, nausea, and vomiting. However, an increasing number of severe and life-threatening complications have also been reported.

As a tertiary referral center, our institution has acquired extensive experience with laparoscopic radiofrequency ablation (RFA) of liver tumors. After 10 years of the liver ablation program, we observed an initial case of acute kidney injury (AKI) and myoglobinuria in a patient following this procedure. An extensive search of the literature failed to reveal significant information about this complication. For this reason, we decided to analyze and try to identify factors that could be related to this complication after RFA.

Patients and Methods

After the initial case of AKI, we decided to include additional laboratory parameters to our existing prospective study for unresectable primary and metastatic liver tumors. Routine preoperative studies include triphasic spiral computed tomography, complete blood count, and complete metabolic panel which includes liver function tests and coagulation studies (prothrombin time/partial thromboplastin time) within 1 week of surgery. After the initial case, we added quantitative urine myoglobin, serum creatinine kinase, and serum creatinine levels to our preoperative and postoperative routine. The Roche® chemiluminescence assay was used for quantitative myoglobin detection in this group of patients. This assay does not cross-react with hemoglobin or any of the known liver-derived proteins.

Prospective data were collected on 41 consecutive patients undergoing laparoscopic RFA at our institution over a 9-month period. Data are expressed as mean ± standard error. The data were entered into an institutional-review-board-approved database. The data from these patients were compared with the rest of the patients in the database.

Laparoscopic RFA Procedure

The technique has been described in detail in the literature.[2] In brief, the operation is performed with the patient under general anesthesia and in the supine position. We routinely use the optical trocar to gain access to the abdominal cavity. Two 11-mm trocars are used in the right subcostal region. The initial step is performing a diagnostic laparoscopy to assess for extrahepatic disease. We then perform laparoscopic ultrasound (US) to identify the liver lesions using a 7.5-MHz side-viewing 10-mm laparoscopic transducer (Aloka Co., Ltd., Wallingford, CT, USA) and the Aloka 5500 ultrasound machine. The lesions are assessed with color flow Doppler imaging to evaluate vascularity. A US-guided liver biopsy of the lesions is performed with an 18-gauge spring-loaded biopsy gun to confirm the histology. After the lesions have been properly identified, the radiofrequency thermoablation catheter is placed percutaneously under US guidance, and ablation is performed using standard parameters.

Statistical analysis was performed with Predictive Analytics Software version 17 for Mac. The *t* test and chi-squared were used as considered appropriate to compare data. A p value was considered statistically significant when <0.05.

Results

Table 1 summarizes the comparison between different variables among the groups. Two patients were excluded from the study due to preoperative myoglobinuria of unknown etiology. Of the remaining 39 patients, three developed dark urine with significant myoglobinuria on postoperative day 1. Two of these patients had neuroendocrine liver metastases; the remaining patient had colorectal liver metastases. The number of tumors ablated in these patients was 14, 11, and 3 vs. 2.4±0.4, respectively. Ablation times were 56.3±11.2 vs. 21.4±2.1 min, respectively. Two grounding pads were used in the three patients that had a complication vs. four pads in the rest of the patients. Dark urine was identified promptly intraoperatively and treated aggressively. All of these patients required intensive care unit admission and had a prolonged hospital stay. Marked elevation of transaminases and creatinine kinase as well as a drop in hematocrit and platelet count was observed in these three patients. One patient died related to an anastomotic leakage from a concomitant right hemicolectomy, within 30 days of the RFA procedure.

We retrospectively reviewed the data of our series of 706 patients who underwent liver RFA in the past 10 years. It was observed that total tumor volume was larger in the group of patients who developed the complication vs. those who did not (127.9±59.5 vs. 48±3 cm^3; $p=0.14$). Ten or more lesions (11.9±0.4) were ablated in 27 patients (3.8%) without significant elevation in serum creatinine postoperatively. Twenty-two out of 706 patients (3.2%) were found to have elevated creatinine after liver RFA, with return to baseline in all but seven patients in follow-up.

Discussion

Radiofrequency thermal ablation is a common procedure used today to treat unresectable liver tumors. In general,

Table 1 Comparison of Different Variables Among Two Groups of Patients Undergoing Laparoscopic Radiofrequency Ablation of Unresectable Liver Tumors

	Myoglobinuria	Control	*p* value
Number of tumors	9.3 (±5.7)	2.4 (±2.3)	0.17
Tumor volume	127.9 (±59.5) cm^3	26.4 (±29.4) cm^3	0.10
Ablation time	56.3 (±19.4) min	21.4 (± 12.3) min	0.10
Postop myoglobin	49,000 (±75,029) ng/mL	26.3 (±5.9) ng/mL	0.37
Postop hematocrit	31.9 (±5.8)%	36.1 (±4.9)%	0.36
Postop CK	1,079 (±595.4) U/L	93.6 (±89.5) U/L	0.10
Postop AST	752 (±41) U/L	268 (±204) U/L	0
Postop ALT	434 (±21.2) U/L	172 (±112) U/L	0
Preoperative Cr	1.1 (±0.2) mg/dL	1 (±0.2) mg/dL	0.51

Data are expressed as mean ± standard deviation

CK creatine phosphokinase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *Cr* creatinine

RFA is considered a simple procedure without the serious complications associated with cryoablation. This paper highlights an extraordinary complication, myoglobinuria, which can lead to devastating sequelae and studies it in a prospective manner. Complications arising from RFA of liver tumors have commonly been related to the local effects of catheter introduction as well as heat generation. These complications have been described in various reports[3–5] and include thermal injuries to adjacent structures including diaphragm, stomach, duodenum, and transverse colon; skin burns; hemorrhage from the needle tract; cholecystitis; pneumothorax; and pleural effusions. Systemic complications arising after RFA are less common. In our experience, we have previously published minor complications in 3.8% of patients including nausea, ileus, abdominal distension, abdominal pain, fever, and urinary retention. Less common complications involved liver abscess formation, trocar injuries involving small bowel and gallbladder in one patient each.[2]

Myoglobin is a single-chain globular protein that is the primary oxygen binding pigment in muscle tissues. A small number of cases of myoglobinuria after RFA have been described, although specific details are lacking. Acute renal failure after RFA of liver lesions was initially described by Keltner et al.[6]. In this case, it was noted that the serum creatine phosphokinase was elevated and peaked at postoperative day 1. The cause of AKI in this case was unclear, and myoglobinuria was not described. Other authors have noticed a relationship between myoglobinuria and ablation of large tumors.[7,8]

As the criteria for applying RFA to larger tumors and longer ablation time continues to expand, we may face an increase in the incidence of myoglobinuria in this patient population. Other complications have also been related to ablation of large tumors.[9] Although myoglobinuria was not consistently observed in patients with similar characteristics, those with large tumor volumes requiring longer ablation times need to be monitored closely for the development of this complication. Preoperative optimization of patients with large or multiple tumors using intravenous hydration as well as alkalinization of urine should be considered.[5,6] In our study, this phenomenon was recognized intraoperatively and aggressively managed with hydration and alkalinization of the urine. One of these patients died due to anastomotic leakage, but the presence of myoglobinuria was a significant adverse stress on this elderly patient with limited reserve. Therefore, intraoperative recognition of dark urine is critical in these patients.

Our search for the predictors of myoglobinuria did not identify obvious factors. Although the tumor volume was larger in these patients compared to average in the whole series in the database, we identified a number of patients with very large tumor volumes ablated, who clinically did not develop any dark urine or renal dysfunction. There was a hint that the number of grounding pads used could play a role, as we did not see any more cases of myoglobinuria after switching to four pads instead of two pads.

Rhabdomyolysis resulting in myoglobinuria has been described in the open surgery literature under different settings. It is a known complication in bariatric surgery due to prolonged immobilization.[10,11] It has also been related to muscle ischemia caused by massive vasoconstriction secondary to catecholamine release in patient with pheochromocytoma.[12] Patient positioning and prolonged immobilization are the most common causes of rhabdomyolysis in surgical patients. The diagnosis is usually made based on clinical symptoms after the operation (tea-colored urine, myalgia, nausea, vomiting, malaise, or fever) and serum markers such as an elevation of creatine kinase and myoglobin. Review of the parameters in our patients did not reveal levels as high as those seen in rhabdomyolysis, but the questionable role of the grounding pad and the fact that myoglobin is present in skeletal muscle, not in liver tissue, suggest that the mechanism in our index RFA cases could be similar to the open literature. Nevertheless, our third patient with two colorectal liver metastases who had a comparably short case does not follow this hypothesis. However, this patient had a low-flow state, with an ejection

fraction of 20–25%, raising the question as to whether hemodynamics could also play a role in the development of myoglobinuria after RFA.

In conclusion, myoglobinuria after liver RFA is a rare but potentially devastating complication that may lead to AKI with significant morbidity and prolonged hospital stay. The fact that this was not observed in other patients with similar tumor characteristics suggests that patient-related factors might play an important role. Based on our experience from this study, patients who have larger liver volumes ablated, requiring longer operating times, and those with low-flow state should be closely monitored for this complication. The surgeons also need to be familiar with the physics of this procedure and provide sufficient return of the RFA current using an adequate number of grounding pads.

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J Gastrointest Surg (2010) 14:668–678
DOI 10.1007/s11605-009-1132-z

ORIGINAL ARTICLE

Surgical Outcomes and Prognostic Factors for T2 Gallbladder Cancer Following Surgical Resection

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Received: 29 July 2009 / Accepted: 4 December 2009 / Published online: 22 December 2009

Abstract
Background Depth of tumor invasion is an important prognostic factor for gallbladder cancer. The aim of this study was to investigate the clinicopathological prognostic factors of T2 gallbladder cancer.
Methods We retrospectively reviewed the clinicopathological data and survival for 83 patients with T2 gallbladder cancers who underwent surgical resection between January 1995 and December 2007.
Results The overall survival rates were 48.9% at 3 years and 29.3% at 5 years. Univariate analysis revealed that R0 resection ($P<0.001$), extended surgery ($P=0.028$), lymph node dissection ($P=0.024$), non-infiltrative tumors ($P=0.001$), well differentiation ($P=0.001$), absence of lymphatic ($P=0.025$), perineural ($P=0.001$), and vascular ($P=0.025$) invasion, absence of lymph node metastasis ($P=0.001$), negative resection margin ($P=0.016$), and stage ($P=0.002$) were significantly better predictors for survival. A significant difference in survival between Rx and R1 was not found. R0 resection, lymph node dissection, well differentiation, and absence of perineural and vascular invasion were significantly independent prognostic factors for overall survival. Recurrence occurred in 48 patients (57.8%). Age older than 65 years, R0 resection, non-infiltrative tumors, and good differentiation were significant independent predictors of disease-free survival by multivariate analysis.
Conclusions For T2 tumors, radical surgery including lymph node dissection should be performed to achieve R0 resection. Tumors with infiltrative types and suspicious lymph node metastasis in the intraoperative findings were candidates for aggressive surgical management to improve patient survival.

Keywords T2 gallbladder cancer · Cholecystectomy · Radical surgery · Lymph node dissection

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Introduction

The prognosis of gallbladder cancer is poor, and the depth of tumor invasion and the presence of lymph node metastasis have been reported to be important prognostic factors.[1,2] Surgical resection without residual tumor provides a chance of cure and long-term survival.[3–5] However, gallbladder cancer is usually diagnosed at an advanced stage in spite of recent progress in diagnostic modalities.[6] The resectability rate is low, accounting for approximately 30% of cases in a recently reported series,[3,7,8] and the extent of resection for each stage of disease is controversial and debatable.[5] Simple cholecystectomy has been adopted as an adequate treatment for patients with T1 gallbladder cancers invading the mucosa or muscle layers,[9–12] while extended radical surgery is required to improve survival outcomes in T2 (invading perimuscular connective tissue or subserosal layer) and more advanced gallbladder cancers.

On the other hand, in T3 and T4 gallbladder cancers that perforate the serosa or invade adjacent organs, the resectability rate tends to be low and the survival rate is poor.[3,13] Therefore, there is hope for long-term survival after radical resection in T2 cancers,[14,15] and the proportion of T2 cancers that are coincidentally found during or after laparoscopic cholecystectomy has been reported to range from 33.3% to 57.7%.[16–18] The survival outcomes following surgical resection and clinicopathological characteristics of T2 gallbladder cancers are important for improving the prognosis and establishing a treatment strategy.

The aim of this retrospective study was to investigate the clinicopathological characteristics of T2 gallbladder cancer and to evaluate the prognostic factors affecting survival and recurrence. We also investigated the survival outcomes and clinicopathological characteristics according to the presence of lymph node metastasis and recurrence.

Patients and Methods

From January 1995 to December 2007, a total of 200 patients with gallbladder cancers underwent surgical exploration at the Department of Surgery, Korea University Medical Center, Korea University College of Medicine, Seoul, Korea. Of 200 patients, 93 (46.5%) were diagnosed with pT2 tumors. Of the 93 patients, ten underwent cholecystectomy with macroscopic residual disease (R2) due to locally advanced disease with extensive lymph node metastasis (n=4), distant metastasis (n=5), or peritoneal seeding (n=1). Eighty-three patients who underwent R0, R1, or Rx resection were included in the survival analysis to examine the prognostic factors influencing survival and recurrence. The following preoperative demographics and clinical information were retrospectively obtained from the patients' records: age, gender, diagnostic modalities, preoperative diagnosis, and operative factors including operative procedures, operative time, need for transfusion, postoperative complication, adjuvant therapy, mode of recurrence, and treatment.

Macroscopically, we evaluated the tumor location, number, and diameter. The gross morphological features were classified into five groups: polypoid, papillary, protruding or fungating, elevated, and diffusely infiltrative lesions. The microscopic characteristics were evaluated as follows: histologic type, differentiation, the presence of lymphatic, perineural, and vascular invasion, lymph node metastasis, and margin status. R0 describes a microscopically margin-negative resection in which no gross or microscopic residual tumor exists in the tumor bed. R1 indicates removal of all macroscopic diseases, but with microscopic margins that are positive for tumor. R2 indicates gross residual disease. Rx describes the diseases in which the presence of residual tumor cannot be assessed. In this study, the Rx group included patients who underwent simple cholecystectomy for T2 tumors, and the presence of residual disease could not be completely assessed. The resection margin was negative for tumor cells; however, occult cancer could not be completely ruled out. These patients could not be classified as R1 definitely; nevertheless, R0 status could not be guaranteed. Tumor stage was defined according to the pathological tumor node metastasis classification proposed by the American Joint Committee on Cancer (AJCC).[19] The T2 tumors were classified into the following three stages: stage IB (T2N0M0), IIB (T2N1M0), and IV (T2 anyNM1).

Adjuvant therapy after surgical resection was not strictly protocol-driven and was administered at the discretion of surgeons and oncologists in the treatment of patients. When the resection margin was positive for tumor infiltration or lymph node metastasis was present, adjuvant chemotherapy and/or radiation therapy were considered.

Statistical calculations were performed using SPSS, version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Survival was measured from the date of surgery. Disease-free survival was measured from the date of surgery to the date of recurrence. The follow-up of patients was considered complete either at death or on the incised date of June 30, 2008. Overall survival was calculated using the Kaplan–Meier method. Clinicopathologic prognostic factors were analyzed by the univariate Kaplan–Meier method and compared by the log–rank test to identify the prognostic predictors for survival. Multivariate regression analysis was performed using the Cox proportional hazards model to identify the independent prognostic factors for survival. Variables to be entered into the multivariate analysis were selected on the basis of the results of univariate analysis (P<0.1). Comparisons between groups were tested using Pearson's chi-square test. A P value of <0.05 was considered statistically significant.

Results

Clinical Characteristics

Of the 83 T2 gallbladder cancer patients, 39 were men and 44 were women, with a mean age of 66 years (range, 43 to 87 years). In patients with preoperative diagnosis of gallbladder cancer, the diagnosis was made based on the radiological features. During the process of diagnosis, 62 patients (75%) underwent abdominal ultrasonography (US) and 60 patients (72%) underwent an abdominal computed tomography (CT) scan. For further evaluation, 11 patients (13%) underwent magnetic resonance cholangiopancreatography (MRCP). Twenty-five patients by US, 36 patients by

CT scan, and five patients by MRCP were diagnosed or suspected to have gallbladder cancer preoperatively. Of the 83 patients, 40 patients (48%) were diagnosed or at least suspected to have gallbladder cancer preoperatively. Thirteen patients (16%) were diagnosed or suspected to have gallbladder cancer during operation. In the end, 30 patients (36%) were diagnosed with gallbladder cancer after the operation.

The operative procedures are shown in Table 1. Cholecystectomy was performed in 52 patients, and more extended surgery was performed in 31 patients. Lymph node dissection and lymph node biopsy were performed in 32 and nine patients, respectively. Laparoscopic cholecystectomy was completed in 25 patients, and seven patients were converted to open surgery during laparoscopic approach by difficulty in dissection due to adhesion, severe inflammation, or bleeding. Of the 13 patients who were suspected to have gallbladder cancer during operation, conversion to radical surgery during operation was performed in four patients and additional second radical surgery was performed in two patients. Of the 30 patients who were diagnosed with gallbladder cancer after cholecystectomy by permanent pathology, five patients underwent a second radical surgery. The mean operative time was 150 min (range, 33–420 min). Ten patients required an intraoperative transfusion.

One patient who had gallbladder cancer along with choledochoduodenal fistula underwent cholecystectomy with primary repair of the duodenum and died following the operation due to sepsis, resulting in a surgical mortality rate of 1.1%. The following operative morbidity occurred in ten patients (11.1%); intra-abdominal abscess (n=4), jaundice (n=1), pleural effusion (n=1), angina (n=1), and wound dehiscence (n=3).

Adjuvant therapy was performed in 47 patients as follows: chemotherapy in 32 patients, radiation therapy in seven patients, and concurrent chemoradiation therapy in eight patients. Adjuvant radiation therapy was performed with external beam radiotherapy, and adjuvant chemotherapy was performed systemically using a 5-flurouracil-, cisplatin-, or gemcitabine-based regimen for either microscopic residual disease or advanced disease.

Table 1 Operative Procedures for the 83 Patients

Operation				No. of patients
Chole				43
Chole	LND			9
Chole	Liver			4
Chole	Liver	LND		13
Chole	BDR			4
Chole	BDR	LND		5
Chole	Liver	BDR	LND	5

Chole cholecystectomy, *LND* lymph node dissection, *Liver* gallbladder bed resection of the liver, *BDR* common bile duct resection

Pathologic Results

The mean size of tumors was 2.8 cm (0.3–7.5 cm). Six patients had multiple polyps. Five patients demonstrated diffuse carcinoma in situ in the background of the cancer. Gross morphological characteristics included polypoid in 19 patients, fungating and protruding in 11 patients, elevated lesion in 12 patients, papillary in 11 patients, and diffuse infiltrative in 30 patients. Pathologically, the histology of the tumor was identified as tubular adenocarcinoma in 73 patients, papillary in four patients, adenosquamous in five patients, and mixed acinar and papillary in one patient. Tumors were well differentiated in 31 patients, moderately differentiated in 37 patients, and poorly differentiated in 15 patients. Of the 32 patients who underwent lymph node dissection, the median number of retrieved lymph nodes was seven (3–36). The median number of metastatic lymph nodes in lymph node-positive patients was 1.5 (1–5). The resection margin status was positive for cancer cells in 19 patients (22.9%). Para-aortic lymph node dissection was not routinely performed, and para-aortic lymph node metastasis was noted in one patient. The R status of the patients was as follows: R0 and R1 resections were performed in 32 and 18 patients, respectively. Thirty-three patients were categorized as Rx. According to the AJCC 6th TNM classification, there were 65 (78.3%) pathological stage IB (T2N0M0) tumors, 17 (20.5%) IIB (T2N1M0) tumors, and one (1.2%) stage IV (T2N1M1) tumor.

Overall Survival and Prognostic Factors for Survival

Overall survival rates for the 83 patients who underwent R0, R1, or Rx resections were 75.2% at 1 year, 59.6% at 2 years, 48.9% at 3 years, and 29.3% at 5 years (median survival time, 33.2 months; Fig. 1). The 1-year survival rate for the ten patients who underwent simple cholecystectomy resulting in R2 resection was 30.0% and all of the patients died within 15 months after surgery due to disease progression. The 5-year survival rates for R0, Rx, R1, and R2 were 51.8%, 26.0%, 0%, and 0%, respectively (Fig. 2). There was no significant difference in survival between Rx and R1 groups (P=0.242).

Univariate analysis revealed that R0 resection (P< 0.001), extended cholecystectomy (P=0.028), lymph node dissection (P=0.024), non-infiltrative tumor (P=0.001), well differentiation (P=0.001), absence of lymphatic (P= 0.025), perineural (P=0.001), and vascular (P=0.025) invasion, absence of lymph node metastasis (P=0.001), negative resection margin (P=0.016), and tumor stage (P= 0.029) were significantly better predictors for survival

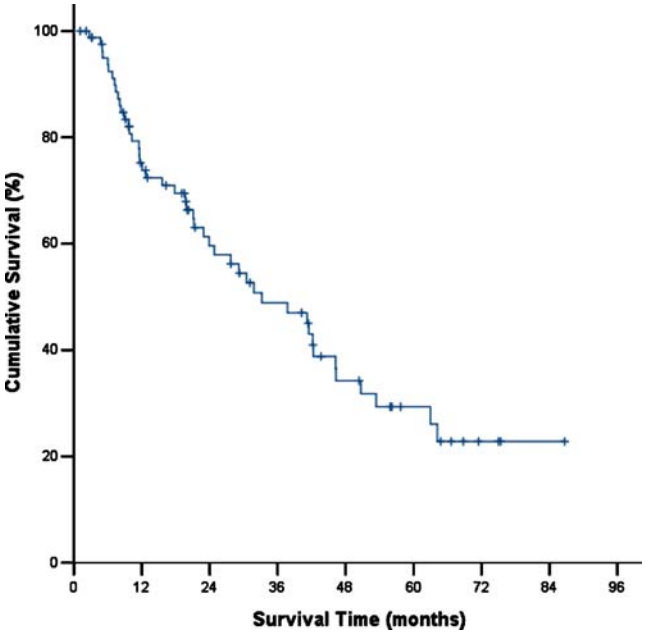

Figure 1 Overall survival curve of 83 patients who underwent surgical resection for T2 gallbladder cancer.

(Table 2). Age, sex, presence of gallstones, transfusion, and adjuvant therapy did not affect overall survival.

Multivariate analysis using a Cox proportional hazards model demonstrated that non-R0 resection (hazard ratio [HR]=8.738), no lymph node dissection (HR=3.584), moderate to poor differentiation (HR=3.181), and presence of perineural (HR=3.428) and vascular invasion (HR=3.989) were significant independent predictors of poor overall survival (Table 3).

Among 32 patients who underwent lymph node dissection and nine patients who underwent lymph node biopsy or sampling upon initial operation, 19 (46.3%) patients were positive for lymph node metastasis. Recurrence occurred in 15 patients who were lymph node-positive at initial operation (P=0.002). Patients who were lymph node-positive at initial operation had a significantly higher incidence of recurrence (P=0.002), non-R0 resection (P=0.001), infiltrative tumor (P=0.005), moderate to poor differentiation (P=0.022), and positive resection margin (P=0.039; Table 4).

Recurrence and Prognostic Factors for Disease-Free Survival

Of the 83 patients, recurrence occurred in 48 patients (57.8%) and, of the 83 patients, 20 patients were excluded from the disease-free survival analysis due to follow-up loss (n=3) and unknown recurrent time and sites (n=17). Disease-free survival rates for the 63 patients were 73.7% at 1 year, 58.5% at 2 years, 45.1% at 3 years, and 34.1% at 5 years (median disease-free survival time, 32.5 months; Fig. 3). Among the 31 patients who suffered recurrence with known recurrent sites, 13 patients showed more than two recurrent sites at the initial detection of the recurrence. The patterns of recurrence were local recurrence in 14 patients (31.8%), distant metastasis in 24 patients (51.1%), and nodal recurrence in nine patients (20.5%). The sites of distant metastasis were as follows: liver in 14 patients, lung in two patients, peritoneum in five patients, port site in two patients, and bone in one patient. Patients with recurrence had a significantly high incidence of age younger than 65 years (P=0.028), non-R0 resection (P=0.013), not performing lymph node dissection (P=0.023), infiltrative tumors (P<0.001), moderate to poor differentiation (P=0.001), presence of lymph node metastasis (P=0.009), vascular invasion (P=0.041), and positive resection margin (P=0.010; Table 5).

Univariate analysis of disease-free survival in 63 patients revealed that age younger than 65 years (P=0.010), non-R0 resection (P=0.009), infiltrative tumors (P<0.001), moderate to poor differentiation (P=0.003), the presence of perineural invasion (P=0.003), positive resection margin (P<0.001), the presence of lymph node metastasis (P<0.001), and advanced stage (P=0.001) were significantly poorer predictors of disease-free survival (Table 6). As shown in Table 7, age younger than 65 years (HR=5.178), non-R0 resection (HR=3.970), infiltrative tumors (HR=3.056), and moderate to poor differentiation (HR=3.427) were significant independent predictors of recurrence by multivariate analysis using a Cox proportional hazards model.

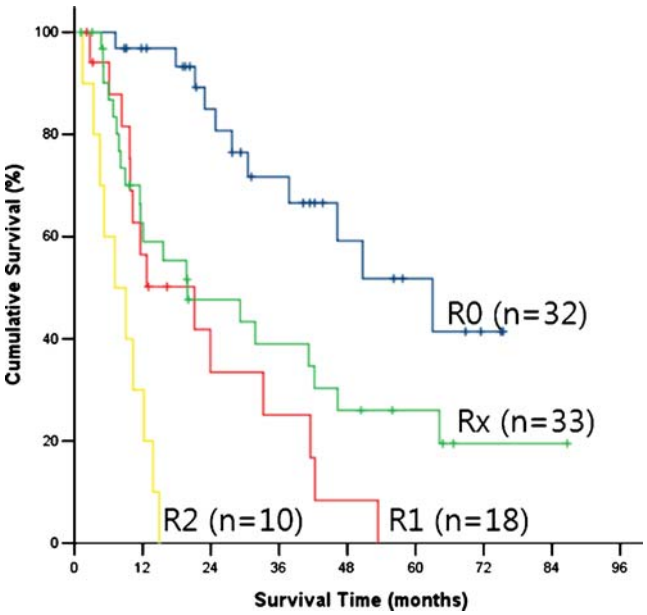

Figure 2 Comparison of survival according to R status. The survival is significantly different according to R status. However, there is no survival difference between R1 and Rx patients (R0 vs. Rx, P=0.005; Rx vs. R1, P=0.242; R1 vs. R2, P=0.007).

Table 2 Univariate Analysis of Prognostic Factors on Overall Survival

Factor		No.	Median	3YSR (%)	5YSR (%)	*P* value
Age	<65	38	31.8	46.1	20.1	0.187
	≥65	45	41.2	51.9	39.0	
Sex	Male	39	42.3	57.2	35.6	0.523
	Female	44	29.1	40.0	23.4	
Stone	No	46	41.2	55.4	33.1	0.242
	Yes	37	21.1	39.3	21.0	
R status	R0	32	63.0	71.7	51.8	<0.001
	R1 or Rx	51	19.9	33.9	16.5	
Transfusion	No	73	33.2	49.6	26.2	0.826
	Yes	10	30.5	43.8	43.8	
Operation	Cholecystectomy	53	23.9	39.8	24.1	0.028
	Extended	30	46.2	63.8	37.6	
Laparoscopy	No	58	24.8	46.2	31.3	0.452
	Yes	25	41.2	54.9	25.7	
Lymph node dissection	No	52	23.5	39.2	17.2	0.024
	Yes	31	63.0	63.5	51.3	
Adjuvant therapy	No	38	37.7	52.8	22.6	0.972
	Yes	45	24.8	46.4	39.8	
Gross	Non-infiltrative	53	46.2	61.3	47.6	0.001
	Infiltrative	30	19.7	26.4	4.4	
Differentiation	Well	30	63.0	76.4	57.5	0.001
	Moderate to poor	49	21.1	36.0	16.7	
Lymphatic invasion	Negative	73	41.2	53.1	30.9	0.025
	Positive	10	9.8	16.9	16.9	
Perineural invasion	Negative	72	42.2	55.3	34.6	0.001
	Positive	11	12.7	12.1	0.0	
Vascular invasion	Negative	77	37.7	51.9	32.9	0.025
	Positive	6	12.1	16.7	0.0	
Resection margin	Negative	63	42.2	55.8	38.0	0.016
	Positive	20	21.0	27.9	7.0	
Lymph node metastasis	Negative	21	63.0	82.1	64.5	0.001
	Positive	19	21.1	25.6	17.1	
Stage	IB	65	41.5	55.1	32.8	0.002
	IIB	17	21.2	28.9	19.3	
	IV	1	6.1	0	0	

Twelve patients with recurrent tumors were treated as follows: repeat operation (n=3), chemotherapy (n=10), and transarterial chemoembolization and percutaneous ethanol injection for the metastatic liver tumor (n=1). Two patients received a palliative operation with systemic chemotherapy.

Discussion

The prognosis for gallbladder cancer is typically dismal because most patients are diagnosed and treated at an advanced stage of the disease. Therefore, the only chance for a cure lies in early detection and complete surgical resection.[5,20,21] In the current study, we investigated and analyzed the survival outcomes and clinicopathological characteristics of patients who underwent R0, R1, or Rx resection for T2 gallbladder cancer that invades the subserosal layer. The 5-year survival rate of T2 gallbladder cancer has been reported to be 49.8–78.3%.[4,10,22,23] The prognosis of gallbladder cancer is influenced by several clinicopathological factors including radical resection, lymph node metastasis, hepatic invasion, bile duct invasion, lymphatic invasion, vascular invasion, residual tumor status and final curability, and tumor stage.[3,4,13,14,23,24]

Operation-related significant prognostic factors that affect the overall survival include R0 resection, extended radical surgery, and lymph node dissection. The 5-year survival rates in patients with T2 disease after simple cholecystectomy and following extended resection have been reported to be 17–40% and 61–90%, respectively.[14,25–27] As shown in the current study, the survival of Rx patients who underwent simple cholecystectomy for T2 gallbladder cancer did not differ from that of R1 patients with microscopic residual tumor (P=0.242). And R0

Table 3 Multivariate Analysis of Prognostic Factors on Overall Survival

Factor		*P* value	HR	95% CI
R0	R0 Non-R0	0.003	8.738	2.064–36.996
Operation	Cholecystectomy Extended surgery	0.848	1.111	0.380–3.251
Lymph node dissection	No Yes	0.026	3.584	1.167–11.011
Gross	Non-infiltrative Infiltrative	0.418	1.468	0.580–3.714
Differentiation	Well Moderate to poor	0.008	3.181	1.622–7.469
Lymphatic invasion	Negative Positive	0.123	2.430	0.787–7.502
Perineural invasion	Negative Positive	0.012	3.428	1.312–8.954
Vascular invasion	Negative Positive	0.018	3.989	1.268–12.543
Resection margin	Negative Positive	0.626	0.817	0.363–1.840
Lymph node metastasis	Negative Positive	0.996	0.998	0.434–2.295

CI confidence interval

resection enhanced the survival significantly. Therefore, radical operations with cancer-free surgical margin (R0 resection) seem to be the treatment of choice for T2 gallbladder carcinoma. However, in the analysis of the early stage gallbladder cancers that were identified from the Surveillance, Epidemiology, and End Results Tumor Registry from 1988 through 2004 in the United States, the proportion of patients having radical surgery for T2 was

Table 4 Comparison of the Clinicopathological Factors According to the Lymph Node Status

Factor		Lymph node (−) (n=21)	Lymph node (+) (n=19)	*P* value
Age	<65	9	12	0.199
	≥65	12	7	
Sex	Male	8	13	0.055
	Female	13	6	
Recurrence	No	15	3	0.002
	Yes	5	15	
	Unknown	1	1	
R status	R0	18	7	0.001
	R1, Rx	3	12	
Operation	Cholecystectomy	7	12	0.059
	Extended surgery	14	7	
Adjuvant therapy	No	10	7	0.491
	Yes	11	12	
Gross	Non-infiltrative	20	11	0.005
	Infiltrative	1	8	
Differentiation	Well	10	3	0.022
	Moderate to poor	9	15	
Lymphatic invasion	Negative	21	16	0.058
	Positive	0	3	
Perineural invasion	Negative	20	18	0.942
	Positive	1	1	
Vascular invasion	Negative	21	17	0.127
	Positive	0	2	
Resection margin	Negative	19	12	0.039
	Positive	2	7	

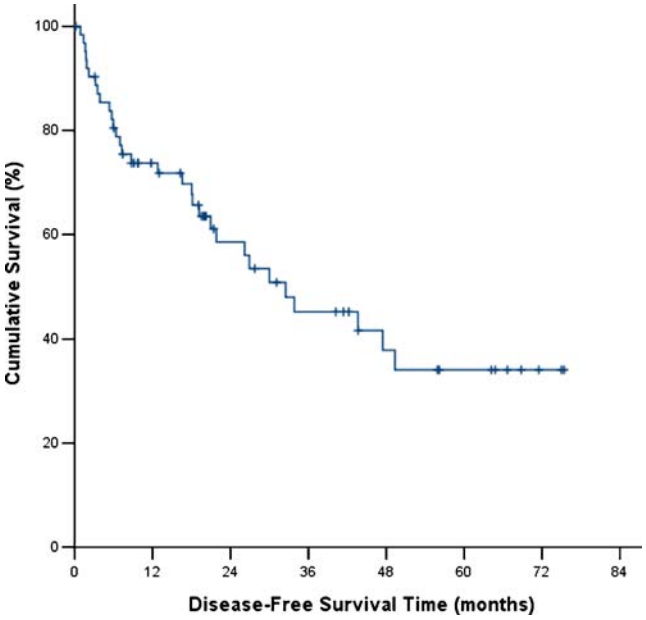

Figure 3 Disease-free survival curve after surgical resection of T2 gallbladder cancers.

5.6%, and therefore, radical resection for gallbladder cancer is significantly underutilized despite a significant survival advantage.[28]

Although gallbladder cancer is diagnosed following laparoscopic cholecystectomy with a low possibility of cancer in the preoperative evaluation, the proportion of cancers advanced more than T2 was relatively high.[16–18] In patients with T2 gallbladder cancer, a second radical resection has been recommended to give a significantly better survival after open or laparoscopic cholecystectomy,[5,14,21] and patients who underwent a second radical resection experienced the same survival benefit as patients who underwent primarily radical resection.[27] However, a relatively low proportion of patients (seven of 25 patients who underwent laparoscopic cholecystectomy) underwent an additional radical surgery in the current study.

The presence of lymph node metastasis has been reported to be 37–50% and is an important prognostic factor in T2 gallbladder cancer,[4,5,14,20,24,29] which is comparable to what was found in the present study. The 5-year survival rate was 70% in the absence of lymph node metastasis and 27% in the presence of nodal involvement in T2 cancers in a previous report.[14] The presence of lymph

Table 5 Clinicopathological Characteristics According to the Recurrence

Factor		No recurrence (n=31)	Recurrence (n=48)	P value
Age	<65	9	26	0.028
	≥65	22	22	
Sex	Male	16	20	0.386
	Female	15	28	
R status	R0	17	13	0.013
	R1, Rx	14	35	
Operation	Cholecystectomy	18	32	0.439
	Extended surgery	13	16	
Lymph node dissection	No	14	34	0.023
	Yes	17	14	
Laparoscopy	No	20	34	0.556
	Yes	11	14	
Adjuvant therapy	No	12	24	0.325
	Yes	19	24	
Gross	Non-infiltrative	28	23	<0.001
	Infiltrative	3	25	
Differentiation	Well	18	10	0.001
	Moderate to poor	12	35	
Lymph node metastasis	Negative	29	33	0.009
	Positive	2	15	
Lymphatic invasion	Negative	28	42	0.700
	Positive	3	6	
Perineural invasion	Negative	29	39	0.123
	Positive	2	9	
Vascular invasion	Negative	31	42	0.041
	Positive	0	6	
Resection margin	Negative	28	31	0.010
	Positive	3	17	

Table 6 Univariate Analysis of Prognostic Factors on Disease-Free Survival

Factor		No.	Median	1YSR (%)	3YSR (%)	*P* value
Age	<65	29	26.2	68.0	21.8	0.010
	≥65	34	–	78.8	63.7	
Sex	Male	32	43.6	73.9	55.0	0.517
	Female	31	26.9	73.3	32.7	
Stone	No	35	47.5	78.5	51.0	0.180
	Yes	28	20.9	67.0	33.3	
R status	R0	29	47.5	89.7	61.5	0.009
	R1, Rx	34	19.2	28.7	23.0	
Transfusion	No	55	26.9	71.8	39.3	0.087
	Yes	7	–	85.7	85.7	
Operation	Cholecystectomy	35	20.9	66.6	42.4	0.400
	Extended	28	32.5	82.1	49.6	
Laparoscopy	No	45	32.5	67.9	47.0	0.454
	Yes	18	26.9	88.2	34.4	
Adjuvant therapy	No	26	30.0	76.0	36.1	0.879
	Yes	37	43.6	72.3	53.1	
Gross	Non-infiltrative	45	–	81.8	56.5	<0.001
	Infiltrative	18	12.8	52.9	15.1	
Differentiation	Well	26	–	92.3	61.8	0.003
	Moderate to poor	34	19.2	62.4	34.3	
Lymphatic invasion	Negative	55	33.8	77.4	47.7	0.083
	Positive	8	5.9	50.0	25.0	
Perineural invasion	Negative	55	43.6	77.4	50.4	0.003
	Positive	8	5.7	50.0	0.0	
Vascular invasion	Negative	60	32.5	74.1	46.0	0.256
	Positive	3	21.8	66.7	33.3	
Resection margin	Negative	48	43.6	84.7	52.9	<0.001
	Positive	15	6.4	40.0	22.2	
Lymph node metastasis	Negative	19	–	89.5	81.3	<0.001
	Positive	16	18.1	53.7	17.9	
Stage	IB	48	43.6	80.6	54.5	<0.001
	IIB	14	18.1	56.3	18.8	
	IV	1	2.2	0	0	

node metastasis was associated with infiltrative tumor, moderate to poor differentiation, and positive margin status in the current study. This can be explained by the fact that there are rich networks of blood and lymph vessels in the subserosal layer of the gallbladder wall through which invading cancer cells can spread.[20] In T2 cancers, lymph node dissection is an essential component of radical surgery, and regional lymph node metastases can be sufficiently managed by lymph node dissection.[14,21] Lymph node dissection could enhance overall survival significantly in the current study; therefore, lymph node dissection should also be performed.

The efficacy of bile duct resection in the treatment of T2 gallbladder cancer still remains controversial. The reason to perform bile duct resection in gallbladder cancers can be either due to the presence of gross involvement or to facilitate the performance of lymph node dissection in the hepatoduodenal ligament.[21] Furthermore, resection of the bile duct may offer a prognostic advantage when perineural invasion exists, even in the absence of bile duct invasion.[30] In order to perform not only a complete lymph node dissection in the hepatoduodenal ligament, but also to remove micrometastasis in the fat tissue, lymphatic duct, or perineural invasion, a combined resection of the bile duct is necessary.[4,23,31] In the current study, 14 patients received combined bile duct resection due to tumor involvement in the cystic duct margin or in order to perform complete lymph node dissection. The direct survival benefit of bile duct resection could not be determined in this study, most likely because the number of patients who underwent bile duct resection was quite small. Combined bile duct resection should be considered in the treatment of T2 gallbladder cancer to achieve oncologic clearance.

The optimal extent of liver resection for T2 gallbladder cancers remains debatable. In T2 gallbladder cancers, achievement of better survival has been reported using an aggressive surgical approach in the order of a S4a + S5 resection, an extended cholecystectomy, and a cholecystec-

Table 7 Multivariate Analysis of Prognostic Factors on Disease-Free Survival

Factor		*P* value	HR	95% CI
Age	≥65 <65	0.003	5.178	1.745–15.366
Transfusion	No Yes	0.174	0.176	0.014–2.152
R0	R0 Non-R0	0.028	3.970	1.165–13.533
Gross	Non-infiltrative Infiltrative	0.031	3.056	1.106–8.446
Differentiation	Well Moderate to poor	0.025	3.427	1.164–10.094
Perineural invasion	Negative Positive	0.412	1.789	0.446–7.172
Resection margin	Negative Positive	0.862	0.906	0.295–2.776
Lymph node metastasis	Negative Positive	0.171	2.030	0.737–5.586

CI confidence interval

tomy.[4] However, in an analysis of 4,243 cases of gallbladder cancers treated during a 10-year period at 112 institutions that belonged to the Japanese Society of Biliary Surgery, for gallbladder cancers without hepatoduodenal ligament invasion and without hepatic invasion, resection of the gallbladder bed was the preferred surgical hepatic procedure. For gallbladder cancers that invade any hepatic sites, a hepatic surgical procedure that can eliminate surgical margins is desirable.[32] Almost all patients in the present study who underwent liver resection received a gallbladder bed resection with a 2- or 3-cm margin.

The recurrence occurred mainly in the intra-abdominal organ. Age younger than 65 years, non-R0 resection, infiltrative tumors, and moderate to poor differentiation were independent prognostic factors of recurrence in the multivariate analysis. Similarly, other investigators have observed that young age group and poor differentiation are common in the early recurrence group and infiltrating type and poor differentiation tumors were independent factors predicting recurrence with stage II gallbladder cancers.[33] For T2 gallbladder cancers, the presence of lymphatic invasion was a significant factor related to disease-free survival.[34] In the analysis of all stages of gallbladder cancers, comparison of patients with and without tumor recurrence after curative treatment for gallbladder cancers indicated that the presence of lymph node metastasis and lymphovascular permeation were significant prognostic factors for recurrence.[3]

In this study, a relatively high proportion of patients were categorized as Rx. R0 resection for T2 tumors was achieved only in 32 patients. This study was based on a retrospective analysis of available medical records, which means that it was difficult to find the exact reason that a surgeon did not perform an extended cholecystectomy, conversion to radical surgery, or additional second operation. According to medical records, some patients rejected additional surgery. Some other patients were excluded from a conversion to radical surgery or second radical surgery because of poor general health. And most patients with gallbladder cancer were older. Therefore, extended surgery was performed on a limited basis. As discussed previously, our review of the literature demonstrated that a small proportion of patients (5.6%) received radical surgery in T2 gallbladder cancer, despite a significant survival advantage for patients with T2 gallbladder cancer who had undergone radical resection.[28]

In conclusion, the prognosis after surgical resection for T2 gallbladder cancers is affected by R status, operation type, lymph node dissection, and aggressive tumor characteristics such as infiltrative tumor, moderate to poor differentiation, the presence of lymphatic invasion, perineural invasion, and vascular invasion, lymph node metastasis, and stage in the univariate analysis. In the multivariate analysis, R0 resection and lymph node dissection significantly enhance the overall survival. The presence of perineural and vascular invasion and moderate to poor differentiation of the tumor had a detrimental prognosis. In the univariate analysis of disease-free survival, age younger than 65 years, R status, infiltrative tumor, moderate to poor differentiation, the presence of perineural invasion, resection margin status, lymph node metastasis, and stage were significant predictors. Furthermore, in the multivariate analysis, age younger than 65 years and non-R0 resection, infiltrative type, and moderate to poor differentiation of the tumor had a significantly poorer disease-free survival. Many pathological factors were not detectable in the preoperative evaluation. Tumors with infiltrative types and suspicious lymph node metastasis in

the intraoperative finding were candidates for more aggressive surgical management. For T2 tumors, R0 resection should be performed because R0 resection with clearly negative resection margin significantly enhances the survival. Therefore, extended radical surgery including lymph node dissection should be performed in T2 tumors because the survival of Rx patients who undergo cholecystectomy alone is similar to that of R1 patients. T2 tumors showing the above-stated aggressive tumor characteristics could be considered potential recipients for adjuvant chemoradiation therapy, although the efficacy of adjuvant chemotherapy for the treatment of gallbladder cancers has not been clearly proven yet. Adjuvant chemoradiation therapy following surgical resection warrants further investigation to improve survival of gallbladder cancer patients.

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J Gastrointest Surg (2010) 14:679–687
DOI 10.1007/s11605-009-1140-z

ORIGINAL ARTICLE

Risk Factors Influencing Recurrence, Patterns of Recurrence, and the Efficacy of Adjuvant Therapy After Radical Resection for Gallbladder Carcinoma

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Received: 24 September 2009 / Accepted: 14 December 2009 / Published online: 22 January 2010

Abstract
Backgrounds Gallbladder carcinoma (GBC) is an aggressive neoplasm, and resection is the only curative modality. Recurrence frequently occurs after the curative resection of advanced GBC. Adjuvant treatment, particularly radiotherapy, is recommended and is used without any evidence of a beneficial effect. The aim of this study was to characterize patterns of recurrence and to identify the factors that influence recurrence and the efficacy of adjuvant therapy after the curative resection of GBC.
Methods The records of patients that underwent surgical resection with curative intent for gallbladder carcinoma from October 1994 and August 2007 were retrospectively reviewed. Recurrence patterns, times to recurrence, and survival rates were analyzed. Sites of recurrence were identified retrospectively and categorized as locoregional or distant.
Results One hundred sixty-six patients underwent surgical resection with curative intent for gallbladder adenocarcinoma. The 5-year recurrence rates of stages IA, IB, IIA, and IIB patients were 0%, 24.3%, 44.9%, and 58.3%, retrospectively. Positivity for lymph node metastases was found to have predictive significance for disease-free survival (p=0.009). Regional lymph node recurrence (27.7%) was observed most frequently. There was no significant disease-free survival rates between the no adjuvant therapy and the adjuvant therapy groups.
Conclusions The regional lymph nodes and the liver were found to be the most common sites of recurrence after curative resection. Lymph node metastases were identified as an independent predictor of tumor recurrence by multivariate analysis. Based on the disease-free survivals observed in this study, the authors find it would be difficult to advocate the routine use of adjuvant radiotherapy and/or chemotherapy

Keywords Gallbladder carcinoma · Predictive factor · Lymph node metastasis · Pattern of disease recurrence · Adjuvant therapy

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Introduction

Gallbladder carcinoma (GBC) was first described by Maximillian Destoll in 1777[1] and is the most frequently encountered malignancy of the biliary system. Although it is a relatively rare disease, with an annual incidence estimated at one to two people per 100,000,[2] it is highly aggressive. Gallbladder adenocarcinoma has traditionally been associat-

ed with a poor prognosis, with an overall survival of from 5% to 10%.[3,4] Complete surgical resection is the only potentially curative treatment for gallbladder cancer,[3,5] and despite advances in imaging techniques, most patients are diagnosed with advanced disease. More recently, extended operations that combine hepatic resection, lymph node dissection, and even common bile duct resection with reconstructive hepaticojejunostomy have been advocated to improve long-term survival.[6,7] However, recurrence remains the main problem after curative resection in cases of advanced disease. Nevertheless, few studies have addressed the recurrence of GBC after curative resection. Furthermore, the roles for adjuvant chemotherapy and radiotherapy have not been properly defined, although both are commonly used. In particular, radiotherapy is often recommended after gallbladder cancer resection, based on the assumption that improving locoregional disease control improves survival.[8,9] The purposes of this study were to identify the factors that affect recurrence, to characterize the pattern of recurrence, and to determine the efficacies of adjuvant therapies after the curative resection of gallbladder carcinoma.

Materials and Methods

The medical records of patients that underwent surgical resection with curative intent for gallbladder carcinoma from October 1994 and August 2007 at our institute were retrospectively reviewed. Only patients with histologically proven adenocarcinoma were included. All operative procedures were performed with curative intent. Resection with curative intent was defined as eradication of whole tumor with potential microscopically negative resection, that is, R0 resection. Patients that underwent R1 resection, palliative procedures, or stage IV patients were excluded.

The medical records of eligible patients were evaluated. These included surgeon's notes, radiologic images, pathology reports, and discharge summaries. Data regarding resection and pathologic variables included overall stage, T classification, N classification, tumor differentiation, and microinvasion. Histological differentiation was classified from well to moderately differentiated, to poorly differentiated. Pathological examination of lymph nodes metastasis was based on a protocol. All lymph nodes in specimen were harvested clearly by pathologist, and the lymph node metastasis status was determined by microscopic examination of individual hematoxylin and eosin-dyed specimens from bisection of resected lymph node. Tumor staging was performed according to sixth edition of the American Joint Committee on Cancer.

Table 1 Patients Demographics and Tumor Pathologic Results

Characteristics	No. of patients (%)
Gender (male/female)	
Male	80 (48.2)
Female	86 (51.8)
Median age, years (range)	61.0 (30–79)
Bilirubin, mg/dl (range)	0.7 (0.2–13.3)
CA19-9, U/ml (range)	17.7 (0.1–28,400)
Stage	
IA	27 (16.3)
IB	56 (33.7)
IIA	14 (8.4)
IIB	55 (33.1)
III	14 (8.4)
Differentiation	
Well/moderate	132 (79.5)
Poor	30 (18.1)
Adjuvant therapy	40 (24.1)
Radiation	22
Chemotherapy	1
Chemoradiotherapy	17

Table 2 Details of Operative Procedures

Operative procedures	No. of patients (%)
Cholecystectomy	33 (19.9)
Cholecystectomy + LN	19 (11.4)
Cholecystectomy + LN + BD	14[a] (8.4)
Cholecystectomy + LN + hepatectomy	82 (49.4)
Type of hepatectomy	
GBBR or wedge resection	21[b] (12.7)
Subsegmentectomy of 4b+5	48 (28.9)
Extended right hepatectomy	8 (4.8)
Extended left hepatectomy	1 (0.6)
Central inferior hepatectomy	1 (0.6)
Right trisectionectomy	3 (1.8)
Cholecystectomy + LN + hepatectomy + BD	18 (10.8)
Type of hepatectomy	
GBBR or wedge resection	3[c] (1.8)
Subsegmentectomy of 4b+5	8 (4.8)
Extended right hepatectomy	5 (3.0)
Right trisectionectomy	2[d] (1.2)
Total	166 (100.0)

LN lymph node dissection, *BD* extrahepatic bile duct resection, *GBBR* gallbladder bed resection (up to 2 cm in depth), *PD* pancreatoduodenectomy

[a] One with pancreatoduodenectomy

[b] One with right hemicolectomy

[c] One with pancreatoduodenectomy

[d] One with pancreatoduodenectomy

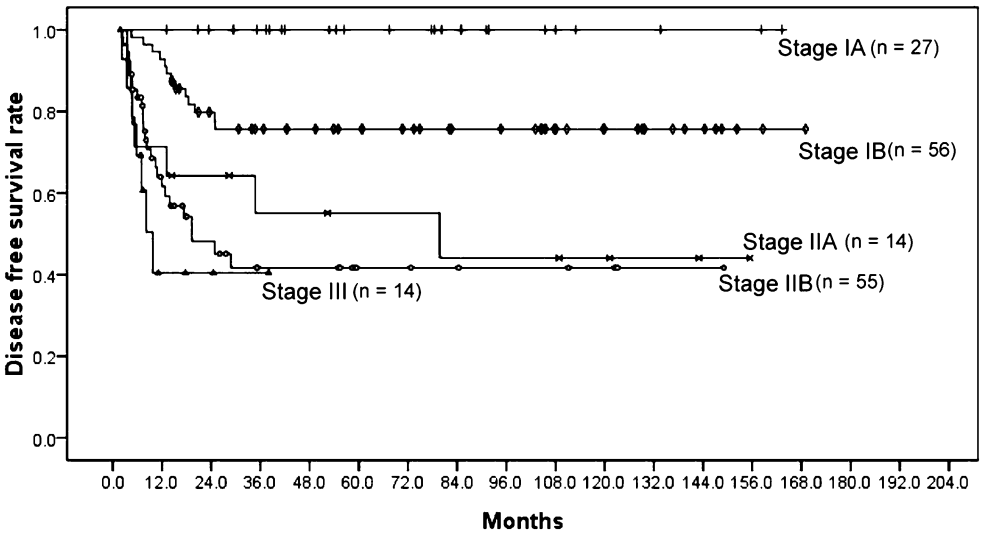

Figure 1 Disease-free survival for patients who underwent curative resection for gallbladder carcinoma.

Sites of first disease recurrence, times to disease recurrence, and survival rates were analyzed. Sites of initial disease recurrence were determined using CT images and were classified as local disease recurrence (hepatic resection margin, bilioenteric anastomosis, or porta hepatis), regional disease recurrence (retroperitoneal and regional lymph node), or distant disease recurrence (intrahepatic, peritoneum, or other organs). With regards to the postoperative adjuvant therapy, decision in each patient was made by the attending surgeon's preference or severity of tumor stage.

Categorical variables were compared using the chi-square test. Survival probabilities were estimated using the Kaplan–Meier method and compared using the log-rank test. Survival (in months) was measured from the date of surgery to date of death or last contact. Cox regression analysis was used to identify independent predictors of disease recurrence using factors found to be significant by univariate analysis. p values of less than 0.05 were considered statistically significant.

Table 3 Patterns of Recurrence after Curative Resection

Site	No. of recurrence (%)
Local	
Hilum	10 (13.9)
Bilioenteric anastomosis	4 (5.6)
Liver (resection margin)	1 (1.4)
Regional	
Retroperitoneal LNs	20 (27.8)
Distant	
Liver (intrahepatic)	16 (22.2)
LNs	10 (13.9)
Peritoneum	5 (6.9)
Lung	4 (5.6)
Bone	1 (1.4)
Abdominal wall	1 (1.4)
Total no. of recurrence	72 (100.0)

Results

One hundred sixty-six patients that underwent surgical resection with curative intent for gallbladder adenocarcinoma between Oct 1994 and Aug 2007 were enrolled in this study. Microscopically curative resections with cancer-free surgical resection margins were achieved in all patients (R0 resection). The demographics of the patient population are summarized in Table 1. Operative procedures performed in the 166 patients are shown in Table 2. Various operations were undertaken from simple cholecystectomy to extended liver resection combined with pancreatoduodenectomy. Extent of lymphadenectomy was the hepatoduodenal ligament, head of pancreas, and common hepatic artery area. A total of 1,286

Table 4 Numbers of Patients with Initial Disease Recurrence at a Locoregional Site Only, Concomitant Locoregional and Distant Site, and a Distant Site Only

	Locoregional site	Concomitant site	Distant site
Stage			
IB	6	1	6
IIA	3	1	3
IIB	9	8	9
III	2	2	3
Total	20	12	21

Table 5 Proportion of Patients with Initial Disease Recurrence at a Locoregional Site only or at a Distant Site (With or Without Concomitant Locoregional Disease Recurrence)

	Locoregional disease recurrence	Distant disease recurrence	*p* value
Stage			
IB	6	7	0.782
IIA	3	4	0.705
IIB	9	17	0.117
III	2	5	0.257
Total	20	33	0.074

Table 6 Univariate Analysis for Predictive Factors Influencing Recurrence After Curative Resection

Variables	No. of patients	Disease-free survival (%)		*p* value
		1 year	5 years	
Age (years)				
<60	79	78.7	67.7	0.645
≥60	87	79.9	63.1	
Gender				
Male	80	82.8	72.0	0.136
Female	86	76.4	58.5	
Bilirubin (mg/dl)				
<1.5	145	79.4	68.7	0.015
≥1.5	21	73.7	34.5	
CA19-9 (U/ml)				
<35	96	86.1	75.8	<0.001
≥35	49	67.1	38.0	
Adjuvant therapy[a]				
No	47	57.7	45.9	0.502
Yes	36	64.5	41.7	
Lymphatic invasion				
Negative	86	84.5	69.4	0.006
Positive	30	64.5	43.0	
Vascular invasion				
Negative	62	80.0	61.2	0.088
Positive	9	75.0	20.0	
Neural invasion				
Negative	93	82.3	69.4	<0.001
Positive	23	62.2	30.5	
Differentiation				
Well/moderate	132	82.1	69.4	0.041
Poor	30	71.2	58.6	
T stage classification				
<3	113	89.2	74.6	<0.001
≥3	53	56.6	42.4	
Lymph node status				
Negative	99	89.8	77.6	<0.001
Positive	64	58.0	39.7	

[a] Over stage IIA

Table 7 Multivariate Analysis for Predictive Factors Influencing Recurrence After Curative Resection, Performed Based on the Result of the Univariate Analysis

Variable	Hazard ratio	95% CI	*p* value
Bilirubin (≥1.5 mg/dl)	0.899	0.217–1.703	0.343
CA19-9 (≥35 U/ml)	0.086	0.462–2.846	0.769
Lymphatic invasion (+)	0.007	0.379–2.872	0.934
Neural invasion (+)	0.556	0.490–4.900	0.456
Poorly differentiation	2.114	0.777–5.502	0.146
T stage (≥T3)	0.381	0.179–2.453	0.537
Lymph node status (+)	6.755	1.313–6.971	0.009

lymph nodes were removed from the 133 patients, a median of 8 (range 1–43) per patients, and lymph node metastasis was found in 221 (17.2%) of 1,286 lymph nodes by microscopic examination. The 64 patients (38.6%) of total patients had regional lymph node metastases. Follow-up periods ranged from 4.6 to 169 months, and the overall median survival time determined using the Kaplan–Meyer method was 34.5 months. Patients were classified by pathological stage: stage IA (n=27), stage IB (n=56), stage IIA (n=14), stage IIB (n=55), and stage III (n=14).

Among 166 patients, 53 patients had tumor recurrence. The median interval between surgery and the diagnosis of disease recurrence was 8 months (range, 2 to 80 months). The 1-year disease-free survival rates of stages IA, IB, IIA, IIB, and III patients were 100%, 92.9%, 71.4%, 64.0%, and 40.4%. The 3-year disease-free survival rates were 100%, 75.7%, 55.1%, 41.7%, and 40.4%, retrospectively (Fig. 1).

The main patterns of recurrence in these 53 patients are shown in Table 3. Regional lymph nodes recurrence (27.7%) was observed most frequently, followed by intrahepatic recurrence (22.2%). Twenty-one patients (39.6%) experienced distant recurrence and 20 (37.7%) locoregional recurrence, and 12 patients (22.6%) had more than one recurrence site (Table 4). No significant difference between recurrence sites was observed between the two groups that were compared in

Table 8 Adjuvant Therapy in Each Stage

	Chemotherapy alone	Radiation alone	CCRT
Stage			
IA	–	–	–
IB	–	4	–
IIA	–	1	3
IIB	–	14	12
III	1	3	2
Total no.	1	22	17

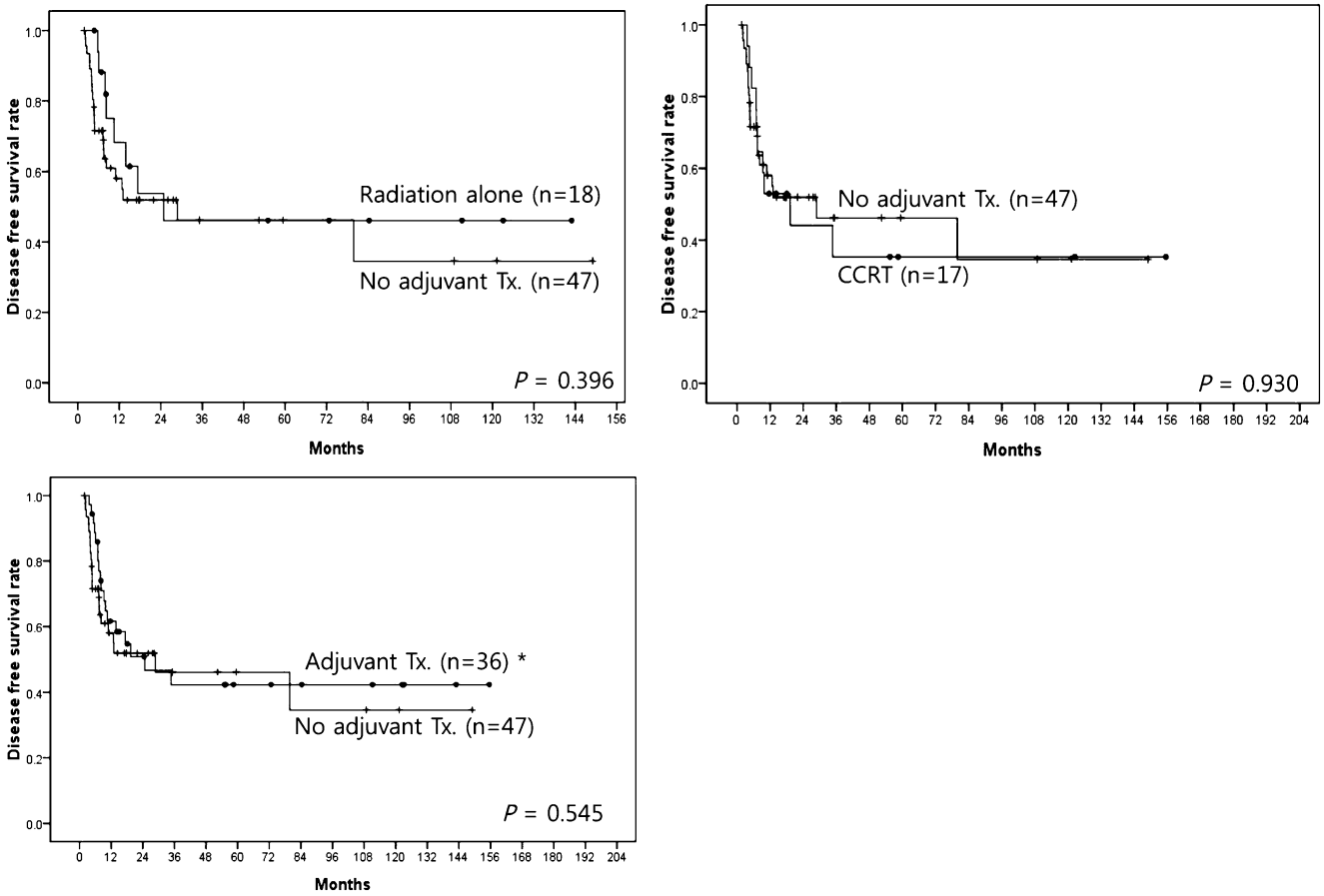

Figure 2 Disease-free survival curve according to radiation alone, concomitant chemoradiotherapy, and adjuvant therapy in stages II and III patients (*asterisk* included one case of chemotherapy).

terms of local regional recurrence alone versus recurrence at a distant site with or without concomitant locoregional recurrence (Table 5).

Univariate analysis conducted to indentify predictors of disease-free survival revealed that seven factors had a significant effect, serum CA19-9 >35 U/ml ($p<0.001$), serum bilirubin concentration >1.5 mg/dl ($p=0.015$), positive lymphatic invasion ($p=0.006$), positive neural invasion ($p<0.001$), a stage exceeding T3 ($p<0.001$), and positivity for lymph node metastases ($p<0.001$; Table 6). Multivariate Cox regression analysis on factors identified by univariate analysis showed that the presence of lymph node metastases significantly influenced disease-free survival ($p=0.009$; Table 7).

Forty-four (24.1%) received adjuvant therapy with chemotherapy ± radiation therapy after resection (Table 8). Chemotherapeutic drugs for adjuvant therapy were 5-fluorouracil (5-FU), cisplatin or capecitabine with single or combination regimen. Radiotherapy consisted of a total dose of 4,400 to 4,500 cGy, divided into 24 to 25 sessions. The majority of patients who received adjuvant treatment were in stage IIB or stage III. Twenty-two of the 44 received only radiotherapy, one received systemic chemotherapy, and 17 received both radiotherapy and systemic chemotherapy. Concerning patients with advanced disease (stage II or III), there was no significant disease-free survival rate when we compared if the patients had adjuvant treatment, radiation, systemic chemotherapy, and concomitant (concurrent) chemoradiotherapy (Fig. 2). Subset analysis by stage failed to detect the significant difference between the no adjuvant therapy and the adjuvant therapy groups (Figs. 3, 4, and 5).

Discussion

Gallbladder carcinoma is more prevalent in Asians than in Caucasians, though the incidence of gallbladder carcinoma is increasing in the West. A recent French study[10] reported a standardized annual incidence of 0.6 cases per 100,000 men and 1.7 cases per 100,000 women. Large-scale studies on gallbladder carcinoma have demonstrated only 2.7% to 15% overall 5-year survival rates in the USA and Europe.[10,11] However, recently published reports have

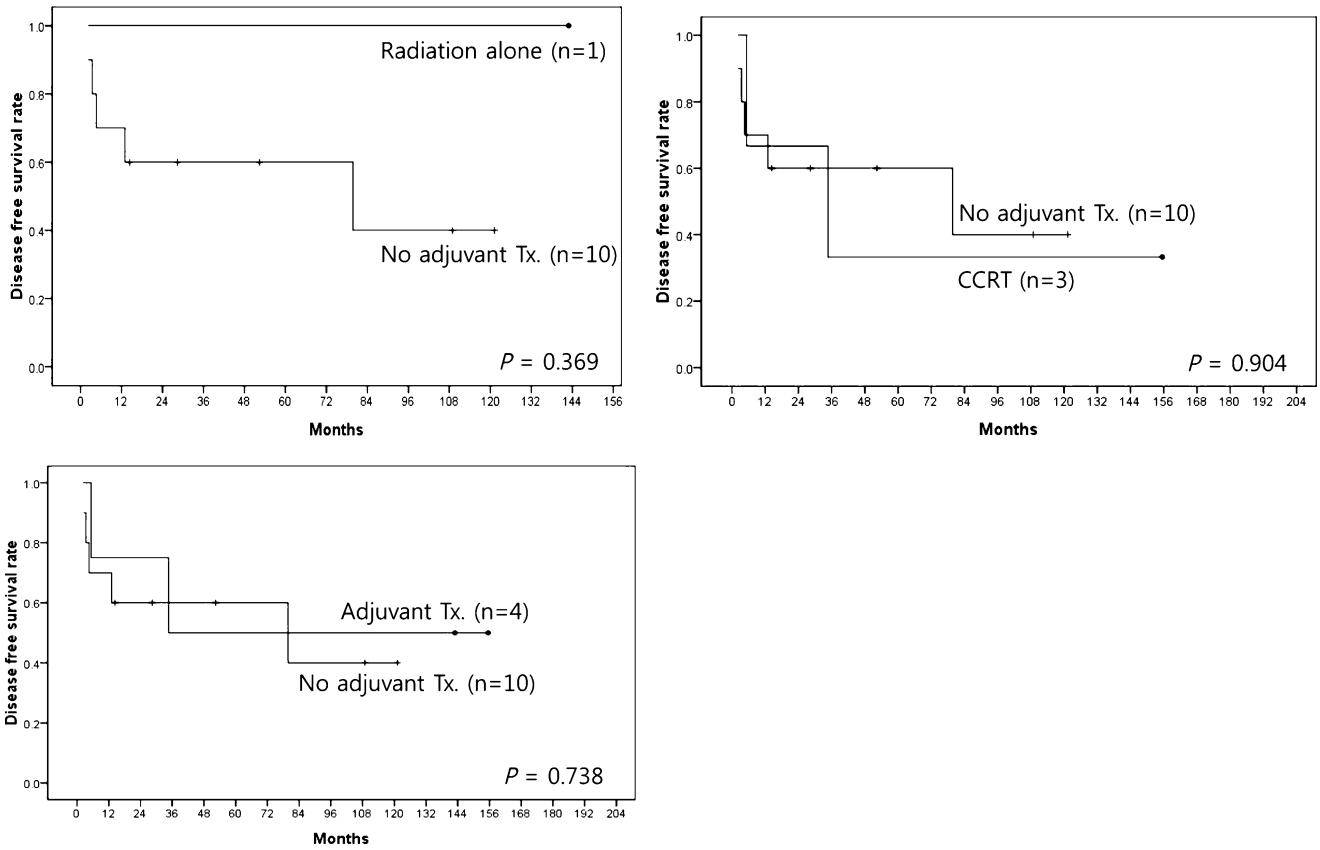

Figure 3 Disease-free survival curve according to radiation alone, concomitant chemoradiotherapy, and adjuvant therapy in stage IIA patients.

shown that aggressive surgical resection for advanced stage carcinoma can improve prognosis.[6,7,12,13]

Many published studies have focused on the prognosis of gallbladder carcinoma.[6,7,12–15] Aramaki et al.[16] reported that the absence of lymphatic vessel invasion is a significant indicator of good disease-free survival and that lymph node, venous, or perineural invasion, and surgical procedure are not significant factors of disease-free survival in patients with T2 gallbladder carcinoma. Park et al.[17] reported that those with an age of <60 years and a poorly differentiated tumor were overrepresented in their early recurrence stage II patient group. Several studies have reported that lymph node metastasis is an important indicator of prognosis,[6,18,19] which concurs with our finding that lymph node metastasis independently predicts tumor recurrence.

As occurs in other malignancies, tumor recurrence after radical resection for gallbladder carcinoma invariably leads to death. However, little information is available regarding disease recurrence patterns after the curative resection of gallbladder carcinoma. In the present study, disease recurrence sites were categorized as locoregional or distant based on proximity to the resection field, possible mechanisms of dissemination, and, in part, on the likelihood that such anatomic sites would be included in postoperative radiotherapy regimens. Locoregional disease recurrence along the resection margin in the porta hepatis or in the retroperitoneum is likely to arise from microscopic residual disease or from disease in the lymphatics and could be included in the radiation treatment field. On the other hand, intrahepatic and recurrences at other distant sites result from hematogenous spread and would not be treated. Aramaki et al.[16] reported that recurrence is commonest in intra-abdominal organs, such as the liver and aortocaval lymph nodes. Chan et al.[20] reported that 12 of 23 patients (52%) that received curative treatment developed tumor recurrence (local recurrence in eight, distant recurrence in four). Park et al.[17] reported that the commonest site of recurrence were the aortocaval lymph nodes and the liver in stage II patients, whereas in the present study, the regional the lymph nodes and liver were more frequently affected.

Radiotherapy is often recommended after gallbladder carcinoma resection based on the assumption that it reduces locoregional disease recurrence rates.[8,9] Several investigators have emphasized the values of chemotherapy and radiotherapy,[21–23] but the value of adjuvant therapy remains

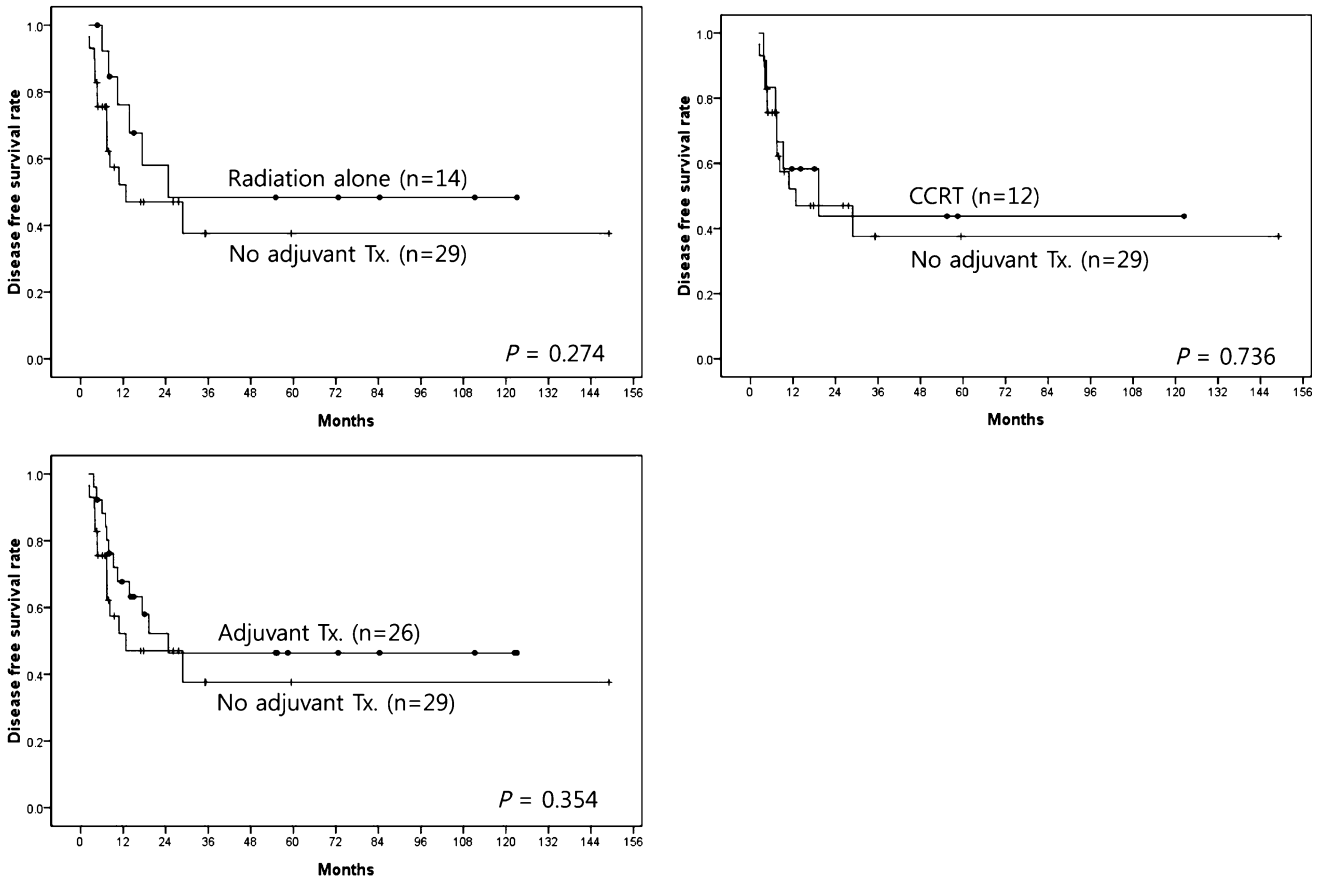

Figure 4 Disease-free survival curve according to radiation alone, concomitant chemoradiotherapy, and adjuvant therapy in stage IIB patients.

controversial.[24,25] In particular, it has not been determined whether adjuvant chemotherapy and/or radiotherapy reduce disease recurrence. This is due largely to the rarity of gallbladder carcinoma and the difficulty of recruiting sufficient cases for randomized trials. Nevertheless, despite this absence of a proven efficacy, adjuvant treatment, particularly radiotherapy, is recommended and frequently used. This practice has been fostered by a number of small, single-institution, nonrandomized studies that have suggested that radiotherapy confers a survival benefit when administered as an adjuvant treatment after gallbladder carcinoma resection.[8,9] Traditional adjuvant chemotherapeutic regimens generally include fluorouracil, and external radiation is often used in conjunction with fluorouracil chemosensitization, but little information is available to support its efficacy. In 2002, Takada et al.[26] reported the findings of a prospective, randomized phase-III trial in which the role of adjuvant chemotherapy in 508 patients diagnosed with resectable pancreaticobiliary carcinoma (112 of whom had gallbladder carcinoma) was examined. Patients were randomized to receive surgical resection alone or resection plus adjuvant 5-FU and mitomycin C chemotherapy. The 5-year survival rate for patients in the adjuvant treatment group was 26%, which compared with 14% in the resection alone control group (p=0.04). de Aretxabala et al.[27] found that chemoradiation had no positive effect and possibly had a detrimental effect in patients with gallbladder carcinoma. In specific cases, better survival was observed when adjuvant radiotherapy was administered to those with a positive surgical margin after radical resection for advanced gallbladder carcinoma.[22,28] An improvement in medium survival was also reported by adding intraoperative and postoperative radiation therapy to patients with residual disease following resection, but there was little evidence that adjuvant therapies conferred benefit in curatively resected gallbladder carcinoma.[22] Jarnagin et al.[29] from Memorial Sloan-Kettering Cancer Center reported the low rate recurrence at locoregional site alone (15%) and so radiotherapy which targeting locoregional recurrence is not likely to have an impact in gallbladder cancer. Based on the disease-free survivals observed in the present study, it would be difficult to advocate the routine use of adjuvant radiotherapy and/or chemotherapy after the curative resection of advanced gallbladder carcinoma.

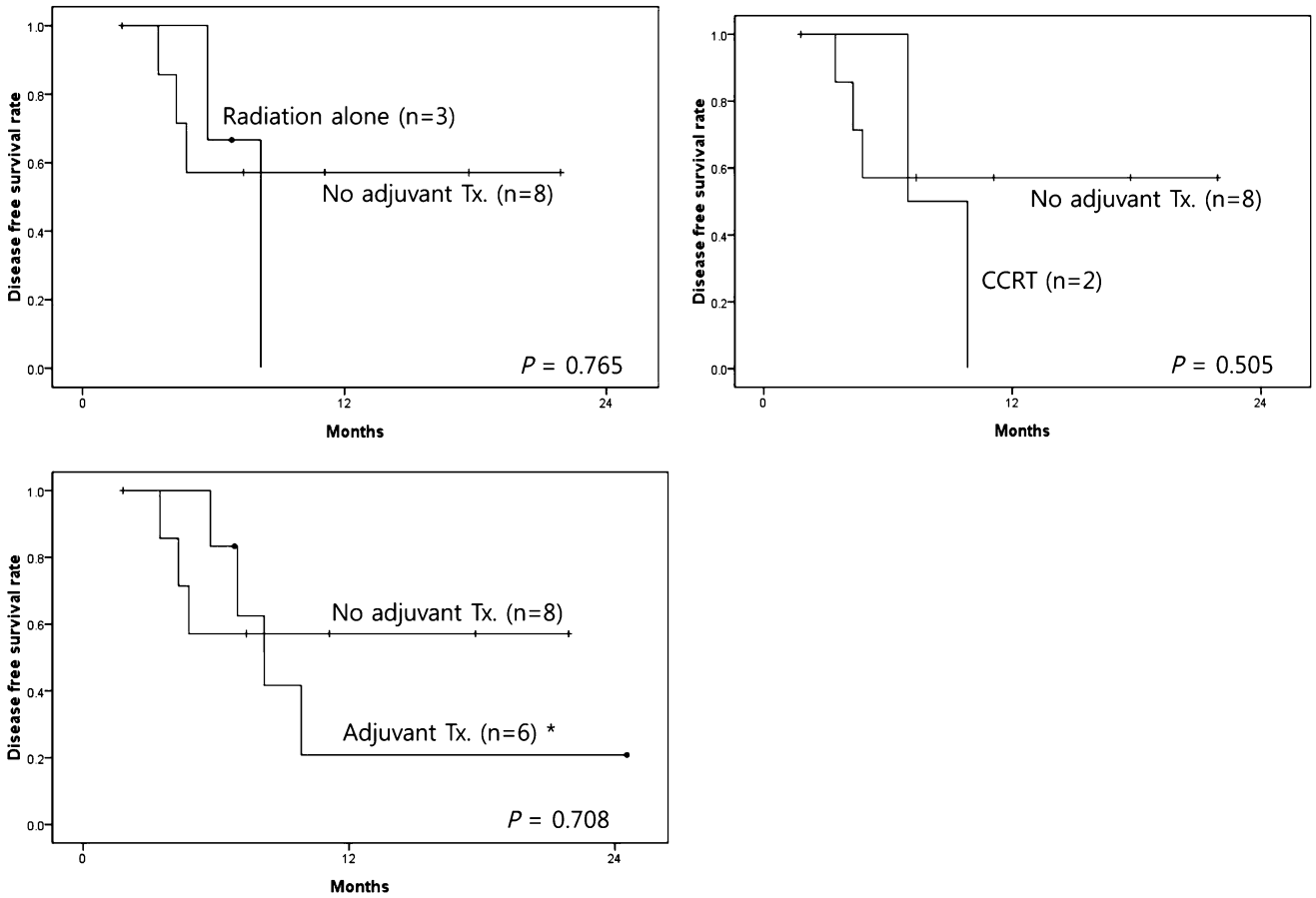

Figure 5 Disease-free survival curve according to radiation alone, concomitant chemoradiotherapy, and adjuvant therapy in stage III patients (*asterisk* included one case of chemotherapy).

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J Gastrointest Surg (2010) 14:688–696
DOI 10.1007/s11605-009-1131-0

ORIGINAL ARTICLE

Biliary Complications Secondary to Post-Cholecystectomy Clip Migration: A Review of 69 Cases

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Received: 11 June 2009 / Accepted: 4 December 2009 / Published online: 5 January 2010

Abstract
Introduction Post-cholecystectomy clip migration (PCCM) is rare and can lead to complications which include clip-related biliary stones. Most have been reported as case reports. This study reviews cases of clip migration reported in the literatures.
Method Searches and reviews of the literatures from "PubMed," "EMBASE," and "Google Scholar" search engines using the keywords "clip migration" and "bile duct stones" were carried out. Eighty cases from 69 publications were identified but details for only 69 cases were available for the study.
Results The median age at presentations of PCCM was 60 years old (range, 31 to 88 years; female, 61.8%) and the median time from the initial cholecystectomy to clinical presentations was 26 months (range, 11 days to 20 years). Of primary surgeries, 23.2% was for complicated gallstones disease. The median number of clips placed during surgery was six (range, two to more than ten clips). Common diagnoses at presentations of PCCM were obstructive jaundice (37.7%), cholangitis (27.5%), biliary colic (18.8%), and acute pancreatitis (8.7%). The median number of migrated clip was one (range, one to six). Biliary dilatation and strictures were encountered in 74.1% and 28.6%, respectively. Of the 69 cases of PCCM-associated complications, 53 (77%) were successfully treated with endoscopic retrograde cholangiopancreatography (ERCP), 14 (20.2%) with surgery, and one (1.4%) with successful percutaneous transhepatic cholangiography treatment. One patient had spontaneous clearance of PCCM. There was no reported mortality related to PCCM.
Conclusion PCCM can occur at any time but typically occur at a median of 2 years after cholecystectomy. Clinical presentations are similar to those with primary or secondary choledocholithiasis. Most can be managed successfully with ERCP.

Keywords Cholecystectomy · Complications · Clip migrations · Iatrogenic biliary stones · Endoscopic retrograde cholangiopancreatography

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Introduction

Gallstones disease is common and cholecystectomy is the treatment of choice for symptomatic disease. Cholecystectomy is one of the most common operations in clinical practice, and in the United States, over half a million procedures are carried out annually.[1] Since the introduction of the laparoscopic technique, laparoscopic cholecystectomy (LC) has become the gold standard for the management of symptomatic gallstones disease.[1,2] Complications in association with LC have been reported to be <5%. However, this is still higher than that of open cholecystectomy (OC).[3–5] Recent reports have shown lower and comparable complications rates.[6] Complications can be categorized into early or late.[7] Early complications include bile duct injuries, bleeding, and wound infections. Fortu-

nately, most are minor and easily managed. However, serious early complications such as major bile duct injuries are associated with prolonged hospital stay, requirement for further surgeries, and potential long-term complications such as strictures, all resulting in increased health care cost.[7,8] They are also associated with litigation.[9] Late complications include biliary strictures and post-cholecystectomy clip migration (PCCM).

Since its introduction, surgical hemostatic clips have been widely used and are generally considered very safe. Migration of clip into the bile duct with resultant stone formations is well recognized.[10] The first case of PCCM was reported in 1978.[11] Despite the increasing number of cholecystectomy being performed annually, PCCM remains rare. Apart from migration into the biliary tree, PCCM resulting in other complications such as duodenal ulcer or clip embolism have also been reported.[12–14] This study reviewed the literatures and presents the characteristics and treatment outcomes of 69 cases of PCCM that had resulted in biliary complications.

Methods

Publications on PCCM were identified from the literatures through three search strategies. The first search strategy involved searches through the "PubMed" and "EMBASE" databases using the keywords "clip migration" and "bile duct stones." The "PubMed" citations were then used to obtain details of the reported cases. The second strategy involved using the "Google Scholar" search engine using the same keywords. The third strategy involved the review of the references for further relevant articles on PCCM cited by relevant publications identified through the initial two strategies.

Overall, 69 publications reporting 80 cases were identified from the three search strategies. Fifty-seven publications were identified from "PubMed" and "EMBASE,"[11,15–70] one from "Google Scholar" which was not indexed in either "PubMed" or "EMBASE,"[71] and finally another 11 publications from reviewing the references of the initial 57 publications.[72–82] The final strategy identified mostly articles published in the non-English literatures. These 11 publications were also not indexed in either the "PubMed" or "EMBASE" database but could be retrieved from the journal website or through the "Google Scholar" search engine using specific details, i.e., title of publications.

The total number of publications and cases reported are shown in Fig. 1. Most of the publications had originated almost equally from the three major continents: Europe (n=20, 29.1%), Asia (n=25, 36.2%), and North America (n=23, 33.3% [United States, n=22 and Canada, n=1]). One publication originated from South America (n=1, 1.4%).

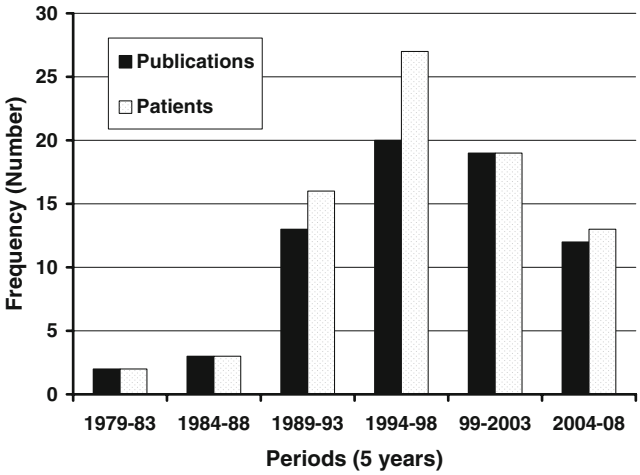

Figure 1 The numbers of publications in 5-year blocks (*dark columns*) and the number of cases reported (*lighter columns*).

Majority of the publications reported a single case and four reported multiple cases (three reported two cases and one reported four cases).

Attempts were made to retrieve all the identified publications. In cases where full articles were not available, the abstracts that had been published in English were carefully reviewed. Only abstracts that had provided adequate details were included. Overall, six publications that had reported a total of 11 cases provided inadequate details and were excluded, leaving 69 cases for the review.[32,40,47,62,63,78] Most of the excluded publications were published in non-English journals. For the articles published in non-English journals and where full publication articles were available, full translations were obtained through interpreters. The corresponding authors were also contacted via e-mail when required. All available publications were carefully analyzed. Clinical data were collected on demographics (age and gender), presentations, diagnoses, primary operative details (OC or LC: uneventful or complicated and details of complications), and number of clips used during the primary operation (stated or counted from radiological imaging provided). Data on the presence of ductal dilatations and strictures (stated or through imaging provided), treatment provided (surgery, endoscopic retrograde cholangiopancreatography [ERCP], or percutaneous transhepatic cholangiography [PTC]) and outcomes, laboratory investigations, and the number of clips found to have migrated were retrieved.

Results

The median age at presentations was 60 years old (range, 31 to 88 years) with more females being affected (n=42, 61.8%). The majority had no premorbid conditions reported.

Most of the cholecystectomies were carried out for symptomatic gallstones diseases with the exception of two cases: one for gallbladder polyp and another was carried out as part of orthotopic liver transplantation (OLT). Overall, 23.2% of the surgeries were done for complicated gallstones disease. Details of indications and types of operations carried out are shown in Table 1. Metal clips were used in all cases except for two cases where absorbable clips were used. The median number of clips used was six (range, two to 14).

The median time from cholecystectomies to clinical presentation of symptoms related to PCCM was 26 months (range, 11 days to 20 years). Three cases of PCCM occurred within 4 weeks of cholecystectomies and all occurred without stone formation.

Reported clinical symptoms and admitting diagnoses of PCCM are shown in Table 2. The most common clinical presentations were abdominal pain, jaundice, and fever. At presentations, the most common admitting diagnoses were obstructive jaundice, cholangitis, and biliary colic.

Table 1 Details of Indications and Initial Operations

Details	*n* (%)
Indications	
Uncomplicated gallstones disease	51 (73.8)
Complicated gallstones disease	16 (23.2)[a]
Others	2 (2.9)[b]
Types of operations	
LC	47 (68.1)
Uneventful	13 (27.7)
Complicated	7 (14.9)
Bile leak	5 (10.6)
Gall bladder rupture	1 (2.1)
Bleeding	1 (2.1)
Converted to OC	3 (6.4%)
No data available	24 (51.0)[c]
OC	25 (36.2)
Uneventful	7 (28.0)[d]
Complicated	4 (16.0)[e]
Converted from LC	3 (12.0)
No data available	11 (44.0)

[a] Included acute or chronic cholecystitis (n=10), acute gangrenous cholecystitis (n=1), gallstones with CBD stone extractions (n=4), and chronic granulomatous cholecystitis (n=1)

[b] Included gallbladder polyp (n=1) and surgery part of OLT (n=1)

[c] Included common bile perforation (n=1), bleeding (n=1), and technical failure (n=1)

[d] Included bile duct exploration (n=3), part of OLT (n=1), operation for gangrenous cholecystitis (n=1), and uneventful OC (n=2)

[e] Included retained stone that passed spontaneously (n=1), bleeding (n=1), stricture formation (n=1), and friable cystic duct stump (n=1)

Table 2 The Clinical Presentations and Diagnoses of Patients with PCCM

	n (%)
Clinical symptoms	
Abdominal pain	58 (84.1)
Jaundice	53 (76.8)
Fever	22 (31.9)
Nausea/vomiting	18 (26.1)
Loss of appetite	5 (7.2)
Pruritus	3 (4.3)
Weight loss	1 (1.4)
Admitting diagnosis	
Obstructive jaundice	26 (37.7)
Cholangitis (± septic shock)	19 (27.5)
Biliary colic	13 (18.8)
Acute pancreatitis	6 (8.7)
Incidental finding	
Abnormal liver function test/pruritus	1 (1.4)
Clip in abnormal position on radiography	2 (2.9)

Overlap occurred as some patients had multiple symptoms and diagnosis

The median number of migrated clip was one (range, one to six). Thirteen cases (18.8%) had clip migrations without inducing stone formations. All of these PCCM occurred within 12 months after cholecystectomies with the exception of one case which occurred at 168 months. Overall, PCCM without stone formation occurred at a significantly shorter time interval between surgeries and presentation of PCCM (median, 5.5 months; range, 0.37 to 168 months) compared to PCCM with stone formations (median, 36 months; range, 3 to 240 months; $p<0.001$, Mann–Whitney test).

Biliary dilatation (Fig. 2) and strictures (Fig. 3) were reported in 74.1% and 28.6%, respectively. Strictures were located near the cystic duct remnant. The postulated mechanisms that contributed to PCCM and subsequent biliary complications included: bile duct injuries secondary to incorrect clip placements, inadvertent placement into the biliary tree, clip slippage resulting in wound dehiscence, bile leak and biloma formation with or without infection, placement of too many clips, and difficult operations either secondary to inflammatory state or bleeding. Mechanisms contributing to stone formation include presence of clip as nidus, lithogenic bile, and bacterobilia. Figure 4 shows the possible mechanisms of PCCM and biliary complications.

Managements

Overall, of the 69 cases of PCCM-associated complications, 53 (77%) were successfully treated with ERCP, 14 (20.2%)

Figure 2 Cholangiogram showing dilated CBD, two metal clips at the cystic duct remnant site, and clip-related stone captured in the basket.

with surgery, and one (1.4%) with successful PTC. One patient had spontaneous passage of clip after PCCM without requiring any intervention. All patients were successfully treated (Table 3). There was no reported mortality directly related to PCCM.

ERCP extractions were attempted in 62 patients and were successful in only 53 (84.5%). This included seven patients who had spontaneous clips/stones passage after failed ERCP extractions. One patient had a successful ERCP extraction of a migrated clip that had occurred within 11 days of cholecystectomy. However, this was complicated by slippage of the remaining cystic duct clip causing bile peritonitis that required surgery. This case was considered as successful ERCP extraction. Two patients required two ERCPs for complete clearance. One patient had failed an initial ERCP and PTC attempts before a successful second ERCP. Another patient had endoscopic surgery (ES)-related bleeding complicating the initial ERCP that was managed with biliary stenting before a successful second ERCP. Overall, failures of ERCP clearances were due to large stone, orientation of stone, or presence of stricture.

Fifteen patients had surgical interventions with a success rate of 93.3%. Four patients had surgery as the initial interventions, while the remainder had surgery after failed ERCP/PTC attempts. Reasons for choosing surgery as the initial interventions were: experienced endoscopist not available (n=1), endoscopic removal facility not available (n=2), and suspected common bile duct (CBD) cancer (n=1). The only patient who failed the initial surgical intervention was a patient who had emergency surgery for perforated secondary bile duct. Laparotomy showed bile peritonitis and the perforation was treated with patch repair. A bile duct stone was missed during surgery. This patient underwent ERCP 3 days later for persistent bile leak. Cholangiography showed bile leak and a stone with a metallic clip at the center. This was successfully extracted after ES with resolution of bile leak.

Three patients had attempted PTC extractions and only one was successful (33.3%). This man (57 years old) had obstructive jaundice 6 years after LC. Initial imaging showed a hepatic mass suspected to be cholangiocarcinoma. This was later diagnosis to be a clip-induced stone and was successfully extracted with PTC. Of the other two cases, a second ERCP performed under general anesthesia was successful in one, while the other case proceeded to surgical extraction as part of another operation.

Spontaneous passage of migrated clip occurred in one patient without requiring any intervention 15 days after LC. This patient had a pre-LC ERCP extraction of two CBD stones after ES. The clip passage resulted in self-limiting acute pancreatitis.

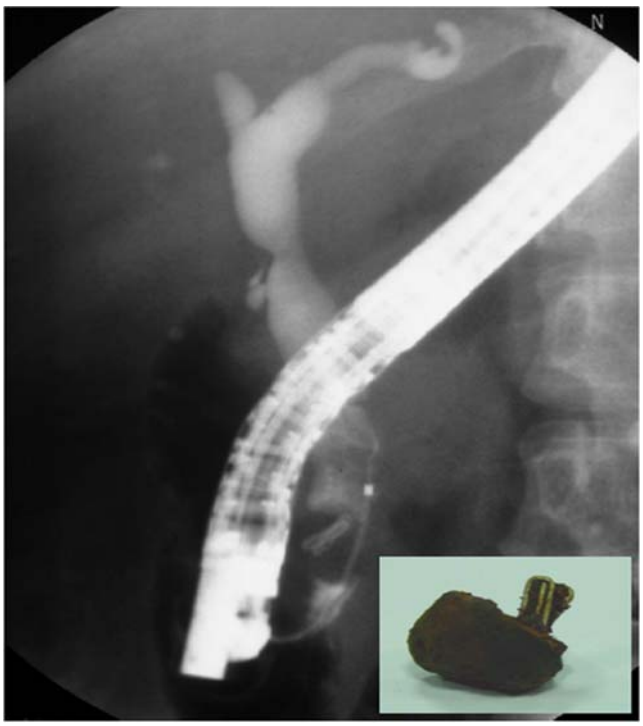

Figure 3 Cholangiogram showing stone with two clips at the center and a stricture at the cystic duct remnant site. There was no significant bile duct dilatation. *Inset* shows extracted stone with two embedded metal clips acting as nidus for stone formation.

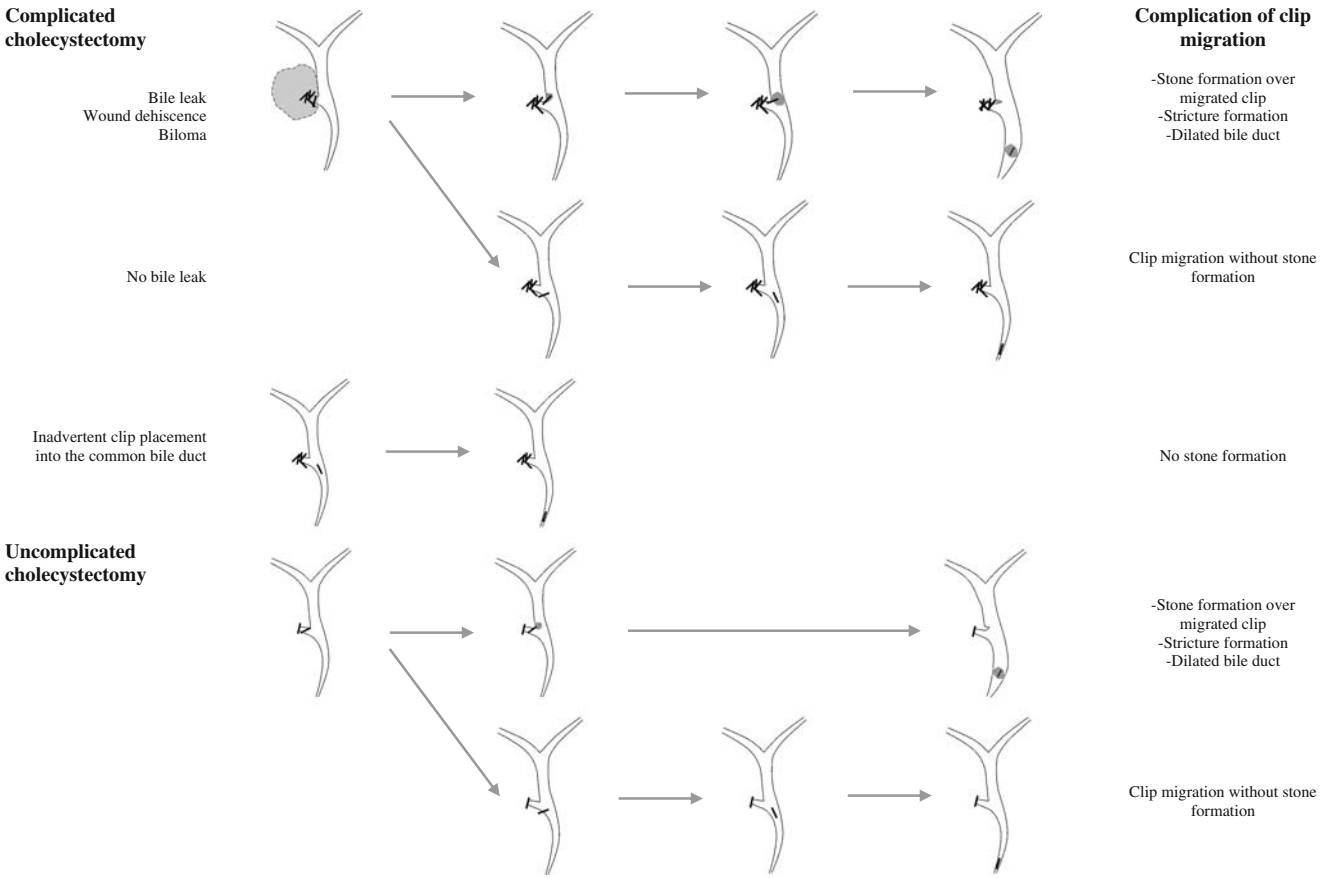

Figure 4 Schematic representations showing the various postulated mechanisms of PCCM.

Discussion

This review showed that PCCM with resultant biliary complications are uncommon with only 80 cases reported despite the large number of cholecystectomies carried out annually. The majority of the published reports had originated from the three major continents (North America, Europe, and Asia), reflecting the large number of cholecystectomies performed in these regions. The number of reported PCCM in the literature peaked in the period of 1994–1998 and this correlated with the introduction of LC. This also correlated with higher complication rates of LC reported during the initial period and this had been attributed to the learning curve for this procedure.[83] As LC became the standard management of gallstones disease coupled with better training programs, complication rates of LC declined. This probably accounted for the subsequent decline in the number of cases reported.[8] There were only 13 cases reported in 12 publications in the last 5-year period (2004–2008).[51–58,66–73]

The gender and age predilections for PCCM reflected the epidemiology of gallstones disease which is more common among females and the older age group.[84] Similarly, the manifestations of PCCM-related biliary complications were not different from the non-iatrogenic choledocholithiasis. Most of the patients presented with typical symptoms of choledocholithiasis. Imaging will be required to distinguish between post-cholecystectomy primary CBD stones from PCCM-related biliary complications. Simple abdominal radiography may show abnormal positions of the metal clips.[32,65]

The managements of PCCM with biliary complications are similar to that of non-iatrogenic choledocholithiasis. Based on current recommendations, ERCP should be the modality of choice with surgery or PTC reserved as rescue procedures especially in the presence of difficult biliary strictures or large stones.[85,86] Surgical extractions were utilized in the earlier period as ERCP techniques were still at its infancy and facilities and expertise were not widely available. This is highlighted by the cases where surgical interventions were chosen as the intervention to deal with biliary complications of PCCM.[11,16,27] Overall, surgical interventions had a success rate of 93.3%. The only case that had failed surgical intervention was due to the failure to detect a CBD stone during surgery.[55] The complicated nature of this particular case was probably an important factor.

Table 3 Details of Management and Outcomes of PCCM

Types of interventions	*n* (%)
ERCP	62 (89.9)
Successful clearance	
ERCP clearance	44
Spontaneous stone passage	7
Failed initial surgical clearance	1
Failed initial PTC clearance	1
Unsuccessful attempts requiring surgery	9[a]
Surgery	15(21.7)
Successful clearance	
Initial open procedure	4
Failed initial ERCP clearance	9[a]
Failed initial PTC clearance	1
Unsuccessful attempt needing ERCP extraction	1
PTC	3(4.3)
Successful	
Initial PTC clearance	1
Unsuccessful	
Successful ERCP	1
Surgical clearance	1
Spontaneous passage without intervention	1(1.4)[b]

Percentages presented in brackets do not add up to 100% due to overlapping of procedures as some patients had different treatment modalities before successful clearance

[a] Reasons: failed cannulation (n=1), stricture/failed extractions (n=2), unsuccessful extraction due to large stone, orientation of stone, and technically difficult ERCP (n=3), no details mentioned (n=2), impacted basket (n=1)

[b] Patient had pre-LC ERCP and endoscopic sphincterotomy

ERCP became the modality of choice in the later period (previous 10 years) with a success rate of 84.5%. This is consistent with the success rate reported for non-iatrogenic choledocholithiasis.[85] Even if we had included the publication that had reported on the six cases of PCCM that were successfully managed with ERCP, the overall success rate was only slightly better at 86.4%.[40] In most cases, only a single ERCP attempt was required for successful clearance. Two ERCP sessions were required in two cases.[43,57] Like the management of non-iatrogenic choledocholithiasis, it is important that an adequate ES is performed as it may facilitate spontaneous passage even if the initial ERCP extraction had failed. Most spontaneous passages of clip/stones had occurred within weeks of ERCP. The presence of strictures or stones that were too big or orientated in difficult positions was an important factor contributing to failures of ERCP extractions.

The exact pathogenesis of PCCM is unknown but is likely to involve complex sets of events occurring simultaneously as previously reported.[10] The underlying pathogenesis probably shares some similarities to the migrations of other foreign bodies into the biliary tree that included surgical sutures, ingested materials such as seeds, vegetables matters, and toothpicks, and projectiles objects such as bullet and shrapnel.[10] The process involves the initial migrations of clip into the biliary tree and later followed by stone formations.

There are many factors that contribute to the migration process. These include inaccurate clip placements with resultant bile duct injuries, local suppurative inflammatory processes, bile leak with resultant biloma formation, and local infective processes.[10] In fact, it has been shown that, once a clip gets embedded within the bile duct wall, the process of clip migrations will continue.[37] The location of the stricture indicated the probable site of clip injury and migration. Inadvertent placement of clips inside the bile duct during the initial operation has also been suggested. This can lead to early manifestations and probably accounted for those cases of early presentations soon after the initial surgeries. The number of clips used during the initial surgery is also an important factor. The use of more than four clips had been shown to be associated with clip migrations.[37] The median numbers of clips used in the cases of PCCM were six. The indications for cholecystectomy were also important. In the acute inflammatory settings of acute cholecystitis or pancreatitis, dense adhesions and inflammations will distort the anatomy, increasing the risk for injuries. In our review, complicated gallstones disease accounted for 23.2% of cases with PCCM with resultant biliary complications. However, this number might have been higher as the full details of the initial surgeries were not available in some of the reports. LC itself may be a risk factor for complications. Generally, LC is technically more difficult and complications rates have been reported to be slightly higher compared to OC.[5] Previous abdominal surgeries will further increase the risk.[87] Apart from biliary complications, PCCM resulting in nonbiliary complications such duodenal ulcer and embolizations had also been reported and the underlying pathogeneses are probably similar.[12–14,88,89]

In order to avoid PCCM complications, all the discussed factors need to be considered and avoided. Ideally, only two clips should be left behind after cholecystectomy. Others have advocated to the use of absorbable clips. However, PCCM have also reported where absorbable clips had been used.[19,67] Clipless cholecystectomy using ultrasound-activated harmonic scalpel may be an option. It has been shown to be effective, efficient, and a safe alternative for dissection and hemostasis.[90–92] In addition, harmonic scalpel has also been shown to be associated with fewer complications (mild or major bile leaks and gallbladder perforation) and shorter operation time. Use in acute cholecystitis has also shown to be safe.[93]

As technology advances, newer and less invasive techniques are being developed and adapted for the management of many clinical disorders including gallstones disease. These

include the use of fewer or single port LC and the natural orifice transluminal endoscopic surgery. In fact, such modalities have been shown to be feasible for the management of gallstones disease and are already being used in some centers.[94–96] Therefore, it will be interesting to see if there will be an increase in the number of complications related to these newer modalities as complications are associated with the learning curve for these procedures.

Overall, PCCM is rare. However, it is possible that the true incidence of PCCM with resultant biliary complications is underestimated. First, clip migrations may go unnoticed as spontaneous clip passages had been reported. Seven of the reported cases had spontaneous clips/stones migrations either after failed ERCP extractions or after LC.[20,29,33,36,38,63,69] All had ES done during ERCP. Therefore, the routine use of precholecystectomy ERCP with ES may be an important factor. Second, it is possible that additional publications especially in the non-indexed, non-English journals might have been missed. Finally, cases of PCCM might have gone unreported or have been included as part of other type of publications.[40] However, the overall number of missed cases is likely to be small.

In conclusion, although rare, PCCM with biliary complications need to be considered in the differential diagnosis for patients presenting with typical symptoms even many years after cholecystectomies. The clinical manifestations are similar to that of primary or secondary non-iatrogenic choledocholithiasis and ERCP is currently the treatment of choice. The recent number of reported cases of PCCM with biliary complications has shown a declining trend, probably as a result of better training programs. However, it will be interesting to see if the there will be any increase in the complications rates of cholecystectomies, including PCCM, as newer techniques are being introduced for the management of symptomatic gallstones disease.

Permission to use Figs. 2 and 3 has been obtained from the publisher (Singapore Med J. 2004;45(11):533–535).

Acknowledgement We would like to acknowledge the assistance of Chong VS and Lim KC for retrieving some of the identified publications, Chong CM for the figure illustration (Fig. 4), and Ms. Lim Ai Giok for the preparation of the manuscript.

Conflict of Interest None.

Financial Disclosure None.

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J Gastrointest Surg (2010) 14:697–704
DOI 10.1007/s11605-009-1134-x

ORIGINAL ARTICLE

Success and Complication Rates of Two Precut Techniques, Transpancreatic Sphincterotomy and Needle-Knife Sphincterotomy for Bile Duct Cannulation

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Received: 25 August 2009 / Accepted: 4 December 2009 / Published online: 7 January 2010

Abstracts

Background The majority of literature on the precut technique is concerned with needle-knife sphincterotomy, whereas the comparison of transpancreatic sphincterotomy and needle-knife sphincterotomy has been rarely reported.

Aim The aim of the study was to compare the success and the complication rates of transpancreatic sphincterotomy with needle-knife sphincterotomy.

Methods During May 2006 and April 2007, 3,178 consecutive endoscopic retrograde cholangiopancreatography (ERCP) procedures were performed in a prospective multicenter study on ERCP-related complications. From the files of these patients, data of cases undergoing precut sphincterotomy, including transpancreatic sphincterotomy and needle-knife sphincterotomy, were retrospectively extracted and analyzed.

Results Overall, 216 patients with precut sphincterotomy were identified; 140 cases received transpancreatic sphincterotomy, and 76 received needle-knife sphincterotomy. There was no significant difference in the initial and eventual success rates between transpancreatic and needle-knife sphincterotomy (82.9% vs. 90.8% and 90.0% vs. 90.8%, respectively). The overall incidences of complications and acute pancreatitis were not significantly different between the two groups (14.3% vs. 18.4% and 11.4% vs. 11.8%, respectively).

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Conclusions Transpancreatic precut sphincterotomy results in similar success and complication rates when compared with needle-knife sphincterotomy. This new precut technique seems to be a safe alternative to needle-knife sphincterotomy with reasonable success rates. However, prospective randomized controlled studies are required to verify our findings.

Keywords Transpancreatic sphincterotomy · Needle-knife sphincterotomy · Biliary cannulation · Endoscopic retrograde cholangiopancreatography (ERCP)

Introduction

Selective cannulation of the biliary duct is a prerequisite to successful biliary therapy during endoscopic retrograde cholangiopancreatography (ERCP). Despite the use of various accessory devices such as catheters, sphincterotomes, and guidewires, selective biliary cannulation with standard techniques has been reported to fail in 5–20% of cases.[1,2] In cases of biliary cannulation failure, several supplementary techniques of precutting have been recommended to facilitate access to the bile duct.

The most frequent precut technique is needle-knife precut sphincterotomy that has been used since the 1980s.[3]This technique uses the free-hand needle knife, a catheter with a thin wire extending beyond its tip to cut into the papilla and enter the bile duct. Needle-knife sphincterotomy is highly successful when performed by an experienced endoscopist but has an increased potential for complications, including bleeding, perforation, and pancreatitis.[4–10]

Transpancreatic precut sphincterotomy is a relatively new precut technique, first described by Goff in 1995.[11] It is performed by a standard traction sphincterotome wedged into the pancreatic orifice, with a cutting wire aimed in the biliary direction. As a new precut technique, transpancreatic sphincterotomy takes advantage of the fact that the pancreatic duct is cannulated unintentionally, and the procedure is performed with a standard traction sphincterotome. Thus, an exchange of a free-hand needle knife is not required, and the depth of incision is easier to control compared with needle-knife sphincterotomy. It has been shown that transpancreatic precut sphincterotomy using a soft guide wire is a safe and effective procedure in patients with difficult bile duct access where classic cannulation techniques or needle-knife procedures fail.[12] Previous studies have found that this precut procedure produces a higher rate of successful cannulation with a similar complication rate, compared with needle-knife sphincterotomy.[13–15]

The aim of this retrospective study was to compare the success and the complication rates of transpancreatic sphincterotomy in comparison with needle-knife sphincterotomy in a study with large number of subjects.

Patients and Methods

Patients and Data Collection

Between May 2006 and April 2007, a prospective multicenter study aiming to determine ERCP-related complications was conducted, with the period of data collection varying from 3 to 12 months among 14 participating centers. Overall, 2,691 patients received 3,178 consecutive ERCP procedures, which included all procedures where an endoscope was inserted with the intention of cannulating the bile duct, the pancreatic duct, or both; however, procedures where papilla of Vater was not reached and stent removal procedures without ductal cannulation were excluded. Patients with high serum amylase levels before ERCP were excluded. The results of this prospective study have been published elsewhere.[16] In the present study, the medical records of patients who underwent precut sphincterotomy were retrospectively analyzed.

Demographic data including gender, age and previous history of sphincterotomy, and other surgical interventions were collected before the ERCP procedure in the above-mentioned prospective study. Details of ERCP, including ERCP indications, cannulation techniques, deep biliary cannulation (i.e., whether catheters or sphincterotomes were deeply placed into the bile duct), and other therapeutic procedures were recorded at the same time of the procedure. All enrolled patients were hospitalized for at least 2 days after ERCP, even if complications were not present. Prolongation of hospitalization was at the discretion of the physician. All patients were closely followed up until discharge to monitor for the development of ERCP-related complications.

Techniques of Precut Sphincterotomy

The precut techniques were carried out by experienced endoscopists, who had previously performed more than 100 ERCP procedures per year. After multiple unsuccessful attempts to selectively cannulate the bile duct using catheters or sphincterotomes with or without guidewires, precut sphincterotomy was carried out. The specific precut technique, including transpancreatic or needle-knife sphincterotomy, was carried out, depending on the endoscopist's preference and on whether or not the pancreatic duct was cannulated (i.e., transpancreatic sphincterotomy if the pancreatic duct was cannulated and needle-knife sphincterotomy if not).

Transpancreatic sphincterotomy was performed as follows: A guidewire was inserted deeply into the pancreatic duct; then, the tip of a standard traction sphincterotome was wedged into the pancreatic orifice; and a sphincterotomy was performed with a cutting wire along the biliary direction at 11 o'clock (Fig. 1). The incision was made through the septum between the pancreatic and biliary duct with the aim of exposing the bile duct orifice. The bile duct orifice was exposed to the left and either below or above the pancreatic orifice, depending on the length of the common channel (short or long, respectively), as described by Akashi et al.[17] After transpancreatic sphincterotomy, the biliary orifice cannulation was attempted by using a catheter or sphincterotome, either with or without a guidewire preloaded.

Needle-knife sphincterotomy was carried out in a standardized fashion. With the needle partially extended beyond tip of the catheter, an incision was made to expose the opening of the distal bile duct. The incision was made toward the intraduodenal segment of the bile duct in the 11 o'clock direction, starting at the papillary orifice and extending upward for a variable distance depending on papillary size and position (Fig. 2). An alternative involved making a puncture into the papilla above the orifice and then cutting downward toward the orifice. After cannulation of the bile duct, the biliary sphincterotomy was extended, when indicated, by using a standard traction sphincterotome.

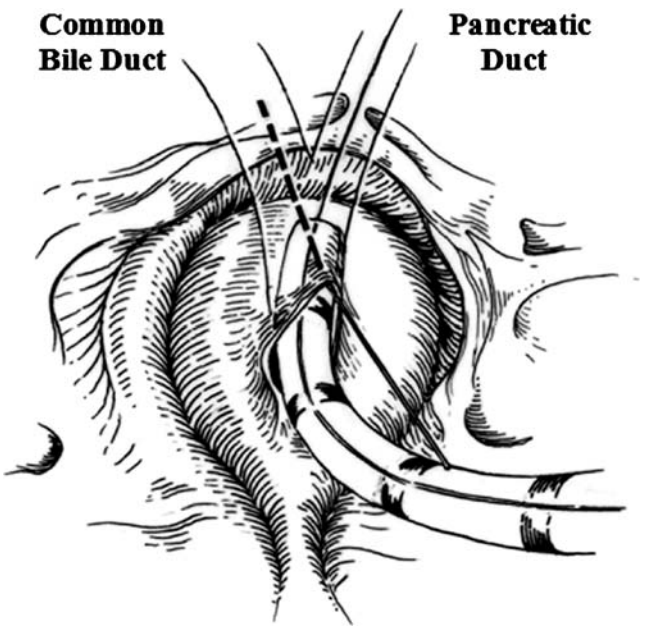

Figure 1 Transpancreatic sphincterotomy. A guidewire was inserted deeply into the pancreatic duct. Then a standard traction sphincterotome was wedged into the pancreatic orifice, followed by sphincterotomy along the biliary direction at 11 o'clock (direction of the *dotted line*).

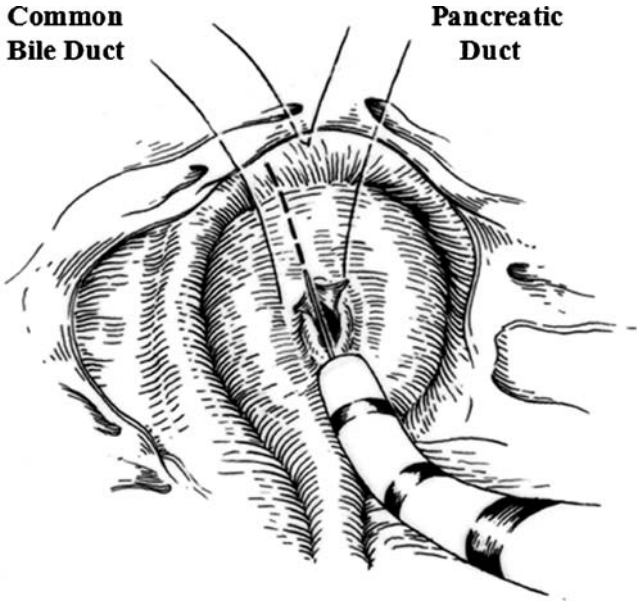

Figure 2 Needle-knife sphincterotomy. The needle partially was extended beyond tip of the catheter. Then an incision was performed toward the intraduodenal segment of the bile duct in the 11 o'clock direction, starting at the papillary orifice (direction of the *dotted line*).

Definitions of Successful Cannulation and Procedure-Related Complications

Successful cannulation was defined as free and deep placement of catheters or sphincterotomes into the bile duct as evidenced by the injection of a contrast medium. Successful biliary cannulation at the time of precut sphincterotomy was considered as initial success. In cases where the first biliary cannulation failed after precut sphincterotomy, ERCP was repeated within 2 to 5 days with the consent of the patient, and a standard cannulation technique without precut was performed at a second ERCP attempt. Successful biliary cannulation at the first or second ERCP attempt was considered to be eventual success.

Definitions of individual complications after ERCP were similar to those reported by Cotton et al.[18] Post-ERCP pancreatitis was diagnosed when new-onset or worsened abdominal pain lasted for more than 24 h, and was associated with an increase in the serum amylase level of at least three times greater than the normal upper limit at 24 h after the procedure. The severity of the pancreatitis was graded mild when hospitalization was prolonged by 2 to 3 days, moderate by 4–10 days, and severe by more than 10 days.[18] In addition, the severity was graded as severe when hemorrhagic pancreatitis, necrosis, abscess, or pseudocyst lesion occurred, or an intervention procedure (e.g., percutaneous drainage or surgery) was needed.[18] Hemorrhage was based on a clinical (i.e., hematemesis and/or melena) and/or endoscopic evidence in association with a decrease in the hemoglobin level by greater than 2 g/dL.

Perforation referred to perforation of retroperitoneum or bowel walls documented by any of radiographic techniques. Cholangitis was defined as inflammation of the bile duct with an elevation in the temperature to more than 38°C without evidence of other concomitant infections.

Statistical Analysis

The data were analyzed with a statistical package (SPSS 15.0, SPSS Inc., Chicago, IL, USA). Continuous variables were described as means ± standard deviation and compared using the two-sided Mann–Whitney's U test. Categorical variables were tested using χ^2 test, with or without Yates' correction or Fisher's exact test, when necessary. Statistical significance was indicated by a two-tailed P value of less than 0.05.

Results

Characteristics of Patients

A total of 216 therapeutic ERCP procedures with precut techniques were performed, 140 received transpancreatic sphincterotomy and 76 needle-knife sphincterotomy. The clinical characteristics were compared between the two groups of transpancreatic and needle-knife sphincterotomy (Table 1). There were no significant differences in gender; age; previous histories of surgeries such as sphincterotomy, Billroth II gastrectomy, and cholecystectomy; the presence of peripapillary diverticulum; indications for ERCP; or average case volumes of each endoscopist between the two groups. Pharmacologic therapy was not used to prevent post-ERCP pancreatitis before ERCP. As for the ERCP-related procedures, patients receiving transpancreatic sphincterotomy were more frequently noted to have cannulation time >10 min (i.e., the duration between the time when the cannula or papillotome was advanced out of the endoscope channel in front of the papilla and the time when successful deep cannulation was evidenced by injection of contrast or the time when the procedure was abandoned due to unsatisfactory cannulation, 82.9% vs. 69.7%, P=0.026) and pancreatic deep wire pass (100% vs. 23.7%, P<0.001), compared with those receiving needle-knife sphincterotomy. In addition, pancreatic stenting was only supplemented in 13.0% of patients with the precut techniques, 18.6% for transpancreatic sphincterotomy, and 2.6% for needle-knife sphincterotomy (P=0.001). However, there was no significant difference in the proportion of patients with pancreatic contrast injections between the two groups (Table 1).

Successful Cannulation Rates

In the 76 patients receiving needle-knife sphincterotomy at the first ERCP attempt, the initial cannulation successful rate was 90.8% (69/76) (Fig. 3, Table 2). Four of the seven patients with initial cannulation failure underwent a second ERCP without precut 2–5 days after the first attempt, but without success. Thus, the eventual success rate of needle-knife sphincterotomy remained 90.8% (69/76) (Fig. 3, Table 2). In the 140 patients receiving transpancreatic sphincterotomy at the first ERCP attempt, the initial cannulation successful rate was 82.9% (116/140) (Fig. 3, Table 2). In the 24 cases with biliary cannulation failure at the first ERCP attempt with transpancreatic spincterotomy, 10 cases underwent a second ERCP attempt without precut after 2–5 days and achieved successful deep biliary cannulation. Thus, the eventual success rate of transpancreatic sphincterotomy was 90.0% (126/140) (Fig. 3, Table 2). There was no significant difference in the initial and eventual success rates between transpancreatic and needle-knife sphincterotomy (82.9% vs. 90.8% and 90% vs. 90.8%, respectively) (Table 2).

ERCP-Related Complications Rates

Overall, complications occurred in 20 cases in the transpancreatic sphincterotomy group and in 14 cases in the needle-knife sphincterotomy group. Complication rates of precut sphincterotomy in the two groups are shown in Table 2. The most common complication in both groups was acute pancreatitis—16 cases in the transpancreatic sphincterotomy group and nine cases in needle-knife sphincterotomy group. One patient who received needle-knife sphincterotomy and had a history of Billroth II gastrectomy developed hemorrhage and perforation. This patient underwent an emergency surgery 6 h after the procedure, the complications were managed surgically, and the patient was discharged 40 days after the operation. There was no procedure-related mortality in the patients receiving precut sphincterotomy. The incidences of overall complications and specific complications, including pancreatitis, hemorrhage, perforation, and cholangitis, did not differ significantly between the two groups (Table 2).

Discussion

Gaining access to the biliary duct is the necessary step for a successful therapeutic biliary endoscopy. However, difficulties in selective cannulation of the bile duct with standard techniques are reported in about 5–20% of ERCP procedures.[1,2] In the cases with difficult biliary cannulation during ERCP, several options exist for successful biliary

Table 1 Clinical Characteristics of Patients Who Underwent Precut Sphincterotomy

	Transpancreatic sphincterotomy (n=140)	Needle-knife sphincterotomy (n=76)
Gender (N (%))		
Male	78 (55.7)	47 (61.8)
Female	62 (44.3)	29 (38.2)
Age (years, mean ± SD)	58.5±18.0	61.3±15.7
History of surgery and ERCP (N (%))		
Cholecystectomy	34 (24.3)	25 (32.9)
Billroth II gastrectomy	0 (0)	3 (3.9)
Sphincterotomy	2 (1.4)	0 (0)
Peripapillary diverticulum (N (%))	30 (21.4)	11 (14.5)
Indications for ERCP (N (%))		
Choledocolithiasis	72 (51.4)	40 (52.6)
Malignant biliary obstruction	58 (41.4)	28 (36.8)
Benign biliary stricture	5 (3.6)	6 (7.9)
Suspected SOD	3 (2.1)	1 (1.3)
Biliary leak	0 (0)	1 (1.3)
Primary sclerosing cholangitis	2 (1.4)	0 (0)
ERCP-related variables (N (%))		
Cannulation time >10 min[a]	116 (82.9)	53 (69.7)*
Pancreatic contrast injection	49 (35)	28 (36.8)
Pancreatic deep wire pass	140 (100)	18 (23.7)**
Pancreatic stent placement	26 (18.6)	2 (2.6)**
Case volumes of endoscopist ≤3/week[b]	35 (25)	21 (27.6)

*P<0.05; **P<0.01, respectively, compared with cases receiving transpancreatic sphincterotomy

[a] Cannulation time was measured between the time when the cannula or papillotome was advanced out of the endoscope channel in front of the papilla and the time when successful deep cannulation was evidenced by injection of contrast or the time when the procedure was abandoned due to unsatisfactory cannulation

[b] The endoscopist performed less than three ERCP procedures per week

cannulation, such as a repeat ERCP at a later date, referral to a tertiary center, a percutaneous–endoscopic rendezvous procedure, surgical intervention (when appropriate), and precut sphincterotomy. Of these options, precut sphincterotomy is the most commonly used approach, because it can be performed during the initial ERCP, avoiding additional procedures and thus additional risks and costs.

Needle-knife sphincterotomy is the precut technique which is most widely used to expose the orifice to the bile duct. Rabenstein et al. reported the largest series of needle-knife sphincterotomy with 694 procedures in 1997.[8] In the study, the initial and eventual success rates were 70% and 85.2%, respectively, and complications were observed in 7.3% without any mortality. In other previous studies, initial success rates ranged from 35% to 97%, and complication rates between 3% and 34% were reported.[4–10] These wide ranges of the success and complication rates may be attributable to the differences in indications, anatomic factors and characteristics of patients selected for precut, the timing of needle-knife precut, and endoscopists experience. In the present study, we reported a success rate of needle-knife sphincterotomy during the initial ERCP (90.8%), which was also comparable to the rate reported by Rabenstein et al. The overall complication rate (18.4%) in our needle-knife series was much higher than that reported by Rabenstein et al., but was among the range reported in other studies.

Goff was the first author who reported transpancreatic sphincterotomy in 1995 and then his long-term experience in 1999.[11,19] When he combined the results of his two studies, the initial and eventual success rates were 94.0% and 97.6%, respectively, with a complication rate of 6%, pancreatitis in 4.8%, and contrast extravasation in 1.2%. In his studies, pancreatic injection of contrast was used to confirm that a sphincterotome was placed in the pancreatic duct. However, pancreatic duct guidewire placement was not described by Goff.

In our study, however, placement of a soft guidewire into the pancreatic duct was performed to orientate the correct placement of a sphincterotome and to assist in transpancreatic sphincterotomy. Eventual successful bile duct cannulation was achieved in 90.0% of 140 patients. We

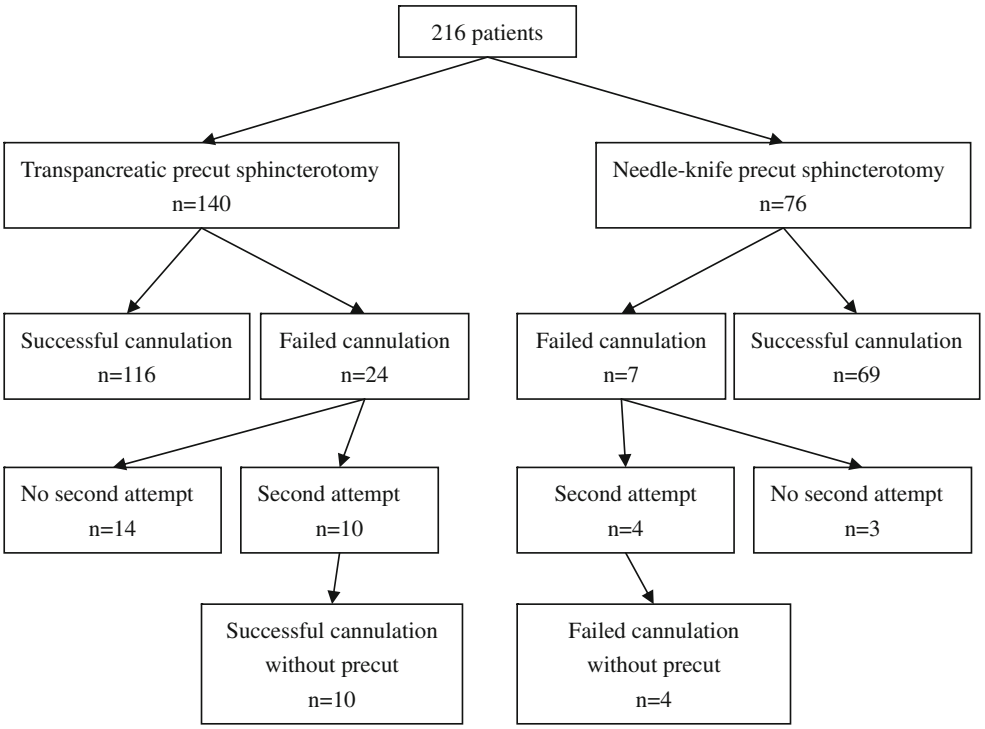

Figure 3 Flow chart showing the outcomes of deep biliary cannulation when transpancreatic and needle-knife precut sphincterotomy were used.

observed an overall complication rate of 14.3% (20 of 140 patients). The observed complications included 14 patients with mild pancreatitis, two with moderate pancreatitis, two with hemorrhage, and two with cholangitis. Weber et al. also performed the wire-guided transpancreatic sphincterotomy on a total of 108 patients and reported similar results.[12] Overall, biliary cannulation was eventually successful in 95.4%, and complications developed in 11.1%, including pancreatitis in 5.6% and hemorrhage in 5.6%.

Two other earlier studies[17,20] evaluating the efficacy and safety of the transpancreatic precut technique without a guidewire as described by Goff have reported the results in accordance with our findings. Akashi et al. studied a total of 172 patients who underwent a precut sphincterotomy for biliary access by placing a sphincterotome into either the pancreatic duct or the common channel without using a guidewire and found that biliary cannulation was initially successful in 163 (94.8%) patients, and complications developed in 17 (9.9%) patients, including mild pancreatitis

Table 2 Success and Complications Rates of Precut Sphincterotomy for Deep Biliary Cannulation

	Transpancreatic precut sphincterotomy (n=140)		Needle-knife precut sphincterotomy (n=76)		P value
	Number	Percent (%)	Number	Percent (%)	
Success cannulation					
Initial success	116	82.9	69	90.8	0.112
Eventual success	126	90	69	90.8	0.852
Complications					
Pancreatitis	16	11.4	9	11.8	0.928
Mild	14	10	8	10.5	0.903
Moderate	2	1.4	1	1.3	1.000
Hemorrhage	2	1.4	3	3.9	0.483
Perforation	0	0	1	1.3	0.352
Cholangitis	2	1.4	2	2.6	0.922
Total	20	14.3	14[a]	18.4	0.425

[a] One procedure had two complications (hemorrhage and perforation)

in 10 (5.8%), cholangitis in five (2.9%), and hemorrhage in two (1.2%).[17] Kahaleh et al. performed this technique in 116 patients with an immediate successful biliary access in 85% and a complication rate of 12% (pancreatitis 7.7%, hemorrhage 2.6%, and perforation 1.7%).[20] These authors performed transpancreatic sphincterotomy after placing a sphincterotome in the pancreatic duct, which was following the pancreatic injection of contrast. However, we used a guidewire to recognize the pancreatic duct for the precut technique as described above. The above data indicate that transpancreatic precut sphincterotomy assisted with pancreatic guidewire placement and transpancreatic precut sphincterotomy following pancreatic contrast injection may achieve similar success and complication profiles, although "head-to-head" comparison studies are required.

Comparison of needle-knife sphincterotomy and transpancreatic sphincterotomy has recently been reported in a prospective randomized study by Catalano et al.[13] They found that transpancreatic sphincterotomy had a higher success rate (29/29; 100%) compared with needle-knife sphincterotomy (26/34; 77%; P=0.01) in per protocol analysis. Although, in the intent-to-treat analysis, the difference in success rate between the two groups was statistically insignificant (94% [29/31] vs. 75% [24/32], P=0.08), the success rate of transpancreatic sphincterotomy was still higher than needle-knife sphincterotomy. Complications were less frequent in the transpancreatic sphincterotomy group (1/29; 3.5%) compared with the needle-knife sphincterotomy group (6/34; 17.7%), but this result was not statistically significant (P=0.12), even in per protocol analysis.[13] In a retrospective study, Kapetanos et al. included a series of 55 patients with precut sphincterotomy (34 with transpancreatic sphincterotomy, 15 with needle-knife sphincterotomy, and six with both techniques).[14] They found that there was no significant difference in the incidence of complications among the three groups (5.9%, 13.3%, and 16.7%, respectively), and the eventual success rate (75% vs. 71.4%) was similar between transpancreatic and needle-knife sphincterotomy. In another retrospective study of 262 cases with transpancreatic sphincterotomy and 157 cases with needle-knife sphincterotomy, Halttunen et al. reported that transpancreatic sphincterotomy had a significantly higher success rate, compared with needle-knife sphincterotomy (97.3% vs. 71.3%, P< 0.001), with similar post-ERCP pancreatitis rates between the two techniques (8.8% vs. 5.1%).[15]

In our series, the initial success rate of transpancreatic sphincterotomy at the first ERCP attempt (82.9%) was lower than that of needle-knife sphincterotomy (90.8%), although the difference between the two groups was not statistically significant, which was different from the result described by Catalano et al. and Halttunen et al.[13,15] A possible explanation is that transpancreatic sphincterotomy was more frequent following antecedent repeated cannulation attempts than needle-knife sphincterotomy. Under the circumstances of repeated cannulation, it is difficult to identify the bile duct orifice because of edema and inflammation at the papilla. Thus, once the edema and inflammation at the papilla had subsided, deep biliary cannulation was achieved at a second ERCP attempt in all 10 cases with failed transpancreatic sphincterotomy, giving an eventual success rate of 90.0%. In future studies, the early implementation of transpancreatic sphincterotomy may improve successful rate at the first attempt and also reduce the higher risks associated with excessive papillary trauma induced by persistent cannulation.

Our study suggests that the complication rates for these two precut techniques were not statistically significant; however, the complication rate of transpancreatic sphincterotomy was still considerably high in our study (14.3%), compared with the result reported by Catalano et al. and Kapetanos et al.[13,14] Most cases of complications were mild pancreatitis (10%). A possible explanation is that the precut technique is associated with pancreatic guidewire insertion under the circumstances of repeated and difficult cannulation. In addition, prophylactic placement of a pancreatic stent during the wire-guided precut was only performed in minority procedures.

Obviously, the major limitation in our retrospective study is the specific precut techniques compared in a non-randomized fashion. Patients with transpancreatic sphincterotomy were more likely to have other procedure-related risk factors of complications and pancreatitis, such as pancreatic deep wire pass and cannulation time >10 min,[16,21,22] compared with needle-knife sphincterotomy. In addition, pancreatic duct stenting, the protective factor for pancreatitis, was only supplemented in minority procedures of two precut techniques although transpancreatic sphincterotomy was frequently associated with placement of pancreatic stent, compared with needle-knife sphincterotomy. Therefore, randomized controlled trials are required to confirm our findings and to control for factors such as manipulation of the pancreatic duct and the timing of precut between the two precut techniques.

In conclusion, transpancreatic sphincterotomy seems to be an effective alternative to needle-knife sphincterotomy and has an acceptable complication profile. However, since our study was not a randomized controlled trial, these results may be regarded as preliminary evidence. Further randomized controlled trials comparing the success and complications of two precut techniques would identify the optimal precut strategies.

Acknowledgments We would like to thank all those endoscopists and physicians who assisted in data collection. This study was partially supported by a grant from Boston Scientific Corporation, China.

Competing interests None.

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J Gastrointest Surg (2010) 14:705–710
DOI 10.1007/s11605-009-1125-y

ORIGINAL ARTICLE

Peng's Binding Pancreaticojejunostomy After Pancreaticoduodenectomy: A French Prospective Study

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Received: 9 July 2009 / Accepted: 30 November 2009 / Published online: 7 January 2010

Abstract
Background Pancreatic fistula (PF) is the single most important complication after pancreaticoduodenectomy. Recently, a 0% rate of PF was reported using a binding pancreaticojejunostomy with intussusception of the pancreatic stump. The aim of this study was to assess the safety of this new binding pancreaticojejunostomy in condition most susceptible to PF, i.e. soft pancreas and non-dilated main pancreatic duct.
Methods Forty-five consecutive patients with soft pancreas and non-dilated main pancreatic duct underwent a binding pancreaticojejunostomy. Post-operative PF was defined according to the International Study Group of Pancreatic Fistula.
Results Four patients (8.9%) developed a PF. In one case, PF developed on post-operative day 3 due to a technical deficiency. In the three other cases, pancreatic fistula developed after the tenth post-operative day; all the patients had local and/or general co-morbidities before PF occurrence.
Conclusions Binding pancreaticojejunostomy according to Peng is a safe and secure technique that improves the rate of pancreatic fistula, especially in case of soft texture of the pancreas remnant. However, a 0% rate seems to be hard to achieve because other abdominal and general complications are frequent and can lead to secondary leakage of the pancreatic anastomosis.

Keywords Pancreaticoduodenectomy · Pancreaticojejunostomy · Intussusception · Pancreatic fistula

Abbreviations

BPJ	Binding pancreaticojejunostomy
ISGPF	International Study Group of Pancreatic Fistula
MPD	Main pancreatic duct
PAF	Pancreatic anastomotic failure
PD	Pancreaticoduodenectomy
PF	Pancreatic fistula
POD	Post-operative day

Presented at the *3ème congrès Francophone de Chirurgie Digestive et Hépatobiliaire*, December 6, 2007, Disneyland® Resort Paris, France.

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Introduction

Anastomotic leakage of the pancreatic anastomosis is the commonest complication after pancreaticoduodenectomy (PD) and remains the most important determinant of post-operative morbidity.[1–3] Most of the large series of PDs have reported rates of pancreatic fistula (PF) over than 10%.[2–12] The most important risk factor is the remnant pancreatic texture. The presence of PF is <5% in case of hard pancreatic texture, although it rises near 20% when texture is soft.[3,5–11,13,14] Neither the technique of pancreatic anastomosis nor the administration of somatostatin analogues has shown a clear benefit in an attempt to reduce the incidence of PF.[4,10,11] Recently, Chinese authors have described a new technique of binding pancreaticojejunostomy (BPJ) after PD.[15–18] This technique revives the concept of the intussusception of the body of the pancreas remnant into the jejunum. The originality lies in the chemical or thermal destruction of the mucosa of the jejunum to create a large surface of adherence with the body of the pancreas. They

have published three retrospective studies and one randomised comparative trial with this technique.[15–18] They reported a 0% of PF, which is obviously the lowest ever published in the literature.

The aim of this prospective, non-comparative study was to test this technique in the French population and assess its reproducibility. Although soft pancreas without dilated main pancreatic duct (MPD) is the one most susceptible to a PF, we chose to apply this technique only to this subset of patients.

Materials and Methods

Study Population

From May 2005 to January 2009, 105 patients underwent a PD in our unit. Among them, 47 patients (44.7%) with soft or fatty pancreas and normal MPD were eligible for having a BPJ. Two patients (4.25%) were excluded because of high discrepancy between small jejunum and large pancreas remnant. Finally, 45 patients were included in this prospective single centre study.

Surgical Technique

Surgical procedure was performed under both general anaesthesia and epidural analgesia with a bilateral subcostal incision. After assessing resectability, a pylorus preserving PD was performed. Texture of the remnant of the pancreas and size of the MPD were assessed after resection. Inclusion criteria for a BPJ were soft and/or fatty pancreas without MPD dilatation (MPD <3 mm). Patients were definitively included after confirmation of lack of pancreatitis or fibrosis at the final pathologist report. A BPJ was always performed by the same surgeon (EB) according to Peng's technique (Fig. 1). After resection, the cut edge of the body of pancreas was mobilised for about 3 cm. Splenic artery was dissected and displaced upward to avoid risks of injury during the last phase of the anastomosis. The first jejunal loop was prepared for anastomosis. The distal edge of the loop was everted by means of three single sutures, about 3 cm proximally to the cut end. Destruction of the mucosa of the everted part was carried out with argon beam, which allows superficial destruction without deep injury. Creases of the mucosa were carefully stretched in order to uniformly burn the whole surface. An end-to-end pancreaticojejunostomy anastomosis was performed between the jejunal everted non-burned mucosa and the cut edge of the pancreas. MPD was not always included in the posterior row of sutures. Once achieved, the stitches used for evertion were cut, and the everted part of the jejunum was turned around the body of the pancreas. Then, the end of the jejunal loop was sutured to the pancreas by means of U stitches of polypropylene 3/0. Care was taken to preserve the splenic artery and the MPD in this last phase of the anastomosis. Finally, a polypropylene 0 loop was tied around the mid-part of the anastomosis through an avascular window in the jejunal mesentry to secure the coagulated mucosal surface against the pancreas. A multitubular silicone sheet was placed behind the BPJ. The rest of the surgical procedure was then similar to classic Child's procedure.[19] Duration of the total procedure was recorded.

Post-operative Management

After operation, oral fluid administration was allowed on post-operative day (POD) 1 and oral feeding on POD 2. Amylase fluid and quantitative drain output (amount of drainage fluid) were measured everyday from POD 3–10. Drain was mobilised on POD 3 and then every 2 days and was removed on POD9 except in presence of pancreatic leak. CT scan was performed only when an intra-abdominal complication is suspected. Analogues of somatostatin were not administered, either pre-operatively or post-operatively.

Study End Points

PF was defined according to International Study Group of Pancreatic Fistula (ISGPF), i.e. drain output of any measurable volume of fluid on or after POD 3 with an amylase content greater than three times the serum amylase activity.[1] Morbidity and mortality were assessed until hospital discharge and graded according to the classification of Clavien.[3]

Results

Forty-five patients (23 male and 22 female) were included in the study. Mean age at diagnosis was 67.2 years (28–82 years). Indications of resection are shown in Table 1. Mean size of the MPD was 2 mm (1–3 mm), and mean duration of the total procedure was 295 min (195–480 min).

Post-operative Morbidity and Mortality

Twenty-four patients presented at least one post-operative complication (53.3%). Of which, according to the classification of surgical complications adopted for pancreatic surgery,[3] four patients (8.9%) had grade I complications, eight patients (17.8%) had grade II, eight patients (17.8%) had grade III, and two patients (4.4%) had grade IV (Table 2). Five patients required a total of

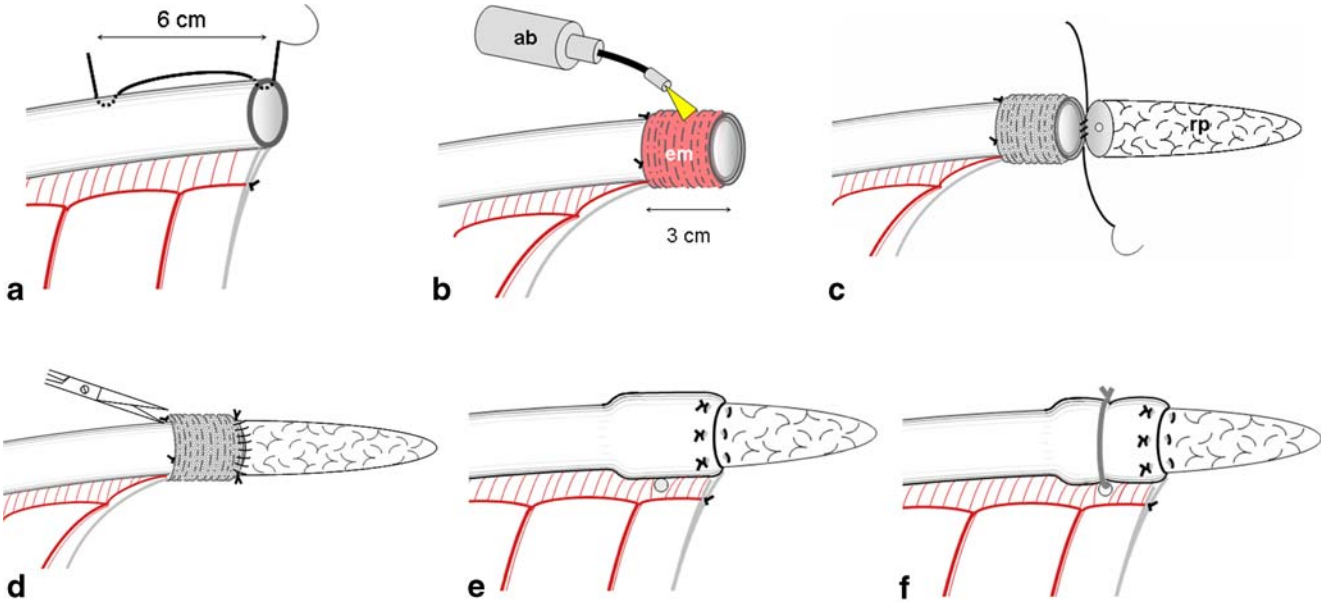

Figure 1 Technique of BPJ according to Peng; **a** eversion of the distal edge of the jejunum by sutures all around the circumference; **b** destruction of the 3 cm of the everted mucosa (*em*) using argon beam (*ab*); **c** first part of anastomosis: end-to-end anastomosis between mucosa of the jejunum and remnant pancreas (*rp*); **d** end of first part of anastomosis. The everted sutures are cut to prepare for intussusception; **e** second part of anastomosis: U sutures between the end of the jejunum and the body of the pancreas. A window is opened in the mesentery for the final loop (*arrow*); **f** final aspect of the BPJ. A loop of polypropylene 0 is tied around the mid part of the anastomosis.

eight reoperations. Indications were haemorrhage (n=3), PF(n=2), biliary fistula (n=1), sub-phrenic abscess (n=1) and colonic fistula (n=1). Two patients (4.4%) died post-operatively (one bilateral pneumonia on POD 12 and one pulmonary embolism on POD 8). Mean hospital stay was 19.5 days (10–200 days). PF occurred in four patients (8.9%).

Table 1 Indications for Resection

Aetiology	Number of patients	Per cent
Malign	24	53.3
Ampullocarcinoma	6	13.3
Malign IPMN[a]	4	8.9
Cholangiocarcinoma	4	8.9
Adenocarcinoma of the pancreatic uncus	3	6.7
Adenocarcinoma of the pancreatic head	2	4.4
Mucinous cystadenocarcinoma	2	4.4
Duodenal adenocarcinoma	2	4.4
GIST of the duodenum	1	2.2
Benign	21	46.7
Neuro endocrine tumour	8	17.8
Benign IPMN[a]	5	11.1
Mucinous cystadenoma	4	8.9
Others	4	8.9

[a] Intraductal papillary mucinous neoplasm

Description of Every PF

The first patient was a 64-year-old woman with diagnosis of neuroendocrine tumour. PF appeared on POD 18, after three reoperations for intra-abdominal haematomas and leak

Table 2 Grading System for Post-operative Complications[3]

Complication grade[3]	n (%)	Complications
I	4 (8.9)	2 wound infections
		1 biliary fistula
		1 post-operative pancreatitis
II	8 (17.8)	3 delayed gastric emptying
		1 urinary tract infection
		1 pancreatic fistula
		1 portal thrombosis
		1 pneumonia
		1 retro gastric collection
III	8 (17.8)	2 pancreatic fistulas
		2 haemorrhages
		1 subphrenic abscess
		1 splenic aneurysm
		1 biliary fistula
		1 colonic fistula
IV	2 (4.4)	1 pancreatic fistula
		1 post-operative pancreatitis
V	2 (4.4)	1 pulmonary embolism
		1 bilateral pneumonia

of the bilioenteric anastomosis. Amylase fluid was normal until POD 17 (<150 UI/mL) and increased to 2,310 on POD18. Adequate drainage was established by a re-operation. Post-operative course was long (200 days), but the fistula finally healed.

The second patient was a 71-year-old man with an adenocarcinoma of the head of the pancreas. PF was diagnosed on POD 3 by observation and exit of brown colour fluid in the drain with increased amylase level. Reoperation showed necrosis of the stump by mesenteric ischemia due to injury of the vascular arcade of the loop (Fig. 2). Resection of the distal jejunum and a new BJP were performed. A stent was placed in the MPD to decrease the risk of recurrent PF. Post-operative course was uneventful. Patient was discharged on POD 45.

The third patient was an 80-year-old woman with a cholangiocarcinoma of the lower bile duct. During surgery, pancreas was large and difficult to slip into the jejunal loop. PF was observed on POD10 after increase level of amylase fluid in the drain. No oral restriction was carried out and spontaneous healing occurred without any other complication. Total hospital stay was 36 days.

The fourth patient was a 51-year-old woman with gastrointestinal stromal tumour of the duodenum invading the right transverse colon. A PD with segmental colonic resection and manual end-to-end colo-colic anastomosis was performed. The patient presented an abdominal sepsis on POD5 and re-operation showed colonic leak without pancreatic leak. A colostomy was performed. Pancreatic leak occurred on POD 8, and the patient was re-operated three times: one for drainage, one for haemorrhage of the splenic vein and one for salvage pancreatogastrostomy.[20] Post-operative course was long but discharge occurred after 3 months.

Comment

PF is well-known to be the major complication after PD with a related morbidity of 30–50% reported in the literature.[1] Risk factors for pancreatic leakage are soft pancreas, fatty pancreas and non-dilated MPD.[6,7,13,14] High rate of PF have been reported whenever one or more of these factors are involved, ranging from 20% to 50%.[5–7,10] In this study, the rate of PF was 8.9%, which is lower than published previously by our institution (17.6%).[21] In addition, it is one of the lowest ever published when soft pancreas and normal MPD are involved. Many technical variations have been developed and published in an attempt to reduce the rate of PF. None have shown a clear benefit, except the external drainage of the MPD studied by Poon and coworkers.[7] However, even in their study, the percentage of PF in the subgroup of patients with soft texture was higher than in our study (14.3% vs.8.9%, respectively).

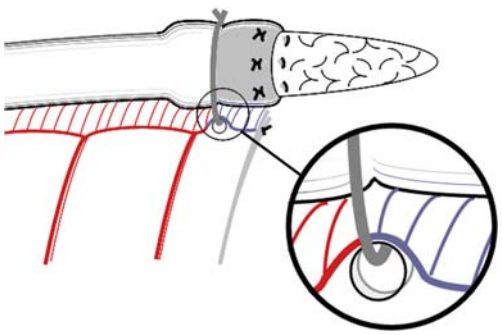

Figure 2 Position of the final loop, causing mesenteric ischemia (*grey zone*).

Peng et al.[15] in 2002 were the first to report a 0% of PF in a study of 115 patients. Their technique of pancreaticojejunal anastomosis is based on the concept of intussusception. Originality lies in the thermal or chemical destruction of the jejunal mucosa of the stump in order to create a large surface of adhesion around the body of the pancreas. An experimental study performed by the same group endorsed the strength of their anastomosis by measurement of the tolerance pressure, which was increased by twofold compared to classic pancreaticojejunal anastomosis.[22] In 2003, they published a new series of 150 patients with no fistula using this same technique.[17] Then, a prospective randomised study was conducted in 2007 on 200 patients and showed superiority of the BPJ in comparison with classic pancreaticojejunal anastomosis.[18] However, in these studies, texture of the pancreas and size of the MPD were heterogeneous or not well-described. Furthermore, definition of PF was not standardised. In this scenario, PF could be misdiagnosed or under-evaluated. In order to eliminate these biases, PF was defined in our study according to the ISGPF criteria. Moreover, only soft and/or fatty pancreas with MPD normal in size were included to homogenise the series and to specifically assess the efficacy of this technique in the group of patients who are more prone to developing a PF. Despite these adverse conditions, our study supports and reproduces the excellent results of Peng's BPJ.

However, it is interesting to note that, despite a low rate of PF, overall morbidity (53.3%) and rate of reoperations (11.1%) were not decreased in comparison to other studies that used the classification of Clavien.[3,23,24] Three hypotheses can explain these results. The first hypothesis is that post-operative fluid collections can lead to complications not related to PF. These post-operative collections are very frequent, not necessarily symptomatic or infected, and can be misdiagnosed. In our series, one splenic aneurysm and one portal vein thrombosis were diagnosed without PF and with non-infected fluid collection in the operative area. Pancreaticojejunal anastomosis is thought to generate high

rate of fluid collections due to larger residual peri-anastomotic space compared to the pancreaticogastric anastomosis.[4] Thus, post-operative complications are more frequent (particularly biliary leak and delayed gastric emptying) and increase post-operative morbidity.[4]

The second hypothesis is that PF, as defined by the ISGPF, may under-estimate the true rate of complications of the pancreatic anastomosis. Thus, the entity "pancreatic anastomotic failure" (PAF) has been introduced recently by Strasberg et al. [25]. It re-groups all the complications due to failure of the pancreaticodigestive anastomosis, including not only the PF but also the other post-operative events like infected fluid collections, abscesses, peritonitis and haemorrhages that do not fit in the definition of PF according to the ISGPF. The rate of PAF is higher than PF and can explain the higher post-operative morbidity (one retrogastric collection, one sub-phrenic abscess and one haemorrhage in this study).

Finally, the last hypothesis is that decrease in PF does not implicate necessarily a decrease in post-operative complications. Poon and coworkers,[7] in their randomised controlled study (external drainage versus not), found no decrease of complication rate, although rate of PF was significantly low in the "external drainage" group. In the same way, Berger and coworkers [23] compared two techniques of anastomosis (duct-to-mucosa versus invagination) and failed to show any difference in term of complication rates (55% vs 49%, respectively), whereas the rate of PF was significantly different (24% vs 12%, respectively, $p<0.05$). These studies corroborate our result: Even with a low rate of pancreatic fistula, post-operative complications are not firmly decreased. We hypothesise that a part of PFs is the consequence rather than the cause of post-operative complications, by the way of local or general sepsis, hematomas and ileus; in these conditions, quality of the pancreatic anastomosis is probably decisive to resist to anastomotic failure. Similarly, Bassi and coworkers[4] compared two techniques of anastomosis (pancreaticojejunal vs pancreaticogastric). They found that even the same rate of pancreatic fistula, intra-abdominal fluid collection, biliary fistula and delayed gastric emptying were significantly more frequent when a pancreaticojejunal anastomosis was performed. They proposed that the stomach had an effect of "sealing" and decrease the anatomic peri-anastomotic space, thus reducing post-operative morbidity. This study confirms that each step of the overall surgical procedure can play a role in reducing post-operative complications, independently of the occurrence of a pancreatic fistula.

Our study pointed out some contra-indications and limits of the BPJ anastomosis. Firstly, BPJ is a safe technique, but the risk of PF is still present. The first and the fourth patients developed conditions that enhance the risk of developing PF, irrespective of the technique of anastomosis: (a) multi-organ failure and/or general sepsis with alteration of tissue perfusion, (b) local ischemia secondary to intra-abdominal sepsis, (c) contamination of the operative site by several successive surgical procedures, (d) traumatism to the BPJ by manipulations at re-operations and (e) paralytic ileum due to intra-abdominal complications and multiple surgical procedures. Integrity of an anastomosis is not only a technical challenge as we all know. PD is a major surgery and often leads to abdominal and general complications that enhance risks of PF, whatever the technique used for the anastomosis. Therefore, it may be very improbable to obtain a 0% rate of PF even in high volume centres, except in selected patients with no major comorbidities.

Secondly, BPJ seems to be an easy technique; however, it is a technically demanding anastomosis because of a lot of successive but important steps that must be followed. Good vasculature of the distal stump, whole destruction of the mucosa, safe first anastomosis, intussusception, a second anastomosis and final loop placement are all steps that need high attention of the surgeon. Learning curve can be long as shown in our experience: Our first technical fault (mesenteric ischemia by incorrect final loop placement) underwent on the 18th patient. We also advise to train on cadavers or animal models to improve the learning curve in this technique of pancreaticojejunal anastomosis.

Thirdly, BPJ cannot be performed in all patients. Peng et al. did not describe any contra-indication to their technique. However, the Orientals may have certain ethnical and anatomical variations as compared to the Caucasians. In the original paper, the aim of the final loop around the stump was to press the intussuscepted jejunum around to the whole body of the mobilised pancreas and to prevent pancreatic juice to go out of the jejunum. In our French experience, this loop was really necessary only in about one third of cases. For others patients, loop was placed, but it was evident that the pancreas was larger than the jejunum with lack of space between these two organs. Furthermore, in two cases, we tried to perform a BPJ, but we failed because of large discrepancy between the size of the pancreas and the size of the jejunum. Finally, a classic pancreaticojejunal end-to-side anastomosis was performed. We believe that our third fistula can be explained by the same pathophysiology. In this last case, even though it was technically difficult, we persisted with a BPJ because the patient was old with much co-morbidity and presented a very fatty pancreas, thereby making her a high risk candidate for PAF. PF can be attributed to ischemia due to excessive manipulation of the jejunal stump and excessive distension of the jejunal stump leading to secondary necrosis. It is also interesting to note that two other patients (4.4%) developed a post-operative pancreatitis. Pathophysiology of this complication is probably obstructive because of

excessive encasement of pancreas remnant and compression of the MPD, favoured by soft texture. Finally, all these cases suggest that the ratio of the diameter of pancreas to the diameter of jejunum is higher in the Caucasians as compared to the Orientals. A high discrepancy in the size of these two organs may be considered as a contraindication for BPJ.

Conclusion

Peng's BPJ is a safe and secure technique for reconstruction after PD. It is a worthwhile procedure to decrease the rate of pancreatic fistula, especially in case of soft texture of the pancreas and normal MPD. Too large discrepancy between pancreas and jejunum is a relative contra-indication to perform this anastomosis because it can increase the risk of pancreatic fistula. However, PD is a major procedure performed sometimes in patients with high comorbidities. It leads inevitably to post-operative complications and jeopardises the pancreatic anastomosis with high risk of fistula. Therefore, it seems very difficult to obtain a 0% rate of pancreatic fistula, whatever the technique and whoever the technician is.

Acknowledgement Authors' potentials conflicts of interest: none declared.

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J Gastrointest Surg (2010) 14:711–718
DOI 10.1007/s11605-009-1147-5

ORIGINAL ARTICLE

Impact of Postoperative Pancreatic Fistula on Surgical Outcome—The Need for a Classification-driven Risk Management

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Received: 2 July 2009 / Accepted: 16 December 2009 / Published online: 22 January 2010

Abstract
Background The International Study Group of Pancreatic Fistula (ISGPF) classification allows comparison of incidence and severity of postoperative pancreatic fistula (POPF). Its post hoc character, however, does not provide a guideline for the treatment of POPF in individual patient. We therefore studied the association of POPF type A-C on secondary surgical morbidity and mortality in patients undergoing pancreatic resection.
Patients and methods Between 3/2001-12/2007, 483 patients underwent pancreatic resections. POPF were classified according to the ISGPF classification. All patient data were entered in a clinical data management system prospectively.
Results Patients who developed POPF had significantly more vascular but not other surgical complications than patients without POPF. Patients with POPF A had no vascular or surgical complications. Twenty one of the 29 patients with POPF C had surgical complications (17 vascular complications). Mortality attributed to surgical complications after POPF C was 5/29. A soft pancreatic consistency (OR 8.5; $p<0.008$) and a high drain lipase activity on postoperative day 3 (OR 4.4; $p=0{,}065$) were predictors for the development of POPF C.
Discussion POPF C is associated with vascular complications like erosion bleeding and other surgical complications like delayed gastric emptying or pleural effusions. A soft pancreatic consistency and a high drain lipase activity on postoperative day3 are early predictors for the development of POPF C.

Keywords Secondary morbidity · POPF · Pancreatic surgery · Vascular complications

Introduction

Postoperative pancreatic fistulae (POPF) remain the major contributor to morbidity after pancreatic resection even in high volume centers.[1] A number of factors are associated with the development of POPF, most of them attributable to pancreatic anatomy,[2,3] but also to surgical technique.[4–6] Pharmacological prevention of POPF with somatostatin and analogs has not been unequivocally accepted due to conflicting results among several randomized controlled trials.[7–9] One of the problems in studies addressing POPF was the heterogeneity of definition of pancreatic fistula. In order to overcome that heterogeneity, a definition of the severity of pancreatic fistula was developed, based on the need for clinical treatment of POPF.[3] While that definition allows the comparison of different studies on POPF treatment and prevention, its post hoc character is susceptible to bias in treatment selection and does not provide a guideline for the timely treatment of POPF in an individual patient. Furthermore, it is unknown if the different grades

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of POPF have further sequelae like erosions of biliary and intestinal anastomoses or blood vessels and might thus be a cause for additional surgical morbidity and mortality.[10]

We therefore performed the present study in order to analyze the association of POPF type A-C, with secondary surgical morbidity and mortality in almost 500 patients undergoing pancreatic resection at a high volume center. To overcome the problems of a post hoc classification system on the prospective treatment plan for patients, we furthermore analyzed the influence of postoperative elevated drainage lipase activity on postoperative secondary morbidity and mortality.

Patients and Methods

Patient Data

Between 3/2001 and 12/2007, some 650 patients underwent abdominal exploration for pancreatic disease, while resection was performed in 483 cases. As of 3/2001, patient data was collected prospectively in a Standard Assessment Procedure (SAP)-based databank. As of 01/2002, standardized patient management was introduced into clinical practice in terms of clinical pathways (CPs). This CPs run on the same SAP-based system as the database for data collection. Data collected in that system include all biographic and disease-related data, perioperative and postoperative clinical data, as well as CP associated economic data like time and resource utilization.[11,12] All data is entered prospectively and analyzed retrospectively for this study.

After publication of the International Study Group of Pancreatic Fistula (ISGPF) definition of pancreatic fistulae in 2005, patient complications were graded in a prospective fashion accordingly. Patients having been treated before that introduction were graded accordingly in a retrospective fashion using the database mentioned above.

Surgical Technique

Pancreaticointestinal anastomosis were performed in a double layer duct-to-mucosa technique where the intestinal mucosa was stitched to the pancreatic duct with 6-0 absorbable monofilament sutures (polydioxanone; PDS, Ethicon, Norderstedt, Germany) and the edge of the parenchymal resection surface to the serosa of the small bowel using similar 5-0 single sutures. In patients undergoing distal pancreatic resection, the pancreatic duct was occluded with a Z type 5-0 PDS suture and a separate interrupted parenchymal suture with 4-0 PDS. Consistence of the pancreatic parenchyma was assessed as described previously.[13] A drainage (easy flow drain 30 Wolkersdorf, Austria) was placed behind the pancreaticointestinal anastomosis. Drains were removed routinely on the fifth postoperative day if no elevated drain lipase activity was detected. In patients developing pancreatic fistula, drains were removed after cessation of the fistula. Oral feeding was started between the first and fifth postoperative day in all patients, depending on the presence of a delayed gastric-emptying syndrome.

Fistula and Complication Definition

Starting in 2005, POPF were classified according to the ISGPF classification.[3] Prior to that classification, a three-fold increase of the drainage lipase activity over the serum lipase activity was considered a fistula. Patients, who had a fistula in that classification, were reclassified according to the ISGPF criteria.

The type A POPF requires little change in management or deviation from our normal clinical pathway with little clinical impact. In that group, no patients required antibiotic or somatostatin analogs treatment and no insignificant delay was found in hospital discharge. The intraoperatively placed drainages were managed by slow removal within 3 weeks on an outpatient basis.

The type B POPF required a change in management of our clinical pathway. Nearly all patients affected developed delayed gastric emptying and were therefore supported by partial or total parenteral nutrition up to 4 weeks postoperatively. The peripancreatic drains were usually left in place. All patients placed on antibiotic therapy; in some cases, somatostatin analogs were administered. In that group, hospital discharge was significantly delayed or readmission after previous discharge was required. Nearly all patients in that group were discharged with drains left in place and followed in our outpatient clinic.

If an invasive procedure was required, the POPF was graded as type C. In that group, a major change in clinical management or deviation from the normal clinical pathway was required. Usually, total parenteral nutrition combined with systemic antibiotics and/or somatostatin analogs was instituted. Computed tomography scan or ultrasound imaging often showed peripancreatic fluid collection, which were treated with percutaneous drainage wherever possible. Patients typically required an extended hospital stay with a major delay in hospital discharge.

However, patients with deteriorating clinical status, progressive sepsis, remote organ failure, or vascular complications required re-exploration. Secondary surgery consisted of revision of the primary procedure such as establishment of a new pancreatico-enteric anastomosis, pancreatectomy or simply in placement of optimized drainages. Postoperative mortality was markedly elevated in that subgroup.

Any deviation from our standard clinical pathway was considered a “complication” and was recorded online

during rounds. Medical complications were classified as surgical or non-surgical complications.[13] Superficial or deep wound infections and intraabdominal abscesses, delayed gastric emptying,[13,14] biliary or intestinal leakage or perforations, vascular erosions, and bleeding or thrombosis as well as pleural effusions, pneumonia, or pulmonary embolism were considered to be directly or indirectly attributable to the surgical procedure and were therefore considered as surgical complications. This included systemic inflammatory syndrome and/or sepsis arising from such complications. All other complications were considered non-surgical, including cardiac arrhythmias, requirement of inotropic support or cardiac failure, not associated with sepsis or systemic inflammatory response syndrome.

Vascular Complications

We categorized vascular complications as intraabdominal hemorrhage or arterial occlusion of large gastrointestinal arteries later than 72 h postoperatively. We consider this period of time as being adequate to distinguish between vascular complications related to the primary procedure and complications resulting from complicated fistulae.

Statistics

Data from the databases were linked and analyzed retrospectively using Statistical Package for the Social Sciences software (SPSS, Chicago, Illinois, USA). Relative risks including 95% confidence intervals were calculated from contingency tables. Data are given as absolutes or as mean ± SEM. Differences between groups were calculated by analysis of variance followed by the recommended post hoc test. Mann-Whitney *U* test was used for non-parametric assessing whether two independent samples of observations come from the same distribution comparisons. The Kruskal-Wallis one-way analysis of variance was used in cases of three or more groups. A $p<0.05$ was considered to be statistically significant. Odds ratios were used to describe the association between the incidence of POPF C and various risk factors for POPF. Account was taken of factors that could potentially confound the association to the occurrence of POPF C by fitting multivariable logistic regression models and obtaining adjusted odds ratios and 95% confidence intervals for the odds ratios.

Table 1 Biographic Data of 483 Consecutive Patients Undergoing Pancreatic Resection

Parameters	*n*	Percentage
	483	100
Gender [f/m]	212/271	44.8/56.1
Age [years; mean ± SEM]	60.7±13.9	
Range	9-87	
Age [≤70 years]	352	72.9
Age [>70 years]	131	27.1
ASA[a]		
I	14	2.9
II	280	58
III	178	36.8
IV	11	2.3
Malignant tumors	273	56.5
Benign pancreatic tumor	106	21.9
Chronic pancreatitis	104	21.5

[a] American Society of Anesthesiologists score

Table 2 Operative Details for 483 Consecutive Patients Undergoing Pancreatic Resection

Parameters	*n*	Percentage
Partial duodenopanreatectomy	323	66.8
Pylorus preserving	283	58.6
Kausch-Whipple	40	8.2
Distal resection	73	15.1
Central resection	15	3.1
Duodenum-preserving resections	22	4.5
Other resections	50	10.5
Vascular resection/reconstruction		
No	425	88
Yes	58	12
No lymphadenectomy	246	50.9
Standard	102	21.1
Extended lymphadenectomy	135	28
OR time [h; mean ± SEM][a]	4.27±1.33	
Blood loss [ml]		
500 ml	314	65
>500 ml	169	35

[a] Operation time

Table 3 Intraoperative Classification of Pancreatic Parenchyma Density in 218 Consecutive Patients Undergoing Partial Duodenopancreatectomy

Parameters	*n*	Percentage
Pancreatic density	218	100
Soft	83	38.0
Intermediate	57	26.2
Hard	78	35.8

Table 4 Morbidity and Mortality After Pancreatic Resection

Parameters	*n*	Percentage
POPF		
None	344	71.2
Type A	62	12.8
Type B	48	10.0
Type C	29	6.0
biliary leakage	28	5.8
GI leakage	0	0.0
Vascular complications	19	3.9
Wound infection	37	7.6
Intraabdominal abscess	53	11.0
Delayed gastric emptying	56	11.6
Pneumonia/pleural effusion	72	15.0
Reoperation/reintervention	56	11.6
IHOS (days; mean ± SEM)	18.3±0.6	
Range	1-126	
ICU stay (days; mean ± SEM)	4.4±0.3	
Range	1-94	
Mortality	12	2.48

POPF postoperative pancreatic fistula, *GI leakage* gastrointestinal leakage, *IHOS* in hospital stay, *ICU* intensive care unit

Results

Biographic and Operative Data

Out of 650 patients undergoing abdominal explorations for pancreatic disease, 483 underwent resection (212 female and 271 male patients, mean age 60.7±13.9 years). The indication was a benign or malignant tumor in 106 and 273 patients, respectively, and chronic pancreatitis in 104 patients (Table 1).

Three hundred twenty-three patients underwent partial pancreatoduodenectomy, mostly performed in the pylorus preserving technique described by Longmire and Traverso (n=283), while the remaining patients following the technique by Kausch-Whipple. Three hundred thirty-eight patients underwent pancreatic resections and subsequent pancreaticointestinal anastomosis. Of the patients with pancreatic malignancies, 86.8% underwent extended lymphadenectomy. Two out of three patients had a blood loss of less than 500 ml requiring no transfusion of blood products (Table 2). In 218 patients, intraoperative data of the pancreatic parenchyma consistency were documented. Of these patients, 38.0% had soft and 35.8% hard pancreatic parenchyma (Table 3).

Table 6 Multivariate Analysis of Association of Pancreatic Parenchyma Density and Lipase Drainage Activity with POPF C in 483 Patients Undergoing Pancreatic Resection

Variables	OR	95% CI	*p*
Lipase>5,000U/L 3rd POD	4.432	0.912-21.551	0.065
Lipase>5000U/L 5th POD	1.318	0.245-7.086	0.747
Soft pancreatic density	8.519	1.764-41.131	0.008

OR odds ratio, *CI* confidence interval, *POD* postoperative day

Complications

One hundred thirty-nine patients (28.8%) developed a POPF of any type. Of those patients, 79.1% had a fistula type A and B, not requiring any further treatment. Twenty nine patients (6.0%) had a POPF C. A total of 237 further complications were considered surgical complications or surgery-related complications like wound infections (n=37; 7.6%), intraabdominal abscess (n=53; 11.0%), delayed gastric emptying (n=56; 11.6%), vascular complications (n=19; 3.9%), or pleural effusion and pneumonia (72; 14.9%), many of them in combination with others. Of all patients, 11.6% required re-interventions mostly in form of percutaneous drainage of intraabdominal abscesses or reoperation for vascular complications. Those complications had a lethal outcome in 12 patients (2.5%, Table 4).

As seen previously, the intraoperative classification of the pancreatic parenchyma as being of soft consistency correlated with the development of a POPF type C with an

Table 5 Univariate Analysis of Association of Pancreatic Parenchyma Density and Lipase Drainage Activity with POPF C in 483 Patients Undergoing Pancreatic Resection

Variables	OR	95% CI	*p*
Lipase>5,000U/L 3rd POD	9.665	4.152-22.497	0.0001
Lipase>5,000U/L 5th POD	5.934	2.499-14.093	0.0001
soft pancreatic density	11.328	2.442-52.560	0.002

OR odds ratio, *CI* confidence interval, *POD* postoperative day

Table 7 Mortality in Patients with and Without POPF

Parameters	*n*	Death	*p*
No POPF	344	7	
POPF A-C	139	5	0.374
A	62	0	
B	48	0	
C	29	5	0.0001

Table 8 Details About Patients with Vascular Complication, Classified as Arterial Erosion or Thrombosis After Pancreatic Surgery

Parameters		Arterial erosion	Arterial thrombosis	*p*
Patients		12	7	NS
Age [years; mean ± SEM]		66.58±8.85	67.00±7.61	NS
Age [>70 years]		4	3	NS
Gender [female]		4	2	NS
ASA	I	0	1	NS
	II	6	5	NS
	III	6	1	NS
	IV	0	0	NS
Malignancy		7	2	NS
Chronic pancreatitis		3	1	NS
Benign pancreatic tumor		2	4	NS
OR time [h; mean ± SEM]		5.53±0.29	3.40±0.45	NS
Blood loss [ml; mean ± SEM]		1,004±220	835±264	NS.
Number of transfusion		2.08±0.05	2.25±0.06	NS
IHOS [days; mean ± SEM]		44±9	25.6±5.1	NS
ICU stay [days; mean ± SEM]		22±5.9	8.7±4.1	0.028
Reoperations (*n*; %)		7 (58.3)	4 (57.1)	NS
Surgical mortality after reoperation (*n*; %)		4 (33.3)	3 (43)	NS
Surgical mortality (*n*; %)		5 (41.6)	3 (42.8)	NS

ASA American Society of Anesthesiologists, *OR* operation time, *IHOS* ⁱn hospital stay, *ICU* intensive care unit, *NS* not significant

odds ratio of 11.3 (Table 5). Multivariate analysis identified a soft pancreatic tissue as the strongest risk factor for the development of POPF type C with an odds ratio of 8.5 (CI 1.7-41.1, Table 6).

The development of POPF of any type was no risk factor for postoperative death; however, the development of POPF type C was associated with a significantly increased mortality (five out of 29 patients; Table 7).

Interestingly, patients with a high drain lipase activity (lipase>5,000U/L) who developed further surgical complications associated with POPF had a mortality of 33.3% (5/15, Fig. 3). This was not the case in patients with a low drain lipase activity or with a high lipase activity without further surgical complications.

POPF was the most common complication, defined as A, B, and C occurred in 12.4%, 10.0%, and 5.8% of patients, respectively. In this series, no leakage of gastrointestinal anastomosis was observed. Wound infections and intraabdominal abscess were seen in 7.6% and 11.0%. Of the patients, 11.6% underwent secondary surgery. In hospital stay (IHOS) and intensive care unit (ICU) stay was 18.3±0.6 (range 1-126 days) and 4.4±0.3 (range 1-94 days), respectively. Twelve out of 483 patients (2.5%) died during hospital stay.

In the subset of 19 patients with vascular complications (VC), 17 (89.5%) had proven fistula prior to onset of VC. The median age was 66.58±8.85 in arterial erosion (AE) and 67.00±7.61, respectively, in arterial occlusion (AO). AE was found in 12 patients, while seven patients had AO;

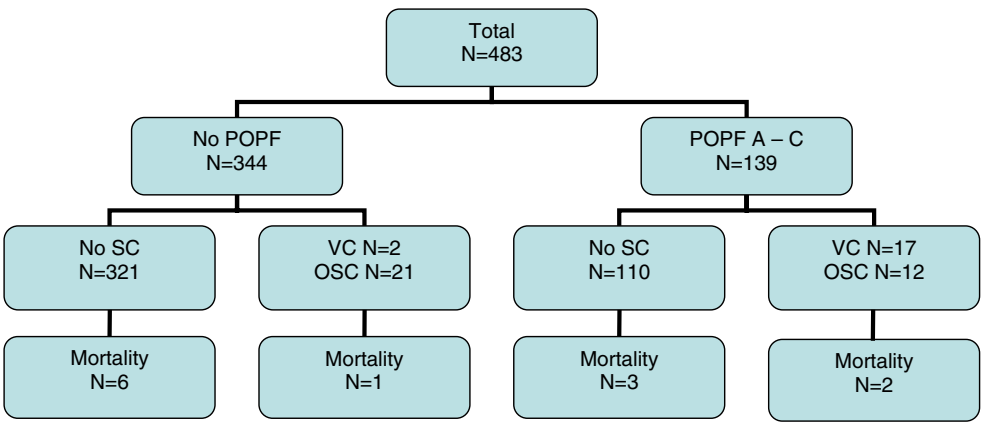

Figure 1 Postoperative mortality of patients with and without postoperative pancreatic fistula (POPF) related to no surgical complications (SC), vascular complications (VC), and other surgical complications (OSC).

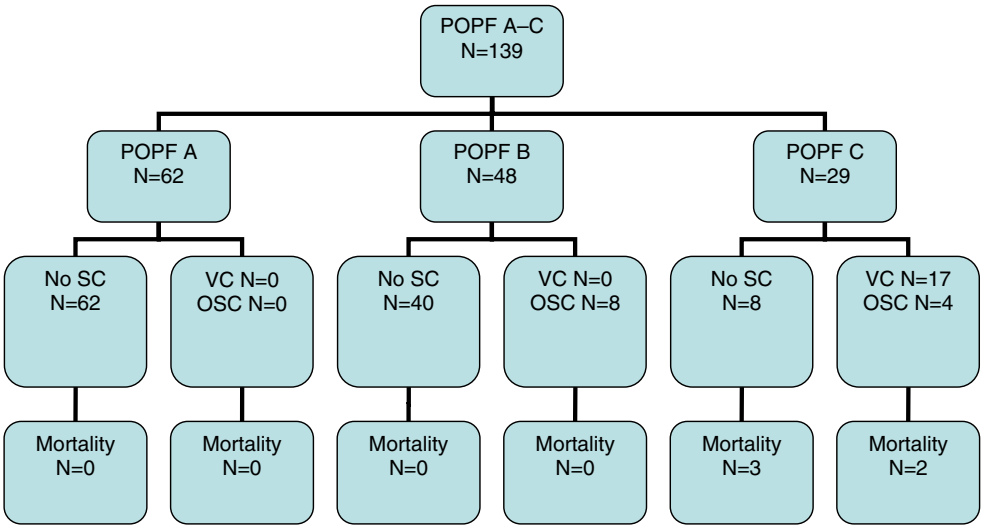

Figure 2 Postoperative mortality of patients with postoperative pancreatic fistula type A, B, and C classified to ISGPF criteria, related to no surgical complications (SC), vascular complications (VC), and other surgical complications (OSC).

hereunder, eight (42.1%) patients were primarily objected to observational monitoring without interventional procedures in cause of clinically stable condition. The event of AE was between 4 and 34 postoperative day (POD; 11± 1.9, data not shown), respectively, AO between 7 and 18 POD (10.1±1.4, data not shown). In 11 of 19 patients (57.9%), reoperations were required. Seven patients with AE underwent emergency surgery mandated by abdominal drains or severe hemodynamic instability (Table 8). AO were suspected by clinical instability either due to intestinal blood loss or fecal secretion via drains secondary to transmural ischemia. Two patients subsequently required a colon segment resection, one a subtotal colectomy and one a two-thirds gastric resection.

In statistical analysis, no significant difference between these two subgroups of VC was found except in length of ICU stay (p=0.028).

Secondary Morbidity Associated with POPF

The majority of the patients who did not developed POPF did not develop any other surgical complications (321/344; 93.3%), resulting in a low mortality rate of 2.0%. Out of the 344 patients without POPF, 23 developed other surgical (OSC) or VC. One single patient without POPF died from a surgical complication in his postoperative course. One hundred ten of 139 patients with POPF had no SC (79.1%), and subsequently a mortality of 2.7%. Of the remaining 29 patients who developed OSC or VC after POPF, two patients died (6.9%, Fig. 1).

No patient with a POPF A developed OSC and there was no fatality in that group. Likewise, no patient with POPF B died. However, eight out of 48 patients (16.7%) in that group developed OSC. In contrast, patients with POPF C 21/29 (72.4%) developed OSC, mostly VC (17/21; 81.0%),

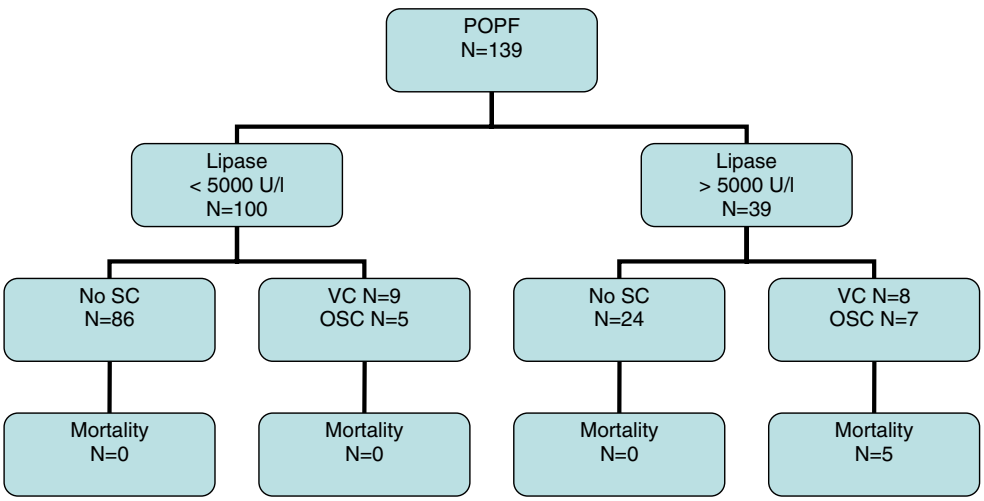

Figure 3 Postoperative mortality of patients with postoperative pancreatic fistula according to ISGPF criteria, related to lipase activity at third postoperative operative day in drains.

leading to a mortality of 5/29 patients in that group (17.2%, Fig. 2).

In patients who developed POPF, 100 patients had a low drain lipase activity. Out of those patients, 86 (86.0%) had no further complications, while 14 (14.0%) did have further VC or OSC. However, no patient with a low drain lipase activity on POD3 died as a consequence of surgical morbidity. In patients with a high level of drain lipase activity without further surgical complications, mortality was zero (0/24). However, in case of OSC or VC, mortality increased to 33.3% (5/15, Fig. 3).

Discussion

The major findings of this study are the association of POPF type C with subsequent surgical complications, vascular complications, delayed gastric emptying, and pleural effusions. The combination of POPF type C with vascular complications and infections significantly increased morbidity and mortality after pancreatic resection. Type C POPF developed predominantly in patients with a soft pancreas and the development of a type C POPF was preceded by a high drain lipase activity on POD3.

The ISGPF definition of POPF was developed to allow a realistic comparison of surgical experiences between different hepatopancreatobiliary centers or to evaluate new surgical techniques or pharmacological interventions. On one hand side, grade A POPF is a biochemically apparent fistula only, evident by drainage fluid with an increased of pancreatic enzyme activity, without further clinical consequences. On the other hand side, type C POPF severely alters the postoperative course of the patient, requiring prolonged and specific treatment, but potentially leading to a lethal outcome.[3] Type B POPF comprises an intermediary type. The ISGPF classification has recently been validated in a series of 176 patients.[1] In that series, Pratt and colleagues, where able to demonstrate the association of type C fistulas with higher rates of complications, surgical or radiological interventions, ICU and overall hospital stay, and increased overall cost. Those findings are in line with the data presented in this present series overlooking nearly 500 patients. With the post hoc character of the ISGPF definition of POPF, these data come as no surprise. However, we were able to further specify and quantify the complications associated with type C fistulas in our data. Since intraoperative drainages were placed in all patients in this series, postoperative interventions to drain fluid collections are rarely required and surgical re-explorations are only necessary in patients with severe bleeding or uncontrollable sepsis.[10]

Somatostatin analogs therapy in patients with established type C fistulas is of questionable value in our experience.[7–9] We demonstrate that type C fistulas predominantly occur in patients with soft pancreas, which might have consequences for pharmacological preconditioning in patients undergoing pancreatic resection.[15,16] Type C fistulas were preceded by a high drain lipase activity on POD3. Lipase activity cutoff points other than 5,000U/L, amylase activity or enzyme activity measured on POD5 or 7 were not predictive for the development of type C fistula (data not shown).

While that finding needs validation and confirmation in other specialty surgical units, a linear correlation of high drain lipase activity with the grade of POPF was also seen in Pratts study.[1] While the use of amylase activity in the definition of POPF has failed to lead to a broadly accepted fistula classification, the clear cutoff point of high drain lipase activity has prompted us to alter our clinical pathway for the postoperative treatment after pancreatic resection.

In our analysis, we found that both the soft quality of the pancreas and an elevation of lipase activity in drainage fluids on POD3 significantly increase the risk for the development of a type C fistula. To prevent such a development, we introduce somatostatin analogs treatment and antibiotic therapy as soon as lipase activity above 5,000 U/L in drainage fluids is detected. As defined by our CPs, drainage fluids are analyzed on POD3 and 5. Intraoperatively placed drains are left in place until fistulae heal. However, in case of severe pancreatic fistula, further management depends on rapid decision for re-exploration, especially in cases of vascular complications.

In conclusion, this is so far the largest study that validates the ISGPF classification on postoperative pancreatic fistula. Namely the association of soft pancreatic tissue and the development of POPF type C together with the association of high drain lipase activity and type C fistula might guide future allocation of postoperative surveillance resources in patients undergoing pancreatic resection.

Acknowledgment We thank Berit Kopp for her diligent help in data collection.

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J Gastrointest Surg (2010) 14:719–728
DOI 10.1007/s11605-010-1156-4

ORIGINAL ARTICLE

Lymph Node Involvement and Not the Histophatologic Subtype Is Correlated with Outcome After Resection of Adenocarcinoma of the Ampulla of Vater

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Received: 22 October 2009 / Accepted: 4 January 2010 / Published online: 27 January 2010

Abstract
Background Intestinal and pancreaticobiliary types of Vater's ampulla adenocarcinoma have been considered as having different biologic behavior and prognosis. The aim of the present study was to determine the best immunohistochemical panel for tumor classification and to analyze the survival of patients having these histological types of adenocarcinoma.
Method Ninety-seven resected ampullary adenocarcinomas were histologically classified, and the prognosis factors were analyzed. The expression of MUC1, MUC2, MUC5AC, MUC6, CK7, CK17, CK20, CD10, and CDX2 was evaluated by using immunohistochemistry.
Results Forty-three Vater's ampulla carcinomas were histologically classified as intestinal type, 47 as pancreaticobiliary, and seven as other types. The intestinal type had a significantly higher expression of MUC2 (74.4% vs. 23.4%), CK20 (76.7% vs. 29.8%), CDX2 (86% vs. 21.3%), and CD10 (81.4% vs. 51.1%), while MUC1 (53.5% vs. 82.9%) and CK7 (79.1% vs. 95.7%) were higher in pancreatobiliary adenocarcinomas. The most accurate markers for immunohistochemical classification were CDX2, MUC1, and MUC2. Survival was significantly affected by pancreaticobiliary type (p=0.021), but only lymph node metastasis, lymphatic invasion, and stage were independent risk factors for survival in a multivariate analysis.
Conclusion The immunohistochemical expression of CDX2, MUC1, and MUC2 allows a reproducible classification of ampullary carcinomas. Although carcinomas of the intestinal type showed better survival in the univariate analysis, neither histological classification nor immunohistochemistry were independent predictors of poor prognosis.

Keywords Ampulla of vater · Adenocarcinoma · Immunohistochemistry · Mucins · Prognostic factor

Introduction

Neoplasms arising from the ampulla of Vater are relatively rare; the incidence is estimated at five to seven cases per million per year, accounting for 0.2% of gastrointestinal tract cancers and 6% to 20% of periampullary tumors.[1–3] Ampullary cancers present earlier and are more likely to be resectable at the time of diagnosis than other periampullary tumors; moreover they have a better prognosis after curative resection compared with pancreatic head or extrahepatic bile duct carcinoma.[3–5] Surgical resection is considered the ideal therapy for patients with ampullary carcinoma, and survival is related to tumor stage, lymphatic metastasis, and tumor grade.[3,4,6,7] Tumors with the same stage and similar prognostic factors do not always evolve in a similar way after surgery, suggesting the existence of biologic differences.[8,9]

Support: FAPESP, Fundação de Amparo à Pesquisa do Estado de São Paulo.

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Ampullary carcinoma may arise from two different types of mucosa: The intestinal type covers the papilla, and the pancreaticobiliary type arises from the epithelium of the distal common bile duct, distal pancreatic duct, or common ampullary channel. Kimura et al.[10] were the first to distinguish pancreaticobiliary and intestinal types of ampullary carcinoma. Albores-Saavedra et al.[11] classified the ampullary tumors in two main types, intestinal and pancreatobiliary. Based on this classification, a series of studies examined the molecular histogenesis of ampullary carcinomas. Matsubayashi et al.[12] successfully separated these two types of tumors by immunohistochemical expression of apomucin MUC2 in intestinal types. Zhou et al.[13] suggest a classification of these neoplasms using immunohistochemical detection of the expression of cytokeratin CK20 in the intestinal type and CK7 in the pancreaticobiliary type. Chu et al.[14] proposed a classification using markers of apomucin and were the first to identify CDX2 as a marker for the intestinal type of ampullary cancer. They also used CK17 as a useful marker in separating pancreaticobiliary adenocarcinomas from extrapancreatobiliary non-mucinous adenocarcinomas, including colon tumors.

Some studies have attempted to demonstrate a prognostic difference between the histologic types of differentiation for ampullary adenocarcinoma.[3,7,10,11,13,15–18] Some authors have found no statistical difference in survival between patients having the intestinal type and those having the pancreatobiliary type,[3,10,11,13,17] while other authors have found worse survival among patients having the pancreaticobiliary type, but only in multivariate analysis[16,18] or in analyses that included other types of periampullary tumors.[15]

In the present study, adenocarcinomas of Vater's ampulla submitted to surgical resection with curative intention were analyzed, and the histomorphologic classification proposed by Albores-Saavedra[11] was correlated with patient outcome and with an immunohistochemical panel containing cytokeratins, mucins, CDX2 and CD10.

Patients and Methods

Between 1985 and 2006, 97 patients diagnosed with adenocarcinomas of the ampulla of Vater were treated surgically with curative intent in the Digestive Surgery Division of the Gastroenterology Department of the University of São Paulo School of Medicine. Formalin-fixed, paraffin-embedded tissue blocks were retrieved from the archives of the Pathology Department.

Clinical data were obtained from medical records review. Follow-up of patients was done through outpatient consultations, and patients without outpatient follow-up were contacted by telephone call.

Histological and Immunohistochemical Study

Histology of all tumors was reviewed by two experienced pathologists (RP and IC), without knowledge of patients' evolution. The tumors were characterized by degree of differentiation into well, moderately, and poorly differentiated tissue; surgical margin condition; adjacent structure infiltration; occurrence and number of lymph node metastasis; and vascular, lymphatic, and perineural invasion. Size of the tumor at its largest axis was recovered from the original report of pathological examination. All tumors were staged using the TNM classification for ampullary carcinomas.[19]

Tumors were classified by the pathologist examiner in intestinal and pancreatobiliary-type adenocarcinomas, based on cytological and architectural features, as described by Albores-Saavedra.[11] Tumors with a mixed histologic pattern were classified according to the predominant type.

Tissue microarrays (TMA) were prepared by selecting an area of interest from the H&E slides. The same areas were marked in the paraffin blocks of tissue donors. Cylinders of 1.0 mm diameter of the areas marked in donor paraffin blocks were transported to a recipient paraffin block using a precision mechanical system (Beecher Instruments) with an interval of 0.3 mm between the cylinders. In total, the constructed TMA contained two samples per case plus nine samples of control tissues (duodenum and ampulla of Vater mucosa). Once ready, TMA blocks were cut into histological sections of 3 μm (Leica Instruments).

Using the avidin–biotin complex technique, slides were stained with monoclonal antibodies. Briefly, 4-μm sections were deparaffinized and rehydrated in graded alcohol and washed in PBS (pH 7.4), the buffer used for all subsequent washings. Slides were stained with the following monoclonal antibodies: CK7 (OV-TL-12/30, Dako) at 1:25,000 dilution, CK17 (E3, Novocastra) at 1:50 dilution, CK20 (Ks20-8, Dako) at 1:400 dilution, MUC1 (MA698, Novocastra) at 1:1000 dilution, MUC2 (Ccp58, Dako) at 1:50 dilution, MUC5AC (CLH2, Novocastra) at 1:200 dilution, MUC6 (CLH5, Novocastra) at 1:125 dilution, CDX2 (AMT28, Novocastra) at 1:50 dilution, and CD10 (56C6, Novocastra) at 1:100 dilution. Negative controls were obtained by leaving out the primary antibody. Appropriate positive controls were performed. The slides were mounted in Entellan for analysis of results.

Immunohistochemistry analysis was performed by one experienced pathologist (RP). All histological sections were examined using a pre-defined ranking system. The nuclear or cytoplasmic reactivity was scored semiquantitatively on a scale from 0 to 4 for distribution (distribution: 0 = absence of staining in the sample stained, 1 = sparse positive cells, 2=5–10% positively stained tumor cells, 3= 10–50%, and 4≥50%). The normal staining pattern for MUC1, MUC2, MUC5AC, and MUC6 was cytoplasmic; for CK7, CK17, CK20, CDX2, and CD10, staining was

observed at the membrane and in the cytoplasm. Scores 0 and 1 were regarded as negative and scores 2–4 as positive.

Statistical Analysis

Data analysis was performed using SPSS® 14.0 software (SPSS, Chicago, IL, USA). Values of $p < 0.05$ were considered significant. Statistical correlation between clinicopathologic, morphologic, and immunohistochemical parameters was tested using a Chi-squared test or two-sided Fisher exact test. Continuous variables were compared by Student's t test. Histological markers were analyzed by the generalized linear model (GLM)[20] using binomial distribution and a logistics link to identify the probability of pancreatic origin. When the effect was protective (negative coefficient), the result was presented as a chance of intestinal origin. To classify tumors using immunohistochemical markers, the GLM was applied to each case, and the probability of being pancreaticobiliary was determined. To classify the patients by tumor type (intestinal or pancreatobiliary), it was necessary to find a cut-off point that maximized sensitivity and specificity on the ROC curve. To estimate probabilities of distribution for the cut-off, a re-sampling (bootstrap) technique was adopted. The median cut-off points obtained after 5.000 re-sampling were used to classify the patients. We calculated the sensitivity, specificity, and accuracy of this new classification. The analysis of agreement intensity between histological and immunohistochemical classifications was evaluated by Kappa method.

Kaplan–Meier actuarial time-to-death, stratified by patient and tumor characteristics, was calculated and compared using the log-rank test. A Cox proportional hazard model was used to identify risk factors for patient death. Variables with $p<0.05$ in the univariate analysis were entered into the multivariate analysis.

Results

Histopathological Study

Fifty-eight men and 39 women with a mean age of 59.3 (23–83) years and with adenocarcinoma of the Vater's

Table 1 Clinical and Pathologic Comparison of Intestinal and Pancreaticobiliary Ampullary Adenocarcinomas

	Intestinal type (n=43)	Pancreaticobiliary type (n=47)	p value[c]
Gender			0.898
Male	28 (65.1%)	26 (55.3%)	
Female	15 (34.9%)	21 (44.7%)	
Age[a]	60.5±12	57.8±13.6	0.438
Pre-operative bilirubin level[a]	5.42±7.9	10.4±10.9	0.022
Maximum tumor diameter[a]	2.66±1.52	2.32±1.16	0.152
Lymph node metastasis			0.005
Yes	8 (18.6%)	22 (46.8%)	
No	35 (81.4)	25 (53.2%)	
Staging			0.019[b]
IA	13 (30.2%)	11 (23.4%)	
IB	14 (32.6%)	4 (8.5%)	
IIA	7 (16.3%)	10 (21.3%)	
IIB	9 (20.9%)	20 (42.6%)	
III	0	1 (2.1%)	
V	0	1 (2.1%)	
Grade of differentiation			0.084
G1	13 (30.2%)	6 (12.8%)	
G2	26 (60.5%)	32 (68.1%)	
G3	4 (9.3%)	9 (19.1%)	
Vascular invasion			0.679[b]
Yes	2 (4.7%)	4 (8.5%)	
No	41 (95.3%)	43 (92.5%)	
Lymphatic invasion			0.039
Yes	8 (18.6%)	18 (38.3%)	
No	35 (81.4%)	29 (61.7%)	
Perineural infiltration			0.005[b]
Yes	4 (9.3%)	16 (34%)	
No	39 (90.7%)	31 (66%)	

[a] Mean ± SD deviation

[b] Fisher exact test

[c] Chi-squared test, when not otherwise specified

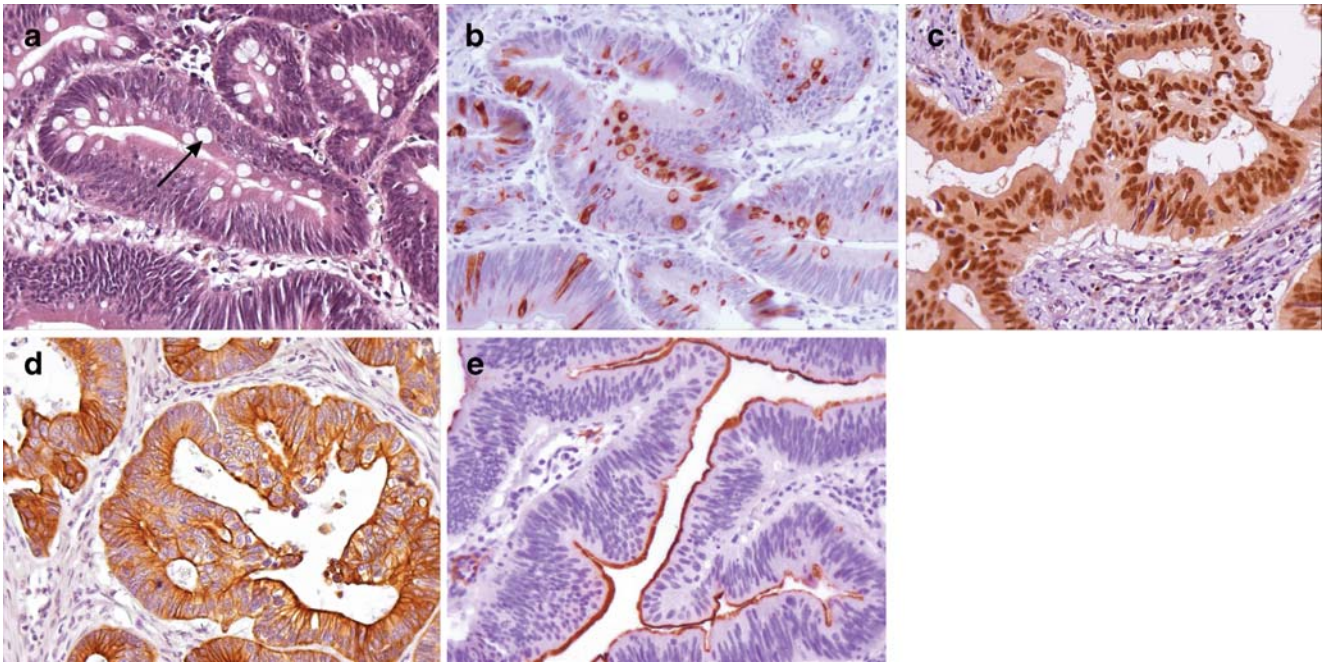

Figure 1 Histology and immunohistochemistry of intestinal type of Vater's ampulla adenocarcinoma: **a** H&E, ×400; **b** MUC2 expression, ×400; **c** CDX2 expression, ×400; **d** CK20 expression, ×400; and **e** CD10 expression, ×400.

ampulla underwent surgical resection between January 1985 and December 2006. The average tumor size was 2.54 cm±1.36 cm. Thirty-three patients (34%) had lymph node metastasis. All patients were staged according to UICC[19] as: stage IA, 25 patients (T1N0M0, T1: limited to the ampulla of Vater or sphincter of Oddi); stage IB, 19 patients (T2N0M0, T2: invading the duodenal wall); stage IIA, 19 patients (T3N0M0, T3: invading the pancreas); stage IIB, 32 patients (any T, N1M0, N1: metastasis in regional lymph nodes); stage III, one patient with portal vein invasion (invasion of the soft peri-pancreatic tissue, or other adjacent organs or structures); stage IV, one patient (any T, any N, presence of metastasis). A total of 22 tumors (22.7%) were well differentiated [grade (G1)]; 63 (64.9%) were moderately differentiated (G2); and 12 (12.4%) were poorly differentiated (G3).

Forty-three cases were classified as intestinal type, 47 as biliopancreatic type and seven as other types (five mucinous adenocarcinoma, one adenosquamous carcinoma, and one clear cell adenocarcinoma). The intestinal and biliopancreatic types were compared with regard to clinical and pathological characteristics (Table 1). Statistically significant differences were demonstrated between the two groups regarding the values of pre-operative bilirubin, lymph node involvement, TNM staging, and lymphatic and perineural invasion.

Immunohistochemical Study

The intestinal type had a significantly higher expression of MUC2, CK20, CDX2, and CD10, while MUC1 and CK7 expression were higher in pancreatobiliary adenocarcinomas (Figs. 1 and 2, Table 2). CDX2 (82.2%) followed

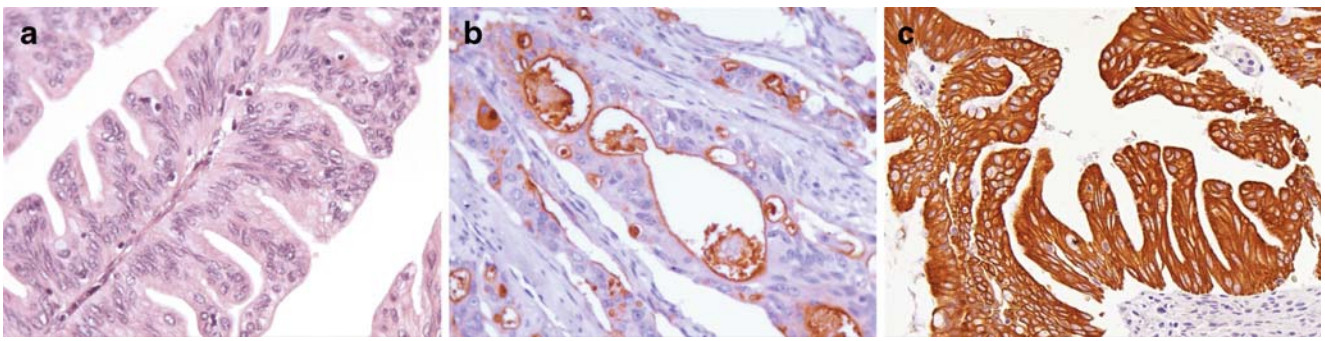

Figure 2 Histology and immunohistochemistry of pancreaticobiliary type of Vater's ampulla adenocarcinoma: **a** H&E, ×400; **b** MUC1 expression, ×400; and **c** CK7 expression, ×2,400.

Table 2 Positivity of Immunohistochemical Staining for Intestinal and Pancreaticobiliary Types of Vater's Ampulla Adenocarcinoma

	Intestinal type (n=43) n (%)	Pancreaticobiliary type (n=47) n (%)	p value[a]
MUC1	23 (53.5%)	39 (82.9%)	0.001
MUC2	32 (74.4%)	11 (23.4%)	<0.001
MUC5AC	29 (67.4%)	33 (75%)	0.436
MUC6	19 (44.2%)	21 (44.7%)	0.566
CDX2	37 (86%)	10 (21.3%)	<0.001
CK7	34 (79.1%)	44 (95.7%)	0.041
CK17	27 (62.8)	37 (78.7%)	0.096
CK20	33 (76.7%)	14 (29.8%)	<0.001
CD10	35 (81.4%)	24 (51.1%)	0.002

[a] Chi-squared test

by MUC2 (75.5%) and CK20 (73.3%) were the markers with greater accuracy in the intestinal type. MUC1 and CK7 have good sensitivity (84.8% and 95.7%, respectively) but low specificity (46.5% and 20.9%, respectively) in the pancreaticobiliary type. Higher positive predictive value was achieved by CDX2 (78.7%) in the intestinal type and MUC1 (62.9%) in the pancreaticobiliary type.

Through generalized linear model analysis, it was determined that MUC1, MUC2, and CDX2 (Table 3) were the key markers for differentiation of the histological type. Applying the GLM model, the probability that a MUC1−/MUC2+/CDX2+ tumor would differentiate to the intestinal type was 91.7%. Such a tumor was 19.13 [95% CI 4.12; 88.85] times more likely to be intestinal when compared to a MUC1+/MUC2−/CDX2− tumor (Table 4).

Immunohistochemical results for CDX2, MUC2, and MUC1 markers led to a new classification of histological type. We determined each patient's likelihood of having a pancreaticobiliary-type tumor, according to the logistic model. A cut-off value of 0.534 was selected by bootstrap method on the ROC curve (Fig. 3). The immunohistochemistry classification shows 47 intestinal-type tumors and 40 pancreatobiliary tumors, excluding three cases which could not be analyzed and seven unusual tumors (Table 5). The sensitivity, specificity, and accuracy of this classification in determining histologic type were, respectively, 80%, 90.5%, and 85.1%. Immunohistochemistry and histological classification were in agreement (Kappa of 0.702, p <0.001).

A significant relationship between absence of perineural infiltration and CDX2 positivity (p=0.027) or CD10 positivity (p=0.04) was found. The presence of lymphatic invasion was significantly associated with positivity for MUC1 (p=0.029). MUC1 positivity was also significantly associated with moderately and poorly differentiated carcinomas (p=0.03); MUC2 positivity was associated with well-differentiated carcinomas (p=0.045).

Survival Analysis

The average patient follow-up was 80 months, ranging from 9 to 321 months. The overall survival was 90.3% in 1 year, 71.5% at 3 years, and 64.2% at 5 years. The mean survival was 150.4 months (median of 128.2). Fourteen patients were lost during follow-up, but only seven before reaching 5 years of survival. Three cases of in-hospital death were excluded from survival analysis. Clinical and pathological factors were analyzed to determine those that affect survival.

Presence of lymph nodes metastasis, TNM stage, lymphatic invasion, and histological classification in univariate analysis were associated with worse survival (Table 6, Fig. 4). Lymph node involvement was an independent prognostic factor (p<

Table 3 Generalized Linear Model to Identify the Main Immunohistochemical Markers for the Determination of Histological Type

Coefficient	Estimate	Standard error	HR	95% CI	p value
Intercept	0.9507	1.2550	0.7213	(0.18; 0.97)	0.448
MUC1	1.5025	0.7331	4.49295	(1.07; 18.9)	0.040
MUC2	−1.6284	0.7471	5.0957[a]	(1.18; 22.4)	0.029
MUC5AC	0.1424	0.7748	1.1530	(0.25; 5.26)	0.854
MUC6	−0.1200	0.6995	1.1275[a]	(0.29; 4.44)	0.863
CK7	0.9899	0.8678	2.6910	(0.49; 14.74)	0.254
CK20	0.2685	0.8350	1.3080	(0.25; 6.72)	0.747
CD10	−0.8099	0.7962	2.248[a]	(0.47; 10.7)	0.309
CDX2	−2.7204	0.7610	15.1864[a]	(3.42; 67.49)	0.001

HR hazard ratio, *CI* confidence interval

[a] HR>1 indicates increased probability of intestinal type

Table 4 Generalized Linear Model to Identify the Effects of CDX2/MUC2 and MUC1/MUC2/CDX2 Associations

Coefficients	Estimate	Standard error	HR[a]	95% CI	*p* value
Intercept	2.3979	0.7385	0.9167	(0.72; 0.98)	0.001
MUC1−/CDX2+/MUC2+	−2.9513	0.7835	19.1423[a]	(4.12; 88.85)	<0.001

HR hazard ratio, *CI* confidence interval

[a] HR>1 indicates increased probability of intestinal type

0.001) in multivariate analysis (Table 7a). Excluding lymph node metastasis and T stage eliminated redundancies among these variables; lymphatic invasion (p=0.012) and TNM stage (p<0.001) were identified as independent prognostic factors (Table 7b).

Discussion

Histologic classification of ampullary adenocarcinoma based on the epithelium of origin has become necessary to compare the incidence and behavior of these tumors. The collection of the Memorial Sloan-Kettering Cancer Center included 140 cases of Vater's ampulla adenocarcinoma: 49% were intestinal type and 22% were pancreaticobiliary.[11] In Kimura's collection, the intestinal subtype amounts to only 25% of all samples studied, whereas pancreaticobiliary subtypes represent the largest group, with 72% of cases.[10] On the other hand, Zhou et al.[13] studied 55 cases and classified 44% as pancreaticobiliary, 27% as intestinal, and 29% as unusual or mixed type. Likewise, in the Roh et al. study, the pancreaticobiliary subtype predominated (64.7%) over the intestinal subtype (35.35%).[17] In our series, the subtype incidence was similar: intestinal type adenocarcinomas, 44.3%; pancreaticobiliary type, 48.5%; and unusual types, 7.2%.

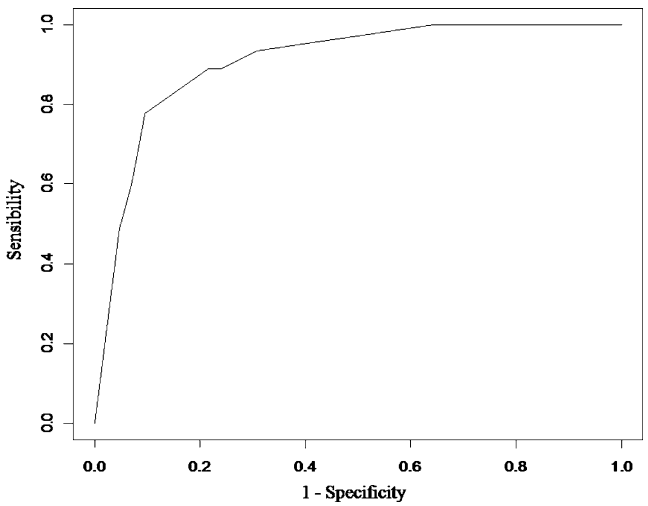

Figure 3 ROC curve to determine the pancreatobiliary type as change in the value of the cut-off.

Using the criteria described by Albore-Saavedra,[11] specialized pathologists are able to classify the tumor subtype (intestinal or pancreatobiliary) in approximately 90% of cases.[7] Immunohistochemical expression is used to better characterize the tumor types, but most of the marker panels used are not uniform. Some authors used only cytokeratins,[13,17] or apomucins,[12] and others used mixed markers.[17,21]

In this study, a broad panel of markers was analyzed, including all markers tested previously, but not together, for ampullary carcinomas (CK7, CK17, CK20, MUC1, MUC2, MUC5AC, MUC6, and CDX2) and CD10. The markers that showed significantly higher frequency of positivity for the intestinal type of tumors were MUC2, CK20, CD10, and CDX2; for the pancreaticobiliary type, these markers were CK7 and MUC1. The logistic regression model showed that CDX2, MUC2, and MUC1 markers had greater ability to predict histological type. Furthermore, this study showed that CDX2 positivity, even independently, represents a 16 times greater chance that the tumor will be intestinal. Furthermore, the CDX2+/MUC2+/MUC1− association increases the possibility of classification by more than 19 times. We reclassified all adenocarcinomas using only these three markers, which resulted in good agreement with histological classification (κ coefficient=0.702).

Zhou et al. used only the CK7/CK20 combination to classify ampullary carcinomas and observed good agreement between the pancreaticobiliary tumors and CK7+/CK20− expression (87.5%). However, CK7−/CK20+ expression was present in over 60% of intestinal tumors.[13] Mucin was used initially by Matsubayashi et al. in a series of 52 cases, including 23 ampullary carcinomas, 24 adenomas with carcinoma, and five adenomas.[12] The

Table 5 Comparison of Histological Classification and Immunohistochemical Classification of Vater's Ampulla Adenocarcinoma

	Histologic types[2]		
	Intestinal	Pancreaticobiliary	Total
Immunohistologic types			
Intestinal	38	9	47
Pancreaticobiliary	4	36	40
Total	42	45	87

intestinal tumors had a higher frequency of intraductal components, adenomatous components, and MUC2 expression than pancreaticobiliary tumors. Roh et al. showed that MUC2 and CK7/CK20 expression are significantly decreased in intestinal and pancreaticobiliary types; however, the cytokeratins had lower specificity.[17] Chu et al. also demonstrated that expression of MUC2 and CDX2 were associated with the intestinal phenotype, whereas MUC1 and CK17 were associated with the pancreatobiliary tumors.[14] The expression of CK17 in our study was also slightly more common in the pancreaticobiliary type than in the intestinal type, but without significant difference.

CDX2 has been demonstrated as a good marker for adenocarcinomas of intestinal origin.[16,21] Hansel et al.[21]

Table 6 Clinical and Pathologic Factors Associated with 5-Year Survival in Vater's Ampulla Adenocarcinoma

Variable	Samples	Survival mean (months)	*p* value[a]
Gender			0.716
Male	55	47.7±2.7	
Female	39	47.7±3.0	
Age			0.442
< 60 years	40	47.4±3.0	
>61 years	54	48.0±2.6	
Jaundice			0.413
Yes	65	46.9±2.4	
No	20	49.4±4.0	
Tumor diameter			0.633
>2 cm	50	46.4±2.8	
≤2 cm	44	49.2±2.8	
Lymph node metastasis			<0.001
Yes	32	50.1±2.8	
No	62	43.6±3.3	
pT stage			0.007
pT1 and pT2	56	52.18±2.3	
pT3 and pT4	38	41.5±3.3	
TNM stage			0.001
I	43	53.9±2.6	
II	49	43.8±2.9	
III and IV	2	24.8±2.0	
Histological type[2]			0.021
Intestinal	41	50.2±2.7	
Pancreaticobiliary	46	45.2±3.0	
Immunohistochemical classification			0.084
Intestinal	45	47.1±2.1	
Pancreaticobiliary	39	60.00±0	
Lymphatic invasion			0.004
Yes	26	47.8±2.1	
No	68	57.1±5.6	
Vascular invasion			0.057
Yes	6	31.4±9.3	
No	88	48.9±2.0	
Perineural infiltration			0.288
Yes	21	44.9±4.2	
No	73	48.6±2.3	
Grade of differentiation			0.059
G1	22	56.0±3.3	
G2	59	46.4±2.6	
G3	13	40.9±5.7	
CDX2			0.129
Positive	49	49.37±2.17	
Negative	45	59.92±0.11	

[a] Log-rank test

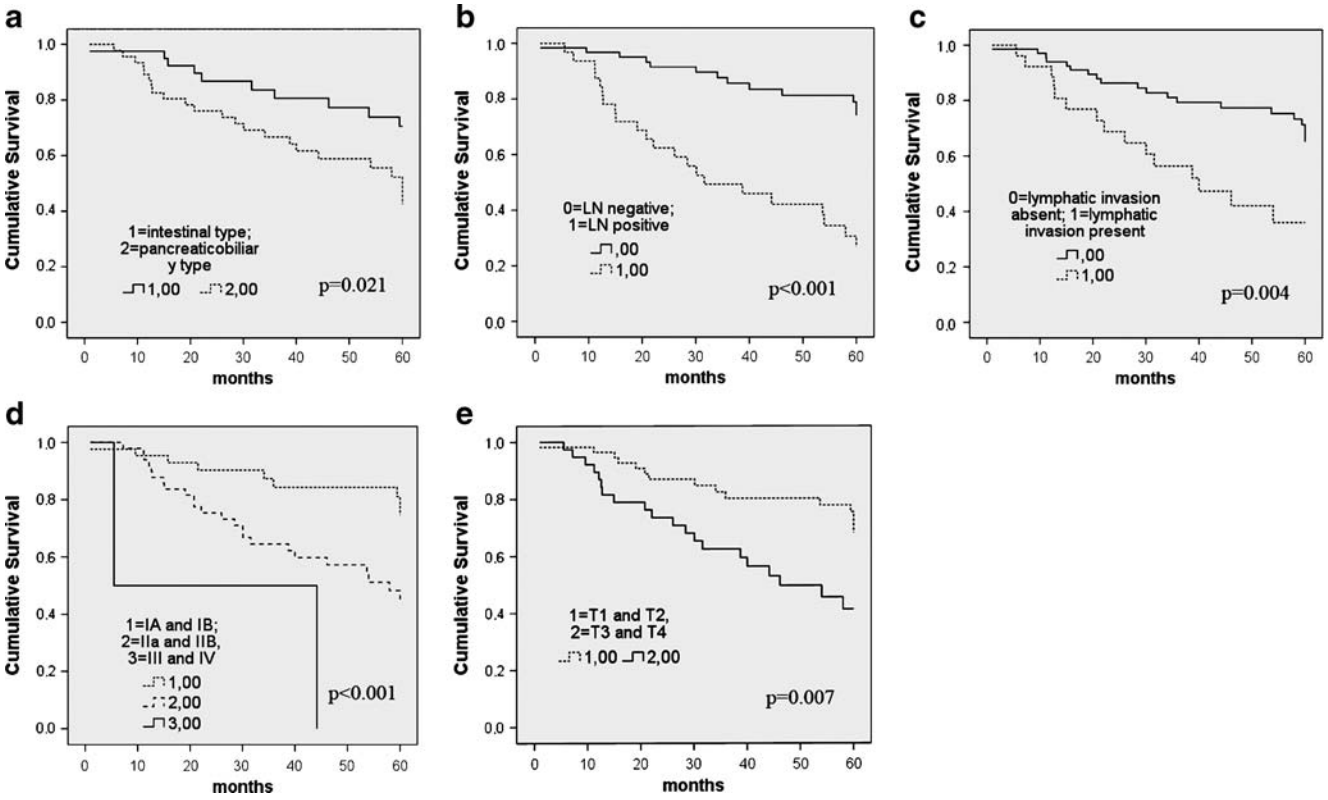

Figure 4 Kaplan–Meier estimates of overall survival: patients stratified by **a** histologic subtype, **b** lymph node status, **c** lymphatic invasion, **d** UICC stage, and **e** pT stage. *p* values shown were calculated using the log-rank test for survival differences. *LN* lymph node, *UICC* International Union Against Cancer.

examined a series of 53 ampullary carcinomas and demonstrated that CDX2 expression alone could identify intestinal-type carcinomas, which are associated with a better prognosis. This finding highlights CDX2 expression as an indicator of independent evolution. Recently, Sessa et al.[16] found 100% of their intestinal ampullary carcinomas expressed these markers. However, as in our series, there is no association between the expression of CDX2 and better survival. CDX2 is related to the differentiation of intestinal and colonic epithelium; loss of its expression is associated with the carcinogenesis of colon cancer.[22,23] On the other hand, its expression in gastric cancer is associated with better prognosis and related to the presence of intestinal metaplasia in the epithelium of the stomach.[24] CDX2 expression in ampullary cancers suggests duodenal epithelial origin, although it is expressed in some pancreatic and biliary tract tumors.[21] In our study, the expression of CDX2 in pancreaticobiliary ampullary tumors occurred in 21.3% of the cases. It is interesting to note that in the analysis of the relationship between biochemical markers and histological type or pathological findings, there are associations between MUC1 positivity and well-differentiated tumors and between MUC2 positivity and poorly differentiated tumors. Sessa et al.[16] studied the association between

Table 7 Multivariate Analyses of Factors Possibly Influencing Overall Survival

Factor	Hazard ratio	IC 95%	*p*
A			
LN metastasis, positive	0.242	0.116; 0.507	<0.001
Lymphatic invasion	0.590	0.211; 1.648	0.314
Histological type pancreaticobiliary	0.583	0.271; 1.256	0.168
pT stage (T1-2*v* T3-4)	1.622	0.565; 4.655	0.369
B			
TNM stage (Ia, Ib, IIa vs. IIb, III, IV)	0.255	0.123; 0.528	<0.001
Lymphatic invasion	0.398	0.194; 0.815	0.012
Histological type pancreaticobiliary	0.529	0.248; 1.125	0.098

LN lymph node

tumor differentiation and markers and found that well-differentiated tumors expressed more CDX2, but without statistical significance.

To our knowledge, there is no study analyzing the expression of CD10 in ampulla of Vater adenocarcinoma. Our study shows that this marker's expression was significantly higher in intestinal tumors (81% vs. 51%). CD10 is associated with the mucous-secreting cells in the pancreas,[25] and it is expressed in the brush border intestinal mucosa cells.[26]

Differences in the expression of immunohistochemical markers seem to prove the origins and different tumorigenic processes for the two histological types of Vater's ampullary adenocarcinoma. Supporting this theory, Ho et al.[27] reported that the mucin genes are regulated independently and that their expression is organ- and cell-type specific. Furthermore, it is possible that most intestinal type adenocarcinomas derive from adenomas, while pancreaticobiliary carcinomas originate from ductal pancreaticobiliary regions, including the common channel.[12] The adenoma–carcinoma sequence has been proposed in intestinal tumorigenesis for colon and rectum,[28] small intestine,[29] and the ampulla of Vater (10% to 91% of cases).[3,30,31] More than 95% of papilla benign tumors are intestinal type adenomas,[2] and the presence of an adenomatous component occurs in 90% of intestinal type adenocarcinomas,[12] suggesting a tumoral origin. Indeed, precursor lesions can lead to both types of intestinal mucosa in the lining of the pancreatic and biliary segments. These tissues can retain cytokeratin and mucin expression.[2] However, in pancreaticobiliary tumors, the evidence of precursor lesions is rare, suggested only by associated pancreatic intraductal lesions.[12,32]

The prognosis in ampullary adenocarcinomas depends on the stage, lymph node involvement, and histological differentiation.[4,6,33–36] In this study, lymph node metastasis, lymphatic invasion, and UICC stage were independent factors related to worse outcome. Although the influence of histologic type is difficult to determine due to the wide variability in terminology and classification methods,[11] our study showed that intestinal histological type was related with better survival in univariate analysis, but failed to prove a ranking difference using immunohistochemistry or the expression of any marker. Several studies have attempted to prove the improved prognosis of intestinal-type tumors. Many studies are composed of small numbers of cases.[10,13,16,17] Some authors found no statistical difference in survival between the intestinal and pancreatobiliary carcinomas.[3,10,11,13,17] Others found worse survival for the pancreatobiliary type, but only in multivariate analysis.[16,18] Westgaard et al.[15] found worse survival for pancreatobiliary-type carcinomas in multivariate analysis, but their series included tumors of pancreatic and biliary origin. We found that pancreaticobiliary tumors were related to increased lymph node involvement and advanced stage and likely for this reason have a worse prognosis in univariate analysis. Nodal stage was the most discriminating risk factor in our tumor analysis. The expressions of some markers related to intestinal type have been related to better prognosis, such as expression of CDX2[21] and apomucin MUC2.[37] However, other studies failed to demonstrate this relationship,[13,14] as in the present study.

Limitations of this study include the use of a single institution, its retrospective nature, and the limited number of cases per year due to the rarity of the disease. The immunohistochemical study was performed by only one experienced pathologist. Finally, we could not control for treatment received after resection; some patients received chemotherapy, which might have influenced overall survival.

In conclusion, our findings support the histological classification of Vater's ampulla adenocarcinoma as intestinal or pancreaticobiliary type, based on the tumor's histogenesis. The expression of MUC1, MUC2, and CDX2 seems to be the best evidence for this differentiation and could be used in clinical practice due to its high accuracy. In our study, intestinal type as determined through histopathologic classification was associated with better survival in univariate analysis. However, neither immunohistochemical classification nor expression of CDX2 identifies a subgroup of tumors with worse outcome. Lymph node invasion, TNM stage, and lymphatic invasion were independent markers of outcome.

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J Gastrointest Surg (2010) 14:729–731
DOI 10.1007/s11605-009-1138-6

CASE REPORT

Prepancreatic Portal Vein in a Patient with Intestinal Nonrotation: Report of a Case

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Received: 20 September 2009 / Accepted: 7 December 2009 / Published online: 12 January 2010

Abstract Prepancreatic portal vein is an extremely rare congenital anomaly. It is even rarer in the setting of intestinal nonrotation. We report a case of prepancreatic portal vein in a 71-year-old female with nonrotation who presented with a pancreatic adenocarcinoma in the tail of the pancreas who underwent a distal pancreatectomy and splenectomy. This anomaly was identified prior to surgery on CT scan of the abdomen.

Keywords Prepancreatic portal vein · Congenital anomaly · Preduodenal portal vein · Anterior position of the portal vein

Introduction

The first reported case of prepancreatic portal vein was described by H.O. Knight, MD, in a 60-year-old cadaver in 1921.[6] Since that time, a number of unique variations of this anatomy have been presented in the literature, some of which have involved associated anomalies such as intestinal malrotation or nonrotation and partial or complete situs inversus.[13] Although rare, identification of this and other portal vein anomalies is important to help avoid intra-operative injury.

Case Report

A 71-year-old female presented with symptoms of abdominal pain with radiation to her back, early satiety, intermittent diarrhea, and a 15- to 20-lbs weight loss over the course of a month. She underwent an endoscopic ultrasound which demonstrated a 2.9×2.3-cm cyst in the pancreatic tail with invasion of the splenic artery and vein. No vascular anatomic abnormalities were identified on EUS. Additionally, no involvement of the celiac access or superior mesenteric artery (SMA) was identified, and the lesion was staged sonographically as T3N1Mx. An FNA of the mass was positive for adenocarcinoma. A pancreas protocol CT scan was also performed which showed a complex mass in the tail of the pancreas with both solid and cystic components, again demonstrating splenic artery and vein involvement. The portal vein was noted to be in an unusual position, running anterior to the pancreas as opposed to its normal posterior location. (Fig. 1) The SMA was noted to be in its normal anatomic position.

The patient underwent a distal pancreatectomy and splenectomy for her disease. The prepancreatic portal vein was identified and carefully preserved (Fig. 2). The ligament of Treitz was notably absent and the duodenum was noted to run caudal to the pancreas and down the right side of the abdomen without the formation of the typical C-loop. The remainder of the patient's operation was uneventful and she was discharged from the hospital without any complications.

Embryology

The portal vein develops originally as a primitive pair of vessels arising on the surface of the yolk sac and passing up the body stalk to enter the primordium of the heart. These

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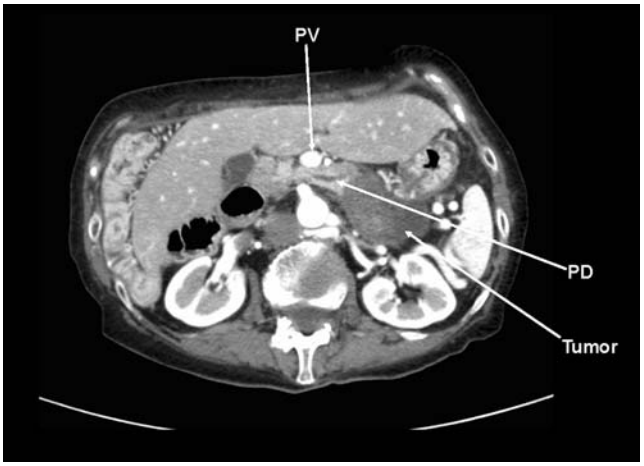

Figure 1 Preoperative pancreas protocol CT scan shows the portal vein (*PV*) coursing anterior to the pancreas. The tumor is seen in the pancreatic tail. *PD* pancreatic duct.

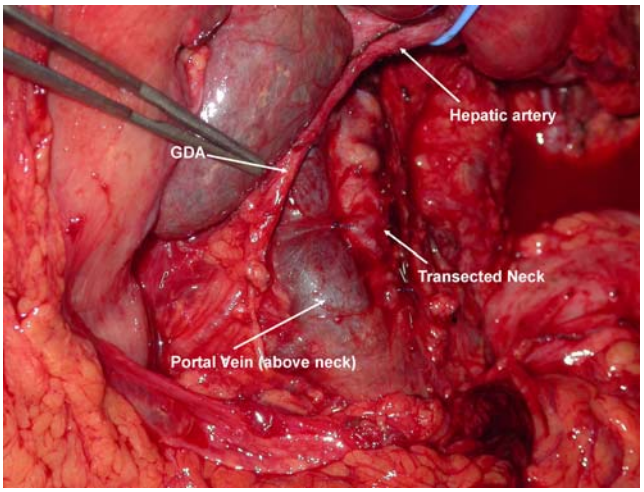

Figure 2 The specimen has been removed and the portal vein is seen adjacent to the cut end of the pancreas. The gastroduodenal artery (*GDA*) is shown in relation to the portal vein.

vessels reach their developmental peak and then begin to decline during the fourth week.[10] By this point, there are three anastomoses between the paired veins—the cranial anastomosis, which lies within the liver, and the middle, and caudal anastomoses, which lie outside the liver. The middle anastomosis passes posterior (dorsal) to the gut while the caudal anastomosis passes anterior (ventral) to it.[4] In normal development, the caudal left vitelline vein, middle (dorsal) anastomosis, and cranial right vitelline vein persist to form the portal vein.[3] A prepancreatic portal vein can form when the caudal (ventral) anastomosis persists instead of the middle one (Fig. 3). An alternative possibility is that the middle anastomosis persists but forms in an anterior instead of posterior position relative to the gut.[4]

In addition to having a prepancreatic portal vein, our patient also had a rotational anomaly of the intestinal tract, namely, nonrotation. In the fourth week of embryological development, the midgut is recognized as a straight tube whose blood supply is derived from the SMA. A proximal or prearterial limb represents the duodenojejunal loop and lies in the midline, superior to the SMA. A distal or postarterial limb represents the ileocecal loop and lies inferior to the SMA. These intestinal loops rotate counter-clockwise through an arc of 270° around an axis formed by the SMA.[12] Between the sixth and tenth weeks of development, the midgut protrudes through the umbilicus before returning to the abdomen between the tenth and 11th weeks. Normally, the proximal prearterial limb returns first and continues its counter-clockwise 270° around the base of the SMA axis. Failure of this event to occur causes a spectrum of abnormalities such as nonrotation, malrotation, reverse rotation, and mesocolic hernias.[12] Nonrotation occurs when the gut rotates only 180° instead of the normal 270°. The distal cecocolic limb enters the abdomen first instead of last, and the duodenum ends up descending straight down to the right side of the SMA. The small

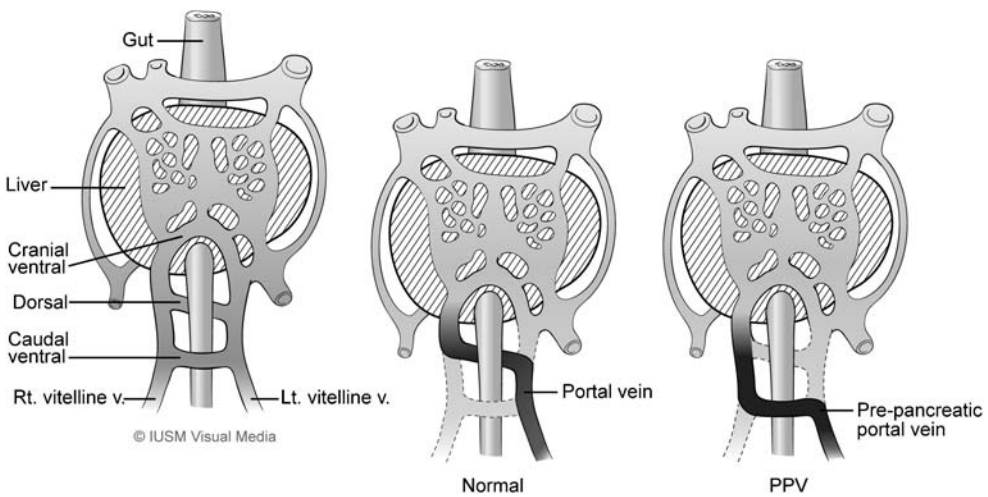

Figure 3 Embryology of the portal vein. *Dark shading* represents the segments that persist to form the portal vein in normal subjects vs. the prepancreatic portal vein (*PPV*) variant.

bowel lies on the right side of the abdomen and the colon lies on the left. This condition is usually asymptomatic.[12]

Discussion

The first reported case of prepancreatic portal vein was identified in an anatomy lab at the University of Texas in 1921.[6] Since then, a number of similar cases have been reported in the literature in both adults and children.[5,8] In 1963, Renner and Child diagrammed the 16 cases known from the world literature to that point and noted the various clinical presentations of this condition.[11] Associated anomalies are common with prepancreatic portal vein and include double portal vein, biliary atresia, partial and complete situs inversus, and intestinal malrotation and nonrotation.[1,2,9] Most of these cases have involved a preduodenal portal vein segment, which in some patients has caused a bowel obstruction from direct mechanical compression of the duodenum.[7,11]

The patient presented here underwent a CT scan of the abdomen that allowed for identification of the prepancreatic portal vein prior to surgery. The portal vein can be clearly seen lying anterior to the pancreas. During surgery, the patient was noted to have intestinal nonrotation with absence of the ligament of Treitz. The duodenum was found to course caudal to the pancreas and continued down the right side of the abdomen without forming the typical C-loop.

This case is similar to several prior cases reported in the literature involving a prepancreatic portal vein in the setting of malrotation or nonrotation. However, these prior cases involved a preduodenal segment of portal vein that often caused a bowel obstruction. In our patient's case, the portal vein did not cross over the duodenum, thus making it a unique anatomic finding that, to our knowledge, has not previously been reported.

Although this patient presented with a mass in the tail of her pancreas, a pancreatic head mass in the setting of a prepancreatic portal vein would also present a challenging case. In this situation, we can only speculate that there would be posterior portal venous tributaries draining the head and uncinate process which would require ligation in order to perform a pancreaticoduodenectomy.

Conclusion

Prepancreatic portal vein is an extremely rare anomaly that originates in the embryologic malformation of the vitelline veins and their anastomoses. Additional congenital anomalies are often found with this condition. Although uncommon, correct identification of a prepancreatic portal vein is important to avoid ligation or transection of this structure, the results of which would be serious, if not fatal.

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J Gastrointest Surg (2010) 14:732–738
DOI 10.1007/s11605-009-1108-z

MULTIMEDIA ARTICLE

Intraperitoneal Virtual Biopsy by Fibered Optical Coherence Tomography (OCT) at Natural Orifice Transluminal Endoscopic Surgery (NOTES)

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Received: 2 September 2009 / Accepted: 9 November 2009 / Published online: 9 December 2009

Abstract
Introduction Fibered optical coherence tomography (OCT) in conjunction with natural orifice transluminal endoscopic surgery (NOTES) could provide a facility for rapid, in situ pathological diagnosis of intraperitoneal tissues in a truly minimally invasive fashion.
Materials and Methods A large porcine model was established to test this hypothesis. A standard double channel gastroscope (Olympus) was used to achieve a transgastric access to the peritoneum and initiate the pneumoperitoneum. Magnetic retraction was used to display the sigmoid colon along with its mesentery. A commercially available fibered OCT probe (NIRIS system, Imalux) was inserted via a working channel of the gastroscope and used to assess intraperitoneal tissues. Separately, OCT images of human tissue specimens ex vivo were contrasted with representative standard histopathological slides.
Results Intraperitoneal OCT provided clear real-time images of both the serosal and muscularis propria mural layers as well as the submuscosal–muscularis interface. Examination of mesenteric lymph nodes (including sentinel nodes) allowed visualization of their subcapsular sinus. Comparison of representative cross-sections however failed to evince sufficient resolution for confident diagnosis.
Conclusion This approach is technically feasible and, if the technology is advanced and proven accurate in human patients, could potentially be used to individualize operative extent prior to definitive resection.

Keywords Optical coherence tomography (OCT) · Natural orifice transluminal endoscopic surgery (NOTES) · Virtual biopsy · Optical biopsy · Sentinel node biopsy

Electronic supplementary material The online version of this article (doi:10.1007/s11605-009-1108-z) contains supplementary material, which is available to authorized users.

Presented in part at the SSAT Video Session, DDW, Chicago, June 3rd 2009.
Supported by EURO-NOTES, European Association of Endoscopic Surgery.

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Introduction

Natural orifice transluminal endoscopic surgery (NOTES) refers to an operative approach to the abdominal cavity that employs flexible instrumentation advanced into a natural orifice (i.e. mouth, anus, vagina, or urethra) to achieve access into the peritoneum and then perform an intervention.[1] Although considerable technical issues remain to be resolved, the concept is proposed to merit 'scarless' surgery (at least in terms of externally visible scarring) and, potentially, reduced postoperative pain and convalescence. Although experience in humans is increasing, the performance of major intestinal resectional surgery by this means remains challenging mostly because of device and instrument limitations. Furthermore, the exact advantages of 'no scar' operating compared to 'one scar' (i.e. single laparoscopic port surgery) or 'multi-mini' scar (standard laparoscopy with mini-instruments) has yet to be defined. However, as much as provide an alternative approach to standard endoscopic intervention, this technique can also provide a minimum access mode to allow improved diagnostic precision to supplement operative care (regardless of how the surgery is actually ultimately performed).[2] While it could clearly provide a means for simple visualization or indeed tissue biopsy for conventional histology, the increasing sophistication of endoscopic optical analysis technology presents intriguing possibilities. Such use as an adjunctive diagnostic implement may then represent a better initial clinical application for natural orifice intervention than many of the more ambitious interventions being proffered.[3,4]

Optical coherence tomography or OCT has its origins primarily in ophthalmology but it is now being increasingly used in interventional gastroenterology and cardiology as a flexible fibered, end-viewing probe. In principle, it utilizes very short-wave near-infrared light with precise interoferometric detection capability to provide real-time cross-sectional images of the tissue of interest. In effect, it measures echo time delay and intensity of light in a manner corresponding to ultrasound except it utilizes optics rather than acoustics and so can provide optical slicing to a depth of 2 to 3 mm in opaque tissues. It is already capable of providing a resolution approaching that of conventional histology (indeed it has demonstrated a capability of detecting single nuclei in the order of 5 μm) and it is certainly considered to have the potential to detect micrometastases (metastatic cell groupings between 0.2 and 2 mm in size) within lymph nodes. OCT has also already been used at the time of laparoscopy to assist in determination and preservation of neurovascular bundles during prostatectomy[5,6] and has been proposed for use in assessing and ensuring marginal clearance of prostate cancers.[7] It has further been suggested as suitable for use in guiding endoscopic transluminal urological surgery.[8]

Here, we demonstrate the use of a commercially available OCT probe (NIRIS System, Imalux Cleveland, OH, USA) employed via a conventional endoscope (Olympus, PA, USA) used to achieve NOTES access to the peritoneum via a transgastric approach in a porcine model. In this way, we aim to clearly document the feasibility and portray the utility of this approach. In addition, we studied OCT images taken on resected human specimens (normal colon wall and lymph node) ex vivo with corresponding conventionally processed (hematoxylin and eosin) histopathological sections to illustrate the current comparative quality of this technology. This latter part was performed to assess the technology's performance on thicker human organ tissue.

Materials and Methods

The facility for use of a fibered OCT probe down the working channel of a standard endoscope was studied in an animal model.

OCT The NIRIS OCT probe was obtained free of charge from Imalux Corporation for use in this protocol. This system consists of an imaging console and a detachable fiberoptic probe. The imaging console contains optical and electrical components, including a super luminescent diode (SLD). The SLD provides near-infrared light, which is directed from the console along the optical fiber within the probe to the patient's tissue. The optical light that is backscattered from the patient's tissue is also collected by the probe's fiber and is then combined with an internal reference signal to produce a high spatial resolution image of the superficial tissue microstructure. Such coherence images are constructed by first measuring the in-depth profile of the backscattered light intensity in the axial (depth) direction. In-depth profiling is performed by measuring the echo time delay against the intensity of the light reflected. Distance or spatial information is then determined from the time delay of reflected echoes according to the formula $z=\Delta T \cdot v$, where z is the distance the echo travels, ΔT is the echo delay, and v is the wave propagation velocity of wave (light or sound). Because light travels at such a high speed (~3×108 m/s), as compared to sound (~1,500 m/s), a light echo time delay system would require ultrafast time resolution which would be impractical and expensive to achieve with modern electronics. For example, an in-depth spatial resolution of 10 μms corresponds to a time resolution of approximately 30 fs. Instead, the NIRIS Imaging System measures OCT echo time delays by comparing the back-reflected light signal to a controlled reference signal. This gives an acquisition rate of 1.5 s per frame for 200 lateral pixel images. To create a two-

dimensional image, the fiber optic beam is moved laterally across the surface (*x*-axis) and in-depth profiles (*z*-axis) are obtained at discrete points along the surface. By obtaining these profiles over a lateral distance, a two-dimensional, cross-sectional image is constructed.

Fibered probes associated with this system are available in lengths of up to 4 m and are easily integrated into working channels of standard endoscopes (the probes have a diameter of 2.7 mm). The probe can be sterilized using the Steris system 1, Sterrad or Ethanol Glutaealdehydrol although a close-fitting sterile sheath is also available for use to ensure exclusion of contaminating microflora. The spatial depth resolution is 10–20 μm in air with a lateral resolution of up to 50 μm while the scanning ranges provided by these probes is up to 2.2 mm in depth (in air) and 1.6–2.4 mm laterally. With a working distance of 0.5 mm, the tip of the probe in effect needs to be directly placed onto the tissue of interest (no coupling agent is required however).

Animal model The study protocol with the involvement of two pigs (mean weight, 62 kg) was approved in full by the appropriate review boards of both institutions. The animals were obtained from a local vendor (Pine View Farms, Valley City, OH, USA). The animals were removed from wood-chip bedding 72 h prior to the planned intervention and were not given anything by mouth during the 12 h immediately prior to their procedure. Anesthesia was induced with 8 mg/kg of intramuscular tiletamine hydrogen chloride and zolazepam, and was maintained with 0.5% to 2% inhaled isoflurane after endotracheal intubation. The animals were mechanically ventilated with 15 to 20 mg/kg of tidal volume at 12 respirations per minute and 100% oxygen. Continuous pulse oximetry monitoring throughout the procedure assisted maintenance of normal physiologic parameters. The studies were planned as acute models and so neither animal was recovered post-procedure.

NOTES procedure A standard double channel gastroscope (Olympus GIF-2T 160) was used to obtain a transgastric access to the peritoneum (see Fig. 1). Once passed per oro into the stomach, the anterior gastric wall was identified by observing for indentation achieved by digital pressure on the abdominal wall (PEG technique). A triple-lumen needle-knife catheter (Microvasive Endoscopy, Boston Scientific Corp, Natick, MA, USA) was then used to make the initial gastrotomy while a 0.89 mm×400 cm Jagwire (Microvasive) was then passed through the abdominal and stomach walls to maintain the conduit. A 20-mm controlled radial expansion through-the-scope esophageal dilating balloon (Microvasive) was used to dilate the channel and allow the tip of the gastroscope enter the peritoneum and then initiate the pneumoperitoneum. With the endoscope in position, the pig was placed in a steep Trendelenburg position to decant the small bowel from the pelvis. A magnet on the tip of flexible tube was passed per ano to lie within the sigmoid colon and was there anchored by a second magnet placed externally on the abdominal wall. By this means the sigmoid colon could be moved and positioned within the abdominal cavity. The tip of the OCT probe was then passed via the working channel of the gastroscope into the peritoneum. Manipulation of the endoscope then allowed direct contact of the tip to any tissues of interest and the resulting OCT image was viewed 'picture in picture' on the endoscope monitor. By this means, high-resolution images of the bladder, small bowel, colon, and mesenteric lymph nodes were obtained. Additionally, to allow lymphatic mapping identify sentinel nodes within the sigmoid mesentery, a sigmoidoscope was passed per ano into the sigmoid colon and used to inject 3 ml of methylene blue submucosally. Blue efferent lymphatic channels were then followed by the intraperitoneal NOTES scope to find first order draining, or 'sentinel', nodes in a manner similar to that previously detailed and these nodes were again examined using the OCT probe.[2]

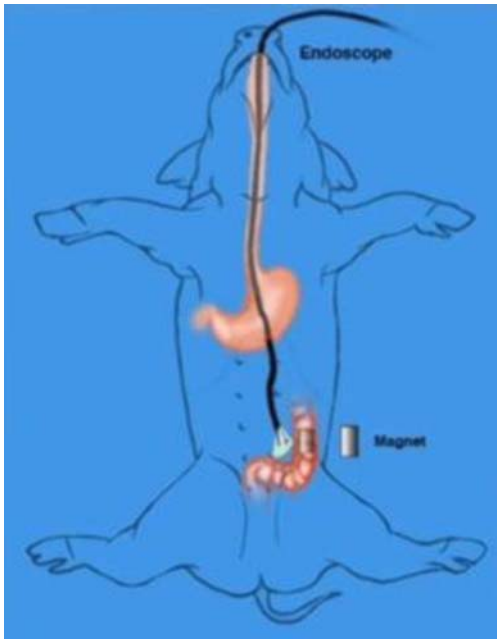

Figure 1 Operative set-up for experimental model. The animal is anesthetized and placed supine. A transgastric NOTES access to the peritoneum is employed while the sigmoid colon and its mesentery is exposed by coupling an intraluminal magnet (placed at the tip of a flexible tube) with a second placed extracoporeally on the anterior abdominal wall.

Ex vivo comparative analysis A similar OCT system (NIRIS, Imalux) was used ex vivo on human tissue by placing the tip of the probe onto resected specimens taken

from two patients undergoing elective operation (both patients had a right hemicolectomy for suspected malignant colonic neoplasia). Comparison between the OCT image and representative slides after standard histological processing of the specimens was made purely for illustrative purposes.

Results

Transgastric access to the peritoneum was readily and safely obtained in both models. Mean access time was 3 min (2.5 and 4 min). There was no apparent damage to any adjacent organs upon exit of the tip of the gastroscope from the stomach. OCT images were easily obtainable in real-time from all organs of interest (see Video A in Electronic Supplementary Material). From the peritoneal aspect, the outer layers of the bladder, small bowel, and colon were readily apparent (see Video B in Electronic Supplementary Material). The subscapsular sinus of mesenteric lymph nodes both before and after lymphatic mapping was also identifiable although resolution was diminished towards the center of the interrogated nodes (see Video C in Electronic Supplementary Material). The images obtained were interpretable by the operators and easily viewed in conjunction with the standard endoscopic image.

Similarly, when placing the tip of the OCT ex vivo onto the resected images from human patients, recognizable images were rapidly produced. The thicker nature of the patient specimens meant however some loss of depth of resolution of the tissue. Comparison was then made between selected still images from the OCT system with corresponding representative slides from the same tissue after histological processing (see Fig. 2). Although gross morphology such as mural sublayers could be identified, sufficiently detailed resolution required for cellular diagnosis was not possible.

Discussions

The emergence of the concept of NOTES as a potential interventional entity has encouraged re-evaluation of the operative approach to early stage malignant disease within the abdomen.[9] In general, the conventional approach for potentially curable patients has been to focus on the exclusion of distant metastases in the preoperative work-up (predominantly by radiological means) and then proceed with radical en-bloc resection of the primary its draining lymphatic basins. Such a procedure certainly offers locoregional control for those with nodal metastases as well as providing histological proof of disseminative lymphatic disease as an indicator for adjuvant systemic therapy. The emergence however of minimum invasive techniques could heighten the focus on patients with truly organ-confined disease (i.e. no nodal metastases) and prompt the suggestion that such patients may be best served by localized resection of the primary alone whether by purely endoscopic or laparoscopic means.[10] Conversely also the facility to correctly perform confined operation as the definitive procedure would reciprocally encourage further development of novel minimal access operations (including single-port laparoscopic procedures as well as NOTES) as these emerging techniques all lack the facility to provide standard degrees of traction–countertraction and tissue tension. Improved means of disease stage identification before resectional surgery has taken place is however clearly required in lieu of awaiting staging by standard pathological processes.

Optical analysis from within the bowel lumen has considerable precedent in the fields of gastroenterology and urology.[11–14] In its technologically simplest form, the use of zoom endoscopy allows magnified views of mucosal surfaces to facilitate in situ distinction between benign and neoplastic changes with further confidence being supplied by the use of surface dyes and ultraviolet examination of the epithelial surfaces. Confocal microscopy and, more recently, OCT, have added further sophistication in the assessment of the inner most layers of hollow organs. Such interferometric imaging techniques are increasingly being determined as indicative of the nature of the disease process and their use can encourage the endoscopist in advocating endoscopic resection of selected lesions.[15–17] However, while intraluminal in situ analysis may facilitate endoscopic partial thickness resection of the earliest neoplastic processes, more advanced (but still early stage) cancers are best treated by margin-free full thickness resection. Clearly these lesions also need careful identification and preselection to minimize the risk of R1 resection. Furthermore, as the risk of lymph node metastases increases in conjunction with increasing transmural propagation, regional staging needs to be assured in the absence of en bloc resection if this latter component of standard resection is to be obviated in certain patients so that optimum oncological outcome is ensured.

Therefore, the facility by which flexible endoscopy outside the lumen could aid surgical endeavor in a means similar to flexible endoscopy inside the bowel requires exploration. In this preliminary work therefore, we proposed the combination of commercially available intraluminal technology for in situ tissue analysis outwith the bowel in a truly minimally invasive means. Furthermore, diagnostic supplementation may provide a niche indication for NOTES as a compliment to more conventional laparoendoscopic techniques rather than this access being proposed immediately as an alternative operative approach. This could be a more suitable initial area for NOTES to

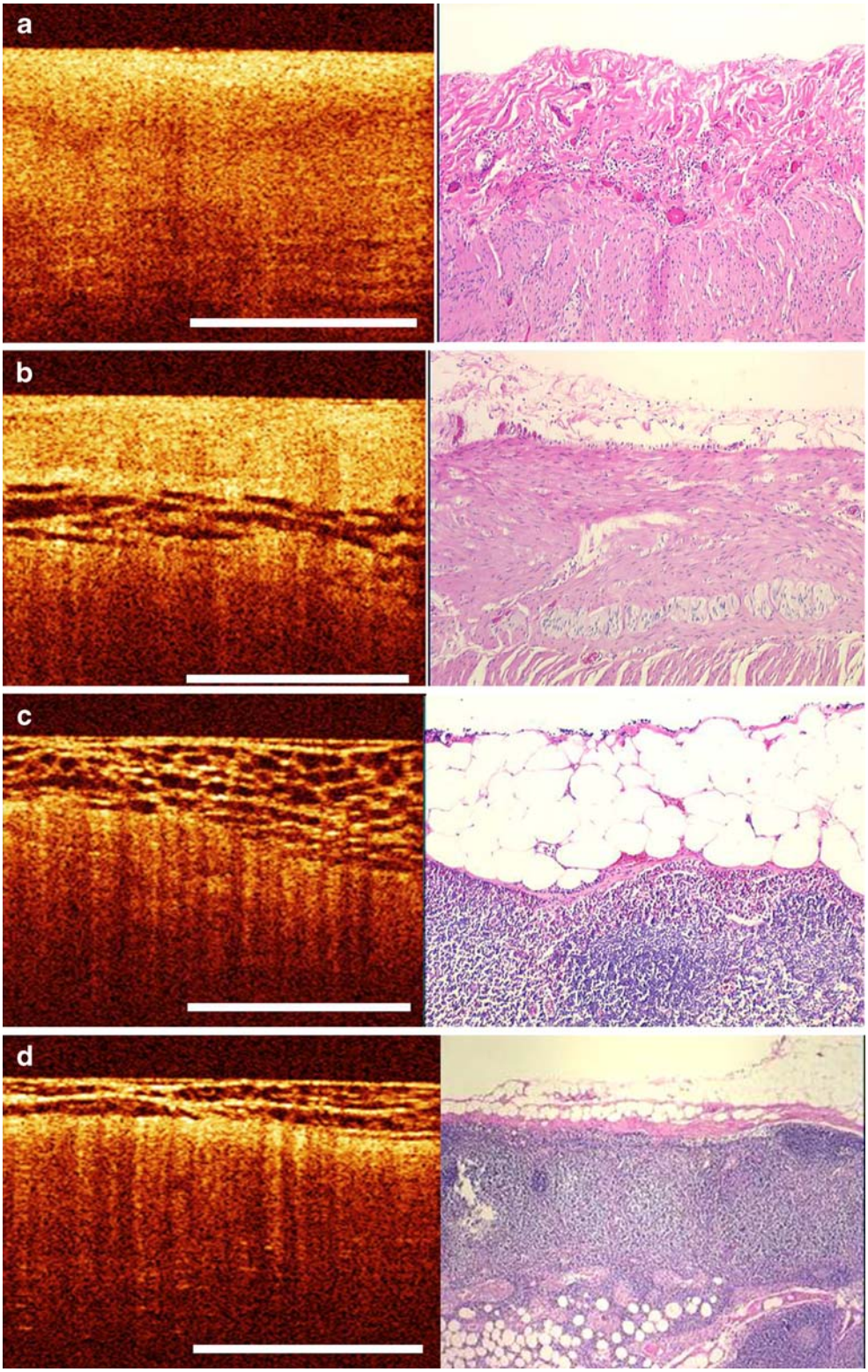

Figure 2 Comparative OCT images with standard pathological sections of ex vivo human tissue in a patient with colon cancer. Representative samples of both colonic (**a** and **b**) and lymph nodal tissue (**c** and **d**) are shown.

progress (assuming safe visceral closure can be assured) rather than the more ambitious resectional operations currently often proposed in experimental scenarios. Although this is an acute study, we have previously developed a technique to provide safe gastrotomy closure for NOTES access at least in such an experimental model[18] and, indeed, we have now begun developing a similar closure system suitable for trialing in a clinical setting.

The use of an end-viewing high-resolution imaging probe proved easy to apply to tissue surfaces. In particular

(and in distinction to radial viewing imaging devices often used intraluminally), it allowed long sections of intestine be rapidly examined. Furthermore, such serosal aspect imaging naturally obviates any luminal distortion or obstruction that may result from the disease process. While very interesting, however, the images provided were not entirely convincing. Although the submucosal–muscularis interface is well seen in the large animal model, the resolution is less apparent in thicker human specimens. This was especially the case with nodal analysis where even the presence of a small amount of covering fat markedly reduced the depth of optical penetration into the substance of the gland. Notwithstanding the fact that the subcapsular sinus (the site of tumor cell clustering in approximately 70% of patients with nodal metastases) was visualized, surgeons and on-site pathologists would be likely to require more evident analogy with standard pathology if therapeutic decisions based on the information provided are to made with confidence.

Relatively simple technical adaptation may help provide such augmented capacity. Needle penetration of the tip of a side-viewing OCT probe could perhaps allow 360° rotational analysis of the substance of the node or indeed bisectioning of an excised node could allow direct examination of the cut surface of the node by an end-viewing tip/use ex vivo. Further technological innovation would seem the more compelling means of improving the quality and resolution of the information obtained and indeed OCT imaging to the level of detection of nodal micrometastases has proven possible ex vivo in developmental systems.[19] In addition, the combination of spectral analysis, high-resolution optical slicing capability and elastrographic assessment within a single probe could provide a combination of complimentary information in order to enhance diagnostic precision. If focused on a precisely selected confined anatomic area (such as a sentinel node), optical biopsy could then potentially provide real-time pathology without excisional biopsy with a high degree of accuracy.

Conclusion

This experimental application of OCT proved a feasible means of providing in situ optical tissue biopsy via a natural orifice access approach. Further technological advance is required to develop the potential of this approach as a means of subselecting patients for specific operative procedures based on the actual extent of their disease at operation and thereby allowing precision tailored intervention.

Acknowledgements The work was supported by an unrestricted grant provided by EURO-NOTES via the European Association of Endoscopic Surgery.

All authors wish to gratefully acknowledge the assistance of Dr. N. Tresser and Mr. J. Spain of the IMALUX Corporation for their expertise in arranging and utilizing the OCT equipment. The NIRIS system was provided for this study free of charge by the IMALUX Corporation. No right of data review was requested by or afforded to this company however prior to composition and submission of this manuscript.

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J Gastrointest Surg (2010) 14:739–742
DOI 10.1007/s11605-009-1114-1

HOW I DO IT

Modified Stapled Transanal Rectal Resection (Starr) for Full Thickness Excision of Rectal Tumour

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Received: 2 September 2009 / Accepted: 12 November 2009 / Published online: 12 January 2010

Abstract
Introduction Traditionally, adenomatous rectal lesions and unexpected malignant polyps that could not be removed endoscopically are referred to surgery. Local excision is the treatment of choice, and several techniques have been proposed. The choice of the approach requires that the tumour is excised intact, with a low recurrence rate and limited morbidity. Local excision can be a straight forward or conversely a demanding procedure due to the restricted space in which the surgeon must work and the difficulty of achieving a satisfactory exposure.
Methods We describe a modified stapled transanal rectal resection for the excision of flat lesions with a diameter up to 2 cm and located between 5 and 12 cm from the anal verge.
Discussion and Conclusion In our experience, it is quick, simple, and easy to teach but it has not previously been reported. It provides full thickness resection with adequate lateral margins. It overcomes some of the limits of the incomplete surgical field exposure and difficult manipulation, since after the confectioning of double half purse-string suture, the suture and sectioning is made by the stapler device.

Keywords STARR · Rectal cancer · Transanal resection

Background

The development of colorectal adenomas is frequent in the Western countries. The estimated lifetime risk is approximately 40%.[1] One third of these lesions will be located in the rectum, and about 10% will turn malignant.[2] Moreover, the constant diffusion of colorectal cancer screening will inevitably lead to an increased detention of adenomas and early rectal cancer. It is therefore expected that more rectal lesions will need endoscopic or surgical management in the forthcoming years.

Even with previous benign biopsies, the presence or absence of malignant cells may be determined only by complete excision (total biopsy). Indeed, unexpected invasive carcinoma can be found in up to 20% of patients after polyp removal.[3]

Traditionally, adenomatous rectal lesions that could not be removed endoscopically (large, sessile, or carpet-like polyps) are referred to surgery. After excision, unexpected malignant polyps are also referred to surgery to complete full thickness 'total biopsy'.

Local excision is the treatment of choice, and several techniques have been proposed. The choice of the approach requires that the tumour is excised intact, with a low recurrence rate and limited morbidity.[4]

There is much evidence that local excision, when complete, can be curative even in polyps containing

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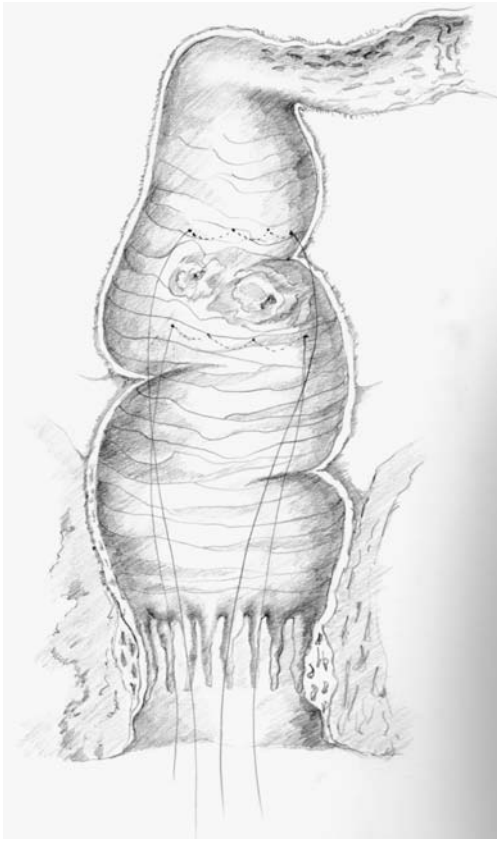

Figure 1 Two purse-string sutures are placed at least 1 cm above and below the lesion.

carcinoma in situ ($T1_{is}$) or initially invasive cancer with infiltration limited to the submucosal layer (T1), provided that pathology features are favourable and that adequate superficial and deep margins are obtained. Local excision of a rectal lesion can be a straightforward or, conversely, a demanding procedure because of the restricted space in which the surgeon must work and the difficulty of achieving a satisfactory exposure. Some of them are related to the characteristics of the polyp itself, such as size, morphology, nature, distance from the anal verge and longitudinal extension, while others are due to extrinsic factors like patient's constitution and health, rectal mobility and, obviously, surgeon's experience.[5,6]

Briefly, the three types of approaches commonly used for local surgical excision[6–13] are the following:

(a) The Kraske dorsal access or the Mason trans-sphincteric approaches or a combination of the two. These offer good exposure and are oncologically very effective but with high complications rate, mainly infectious and faecal fistula.
(b) The Parks transanal approach (and its variations according to Francillon and Faivre) is the most common and effective approach for tumours located up to 12 cm from the anal verge. In expert hands, the recurrence rate is low, approximately 10% but can be as high as 36% with major complications. The tumour is excised using diathermy or harmonic scalpel.

Obviously, the use of a natural orifice (in the Parks approach) is accompanied by reduced space for surgical manipulation, difficult bleeding control (especially for posterior tumours), and incomplete field view (especially for higher tumours). As a consequence, incomplete and imprecise resection may follow.

To overcome these limits, several alternatives have been proposed, such as the use of 'endoscopic transanal resection' via a urologic resection device as initially described by Zinkin et al. for the palliation of obstructing rectal tumour and subsequently implemented for incisions of rectal adenomas and selected low rectal cancers. However, this often does not allow a full-thickness resection, and the recovered multiple specimens represent a challenge for an accurate pathologic evaluation.

(c) The transanal endoscopic microsurgery (TEM) allows full thickness resection under excellent view of the entire rectum (up to 18 cm from the anal verge). The limit is the cost of the device and its accessories and the necessary learning curve.

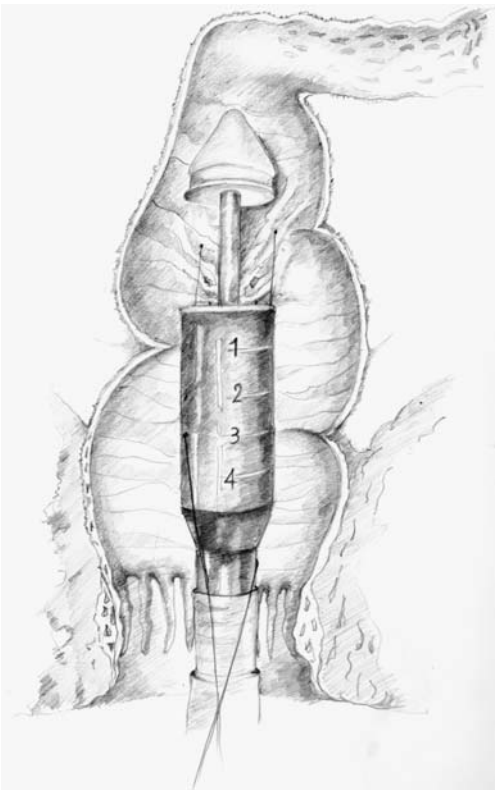

Figure 2 A 33-mm circular stapler is inserted above the lesion and the upper purse-string.

We describe our technique for flat lesions (sessile or carpet-like polyps), $T1_{is}$ and T1 cancer, with a diameter up to 2 cm and located between 5 and 12 cm from the anal verge using a circular stapler device. This represent a modification of the STARR implemented to treat obstructed defecation syndrome (ODS). In our experience, it is quick, simple and easy to teach, but it has not previously been reported. We used this technique in five patients (four males and one female). All patients underwent preoperative lesion biopsies and a full colonoscopy. Patients with proven cancer underwent endoscopic transrectal ultrasound evaluation in order to define the T and the N stages. Proven cancer patients underwent abdominal CT scan and pelvic MRI. Only patients with sessile polyps or T1N0 cancers were considered suitable for this technique. Only lesions less than 2 cm and located within 10 cm from the anal verge were treated. All stapled transanal rectal resections (STARR) provided full-thickness resection with adequate lateral superficial margins (>1 cm). Macroscopic appearance of the specimens was rectangular with a median size 3.54±1.2×2.32±0.6 cm. Median depth of resection was 0.88±0.2 cm. Mean lesion size was 1.48±0.7 cm. Pathology revealed T1 adenocarcinomas in three patients, one $T1_{is}$ carcinoma and one sessile adenoma with moderate dysplasia. During surgery, additional haemostatic sutures

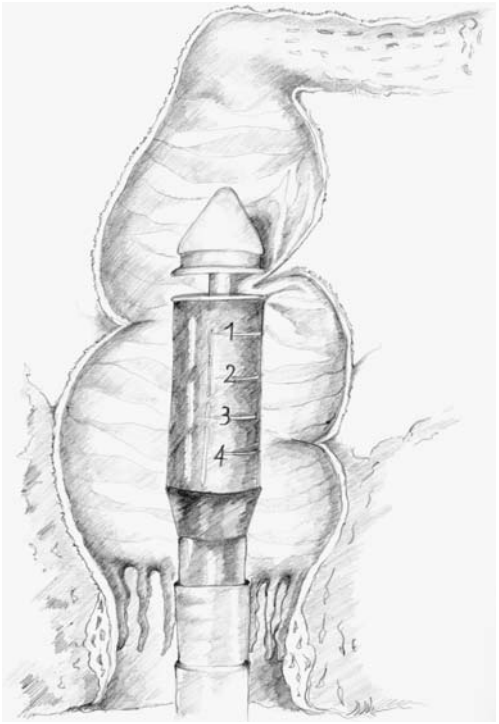

Figure 4 If a full thickness purse-string suture is performed, a full-thickness resection is expected.

Figure 3 The two double ends of the purse-string sutures are pulled down into the stapler.

Figure 5 End of the procedure. After stapler removal the staple line is observed. If bleeding occurs, additional haemostatic sutures are placed over the staple line.

were needed in two cases (3-0 vicryl). We did not observed any complications, and patients were discharged within 4 days. Only one patient experienced longer term tenesmus that lasted up to 5 months after surgery.

In our experience, this technique overcomes some of the limits of the incomplete surgical field exposure and difficult manipulation, since after the placement of the purse-string sutures, the resection is performed by the stapler device.

Surgical Technique

The day before surgery, patients receives a mechanical full bowel preparation. Preoperatively, a cleansing enema is also given. Patients receive routine antibiotic prophylaxis (cefotaxime 2 g and metronidazole 500 mg i.v.) at anaesthesia induction. Surgery is performed under general or caudal anaesthesia in lithotomy position. A circular stapler device is used. A disposable circular anal dilator and a purse-string suture anoscope are used as for a PPH procedure (PPH01, Ethicon Endo Surgery, Inc, Pomezia, Italy). The anal verge is gently lubricated and digitally dilated for 1 min with two fingers. The lubricated obturator is then inserted and left in situ for 1 min. At this point, four radial stitches (0 silk) are used to expose the anal verge and fix the perianal skin to the anal dilator (CAD 33 if a PPH set is used). Using 2-0 prolene (Ethicon, Somerville NJ, USA), a 180° purse-string suture is performed at least 1 cm above the rectal tumour. Purse-string stitches should include mucosa, submucosa, and rectal muscle wall (Fig. 1). A similar purse-string 180° suture is performed below the tumour. The two ends of the purse-string sutures are then secured on the right and left using small clamps.

A 33-mm circular stapler is then opened and the head inserted above the lesion and the upper purse string. The double ends of the purse-string sutures are inserted into the stapler as well as for anopexy or standard STARR for ODS and pulled down (Figs. 2 and 3). If full thickness purse strings have been performed the rectal wall including the lesion should be invaginated into the stapler head after pulling the purse-string ends (Fig. 4).

The stapler is then closed, held for 30 s (Fig. 5) and fired. In female patients with an anterior lesion, the posterior vaginal wall should be checked with fingers before firing. Occasionally, a minimal mucosal bridge with a staple connecting the two edges may occur, and this is easily cut using heavy scissors. If bleeding occurs, the suture line can be reinforced using interrupted 3-0 vicryl suture. The retrieved specimen is then oriented, pinned on a cork pad, properly labelled and sent for pathology evaluation. The presence of the 2-0 prolene stitches (previously used for the two purse-string sutures) in the retrieved specimen aids the identification of the upper and lower resection margins.

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J Gastrointest Surg (2010) 14:743–752
DOI 10.1007/s11605-009-1084-3

REVIEW ARTICLE

Conventional and Laparoscopic Reversal of the Hartmann Procedure: a Review of Literature

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Received: 1 August 2009 / Accepted: 26 October 2009 / Published online: 21 November 2009

Abstract
Purpose The aim of this study was to provide a systematic overview on both laparoscopic and conventional Hartmann reversal. Furthermore, the Hartmann procedure is reevaluated in the light of new emerging alternatives.
Methods Medline, Ovid, EMBASE, and Cochrane database were searched for studies reporting on outcomes after Hartmann reversal.
Results Thirty-five studies were included in this review of which 30 were retrospective. A total of 6,249 patients with a mean age of 60 years underwent Hartmann reversal. Two thirds of patients were classified as American Society of Anesthesiologists (ASA) I–II. The mean reversal rate after a Hartmann procedure was 44%, and mean time interval between Hartmann procedure and Hartmann reversal was 7.5 months. The most frequent reported reasons for renouncing Hartmann reversal were high ASA classification and patients' refusal. The overall morbidity rate ranged from 3% to 50% (mean 16.3%) and mortality rate from 0% to 7.1% (mean 1%). Patients treated laparoscopically had a shorter hospital stay (6.9 vs. 10.7 days) and appeared to have lower mean morbidity rates compared to conventional surgery (12.2% vs. 20.3%).
Conclusion Hartmann reversal carries a high risk on perioperative morbidity and mortality. The mean reversal rate is considerably low (44%). Laparoscopic reversal compares favorably to conventional; however, high level evidence is needed to determine whether it is superior.

Keywords Hartmann · Reversal · Morbidity · Mortality

Introduction

The Hartmann procedure (HP) consists of a sigmoidectomy with rectal stump closure and a terminal colostomy. It is a common operation for left-sided colonic disease, especially in emergency cases. Initially, this procedure was solely performed in cases of neoplastic obstructions. Currently, indications include complicated diverticulitis, traumatic lesions, and perforated tumors of the rectosigmoid and volvulus.[1]

The Hartmann procedure was initially designed to reduce mortality caused by anastomotic dehiscence. However, reestablishing continuity after a Hartmann procedure (Hartmann reversal, HR) is still considered a major surgical procedure and carries serious risk of surgical morbidity and mortality of up to 50% and 5%, respectively, in the published literature.[2,3] Several attempts have been under-

BJM and ESS performed the systematic review and drafted the manuscript. WAD coauthored the writing of the manuscript. ECJC and IAMJB also coauthored the writing and have given final approval of the version to be published.

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taken to perform HR by minimally invasive techniques with the objective to reduce high morbidity and mortality rates. Nevertheless, it has been estimated that approximately half of patients who undergo a Hartmann procedure will not have continuity restored by either a minimally invasive or open technique.[4,5]

Many studies on HR have been published. However, due to the large amount of studies on this subject, it is difficult to determine the characteristics and percentage of patients who undergo reversal and morbidity and mortality rates after both laparoscopic and conventional HR. Furthermore, the HR must be reevaluated in the light of new emerging alternatives. This study provides a systematic overview of the available current evidence to evaluate the aforementioned topics and put the HR in perspective of innovative alternatives.

Material and Methods

Literature Search

A systematic search of the literature was conducted to identify all studies on the reversal of the Hartmann procedure. We performed a duplicate search of the electronic databases PubMed, EMBASE, and the Cochrane library (from October 1987 until May 2009) using the following keywords and text word terms: "Hartmann", "Hartman", "Hartman's", "Hartmann's", "anastomosis", "reconstruction", "reversal", "continuity", and "restoration". The "related articles" function in PubMed was also used to identify additional studies. References of the articles identified were also searched for by title and then subsequent abstract review.

Study Selection

Studies were selected according to the following selection criteria: (1) study is about reversal of Hartmann procedure, (2) publication is not an expert opinion or case report, (3) English language publication, and (4) more than ten patients included. The methodological quality of the included studies was judged in terms of the grades of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence. The methodological quality of the studies was judged independently by two reviewers (BJM and/or ES). Discrepancies between reviewers were resolved by discussion by a senior coauthor (WA).

Data Extraction

Patient-related data (indication of initial Hartmann procedure, age, gender, American Society of Anesthesiologists (ASA) classification), operative and hospital-related data such as the number of Hartmann procedures and reversals, reversal rate, reasons not to perform reversal, time interval between Hartmann procedure and reversal, hospital stay, morbidity (bleeding, wound infection, anastomosis leakage or stricture, and cardiac or pulmonary complications), mortality, operative time of both conventional and/or laparoscopic reversal, conversion rates, and reasons for conversion were gathered and analyzed. The ASA scores were divided in three groups: groups I–II, group III, and groups IV–V. ASA scores I–II represent healthy patients or with mild systemic disease. ASA III represents patients with moderate to severe systemic disease, and ASA IV–V represent patients with severe to life-threatening systemic disease.

Data Analysis and Presentation

Data analysis was limited to basic manipulation because of a lack of statistically relevant data, resulting from large trials. Descriptive statistics including means, counts, and percentages were used to describe the study population for all variables.

Results

Baseline and Patient Characteristics

The search initially yielded 813 articles (Fig. 1). After screening of title and abstract, 747 articles were excluded because they were not about HR. Sixty-six manuscripts were screened using the inclusion criteria. A total of 31 publications were excluded because they were not about HR (19 articles), included less than ten patients (ten articles), and were not about humans or in English (two articles) leaving 36 studies to be included in this review.[1–35]

In Table 1, the authors, year of publication, level of evidence, number of patients who underwent reversal, operative indication, ASA classification, age, and gender are presented. The year of publication ranged from 1987 to 2009. Five studies were prospective and 30 were retrospective.[6] The size of the individual study population ranged from 12 to 3,051 (mean 179) patients. The overall female–male ratio was 1:1.14 and the mean age was 60 years (38–71).

The indication for Hartmann procedure varied among studies. Diverticular disease and its associated complications (mostly fecal and purulent peritonitis followed by abscess, obstruction, and fistula) were the most common indication for Hartmann procedure in 67% of patients. Five studies included patients with diverticular disease only, with fecal and purulent peritonitis also being the most frequent indication for the initial procedure.[3] Colorectal malignancies causing obstruction or perforation were found

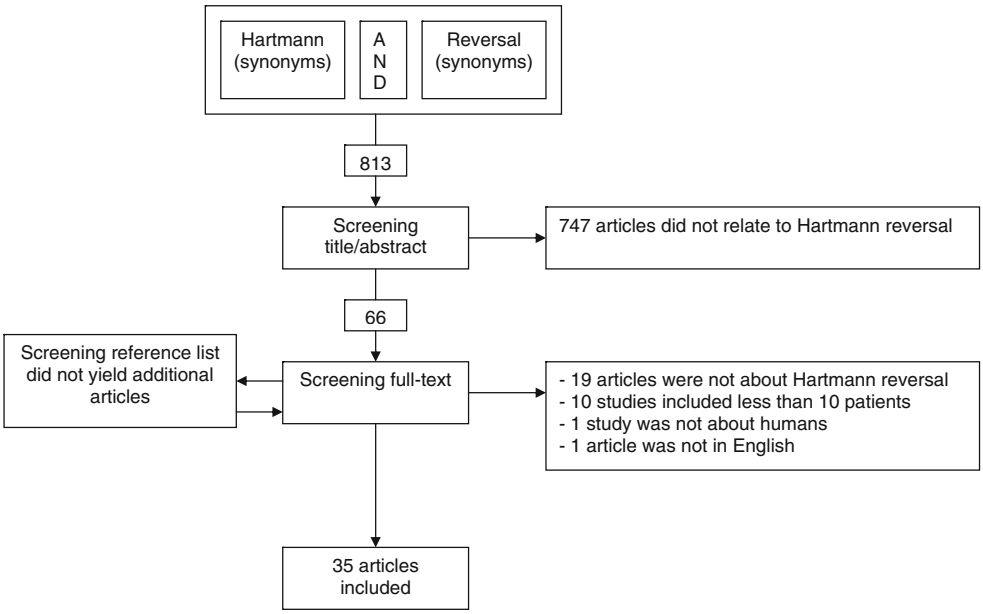

Figure 1 Flowchart describing the selection of studies included in this review.

to be the indication in 17% of patients. Other indications including inflammatory bowel disease, ischemia, volvulus, (iatrogenic) trauma, perforation, and anastomosis leakage following resection with primary anastomosis comprised 16% of cases.

Of the 646 patients who underwent reversal in these studies, 433 patients (67%) were considered relatively healthy (ASA I and II). For moderately healthy patients (ASA III), this amount was 200 patients (31%). A fraction of patients that underwent reversal was considered ASA IV (2%).[3,9,12,21,24] Reasons for performing reversal in this high risk group were not reported. Only two studies reported both the ASA classification of patients who underwent reversal and those that did not. Roque-Castellano et al. studied a population consisting of 162 patients that had an initial Hartmann procedure.[1] Of this group, 63 patients were considered ASA I or II, 72 patients ASA III, and 27 were considered ASA IV. Only 32 out of the 63 ASA I/II patients (51%) underwent reversal as shown in Fig. 2. For the ASA III patients, this amount was nine out of 72 (13%), and for ASA IV, one out of 27 patients (4%). Banerjee et al. reported that three out of 25 ASA IV patients (12%) underwent reversal.[18] The percentages of other ASA classifications were not reported.

Morbidity and Mortality of Hartmann Reversal

In Table 2 and Table 3, the hospital stay and morbidity and mortality rates after conventional and laparoscopic HR are presented. The overall morbidity rate of the HR (conventional plus laparoscopic approach) is considerably high ranging from 3.6% to 50% (mean 16.3%). The most frequent postoperative complication was wound infection which ranged from 5% to 30% (mean 12.5%).[18] Other common postoperative complications include cardiopulmonary complications ranging from 1% to 14.6% (mean 5.3%) followed by anastomosis leakage with a range of 0% to 16% (mean 5.2%) and postoperative bleeding from wound or anastomosis site ranging from 0% to 7% (mean 3.2%). Late complications including anastomosis stricture ranged from 2% to 10% (mean 5.8%).

Mainly because of anastomosis-related complications (leakage and stricture), between 0% and 20% (mean 5.3%) of evaluated patients required secondary surgery after reversal of HP. Of the patients that required a reoperation, 24% to 50% were left with a permanent stoma.[11,14,15,19,22,28–32] This proportion comprises 3% to 12.5% (mean 6.1%) of all patients that underwent HR.

Mortality was largely caused by septic complications due to anastomotic dehiscence or postoperative abscesses.[2,5,7,8,10,12,13,15,18–22,24–26,28,29,31–33] Some studies also reported renal failure and myocardial infarction after reoperation for wound dehiscence and dissipated malignancies as cause of death.[5,8–10,13]

Laparoscopic vs. Conventional Reversal of HP

Five studies compared laparoscopic surgery with the open approach of HR.[10,13] Seven studies were solely about laparoscopic HR.[4,11,21,25,29,31,32] A total of 396 patients had a laparoscopic HR vs. 5,853 patients with conventional HR.

Hospital stay appeared to be notably shorter after laparoscopic HR (mean 6.9, range 3–11 days) compared to conventional HR (mean 10.7, range 3–

Table 1 Baseline and Patient Characteristics of Included Studies

Reference	Year	Level	Reversal (*n* patients)	Age (years)	Gender		Initial indication			ASA classification		
					Female (*n*)	Male (*n*)	Div (%)	CA (%)	Other (%)	ASA I–II (%)	ASA III (%)	ASA IV–V (%)
Sweeney and Hoffmann	1987	IV	19	71	10	9	100	0	0	–	–	–
Basse	1991	IIb	27	50	14	13	50	22	28	–	–	–
Roe	1991	IV	69	67	38	31	70	30	0	–	–	–
Geoghegan and Rosenberg	1991	IV	55	65	–	–	58	31	11	90	10	0
Pearce	1992	IV	80	65	44	36	71	24	5	–	–	–
Keck	1993	IV	50	–	–	–	80	14	6	–	–	–
Sosa[b]	1994	IV	18	38	4	14	50	0	50	–	–	–
Khan	1994	IV	28	58	13	15	100	0	0	–	–	–
Wigmore	1995	IV	178	65	93	85	63	33	4	–	–	–
Macpherson[b]	1996	IV	12	62	7	5	75	17	8	–	–	–
Regadas[b]	1996	IV	20	52.8	10	10	10	20	70	–	–	–
Carcoforo[a]	1996	IV	19	–	9	10	–	–	–	–	–	–
Seetharam	2003	IV	23	–	–	–	84	8	8	–	–	–
Maggard	2004	IIb	765	–	–	–	–	–	–	–	–	–
Banerjee	2004	IV	66	59	30	36	–	–	–	71	25	4
Rosen[b]	2005	IV	22	54	12	10	68	9	23	–	–	–
Albarran	2004	IV	40	60	19	21	55	28	17	63	32	5
Bell	2005	IV	20	56	1	19	55	20	25	–	–	–
Aydin[a]	2005	IV	121	57	54	67	100	0	0	41	56	3
Khaikin[b]	2007	IV	27	–	10	17	70	19	11	56	44	0
Salem and Flum	2004	IV	3,051	–	–	–	–	–	–	–	–	–
Oomen	2005	IIb	65	63	32	33	100	0	0	–	–	–
Roque-Castellano	2007	IV	42	56	7	35	–	–	–	77	21	2
Faure[a]	2007	IIb	34	62	18	16	67	26	7	76	24	0
Boland	2007	IV	39	53.4	17	22	56	15	29	–	–	–
Schmelzer	2007	IV	113	49.5	41	72	38	15	48	61	39	0
Carus[b]	2008	IV	28	–	–	–	–	–	–	–	–	–
Haughn[a]	2008	IV	122	59	68	54	70.5	18	11.5	–	–	–
Leong	2008	IV	28	–	–	–	29	46	25	–	–	–
Mazeh	2009	IV	82	60.5	41	41	58	6.1	35.9	–	–	–
Petersen[b]	2009	IIb	71	–	32	39	–	–	–	–	–	–
Slawik and Dixon[b]	2008	IV	28	66	17	11	67.9	25	8.1	68	32	0
Vermeulen[a]	2008	IV	63	61	26	35	100	0	0	63	23	–
Chouillard	2008	IV	88	57	50	38	75	18	7	–	–	–
David	2009	IV	736	60	335	401	82.6	17.4	0	–	–	–
Total			6,249		1,052	1,195	–	–	–	–	–	–
Mean	–	–	179	60	38	43	67	17	16	67	31	2

Div diverticulitis, *CA* carcinoma

[a] Results of laparoscopic and conventional Hartmann reversal grouped together (conventional > laparoscopic)

[b] Results of laparoscopic Hartmann reversal only

18 days).[14,15,19,22,28,30,34] Furthermore, patients treated laparoscopically appeared to have a reduced mean overall morbidity rate (12.2% vs. 20.3%). This was mainly found for wound infection (mean 10.8% vs. 14.2%), anastomotic leakage (mean 1.2% vs. 5.1%), and cardiopulmonary complications (mean 3.6% vs. 6.9%). Reoperations occurred more often in conventional HR (mean 3.6% vs. 6.9%). The need for a permanent stoma was not reported for laparoscopic HR.

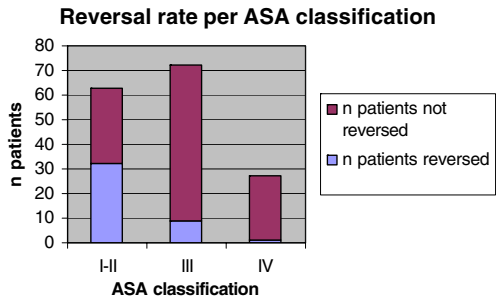

Figure 2 Reversal rate per ASA classification.

However, this percentage was on average 6.1% in the conventional group.

Mortality appeared to be comparable for both techniques (mean 0.9% vs. 1.1%). One study reported a mortality rate of 7% in a study population of 28 patients that were treated laparoscopically.[1,6–13,20,23,25,26,27,31,32,35] In this study, one patient died from a mesenteric embolus secondary to atrial fibrillation, and one patient died from anticoagulation induced hemorrhage.

The operating time was appeared to be comparable for laparoscopic (mean 153 min, range 30–356) and conventional HR (mean 170 min, range 57–500). Conversion from laparoscopy to conventional surgery ranged from 7% to 22% (mean 12.6%). Reasons for conversion were lack of visualization due to dense adhesions (80%), rectal stump perforation (7%), persisting infection of the rectal stump (5%), extensive neoplasm invasion (3%), and lesions to the bladder or spleen (5%).[30] Other intraoperative complications not requiring conversion included splenic lesions (4.5%), accidental enterotomy during adhesiolysis (2.8%), incomplete anastomosis (2.5%), and bladder or ureteral injury.

When comparing the group of patients treated laparoscopically to the group treated conventionally, patients treated laparoscopically appeared to be slightly younger (55 vs. 61 years) and were more often initially treated for other indications (32% vs. 13%), such as inflammatory bowel disease, ischemia, volvulus, and trauma rather than diverticulitis (55% vs. 67%) or malignancies (15% vs. 19%). Furthermore, the mean interval between Hartmann procedure and reversal was considerably shorter for patients treated laparoscopically (5.5 vs. 8.8 months). There were no apparent differences in ASA classification.

Reversal Rate and Factors

Nineteen studies mentioned the amount of patients who initially received a Hartmann procedure and therefore offered the opportunity to calculate the reversal rate (Table 4). A total of 12,302 patients had a Hartmann procedure of which 5,405 subsequently underwent reversal leading to a mean reversal rate of 44% (range 19% to 71%). Fourteen studies mentioned reasons or factors that possibly influenced the choice not to perform a HR. The most frequent reported reason or factor was a high ASA classification mentioned in 12 studies, followed by patient refusal in nine, metastatic disease in seven, and high age in five studies. Three studies reported other reasons which mostly concerned the inability to perform an anastomosis due to persisting rectal stump difficulties. Roque-Castellano et al. published a study focusing specifically on factors related to the decision of restoring intestinal continuity after Hartmann procedure.[1] They found that reestablishment of intestinal continuity was related in a statistically significant matter to male sex, nonneoplastic disorder, younger age, and lower ASA classification. Other studies also supported the fact that high age and ASA classification are associated with a low reversal rate.[1]

The interval between the original Hartmann procedure and its reversal varied widely between studies as demonstrated in Table 5. Two studies included patients who underwent their reversal after an interval shorter than 3 months.[13,28] These studies had comparable outcomes with studies that had a longer time interval. The longest interval reported was 13.5 months and was attributed to a long waiting list in the concerning hospital.[1] The mean interval of all included studies was 6.7 months. Approximately 7% to 16% of patients waiting for reversal died due to disease-related complications (mostly metastatic disease).[30]

Discussion

With this systematic review, we have attempted to summarize all evidence currently available in the literature concerning the indications of HP and the number and characteristics of patients who undergo reversal of this procedure with its morbidity and mortality. Although at this point in time high level studies are lacking, this study indicates that the initial HP is mainly reserved for patients with complicated (Hinchey III–IV) diverticulitis and patients with fecal or purulent peritonitis due to tumor perforation. Approximately 44% of patients undergo bowel continuity restoration after HP with a mean interval of 7.5 months. The majority of patients (mean age 60 years) undergoing reversal are considered ASA I–II. Reversal of HP is accompanied by a considerable risk of complications (mean 16.3%, range 3–50%) and has an overall mortality rate of 1%. When comparing the few studies on laparoscopic HR with conventional surgery, a lower overall morbidity rate is found (12.2% vs. 20.3%). Furthermore, patients treated laparoscopically have a shorter hospital time compared to conventional reversal (6.9 vs. 10.7 days). Mortality, however, is comparable for both operative techniques.

Table 2 Hospital Stay, Morbidity, and Mortality of Conventional Hartmann Reversal

First author (year)	Patients (*N*)	Hospital stay (days)	Morbidity								Mortality (%)
			Permanent stoma (%)	Bleeding (%)	Leakage (%)	Stricture (%)	Reoperation (%)	Wound infection (%)	Cardio/pulmonary (%)	Overall morbidity (%)	
Sweeney (1987)	19	18.1	–	–	16	–	–	5	–	21	0
Roe (1991)	69	14	–	–	4	–	6	10	1	15	3
Basse (1991)	27	3	–	4	4	–	0	–	–	8	0
Geoghegan (1991)	55	–	–	–	–	–	2	8	2	10	2
Pearce (1992)	80	13	8		16	–	–	–	–	16	4
Keck (1993)	50	12		–	4	8	0	20	–	32	2
Khan (1994)	28	12.5	–	–	7	–	4	7	11	25	0
Sosa (1994)	65	9.5	–	–	–	–	–	–	–		–
Wigmore (1995)	161	12	–	–	4	7	4	10	6	27	1
Carcoforo (1996)	12	–	–	–	–	10	–	–	–	10	0
Seetharam (2003)	23	–	–	–	–	–	–	–	–		0
Albarran (2004)	40	15.5	–	–	3	9	3	21	6	39	0
Banerjee (2004)	66	–	3	–	6	2	6	8	–	16	0
Bell (2005)	20	–	–	–	5	–	20	30	15	50	0
Oomen (2005)	65	–	4	2	5	–	17	–	8	15	3
Roque (2005)	42	13.5	–	7	–	–	–	24	–	31	0
Salem (2004)	3,051	7	12.5	–	–	–	–	–	–	–	0.4
Aydin (2005)	111	–	–	–	3	–	19	7	6	16	2
Boland (2007)	39	8	10	–	3	–	3	–	–	3	3
Schmelzer (2007)	113	6.8	–	6	1	–	–	16	2	25	0
Faure (2007)	20	11	–	–	5	–	–	–	–	5	–
Chouillard (2008)	44	6.8	–	–	7.1	–	4.5	20.5	–	27.6	0
Haughn (2008)	61	–	1.6	–	–	1.6	13.1	13.1	9.8	24.5	0
Leong (2008)	28	–	3.6	–	3.6	–	3.6	–	–	3.6	0
Vermeulen (2008)	63	–	–	(1.6)	(3.2)	–	–	(11)	–	15.8	(5)
David (2009)	736	11	–	–	2.3	–	–	11.7	–	14	1.4
Mazeh (2009)	41	8.1	–	2.4	0	–	4.9	19.5	14.6	36.5	0
Mean		10.7	6.1	3.8	5.1	6.3	6.9	14.2	6.9	20.3	0.9

In parentheses were results of laparoscopic and conventional Hartmann reversal grouped together (conventional > laparoscopic)

Table 3 Hospital Stay, Conversion Rate, Morbidity, and Mortality of Laparoscopic Hartmann Reversal

First author (year)	Patients (*N*)	Hospital stay (days)	Conversion (%)	Morbidity								Mortality (%)
				Permanent stoma (%)	Bleeding (%)	Leakage (%)	Stricture (%)	Reoperation (%)	Wound infection (%)	Cardio/pulmonary (%)	Overall morbidity (%)	
Sosa (1994)	14	6.3	22	–	–	–	7	–	7	–	14	0
Regadas (1996)	20	4	15	–	5	–	–	5	10	–	15	0
Macpherson (1996)	12	8	0	–	–	–	–	–	8	8	16	0
Rosen (2005)	20	4.2	9	–	–	–	–	0	18	–	18	0
Khaikin (2007)	23	6	14.8	–	–	0	–	4	20	–	18	0
Faure (2007)	14	9.5	14.8	–	–	–	7.1	7	–	–	7.1	–
Slawik (2008)	28	3	3.6	–	–	–	–	–	7.1	–	7.1	7.1
Carus (2008)	28	8.6	17.9	–	–	3.6	–	7.1	10.7	–	14.3	–
Chouillard (2008)	44	4.8	9.1					2.2	9		11.2	2.2
Haughn (2008)	61	–	–	–	–	–	1.6	3.3	3.8	4.9	10.3	0
Mazeh (2009)	41	6.5	19.5	–	3	0	–	0	14.6	0	17.6	0
Petersen (2009)	71	–	12.7	–	1.4	–	–	–	–	1.4	2.8	1.4
Mean		6.9	12.6	–	3.1	1.2	5.2	3.6	10.8	3.6	12.2	1.1

ASA classification and high age are frequently reported as a reason to abstain from reversal. Although this review was not constructed to address this issue, it is generally thought that these factors are associated with higher morbidity and mortality rates.[16,18,33] Unfortunately, the majority of patients with a colostomy after HP are old and considered ASA III or higher. Therefore, a large group of patients are left with a permanent stoma mainly because reversal is considered risk full due to their fragile state of health. Such a group of patients may benefit from less invasive procedures.

Laparoscopic HR seems to be a promising alternative to open surgery. By reducing the invasiveness of the operation, this review has found decreased postoperative recovery time. Furthermore, the mean overall morbidity rate appears to be reduced for laparoscopic HR. However, there is considerable overlap in range between laparoscopic and conventional HR (2.8–17.6% vs. 3–50%). Conversion rates, ranging from 0% to 22%, reflect the fact that the operation is technically demanding and might also result in elevated morbidity rates. Laparoscopic reversal is a relatively new technique with only small numbers of retrospective case series each containing no more than seven to 71 patients. It is therefore uncertain what the effects of selection bias are on the outcomes after laparoscopic HR. Randomized trials are necessary to determine whether laparoscopic reversal is indeed superior to the conventional technique.

HP has been the operation of choice for complicated diverticulitis and tumor perforation with peritonitis. HP was recommended because it could potentially avoid intra-abdominal sepsis related to anastomotic leakage. However, several studies have demonstrated that primary anastomosis with or without defunctioning ileo- or colostomy after resection could safely be performed in patients with peritonitis and eliminate the need for an invasive second stage reversal. In a recent review, the leak rate of the primary anastomosis was described at 5.5% which compared favorably with the leak rate found in our review after HR (mean 3.2%, range 0–16%).[18,20] However, certain considerations must be taken into account. Firstly, most studies comparing the Hartmann procedure with primary anastomosis with or without defunctioning colo- or ileostomy are retrospective with inherent selection bias. Patients that undergo HP often suffer from more extensive disease when compared to patients who have primary anastomosis. Therefore, solid conclusions cannot sufficiently be drawn regarding this topic, and it therefore may be justified that the choice of operative technique should be considered on an individual basis. In The Netherlands, a trial has been developed to address this issue in the near future. Secondly, reversal of the ileo- and colostomies carry considerable morbidity themselves ranging from 4.6% to 34% with anastomotic leakage occurring in 0–2.2% of patients.[36]

Table 4 Reversal Rate and Reasons for Not Performing Reversal

First author (year)	Patients HP (*n*)	Patients HR (*n*)	Reversal rate (%)	Reasons for not performing reversal				
				High ASA	Patient refusal	Metastatic disease	High age	Other
Sweeney 1987)	30	19	63	X	X			
Roe (1991)	107	69	64	X	X	X		
Geoghegan (1991)	108	55	51	X	X	X		X
Pearce (1992)	145	80	55					
Keck (1993)	111	50	45	X	X	X		X
Khan (1994)	61	28	46	X	X	X		
Wigmore (1995)	345	178	47					
Carcoforo[a] (1996)	43	19	44					
Seetharam (2003)	124	23	19					
Banerjee (2004)	110	66	61	X			X	
Albarran (2004)	74	40	54		X			
Maggard (2004)	1,176	765	65	X			X	
Salem (2004)	5,420	3,051	56				X	
Oomen (2005)	91	65	71	X				
Roque (2007)	164	42	30	X		X	X	
Leong (2008)	70	28	40	X	X	X		
Vermeulen (2008)	139	63	45	X	X	X	X	X
Carus[b] (2008)	34	28	82	X	X			
David (2009)	3,950	736	23.3					
Mean	647	284	44	–	–	–	–	–

[a] Results of laparoscopic and conventional Hartmann reversal grouped together

[b] Studies reporting results of laparoscopic Hartmann reversal only

Moreover, 0–16.7% of colo- and ileostoma are never reversed (reasons are patient refusal, general inoperability, tumor progression, and anal sphincter insufficiency).[37–40] Noteworthy, however, this compares favorably to the reversal rate of 44% after the Hartmann procedure.

This review has several limitations. The analysis of data mainly serves as descriptive purposes identifying characteristics of patients undergoing HR, reversal rates, reasons not to reverse, and morbidity and mortality of laparoscopic and conventional HR. It does not intend to provide direct comparison between laparoscopic HR and conventional HR. Therefore, certain considerations must be taken into account when attempting to compare laparoscopic to conventional HR using results of this review. Firstly, the decision on surgical approach in the studies was based on surgeon's preferences leading to certain amounts of selection bias. Predominantly, the interval between Hartmann procedure and reversal was significantly lower in patients treated laparoscopically. It is difficult to evaluate to what extent this may have biased the results as it remains a controversial topic in the literature. Secondly, a serious confounder could be the moment of publication; studies on laparoscopic surgery were published since 1996, while studies on open reversal were published since 1987. As recent developments have led to shorter hospitalization times in general, more recent publications, such as studies on laparoscopic HR, might report shorter hospital stay compared to older publications such as studies on conventional HR. To date, clear comparison is nearly impossible as studies that attempted to compare laparoscopic HR to conventional HR are retrospective and not randomized.

Recently, an innovative promising technique has been developed which might be a solution for the aforementioned risk-full patients. In 2004, Gagner et al. described an endoscopic procedure to restore bowel continuity after HP in a canine model.[41] This procedure requires a modified HP during which the rectal stump is sutured to the sidewall of the colostomy limb in an end-to-side fashion to enable the opportunity to perform endoscopic reversal. During reversal, a rendezvous procedure is constructed during which a dedicated device is inserted through the colostomy that meets a standard circular stapler introduced through the anus. This procedure has several theoretical advantages. For one, it may eliminate the requirement for general anesthesia and associated morbidity (cardiopulmonary stress, gastrointestinal ileus). Secondly, by avoiding laparotomy or laparoscopy, the risk of postoperative associated complications may be reduced and patients may have shorter recovery time. Thirdly, this technique may be able to

reduce the long time interval between HP and reversal found in this review consisting of approximately 7.5 months. There are certain considerations which must be taken into account. The modified HP may be more difficult in patients who are left with a short rectal stump. In addition, mobilization of the splenic flexure may be necessary which, however, creates an additional risk for complications (3.1%). Furthermore, until now, during endoscopic reversal, the final anastomosis is made without direct visualization of the circular anastomosis.

A comparable endoscopic technique has been performed in 13 patients by Vermeulen et al. Essentially, HR was performed through the stomal opening. Through an incision at the formal stoma side, lysis of intra-abdominal adhesions could be performed manually. The rectal stump was identified intra-abdominally using a transanal club, and an end-to-end colorectal anastomosis was created under manual control. There were two conversions due to strong adhesions in the lower pelvic cavity, and no complications occurred. Unfortunately, as in the technique described by Jacob et al., the anastomosis was made without direct visualization. In the future, an adjusted stapler with a fiber optic viewing channel might overcome this problem.

In conclusion, based on the published literature, reversal of the Hartmann procedure carries a high operative morbidity and mortality and is performed in only 44% of patients. Principally, relatively younger and healthy patients are eligible for reversal. This leaves a considerable group of patients, mainly older with poor health condition, with a permanent stoma. Laparoscopic reversal compares favorably to conventional; however, high level evidence is needed to determine whether it is superior. Endoscopic techniques might be upcoming and may introduce the possibility for the older and fragile patients to undergo reversal.

Table 5 Time Interval Between HP–HR and Mortality During This Interval

First author (year)	Interval between HP and conventional HR (*n* months)	Interval between HP and laparoscopic HR (*n* months)	Mortality in time interval (%)
Sweeney (1987)	5.6	–	–
Geoghegan (1991)	6.5	–	–
Roe (1991)	4.5	–	–
Pearce (1992)	6	–	–
Keck (1993)	8.5	–	–
Khan (1994)	3–6	–	–
Wigmore (1995)	0–3	–	–
Carcoforo (1996)	7.7	–	–
Macpherson (1996)	–	7.5	–
Seetharam (2003)	7.6	–	19
Banerjee (2004)	8.3	–	16
Maggard (2004)	5	–	–
Salem (2004)	5	–	–
Bell (2005)	10.6		–
Boland (2007)	11.5	–	–
Schmelzer (2007)	10.2	–	–
Roque (2007)	13.3	–	–
Faure (2007)	4	6	–
Leong (2008)	9	–	7
Haughn (2008)	14	5.7	–
Vermeulen (2008)	9.1	–	–
Chouillard (2008)	5.1	6.2	–
Carus (2008)	–	2.5	–
Mazeh (2009)	7.7	4.9	–
David (2009)	9.5	–	–
Mean	8.0	5.5	14

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J Gastrointest Surg (2010) 14:753–755
DOI 10.1007/s11605-009-0918-3

GI IMAGE

A Rare Variant of Gallstone Ileus: Bouveret's Syndrome

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Received: 19 February 2009 / Accepted: 15 April 2009 / Published online: 7 May 2009

Abstract
Introduction Bouveret's syndrome (gastric outlet obstruction due to impaction of a stone) is a rare variant of gallstone ileus. A recently observed case led us to review the literature, with the aim to discuss the recent advances in the management of this rare syndrome.
Discussion A 69-year-old woman was admitted with symptoms of high intestinal obstruction. Computed tomography scan of the abdomen showed a large gallstone impacted in the duodenum. One-stage surgery, consisting in enterolithotomy, cholecystectomy, and fistula repair, was carried out. Although several surgical and nonoperative procedures have been used, the optimal treatment of Bouveret's syndrome remains controversial. Surgery still maintains a prominent position, even though nonoperative procedures have an increasing role especially in high risk patients with important comorbidities. The decision should be taken on an individual basis, after evaluating patient's general condition and age, stone size, comorbidities influencing the operative risk, and expertise of surgical and endoscopic teams. One-stage surgery may offer definitive management in selected patients.

Keywords Bouveret's syndrome · Gallstone ileus · Surgical treatment · Nonoperative treatment · One-stage surgery

Case History

A 69-year-old woman was admitted with a 3-day history of colicky upper abdominal pain, nausea, and vomiting. Medical history was unremarkable except for cholecystolithiasis. Over the past 6 months, she had suffered from episodes of biliary colic. On arrival, the patient had temperature of 37.6°C, heart rate of 98 beats/min, and blood pressure of 150/85 mmHg. Physical examination revealed a moderately distended abdomen with tenderness in the right upper quadrant and epigastrium, with no rebound. Abnormal laboratory findings were hemoglobin 10.6 g/dL, hematocrit 34%, and potassium 2.7 mEq/L. Leukocyte count, liver, and pancreas function tests were within the normal range. Intravenous administration of fluids and electrolytes was started. Nasogastric lavage yielded 1 L of gastric fluid. A gastric outlet obstruction was suspected and the patient was sent for a computed tomography (CT) scan of the abdomen which revealed intrahepatic pneumobilia (Fig. 1a), gastric distension, a contracted gallbladder containing air, pericholecystic inflammatory changes, and a large calcified stone in the duodenal lumen (Fig. 1b). The typical Rigler's triad consisting in pneumobilia, ectopic gallstone, and small bowel obstruction was recognized and the diagnosis of Bouveret's syndrome was made. A gastroduodenoscopy confirmed the presence of an impacted stone in the descending duodenum. Due to the large size of the stone, endoscopic retrieval was not attempted and the patient underwent surgical exploration. Intraoperatively, a very dilated stomach was found as a result of obstruction caused by a large stone measuring 5×4 cm impacted in the duodenum (Fig. 2). A cholecystoduodenal fistula was discovered at the site of

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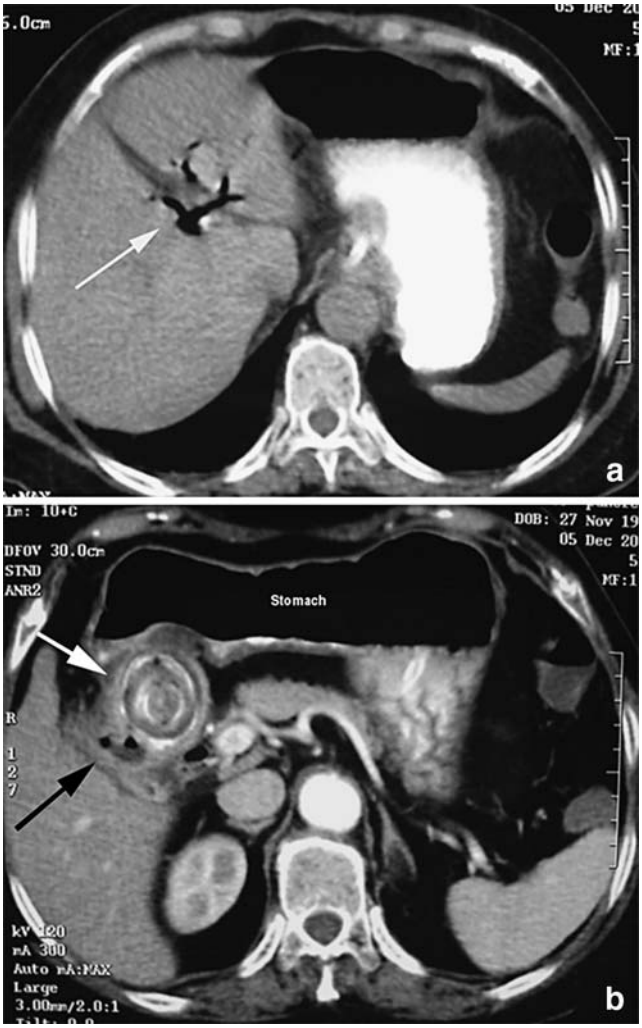

Figure 1 CT scan of the abdomen revealed intrahepatic pneumobilia (**a**, *arrow*) gastric distension, a contracted gallbladder containing air with pericholecystic inflammatory changes (**b**, *black arrow*), and a calcified stone in the duodenal lumen (**b**, *white arrow*).

duodenal bulb. One-stage surgery consisting in enterolithotomy, cholecystectomy, and fistula repair was carried out. We decided on this option, rather than a simple enterolithotomy, given the relatively young age of the patient and the absence of comorbidities. Her recovery was uneventful and she was discharged on postoperative day 8. After 1 year, the patient was asymptomatic and in good health.

Discussion

Gastric outlet obstruction due to impaction of a gallstone (Bouveret's syndrome) is a rare variant of gallstone ileus. Stones of at least 2.5 cm in diameter migrating through a cholecystoduodenal fistula may impact and cause intestinal obstruction, which usually takes place in the terminal ileum.[1–3] Impaction of a stone in the duodenum causing Bouveret's syndrome only occurs in 1–3% of cases.[3,4] The latest detailed review of Bouveret's syndrome found 128 cases published in English up to June 2005.[5] Mortality rate, though reduced with respect to the past, has been reported to be around 12%.[6] Reasons for this finding include advanced age of patients, commonly associated comorbidities, and frequent delay in establishing the correct diagnosis due to its rarity and lack of specific signs.[7,8] Elements of suspicion for Bouveret's syndrome when dealing with a patient with small bowel obstruction are advanced age, history of symptomatic cholelythiasis, and absence of scars from previous abdominal operations.

Figure 2 The gallstone causing Bouveret's syndrome measured 5×4 cm.

The typical Rigler's triad of pneumobilia, ectopic gallstone, and small bowel obstruction can be identified on abdominal X-ray in only 30–35% of all cases of gallstone ileus and even more rarely in Bouveret's syndrome.[8] For years, the gastroduodenoscopy has been considered the mainstay in diagnosis of this rare condition,[2,5] but nowadays, the CT scan has become the most employed investigation.

More than 90% of patients require surgery.[2] Controversies exist in deciding between enterolithotomy alone or enterolithotomy associated to cholecystectomy and fistula repair. Advocators of enterolithotomy as a single procedure argue that resolving the obstruction through the simple removal of the offending stone is the appropriate treatment in most cases.[3,9,10] However, as such an approach does not address the underlying cholecystoduodenal fistula, others emphasize that the persistence of the fistula poses postoperative risks such as recurrent gallstone ileus, cholecystitis, cholangitis, gallbladder carcinoma, and hemorrhage.[1,4,11] One-stage surgery, consisting in enterolithotomy, cholecystectomy, and fistula repair, is conceptually the ideal treatment since the

simultaneous solution of both the obstruction and the underlying biliary pathology prevents the aforementioned complications and avoids the need for further intervention. Disadvantages are higher mortality and morbidity rates when compared to simple enterolithotomy.[4,7] No convincing data to establish which approach provides better outcomes are available.[2] Enterolithotomy alone is advised in elderly patients with associated comorbidities as well as in the presence of significant inflammatory process in the right upper quadrant. One-stage procedure should be restricted to relatively young patients in good overall condition, as in the case described herein. Laparoscopic or laparoscopic-assisted enterolithotomy[12,13] as well as laparoscopic one-stage procedure[7] have been successfully carried out.

Endoscopic lithotripsy and stone retrieval or lithotripsy alone, achieved by using mechanical, electrohydraulic, and laser lithotriptors as well as argon plasma coagulation have recently emerged as nonoperative approaches.[2,5,14–17] Extracorporeal shock wave lithotripsy has also been used with some success.[15] Endoscopic fragmentation of stones which are frequently quite large, deeply embedded in the duodenal mucosa, or distally impacted in the duodenum can be challenging and sometimes causes distal gallstone ileus.[13] Besides, endoscopic management often requires a combination of various endoscopic facilities that are not always available.[14,15] Nevertheless, nonoperative approaches have gained importance because of their ability to relieve the obstruction with low morbidity and insignificant mortality.

In conclusion, surgery still maintains a prominent position in treatment, even though nonoperative procedures have an increasing role especially in high risk patients with important comorbidities. The decision should be taken on an individual basis, after evaluating patient's general condition and age, stone size, comorbidities influencing the operative risk, and expertise of surgical and endoscopic teams. One-stage surgery may offer definitive management in selected patients.

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J Gastrointest Surg (2010) 14:756–758
DOI 10.1007/s11605-009-0932-5

GI IMAGE

Intraabdominal Bronchogenic Cyst

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Received: 2 May 2009 / Accepted: 11 May 2009 / Published online: 28 May 2009

Abstract
Introduction Bronchogenic cyst is pathology of the respiratory track. It consists of a defect during the embryological development of the tracheobronchial tree. Most common presentation is as a solid or cystic mass located in mediastinum, and it is usually diagnosed in relation to respiratory problems or recurrent infections in children. In adulthood, it is a rare pathology, and its diagnosis is usually incidental.
Case Report We present a case of a patient with a paraesophageal cystic mass suggestive of intraabdominal esophageal duplication cyst but, after the histopathological examination, was discovered to be a bronchogenic cyst, something extremely rare as in most cases of subdiaphragmatic location; bronchogenic cysts appear as retroperitoneal lesions.
Discussion After we review the current literature, surgical extirpation appears to be the treatment of choice due to potential complications, and laparoscopic approach is a feasibily and safe procedure for this pathology up to date.

Keywords Intraabdominal · Bronchogenic cyst · Laparoscopic approach

Introduction

Bronchogenic cyst is a cystic lesion with ciliary epithelium and cartilage that produce mucus and is usually connected to the respiratory tract. Diagnosis is in childhood and associated in most cases in relation with recurrent respiratory infections.[1]

Diagnosis in adulthood is rare and is usually as a result of incidental findings of some imaging test. Most common location is the chest, although there are several cases describing bronchogenic cysts in the neck.[2–4]

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Bronchogenic cyst outside the thoracic cavity is a very rare situation and, in most cases, is described as retroperitoneal mass, result of incidental findings in the course of a computer tomography. Pure intraabdominal location is extremely uncommon.[5]

Absence of symptoms and their incidental diagnosis raise doubts about the most appropriate management of this disease. The problem is potential complications from these masses, such as infection, bleeding, or malignization.[6,7] These reasons and the lack of a certain pathological diagnosis make the surgical resection the current trend.[8]

Case Report

We present a 67-year-old man, without medical or surgical previous history, who underwent examination for chronic low back pain; ultrasonography evidenced the presence of a pelvic "horseshoe kidney" without other significant findings. The study was completed with a computerized tomography, which showed (in addition to those described by ultrasound) a cystic oval mass of 6 cm as maximum diameter, attached to the gastroesophageal junction and next to diaphragmatic crura suggestive of esophageal duplication cyst due to the radiological findings.

Upper endoscopy and esophageal gastric transit were performed in which no alteration was observed, and they did not demonstrate any communication between the digestive lumen and the described structure.

After multidisciplinary consensus and patient consent, surgical resection was decided.

By laparosopic approach in the lesser gastric curvature, we observed a diverticular structure of 6 cm in maximum diameter and macroscopic appearance similar to the stomach wall so it suggested a gastric duplication cyst (Fig. 1). It was originated in the gastroesophageal junction, and there was no communication with the digestive lumen. Laparoscopically, it was desiccated from the digestive tract (Fig. 2), and after its extraction, we performed an upper endoscopy to confirm esophageal and gastric mucosa integrity (Fig. 2). We reviewed the rest of the abdominal cavity, and no other alterations were found. Postoperatory evolution was satisfactory with no complications so far.

Despite the initial radiological diagnosis of esophageal duplication cyst and the possible diagnosis of gastric duplication cyst because of the appearance during the laparoscopy, final histopathological study of the completed specimen showed as a definitive diagnosis: bronchogenic cyst, as it was recovered of ciliar and respiratory epithelium, and no signs of esophageal of gastric wall were found.

Discussion

Sumiyoshi described in 1985 that between the third and seventh weeks of embryologic development, a lack in the closure of the pericardioperitoneal channel can take place; it also can promote the migration of elements of the tracheobronchial tree to the abdominal cavity; thus, it justifies the presence of bronchogenic cysts below the diaphragm.[9]

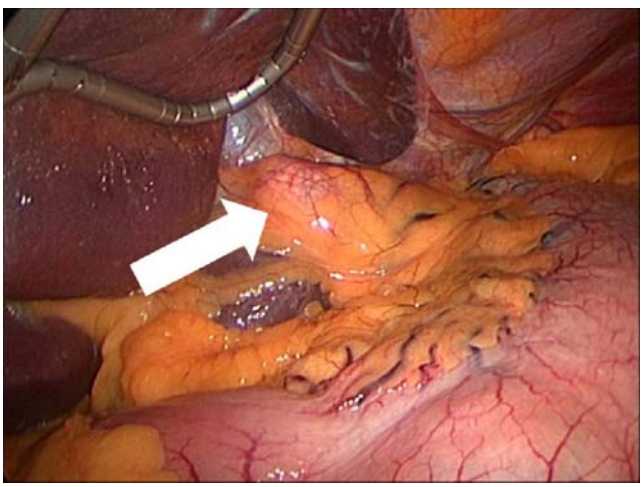

Figure 1 Laparoscopic findings: oval mass similar to gastric wall (*white arrow*).

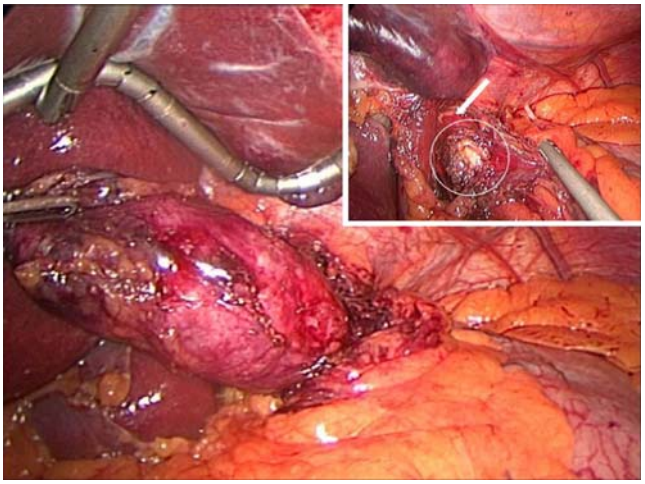

Figure 2 Laparoscopic dissection and resection site after final extirpation (*white circle*) with mucosal integrity. Esophagus (*white arrow*).

This situation is more commonly described as retroperitoneal mass[5] which requires a differential diagnosis with typical cystic tumor as cystic type of lymphangioma, mucinous cyst neoplasm, epidermoid cysts, or solid tumor as mucinous carcinoma or retroperitoneal pseudomyxoma.

In the case of intraabdominal location, differential diagnosis is even more extensive, but given the silent clinical presentation and findings of imaging tests, most common differential diagnosis is established with esophageal duplication cysts.[10] Stromal tumor is another diagnosis to consider as it has been also described as bronchogenic cyst.[11]

It is radiologically described as cystic solid, well-defined mass with thin wall but with possible calcifications. But these features are shared with some of the mentioned tumors; therefore, they are only descriptive findings;[12,13] and, only the histopathological study can confirm the definitive diagnosis up to date.

This fact and the impossibility to exclude the presence of neoplastic disease seem enough to establish the indication for surgical treatment in cases of suspected bronchogenic cyst or esophageal duplication cyst. Potential complications of conservative management can lead to support that the treatment of choise is extirpation. These complications are sobreinfection, bleeding, compression of adjacent structures, and risk of malignization.[6,7]

Once surgical management has been decided, it seems clear that the laparoscopic approach is a safe procedure in expert hands, and it has widely demonstrated its advantages over the laparotomic approach; several cases reported describe successful laparoscopic treatments in these pathologies.[14,15]

Conclusion

Bronchogenic cyst is a rare disease, and even more if located outside the mediastinum. Below the diaphragm, they are usually described as retroperitoneal mass, and intraperitoneal location is extremely rare.

Usually, it is diagnosed incidentally, and the indication of surgical treatment is controversial in asymptomatic cases. But the risk of infection, compression complications, and potential risk of malignancy appears to support the indication of extirpation.

Once surgical treatment has been decided, laparoscopic approach seems to be the standard approach if it is developed by expert laparoscopic surgeons.

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