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EDITORIAL

The Revolution Will be Televised

Jeffrey Matthews

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Ours is a golden age of surgical innovation. Advances in minimally invasive and computer-assisted (robotic) techniques are introduced at an ever-accelerating pace. Biomedical applications of emerging technologies such as novel energy sources, new biomaterials, nanoscale engineering and visualization will continue the revolution in surgical care for many years to come. Video and convergent digital technologies are also changing the way these new innovations can be streamed to a worldwide audience interconnected by personal computers. Surgical training and continuing surgical education have been dramatically impacted by these advances. Members of the "YouTube generation" now find it hard to imagine a time when electronic educational media was not available on demand via desktop or handheld devices.

High-quality video as a means to augment scientific and technical communication has long been popular at surgical conventions, but it has been used somewhat sparingly in traditional scientific peer-reviewed publications. In this issue of the *Journal of Gastrointestinal Surgery*, we feature a series of three articles that include links to video files that beautifully document innovative surgical techniques in minimally invasive liver resection. The Editors encourage authors to take advantage of widely available user-friendly video editing software and the significant electronic capabilities of our publisher Springer Science+Business Media as they prepare their work for peer review. We encourage submission of multimedia and dynamic manuscripts that include imbedded video material as either the heart of the article or as electronic supplementary material. Further information for authors is available at http://www.editorialmanager.com/jgsu.

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Totally Laparoscopic Extended Left Hepatectomy

Andrew A. Gumbs · Barak Bar-Zakai · Brice Gayet

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Abstract This video will discuss the main steps necessary to perform a totally laparoscopic extended left hepatectomy including partial or complete resection of the middle hepatic vein and resection of segment I. Although totally laparoscopic extended liver resections are currently only being performed in several centers with experience in both minimally invasive and hepatobiliary surgery, it will likely become more common, as more surgeons gain expertise in both of these disciplines.

Keywords Extended · Left · Hepatectomy · Laparoscopic

Introduction

Laparoscopic resection of peripheral hepatic segments has become increasingly more common in the surgical treatment of both benign and malignant tumors. The minimally invasive approach to major hepatectomies is still only being currently performed in highly specialized centers. This video will demonstrate the relevant technical maneuvers in the performance of a totally laparoscopic extended left hepatectomy including resection of segment I. Common pitfalls and areas of concern will also be discussed.

Method

This video will illustrate the pertinent issues regarding preoperative patient selection, necessary minimally invasive equipment, trochar placement, intra-operative monitoring, and steps necessary to perform a left hepatectomy including control and resection of the middle hepatic vein and the left aspect of segment VIII using totally laparoscopic techniques. The techniques for removal of segment I will also be demonstrated. The five principal steps of this procedure include mobilization of the liver, control of hepatic inflow, division of hepatic parenchyma, control of hepatic outflow, and removal of the specimen.

Results

At our institution, a total of three extended left hepatectomies have been performed with totally laparoscopic techniques. These procedures included left hepatectomies with the addition of resection of the middle hepatic vein and complete or partial resection of segments V and VIII. Complications included bile leak in one patient that responded to endoscopic placement of biliary stents. Our short- and long-term results have been similar to our open historical controls. No mortalities have been observed.

Conclusion

Minimally invasive techniques in left hepatic resections are feasible, and high volume centers that specialize in these procedures can have results similar to historical open series. Totally laparoscopic extended left hepatectomy should currently only be performed by surgeons with expertise in laparoscopy and hepatobiliary surgery.

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Totally Laparoscopic Central Hepatectomy

Andrew A. Gumbs · Brice Gayet

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Abstract This video will show the pertinent steps to perform a totally laparoscopic central hepatectomy. The main steps of this procedure include control of the hepatic inflow, mobilization of the right liver, control of the hepatic outflow, and specimen removal. This technique is feasible and safe via laparoscopic techniques, but should currently be performed at high volume centers by surgeons with expertise in both HPB surgery and minimally invasive techniques.

Keywords Central · Hepatectomy · Laparoscopic

Introduction

Since the first report of a laparoscopic liver resection in 1992, laparoscopic resection of peripheral hepatic segments has become increasingly more common in the surgical treatment of both benign and malignant tumors. The minimally invasive approach to major hepatectomies, however, is still only being currently performed in highly specialized centers. This is principally because of concerns for gas embolism and difficulty in controlling major hemorrhage via the laparoscopic approach. This video will demonstrate the relevant technical maneuvers in the performance of a totally laparoscopic central hepatectomy.

Method

This video will illustrate the pertinent issues regarding instrument selection, trocar placement, intraoperative monitoring, and steps necessary to perform central hepatectomy using totally laparoscopic techniques. The principal steps of this procedure include control of hepatic inflow, division of hepatic parenchyma, control of hepatic outflow, mobilization of the liver, and specimen removal.

Results

This procedure has been attempted and performed successfully once by totally laparoscopic techniques in a 43-year-old patient with a colorectal metastasis to the liver. The tumor measured 18 cm, and the patient lost 1,000 cc during the operation that lasted 420 min. The postoperative course was complicated by an abscess along the hepatic transection line that was treated by drain placement via interventional radiology. The patient was discharged home on day 18 and was alive and free of disease at 6-months follow-up.

Conclusion

Minimally invasive techniques for central hepatic resections are feasible, and high volume centers that specialize in these procedures can have results similar to historical open series.

Totally laparoscopic central hepatectomy should currently only be performed by surgeons with expertise in laparoscopy and hepatobiliary surgery.

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Video: The Lateral Laparoscopic Approach to Lesions in the Posterior Segments

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Abstract Although some authors believe that laparoscopy is contraindicated for the posterior hepatic segments, we believe that lesions in these segments are actually an indication for the minimally invasive approach. This video will illustrate the pertinent issues regarding instrument selection, trochar placement, intraoperative monitoring and steps necessary to perform laparoscopic resection of the posterior hepatic segments using totally laparoscopic techniques.

Keywords Posterior hepatic · Lateral approach · Deep segments · Laparoscopic

Introduction

Since the first report of a laparoscopic liver resection in 1992, laparoscopic resection of anterior hepatic segments has become increasingly more common in the surgical treatment of both benign and malignant tumors. The minimally invasive approach to lesions in the posterior segments, however, is still only being currently performed in highly specialized centers. This is principally because of concerns for gas embolism and difficulty in controlling major hemorrhage via the laparoscopic approach. Although some authors believe that laparoscopy is contraindicated for the posterior hepatic segments, we use a lateral approach for resections in these segments.

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Methods

This video will illustrate the pertinent issues regarding instrument selection, trochar placement, intraoperative monitoring, and steps necessary to perform laparoscopic resection of the posterior hepatic segments using totally laparoscopic techniques. The hepatic inflow is approached with patients in a modified partial left lateral, with the surgeon between the legs. The hepatic outflow is then controlled laterally, if not already done so retro-hepatically, with the surgeon standing to the right of the patient.

Results

We have safely performed this procedure in >25 patients with a 5% rate of major morbidity and 0% mortality. Average margin is >10 mm for malignant lesions. Long-term results are similar to our open patients.

Conclusions

Minimally invasive techniques for lesions in the deep hepatic segments are feasible, and high volume centers that specialize in these procedures can have results similar to historical open series. The lateral laparoscopic approach to hepatic lesions in the posterior segments of the liver should currently only be performed by surgeons with expertise in laparoscopy and hepatobiliary surgery.

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Vagotomy During Hiatal Hernia Repair: A Benign Esophageal Lengthening Procedure

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Abstract
Introduction This study describes the use of vagotomy in patients during complex laparoscopic esophageal surgery (e.g., reoperative antireflux surgery (rLARS) or paraesophageal hernia (PEH) repair) when, after extensive esophageal mobilization, the gastroesophageal junction cannot be made to reach the abdomen without tension. In doing so, we hope to understand the risk incurred by vagus nerve division in this setting in order to evaluate its role in managing the short esophagus.
Methods One hundred and sixty-six patients underwent rLARS or PEH repair between 1/1998 and 6/2003 at our institution. Clinical data was obtained from a prospectively maintained database and systematic patient questionnaires administered for this study. Follow-up was available for 102 (61%) of these patients, at a median of 19 months (range 6–69 months).
Results Fifty-two patients underwent rLARS while 50 patients underwent PEH repair. Thirty patients had a vagotomy during the course of their operation (Vag Group; 20 anterior, six posterior, four bilateral), 13 in the rLARS group (25%), and 17 in the PEH group (34%). The primary presenting symptoms for rLARS and PEH repair patients were improved in 89% in the Vag Group and 91% in the No Vag Group. Similarly, there was no difference in the severity of abdominal pain, bloating, diarrhea, or early satiety between the Vag and No Vag groups at follow-up. No patient required a subsequent operation for gastric outlet obstruction.
Conclusions Vagotomy during rLARS and PEH repair does not lead to a higher rate delayed gastric emptying, dumping syndrome, or other side effects. Thus, we propose vagotomy to be a legitimate alternative to Collis gastroplasty when extensive mobilization of the esophagus fails to provide adequate esophageal length.

Keywords Vagotomy · Short esophagus · Hiatal hernia · Reoperative surgery · Nissen fundoplication · GERD

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Introduction

A short esophagus is recognized as one of the potential factors associated with recurrence after hiatal hernia repair. While the condition has been reported to be rare (in the range or 2–5% of all patients undergoing fundoplication),[1–3] however, among those with a paraesophageal hernia or recurrent hiatal hernia, it is thought to be more common.[4] This condition is often associated with large sliding and/or paraesophageal hiatal hernias, and it is relatively common in patients who develop a recurrent hiatal hernia (after an operative repair). Achieving a technically satisfactory reconstruction of the cardia by way of an antireflux procedure is substantially more difficult under these conditions. Even when a good repair may be achieved, its durability may be compromised by the continued cephalad tension on the

gastroesophageal junction, which may lead to recurrent herniation. An extensive mobilization of the esophagus from mediastinal structures usually yields the necessary length of intraabdominal esophagus. Another way to deal with the problem is to perform a Collis gastroplasty, a procedure that uses a portion of stomach to create a "pseudo" intra-abdominal esophagus in more severe cases.

A third, not previously reported option to deal with a short esophagus is a vagotomy. Selective division of one or both vagi can substantially increase esophageal length, as most surgeons with experience in dividing the vagus can attest to. While this is routinely seen in patients who undergo vagotomy for peptic ulcer disease or as part of other operations such as esophagectomy, vagotomy has not previously been used to lengthen the esophagus during reconstruction of the cardia because of fear of its potential side effects. Indeed, in some patients who undergo vagotomy for peptic ulcer disease, gastric emptying may be impaired, dumping syndrome may occur, and postoperative changes in bowel habits such as diarrhea and bloating are relatively common.[5] It is interesting to note that the great majority of these patients undergo some form of gastric drainage procedure in addition to the vagotomy and that the side effects previously mentioned occur after both procedures. Because vagotomy without gastric drainage is rarely done, there is little evidence concerning the magnitude of potential problems that may be associated with vagotomy alone. Moreover, there are no data on the morbidity of vagotomy in patients undergoing hiatal hernia repair.

This study describes the use of vagotomy in patients with large or recurrent hiatal hernias in whom, after extensive esophageal mobilization, the gastroesophageal junction (GEJ) cannot be made to reach the abdomen without tension. We describe the rationale for this surgical maneuver, the effects on the esophagus, and the side effects we noted on the follow-up of these patients. In doing so, we hope to understand the risk incurred by vagus nerve division in this setting in order to evaluate its role in managing the short esophagus.

Methods and Materials

Between January 1998 and June 2003, 166 patients underwent a laparoscopic recurrent hiatal hernia or PEH repair at our institution and were identified from a prospectively maintained database. To collect postoperative follow-up data, in 2004, all patients were first mailed patient questionnaires and were then called using the last available contact information and asked to participate in the study. A total of 102 (61%) patients could be contacted and each agreed to participate in the study.

Symptomatic Follow-Up

Each patient who underwent either a paraesophageal or a recurrent hernia repair via the laparoscopic approach had completed a preoperative symptom questionnaire which was stored, along with perioperative testing and interventions, in a prospectively maintained database. Using data from the operation, the patients were then divided into two groups: those who had vagotomy (one or both nerves; Vag group) and those who did not have vagotomy (No Vag Group). For the purposes of this study, all patients were evaluated using a questionnaire that focused on six main symptoms (i.e., heartburn, abdominal pain, bloating, diarrhea, early satiety, and dumping syndrome symptoms). Dumping syndrome was defined for patients as the occurrence of flushing, palpitations, or diarrhea following a meal. This survey, administered by telephone or by mail, includes questions on frequency (reported on a five-point scale (0 = never, 1 = once a month, 2 = once a week, 3 = once a day, 4 = several times daily)) and on severity (0–10, 0 = not present and 10 = equivalent to the worst imaginable). Only frequency scores were queried preoperatively. The patients were also asked to evaluate the overall effectiveness of the operation specific to their symptoms as well as state their general satisfaction with the operation. For the purposes of this study, an improvement in symptoms was acknowledged if symptom frequency was reduced by at least one point, and the patient stated that overall symptoms were better than before the operation.

Postoperatively, patients were asked to be objectively evaluated using a 24-h esophageal pH study and/or manometry test. Data was available for 33 patients who underwent pH studies and 34 patients who underwent manometry tests.

Operative Techniques

Redo laparoscopic antireflux surgery (rLARS) Our operative technique to deal with recurrent reflux or hiatal hernia after antireflux surgery has been described previously.[6–7] In short, it entails access via laparoscopy, take down of adhesions to the anterior abdominal wall and between the stomach and liver, full mobilization of the structures and dismantling of the previous fundoplication to restore the preoperative anatomy. After adequate intraabdominal esophageal length is obtained with transhiatal esophageal mobilization, an assessment of length is made. If there is <3 cm of intraabdominal esophagus, we would have, in the past, consider lengthening the esophagus via a Collis gastroplasty. At this point, a posterior vagotomy is performed; if this is insufficient to achieve the desired length, an anterior vagotomy is added. The crura are, then, reapproximated with sutures, and either a partial (Toupet) or total (Nissen) fundoplication is created.

PEH repair Our operative technique of PEH repair has been described previously.[8] In summary, after laparoscopic access is acquired, the herniated stomach is pulled back into the abdomen (to the extent possible), and the greater curvature is mobilized by dividing the gastrosplenic ligament and short gastric vessels. The herniated sac is excised, with care taken to preserve the vagus nerve. After adequate intraabdominal esophageal length is obtained with transhiatal esophageal mobilization, an assessment of length is made. If there is <3 cm of intraabdominal esophagus instead of considering a Collis gastroplasty, a vagotomy is performed. The hiatus is then closed. Finally, either a partial (Toupet) or total (Nissen) fundoplication is created.

Statistical Analysis

Statistical significance of differences in symptom frequency and severity between those operations with and without vagotomy was compared using Mann–Whitney *U* test and Fisher's exact test. The results are presented as mean ± SD, unless otherwise specified. Values of $P<0.01$ were considered significant.

The institutional review board at the University of Washington approved this study HSD# 02-2724-E 01.

Results

Fifty-two patients underwent rLARS while 50 patients underwent PEH repair. The mean follow-up was 27 months, and the median follow-up was 19 months (range 4 to 69 months). The mean age of the patients was 56, and the median age was 57 (range 18–87). There were 82 females and 43 males. Thirty patients had a vagotomy during the course of their operation (Vag Group; 20 anterior, six posterior, four bilateral), 13 in the rLARS group (25%), and 17 in the PEH group (34%; Fig. 1). Twelve of these vagotomies were intentionally performed to provide esophageal length for a short esophagus (two were bilateral). In the remainder, the vagus nerve (usually the anterior) was divided as it was either part of a large sac of a paraesophageal hernia or intimately adherent to the gastroesophageal junction in patients with a previous antireflux operation. No patient underwent a concomitant drainage procedure. Forty-eight (92%) of patients who underwent rLARS had a Nissen fundoplication. The remaining patients who underwent rLARS had their original wrap taken down without performing a fundoplication. All but one patient (98%) who underwent PEH repair had a Nissen fundoplication. A single patient underwent PEH repair but did not have a concomitant fundoplication but instead underwent reduction of the hernia, closure of the hiatus, and a gastrostomy. Two operations (one rLARS and one PEH repair) required conversion to an open procedure.

The mean and median hospital stay after rLARS or PEH repair was 4 and 2 days, respectively (range 1–21 days). Perioperative complications were rare. Postoperative ileus or gastric distention occurred in seven patients (7%), and in all were self limited resulting in minimal increased length of stay. There were no deaths.

The primary presenting symptoms for patients undergoing rLARS were heartburn (39%), dysphagia (24%), postprandial pain (12%), regurgitation (12%), and chest pain (12%). The most frequent primary symptoms for PEH repair patients were heartburn (25%), dysphagia (25%), chest pain (25%), postprandial pain (11%), and dyspnea (7%). The mean and median duration of primary symptoms before the operation was 99 and 60 months, respectively (range 1–480 months).

At a median follow-up of 19 months, the primary symptom was improved or resolved for 88% of patients after rLARS and 92% of patients after PEH repair overall.

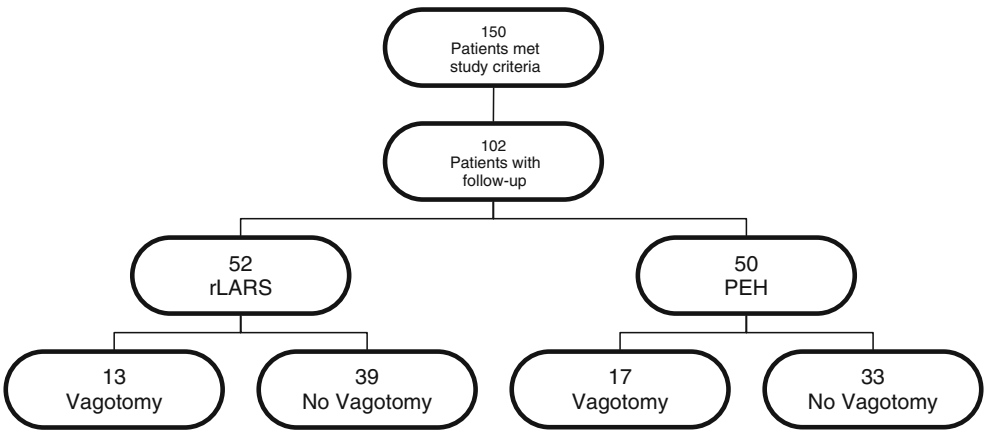

Figure 1 Study sample set distribution.

rLARS – Redo Laparoscopic Anti-Reflux Surgery
PEH – Paraesophageal Hernia Repair

When the groups were compared, the primary symptom was improved in 89% in the Vag Group and 91% in the No Vag Group. Similarly, there was no difference in symptom control between the Vag and the No Vag groups, even when stratified according to rLARS and PEH repair (Fig. 2). When all symptoms are considered, there was no significant difference in the severity of heartburn, regurgitation, abdominal pain, dysphagia, chest pain, bloating, nausea, or diarrhea postoperatively between the two groups of patients (Table 1). Similarly, there was no difference in postoperative symptoms if the operation was rLARS (Table 2) or PEH repair (Table 3). Symptoms that could be thought of as part of the "dumping syndrome" were experienced postoperatively by 18 (25%) patients without vagotomy and 6 (23%) patients with a unilateral vagotomy. All four patients with a bilateral vagotomy experienced occasional symptoms compatible with dumping syndrome, which was a significant difference compared to those patients without vagotomy. The remainder of symptoms queried in the bilateral vagotomy patients, however, did not differ significantly from those with no vagotomy (Table 4) or unilateral vagotomy (Table 5) though with only four patients (bilateral vagotomy), it is hard to draw conclusions about the relative morbidity of bilateral vagotomy.

Postoperatively, 33 patients (32%) underwent 24-h pH studies. Nineteen (58%) of these patients had a normal DeMeester score after the operation; 14 patients (42%) had an abnormal score. The average postoperative DeMeester score (normal <14.7) was 29.0 (range 0.3–192.4); it was 18.2 in the Vag Group, and it was 36.2 among those in the No Vag group. Although the differences between these two groups did not reach statistical significance, the trend suggests better acid control in the Vag group.

We also analyzed the pH monitoring results in the rLARS and PEH groups. The rLARS group had a mean DeMeester score of 11.8±15.8, and 11 out of 16 (69%) had a normal DeMeester score. The PEH group had a mean DeMeester score of 45.3±62.6, and eight out of 17 (47%) had a normal DeMeester score.

Discussion

Of the many factors that can jeopardize the success and durability of hiatal hernia repair and/or fundoplication, the short esophagus defined as one that has less than 3 cm in the abdomen is often referred to as the most important. A short esophagus is believed to cause upward tension on the gastroesophageal junction, potentially, with time, leading to a recurrent hernia. The vagus nerves can provide cephalad traction to the GEJ; thus, division of one or both vagi can release this traction and provide more esophageal length.[9] Vagotomy, performed in the past mostly for peptic ulcer disease, has been associated with significant side effects and, thus, has not been considered by most surgeons as an option to lengthen the short esophagus.[10–11]

It has been our policy to pay specific attention to the integrity of the vagi at the end of an operation on the hiatus. When one of the nerves was divided, usually during the repair of a large paraesophageal hernia or during a redo procedure, we took special note of it. We followed those patients carefully with an eye to early identification of the development of a gastric emptying problems with the idea that some would have to undergo gastric drainage. Our fears were not materialized and we noted that, by and large, patients who had had a vagal injury during these complex procedures did not fare any different than their similar cohorts who had the integrity of the vagi preserved. More importantly, we noted that when one of the vagi was divided—either inadvertently or as a result of a deliberate

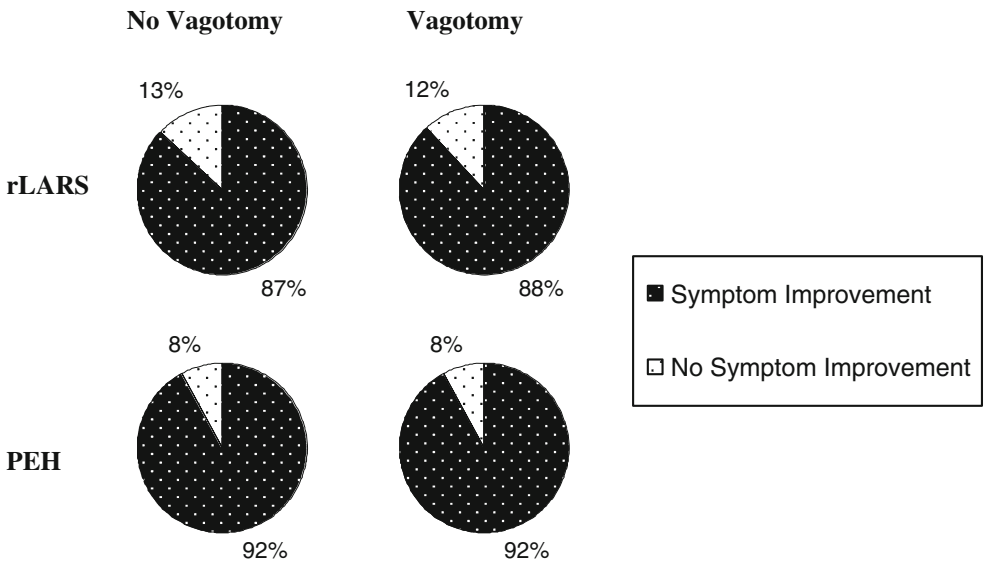

Figure 2 Primary symptom improvement by group.

Table 1 Postoperative Symptom Severity

Symptom	No vagotomy (n=72)	Vagotomy (n=30)	p-value
Heartburn	2.1±3.0	1.7±1.3	.652
Regurgitation	1.0±2.2	0.8±1.0	.408
Abdominal pain	1.7±3.0	1.8±2.8	.749
Dysphagia	1.3±2.4	1.6±2.3	.212
Chest pain	0.8±1.8	0.6±1.6	.607
Bloating	2.2±3.1	2.7±3.3	.481
Nausea	2.1±3.3	1.5±3.1	.483
Diarrhea	2.3±3.6	3.1±3.7	.129
Early satiety	2.0±2.9	2.6±3.4	.313
Dumping	25%	33%	.467
>1/week	21%	30%	.320

Visual analog scale 1–10 (1 = no symptoms; 10 = most severe). Dumping indicated by percentage of patients who experienced symptoms

Table 3 PEH Postoperative Symptom Severity*

Symptom	No vagotomy (n=37)	Vagotomy (n=13)	p-value
Heartburn	2.0±2.9	0.4±1.0	.064
Regurgitation	1.3±2.5	0.2±0.6	.123
Abdominal Pain	1.4±2.9	1.2±2.0	.807
Dysphagia	1.1±2.4	1.2±1.9	.397
Chest Pain	0.7±1.7	0.8±1.9	1.000
Bloating	1.5±2.2	2.5±3.5	.545
Nausea	1.5±2.7	0.1±0.3	.084
Diarrhea	1.7±3.4	2.2±3.3	.459
Early Satiety	1.8±3.0	2.6±2.7	.184
Dumping	19%	31%	.445
>1/week	16%	31%	.420

Visual analog scale 1–10 (1 = no symptoms; 10 = most severe). Dumping indicated by percentage of patients who experienced symptoms

maneuver to free the gastroesophageal junction during a difficult operative dissection, the gastroesophageal junction dropped a couple of centimeters down with ease. Although we did not keep prospective measurements of this, we have consistently noted the lengthening effect of vagotomy in these and other operations (e.g., esophageal and gastric resections).

This led us to start performing unilateral or bilateral vagotomy intentionally and for the sole purpose of achieving appropriate esophageal length in carefully selected patients in whom the esophagus, after a thorough dissection, would not come as far down as desired. This study, which includes both sets of patients (those in whom the vagus was accidentally or purposely divided during the dissection independent of the esophageal length and those in whom the vagotomy was performed for the sole purpose of increasing esophageal length) demonstrated that a vagotomy increases the length of the esophagus and is not associated with side effects. Moreover, those patients with a vagotomy tended to have less heartburn, regurgitation, chest pain, and nausea, as well as a lower acid exposure than those without. Thus, it appears that it should be considered as a viable option for patients with a short esophagus.

The Short Esophagus

A short esophagus is an uncommon problem. Its occurrence is relatively more common among patients who present with recurrence of reflux or a recurrent hiatal hernia after antireflux surgery. Failure of this second operation is higher than after first time antireflux surgery possibly because of this short esophagus or weakening of the hiatus.[12–13] Patients with large paraesophageal hernias also have very high recurrence rates (up to 42%) due to the stomach chronically pulling the GEJ cephalad.[4,14] Indeed it has been

Table 2 rLARS Postoperative Symptom Severity

Symptom	No vagotomy (n=35)	Vagotomy (n=17)	p-value
Heartburn	2.1±3.2	2.8±3.2	.439
Regurgitation	0.7±1.7	1.4±3.3	.686
Abdominal pain	2.1±3.1	2.3±3.3	.809
Dysphagia	1.4±2.4	1.9±2.6	.403
Chest pain	0.8±1.9	0.5±1.4	.477
Bloating	2.9±3.7	2.8±3.2	.899
Nausea	2.6±3.7	2.6±3.8	.850
Diarrhea	2.9±3.8	3.8±3.9	.255
Early satiety	2.1±2.9	2.6±4.0	.931
Dumping	31%	35%	1.00
>1/week	26%	29%	1.00

Visual analog scale 1–10 (1 = no symptoms; 10 = most severe). Dumping indicated by percentage of patients who experienced symptoms

Table 4 Postoperative Symptom Severity

Symptom	Bilateral vagotomy (n=4)	No Vagotomy (n=37)	p-value
Heartburn	1.3±2.5	2.1±3.0	.553
Regurgitation	0±0	1.0±2.2	.315
Abdominal pain	2.3±3.3	1.7±3.0	.492
Dysphagia	3.0±2.5	1.3±2.4	.063
Chest pain	1.3±2.5	0.8±1.8	.667
Bloating	4.3±4.2	2.2±3.1	.206
Nausea	0.8±1.5	2.1±3.3	.577
Diarrhea	6.0±4.0	2.3±3.6	.100
Early satiety	4.5±3.3	2.0±2.9	.154
Dumping	100%	25%	.001
>1/week	100%	21%	.001

Visual analog scale 1–10 (1 = no symptoms; 10 = most severe). Dumping indicated by percentage of patients who experienced symptoms

Table 5 Postoperative Symptom Severity

Symptom	Bilateral vagotomy (n=4)	Unilateral Vagotomy (n=26)	p-value
Heartburn	1.3±2.5	1.8±2.8	.671
Regurgitation	0±0	1.0±2.7	.409
Abdominal pain	2.3±3.3	1.7±2.8	.560
Dysphagia	3.0±2.5	1.4±2.3	.137
Chest pain	1.3±2.5	0.7±1.7	.438
Bloating	4.3±4.2	2.4±3.1	.281
Nausea	0.8±1.5	1.7±3.3	.845
Diarrhea	6.0±4.0	1.7±2.9	.192
Early satiety	4.5±3.3	2.4±3.4	.202
Dumping	100%	8%	.002
>1/week	100%	4%	.001

Visual analog scale 1–10 (1 = no symptoms; 10 = most severe). Dumping indicated by percentage of patients who experienced symptoms

estimated that up to 20% of patients with large hiatal hernias have a foreshortened esophagus[15–17] and that as many as 7% to 14% of these patients require a lengthening procedure in addition to fundoplication.[16,18–20]

There are several options to deal with the short esophagus. They range from aggressive mobilization of the mediastinal esophagus, a Collis gastroplasty, leaving the fundoplication in an intrathoracic position, and/or esophageal resection.[20–25] The approach that is most commonly used is the creation of a neoesophagus from the proximal gastric cardia with a Collis gastroplasty or stapled-wedge gastroplasty.[20–21] Reports have shown the Collis–Nissen procedure to be effective in up to 88% of patients, relieving preoperative symptoms and reducing the likelihood of recurrent herniation.[22–23] However, this procedure is associated with many adverse side effects including dysphagia, slowed esophageal emptying, persistent acid reflux and esophagitis, and delayed gastric emptying in up to 36% of patients.[16,23–24,26] Moreover, a Collis gastroplasty is technically difficult to perform laparoscopically, and it adds to the risk of the operation because it requires resection of a portion of the GI tract. The first method described for laparoscopic use utilized a circular stapler to remove a circle of about 2 cm of stomach and then a linear stapler to separate part of the fundus from the lesser curvature. This is difficult, time consuming, and expensive.[20] As a result, modifications have followed. Swanstrom, for example, described using a linear endoscopic stapler via a right thoracic incision. However, the procedure is still difficult, adds substantial pain, and requires a tube thoracostomy.[16] The most recent modification is a stapled-wedge gastroplasty, described by Terry.[21] While this procedure reduces operation time, similar complications exist as with other gastroplasty techniques. In addition to the time and complexity and the risk involved with division or resection of a portion of the stomach, this operation creates a new "tube" of esophagus formed with stomach and lined with gastric mucosa that secretes acid.

By contrast, a vagotomy is technically a very simple procedure once the esophagus has been completely mobilized. In many of these patients, one or both vagi often act as a point of tension, suspending the GEJ. When we consider performing a vagotomy to lengthen the esophagus, we pay close attention to the amount of tension the vagus is providing. When it is not causing upward traction, we do not divide it. However, in most cases, it does, and in these cases when the nerve is divided, the gastroesophageal junction drops nicely into the abdomen.

The Impact of Vagotomy

The most common reported side effects of vagotomy are symptoms of delayed gastric emptying (e.g., nausea, bloating, early satiety), diarrhea, and dumping syndrome. The patients who had vagotomy in this study did not have more severe symptoms of delayed gastric emptying when compared with those without a vagotomy, though most of our patients had a unilateral vagotomy, and others have shown that unilateral vagotomy is associated with normal gastric emptying.[27] While performance of a bilateral vagotomy (which was done in a small number of our patients) seemed to consistently be associated with the occurrence of at least occasional dumping, unilateral vagotomy does not seem to increase the incidence of dumping symptoms. Moreover, patients experienced improvement in presenting symptoms in more than 90% of cases, statistically similar to results from operations without vagotomy. This raises the question: why do these results seem to go against surgical dogma that suggests that vagotomy inevitably leads to impaired gastric emptying?

Studies have shown that vagotomy whether performed for the treatment of peptic ulcer disease or in conjunction with gastric or esophageal resection for other problems can produce significant side effects, including delayed gastric emptying and dumping.[28–34] In contrast, studies have shown that parietal cell vagotomy or highly selective vagotomy during Nissen fundoplication is not associated with increased side effects, morbidity, or mortality.[35–37] It may be that the difference in outcome may be attributed to the underlying disease rather than to the vagotomy. For example, peptic ulcer disease often leads to gastric and duodenal inflammation and scarring that may more easily compromise the emptying of the stomach and that may cause other motility dysfunction in the rest of the gut. Gastric or esophageal resection distorts the gastric anatomy and may also disturb the migrating motor complex.[32,38] These factors may lead to delayed gastric emptying and

dumping syndrome more than vagotomy itself. On the other hand, the Nissen fundoplication usually results in increased rate of gastric emptying (owing to the loss of receptive relaxation by the fundus), something that may counteract the effects of vagotomy. It is also possible that the extensive dissection required to repair a recurrent hernia or a large paraesophageal hernia may impose changes in the motility of the stomach by itself which minimize the differences (clinically) between patients who had just that dissection and those who had that dissection as well as vagotomy.

We did not perform a gastric emptying procedure of any sort at the time of the vagotomy. Our strategy was to wait until we saw if symptoms of impaired gastric emptying developed before doing so. None of our patients required the addition of a gastric emptying procedure in the follow-up period. Other recent studies have questioned the need for gastric emptying procedures with vagotomy. For example, others have suggested that pylormyotomy and pyloroplasty do not significantly improve outcome after esophageal resections.[39–40] Gastric emptying procedures are certainly associated with an increase in the prevalence of dumping syndrome.

We included objective measures of gastroesophageal reflux disease (GERD) postoperatively, as they are the best measures of the efficiency of fundoplication. While the majority had normal studies, about 40% did not. We think this finding highlights two things. First, the difficulty in maintaining a "perfect" fundoplication in the setting of a PEH or when revising a failed fundoplication; second, only a third of our patients came back for pH monitoring, and almost uniformly did so when they were having problems (like recurrent GERD symptoms). Therefore, we think this prevalence of recurrent GERD detected by pH monitoring is likely an over representation of the entire cohort.

There are potential limitations of our study. As we have discussed, we did not quantify the increased esophageal length obtained with vagotomy. However, each intentional vagotomy was performed for an esophagus with less than 2 cm of intraabdominal length, and in all cases, at least 3 cm existed after this maneuver. The groups that we compared are not perfectly matched. However, those patients that required a vagotomy are more likely to have more complex anatomy, making it more difficult to control their disease. The fact that the vagotomy group had similar outcomes favors the strategy of vagotomy. Also, it could be argued that some of the patients in the "no vagotomy" group had unrecognized vagus nerve injury, and this could explain why there was no difference in outcomes. We would argue that it is only the overt, recognized, or intentional vagotomy that matters clinically. The question is: when faced with the potential need to knowingly cut a vagus nerve in order to lengthen the esophagus, does doing so negatively affect patient outcomes? Our study suggests that the answer is no.

Conclusions

Reestablishing the intraabdominal esophagus is important during recurrent hiatal hernia or large PEH repair. We have shown that when other maneuvers fail (thorough dissection and mobilization), a vagotomy provides additional length in the majority of the patients. This can be done without significant adverse consequences. While bilateral vagotomy usually results in dumping syndrome and should be avoided if possible, unilateral vagotomy does not appear to lead to a higher rate delayed gastric emptying, dumping syndrome, or other side effects commonly believed to be caused by vagotomy.

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The Resection of the Azygos Vein — Necessary or Redundant Extension of Transthoracic Esophagectomy?

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Abstract Due to the increasing use of minimally invasive techniques, some authors have questioned the necessity to dissect the azygos vein as part of the en-bloc esophagectomy in patients with esophageal cancer. This study investigates the nodal clearance associated with resection of the azygos vein. Ninety-two patients with esophageal carcinoma were included in this prospective analysis. In all patients, a standard transthoracic en-bloc esophagectomy was performed including the resection of the azygos vein from the superior vena cava to the level of the diaphragm. After resection, the azygos vein with its adjacent connective tissue was separated from the tubular esophagus. The separated azygos vein specimen was histopathologically examined for the presence of lymph nodes (LN) and possible nodal metastasis. A total of 2,778 LN with a mean of 30.2 LN for each patient were resected. In 60 patients, 216 of 1,666 mediastinal LN (13.0%) were located along the azygos vein. Seven of 39 pN1 patients (17.9%) had LN metastases in the separated azygos vein specimen. In these seven patients, a total of 23 metastatic nodes were detected along the azygos vein. LN metastases along the azygos vein are too frequent to neglect their existence. Therefore, standard en-bloc esophagectomy including dissection of the azygos vein should not be abandoned irrespective of the surgical approach.

Keywords Esophageal carcinoma · Transthoracic esophagectomy · Azygos vein · Lymph node metastasis

Introduction

Transthoracic en-bloc esophagectomy is the standard oncologic procedure for esophageal carcinoma because it allows a radical resection of the primary tumour and an extensive mediastinal lymphadenectomy.[1–4] For this transthoracic procedure, the Dutch prospective trial could demonstrate an ongoing trend towards better 5-year survival compared with limited transhiatal resection.[5,6] In many esophageal centres, the transthoracic esophagectomy includes the en-bloc resection of the azygos vein from the diaphragmatic level to the superior vena cava with dissection of multiple intercostal veins and preservation of the intercostals arteries.[2,3]

Since the first publications of minimally invasive transthoracic esophagectomies, an increasing number of specialized centres take advantage of this approach.[7–10] However, the thoracoscopic approach is still a demanding and complex surgical procedure and it has been suggested to resign on the azygos vein resection in order to facilitate esophagectomy.[7,10,11]

Therefore, this prospective study was done to investigate whether the resection of the azygos vein increases oncologic radicality in terms of nodal clearance.

Methods

Study Population

A total of 92 patients with esophageal carcinoma were included in this prospective evaluation conducted from October 2003 to December 2006. Seventy-four patients

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were male (80.4%) and 18 patients were female (19.6%). The mean age was 61.4 years (range 34 to 79 years). Sixty-one patients (66.3%) had an adenocarcinoma and 31 patients (33.7%) had a squamous cell carcinoma. Because of a locally advanced tumour, 54 patients (58.7%) received neoadjuvant radiochemotherapy according to a standardized protocol.[12]

The local Institutional Review Board (IRB) approved this prospective study and indicated that individual consent could be waived because individual patients were not identified.

Surgery

All patients underwent a transthoracic en-bloc esophagectomy with two-field lymphadenectomy of the mediastinal and abdominal compartment. As an integrated part of this surgical procedure, the azygos vein with multiple intercostals veins was dissected closely to the superior vena cava and just above the level of the diaphragm. Intercostal arteries were intended to be preserved. The surgical procedure always included the resection of the thoracic duct which was ligated above the level of the diaphragm very close to the distal dissection margin of the azygos vein. Reconstruction was done with a high intrathoracic stapled esophagogastrostomy.[3,13] In 89 patients, this was performed as a two-stage procedure with initial laparoscopic mobilization of the gastric conduit followed by the transthoracic esophagectomy and reconstruction 5 days later, as recently described elsewhere.[13] Another three patients underwent a one-stage procedure with open abdominal gastroplasty followed by transthoracic esophagectomy and reconstruction.[3]

In 89 patients (96.7%), a complete resection of the tumour could be achieved (R0 resection). Specific complications related to azygos vein resection were not recorded.

Pathology

The resected lymph nodes of the abdominal compartment were classified according to the Japanese Research Society for Gastric Cancer.[14] The laparoscopic en-bloc abdominal lymphadenectomy comprised the lymph nodes of compartment I with groups 1, 2 and 3 (gastric cardia, gastric fundus, lesser curvature) as well as compartment II with groups 7, 8 and 9 (gastric and hepatic artery, coeliac trunc).

The lymph nodes of the mediastinal compartment were classified according to the Japanese Society of Esophageal Cancer.[15] The azygos vein with its attached connective tissue comprised the lymph node group numbers 108 and 110 which were defined as those located between the azygos vein, the thoracic aorta and the tubular esophagus. As demonstrated in Figs. 1 and 2, the azygos vein with the adjacent connective tissue was separated from the tubular esophagus immediately after removing the complete specimen (Figs. 1 and 2). Then, the separated azygos vein was divided into an upper and lower part at the level of the bifurcational lymph nodes (Fig. 3). This preparation was done in the operating theatre with a senior surgeon (W.S.) performing the operation.

After separation and numbering, the lymph nodes were fixed in formaldehyde and embedded in paraffin. After equatorial sectioning of the lymph nodes at six levels, routine staining with hematoxylin and eosin as well as periodic acid-Schiff (PAS) was performed to examine the nodes histologically for the presence or absence of metastatic disease (pN0/pN1).

The pT and pN stage distribution according to the UICC classification is displayed in Table 1.[16]

Statistics

Descriptive analysis was used to describe data. The prevalence of lymph node metastases was analysed by the Wilcoxon test, and ordinal data by the X^2 test. $P<0.05$ was considered significant.

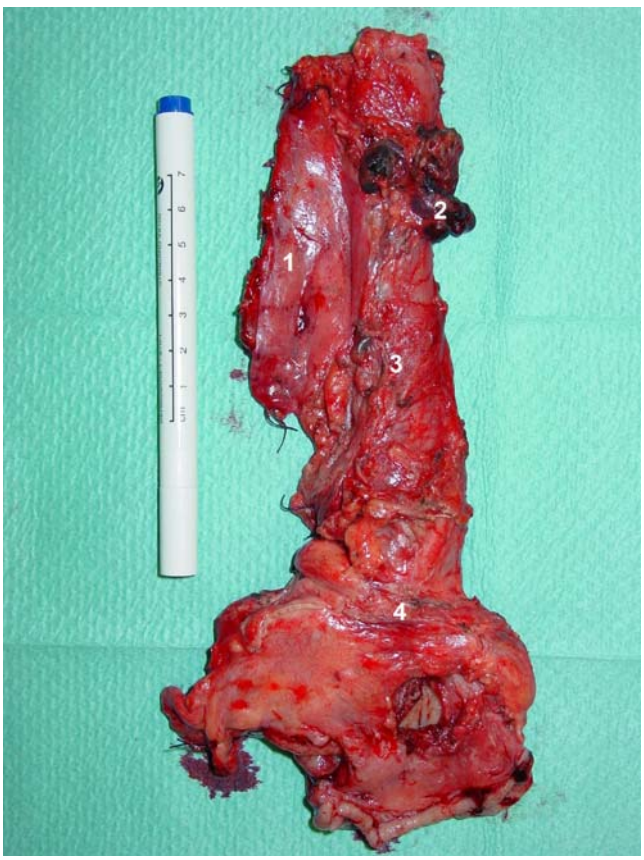

Figure 1 Postoperative preparation of the resected specimen of an esophageal carcinoma (*1* azygos vein, *2* bifurcational LN, *3* tubular esophagus, *4* gastroesophageal junction).

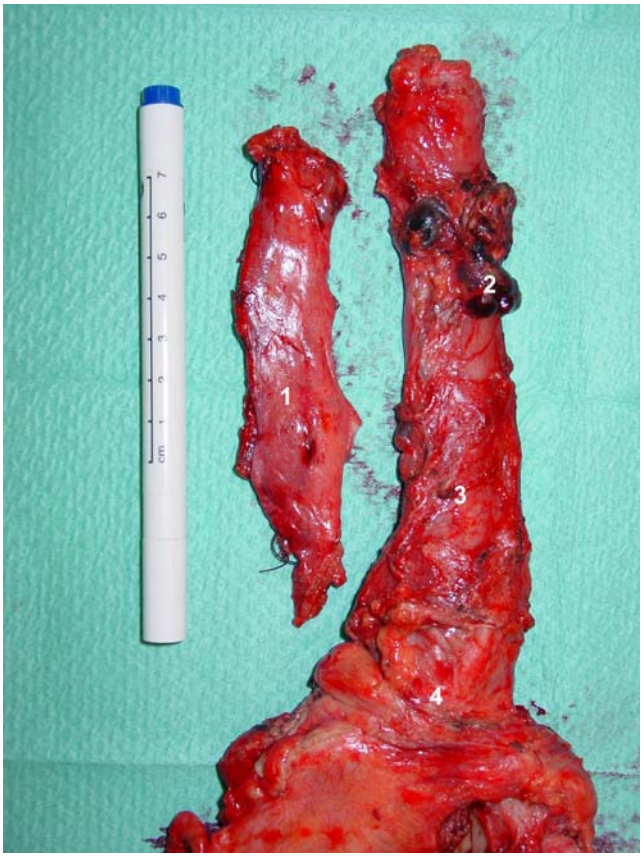

Figure 2 Separation of the azygos vein from the tubular esophagus (*1* azygos vein, *2* bifurcational LN, *3* tubular esophagus, *4* gastroesophageal junction).

Results

In the 92 patients, a total of 2,778 LN with a mean of 30.2 LN for each patient were resected (range 11 to 67). A total of 1,112 LN were located in the abdominal compartment (mean 12.1 LN per patient; range 0–32). A total of 1,666 LN was dissected from the mediastinal compartment (mean 18.1 LN per patient; range 3–45). The mean number of LN harvested in 53 patients who underwent preoperative radiochemotherapy was lower compared to those 39 patients without neoadjuvant therapy though not statistically significant (mean of 28.8 LN vs. mean of 32.2 LN, $p<0.28$). In 39 of 92 patients (42.4%), LN metastases were detected. Sixteen of the 39 patients (41.0%) had abdominal and mediastinal LN metastases, whereas 11 patients had only abdominal and 12 patients only mediastinal LN metastases.

Of the 1,666 LN harvested from the mediastinal compartment 216 LN (13.0%) were located along the azygos vein (mean 2.4 LN per patient; range 0–14 LN). In 60 of the 92 patients (65.2%), LN were histopathologically detected in the separated azygos vein specimen. Thirty-two patients (34.8%) had no LN found along the azygos vein. Table 2 demonstrates the frequency of azygos vein LN. Seven of 92 study patients (7.6%) and of 39 pN1 patients (17.9%) had metastatic LN along the azygos vein. Four patients had one metastatic LN, another three patients 3, 4 and 12 metastatic LN, respectively. Twenty-three of the 216 LN along the azygos vein (10.6%) demonstrated metastatic disease. Thirteen of these 23 metastatic LN (56.5%) were located in the upper part of the azygos vein and 10 in the lower part (43.5%).

Discussion

Various studies have investigated the pattern of nodal metastasis in esophageal cancer and could demonstrate a bidirectional nodal spread to the cervical and abdominal compartment.[1,17–21] In the abdomen, the lymphatic spread is directed along the lesser curvature of the stomach and the left gastric artery to the coeliac trunc. In the upper mediastinal and cervical compartment, LN metastases are predominantly detected along the laryngeal recurrent nerves. This general pattern of nodal disease is irrespective of the tumour localization and the tumour histology. In

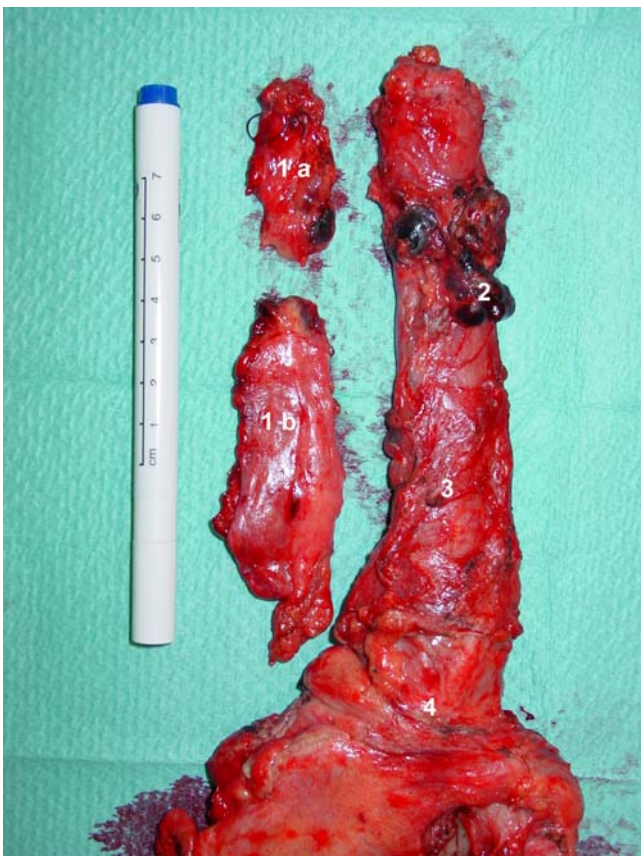

Figure 3 Dissection of the azygos vein into an upper and lower part (*1a* upper azygos vein, *1b* lower azygos vein, *2* bifurcational LN, *3* tubular esophagus, *4* gastroesophageal junction).

Table 1 Histopathological Data of 92 Patients with Esophageal Carcinoma

Histopathological Data	Values
pT stage	
pTx	*N*=2
ypT0	*N*=13
(y)pT1	*N*=17
(y)pT2	*N*=15
(y)pT3	*N*=45
pN stage	
pN0	*N*=53
pN1	*N*=39
Number of resected LN	2,778 LN (mean 30.2 LN)
Abdominal compartment	1,112 LN (mean 12.1 LN)
Mediastinal compartment	1,666 LN (mean 18.1 LN)
53 patients with RTx/CTx	1,524 LN (mean 28.8 LN)
39 patients without RTx/CTx	1,254 LN (mean 32.2 LN)

order to perform a formal three-field or extended two-field dissection all these areas have to be subject of nodal clearance.

Though not statistically significant, the present study confirms previous data that the number of resected LN is less in patients with neoadjuvant radiochemotherapy.[19,22] Therefore, the incidence of LN along the azygos vein before treatment is expected to be even higher. This means that multimodal treatment has no impact on the conclusion drawn from these data.

The increasing use of minimally invasive techniques in the field of oncologic esophageal surgery has questioned the necessity of an extensive mediastinal lymphadenectomy.[10,11] This is due to the fact that, in particular, the lymphadenectomy is complicating the minimally invasive esophagectomy. The thoracoscopic lymphadenectomy of the tracheal bifurcation, along the right and left recurrent nerve in the upper mediastinum and the azygos vein are challenging surgical procedures. However, most esophageal surgeons agree that the type of oncologic dissection should not be influenced by the surgical approach. From this point of view, the extent of lymphadenectomy should not differ for the open or minimally invasive approach.

Table 2 Frequency of LN Detected in the Separated Azygos Vein Specimen

Number of Patients	Percentage of Patients	Number of Detected LN Along the Azygos Vein
32	34.8	0
17	18.5	1
9	9.8	2
12	13.0	3
6	6.5	4
4	4.3	5
5	5.4	6
3	3.3	7
1	1.1	9
1	1.1	13
2	2.2	14
92	100	216 LN (Total)

There are two theoretical advantages of the standard transthoracic en-bloc esophagectomy: first, the safety margin to the primary tumour is increased and therefore the R0 resection rate; secondly, the mediastinal lymphadenectomy is more extensive and therefore the clearance of metastatic nodes.

The main purpose of this morphological study was to investigate the frequency of nodal metastases along the azygos vein and its attached connective tissue. This analysis intended to describe the difference of harvested lymph nodes between the standard en-bloc esophagectomy with azygos vein dissection and a simple dissection of the tubular esophagus. The authors are well aware of the fact that a substantial portion of lower mediastinal connective tissue can be resected without performing a radical en bloc esophagectomy including azygos vein dissection. However, data on the prevalence of LN metastasis may help to decide whether en-bloc dissection of the tubular esophagus with the adjacent mediastinal tissue is a necessary oncologic procedure or not. It was not the aim of the study to analyse the impact of azygos vein resection on staging and survival. These data can be only obtained from a prospective randomized trial. Despite the methodological limitations, two results of this study should be emphasized. First, the majority of patients do have LN which are located in the connective tissue closely to the azygos vein. Secondly, if patients develop nodal metastases (pN1), almost every fifth patient demonstrate nodal involvement along the azygos vein. Most of these LN will be missed if the azygos vein is not dissected and only the tubular esophagus is resected.

From the authors' point of view, this frequency is too high to be oncologically neglected. However, these results are in contrast to a recently published study in which 15 human cadavers underwent en-bloc esophagectomy with azygos vein dissection.[11] The average number of dissected LN located along the azygos vein was only 0.67 LN per patient. Due to the study design, no comments on the frequency of nodal metastasis could be made. The authors of the cadaver study conclude that the preservation of the azygos vein in transthoracic esophagectomy is justified.

With respect to this upcoming discussion on the dissection or preservation of the azygos vein, it has to be kept in mind that the major reason for performing a transthoracic procedure at all is the possibility of an extensive mediastinal lymphadenectomy.[1,2,23] In addition, there is mounting evidence that extensive nodal clearance of the transthoracic procedure is associated with a survival

benefit compared to the transhiatal approach which does not allow the dissection of the azygos vein and the surrounding connective tissue.[5,6]

Disadvantages of the azygos vein resection are the difficult and sometimes time consuming surgical preparation of the posterior mediastinum with dissection of the intercostals veins and preservation of the anatomically close intercostals arteries. Cases of ischemic spinal cord injury with severe neurologic deficits have been reported following transthoracic en-bloc esophagectomy.[24] In addition, severe postoperative bleeding from the dissected hemiazygos vein is also possible. None of these events could be observed in this series of patients. On the other hand, it has been reported that the preservation of the azygos arch can cause a strangulation of the gastric conduit.[25]

Conclusion

The frequency of LN metastases along the azygos vein supports the necessity of its dissection as integrated part of a standard transthoracic en-bloc esophagectomy. The possible advantage of an extensive nodal clearance should not be resigned by altering the surgical approach from an open to a minimally invasive technique.

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Treatment of Thoracic Esophageal Anastomotic Leaks and Esophageal Perforations with Endoluminal Stents: Efficacy and Current Limitations

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Abstract
Background Intra-thoracic esophageal leakage after esophageal resection or esophageal perforation is a life-threatening event. The objective of this non-randomized observational study was to evaluate the effects of endoluminal stent treatment in patients with esophageal anastomotic leakages or perforations in a single tertiary care center.
Methods Thirty-two consecutive patients with an intrathoracic esophageal leak, caused by esophagectomy (n=19), transhiatal gastrectomy (n=3), laparoscopic fundoplication (n=2), and iatrogenic or spontaneous perforation (n=8), undergoing endoscopic stent treatment were evaluated. Hospital stay, mortality and morbidity, sealing rate, extraction rates, complications, and long-term effects were measured.
Results Median time interval between diagnosis and stent treatment was 3 and 5 days, respectively. Eighteen patients had futile surgical closure of the defect before stenting, while in 14 patients, stent placement was the primary treatment for leakage. Stent placement was technically correct in all patients. Functional sealing was achieved in 78%. Mortality was 15.6%. Stent extraction rate was 70%. Overall method-related complications occurred in nine patients (28%).
Conclusions Implantation of self-expanding stents after esophageal resection or perforation is a feasible and safe procedure with an acceptable morbidity even if used as last-choice treatment.

Keywords Esophageal leak · Esophageal perforation · Endoluminal stent · Endoscopy · Esophageal surgery

Introduction

Anastomotic leaks after esophagectomy occur in 4% to 17% of cases. These leaks are the major source of mortality and morbidity, especially when leakage follows an intra-thoracic anastomosis.[1–5] A similar life-threatening situation emerges in esophageal perforations, especially when they are not treated immediately after onset.[6–9] A standardized therapy regimen has not yet been established. Some investigators suggest aggressive surgical reexploration and repair or even disassembly of the anastomosis, whereas others recommend conservative treatment using total parenteral nutrition, perianastomotic drainage with chest drains, or computed tomography (CT)-guided percutaneous drainage of abscesses and broad spectrum antibiotics.[6,9–14] However, surgical treatment is often associated with high morbidity and mortality,[1–3,11,15] and conservative treatment is only indicated in selected patients with asymptomatic and minimal anastomotic leaks.[15,16] In recent years, several

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reports of successful treatment of esophageal anastomotic leakages and perforations with endoscopically applied endoluminal stents have been published.[17–27] However, these reports mostly reflect small series with heterogenous patient selections, a wide variety of stent types, and different management concepts. Therefore, general recommendations and guidelines for treatment with endoluminal stents have not yet been established.[6,11,12]

The aim of the present study was to evaluate the effects of endoluminal stent treatment in a patient group with only thoracic anastomotic leakages or perforations of the esophagus. With regard to other series, the rates of success and complication rates are discussed, and current limitations of endoscopic stent treatment are analyzed. Follow-up examinations were performed to assess the long-term effect of endoscopic stent treatment.

Material and Methods

A non-randomized observational study was performed between 1999 and 2006 on all consecutive patients treated with a covered self-expanding endoluminal metal stent by a single experienced endoscopist (D.T., >200 stent implantations) after the diagnosis of an anastomotic leakage after thoraco-abdominal esophagectomy with an intrathoracic esophagogastrostomy or perforation of the thoracic esophagus if the following criteria were fulfilled:

- Detection of the defect by upper GI-tract endoscopy with simultaneous application of water-soluble contrast dye over the endoscope
- Extravasation of contrast dye into the mediastinum, pleural, or abdominal cavity
- Extent of the defect less than 2/3 of the circumferential anastomosis
- Vital appearance of the mucosa
- Clinical course characterized by systemic inflammation (leukocytosis, elevation of CRP, fever, deterioration of general condition), leading to a stay in the intensive care unit for at least 1 week or at least 2 weeks on the observation ward

Patients with an ischemic gastric tube and avital anastomosis were excluded because they were supposed not to be suitable for endoscopic stent treatment (Fig . 1). In all other patients, stent implantation was performed under analgo-sedation using midazolam and/or propofol or under general anesthesia in intubated patients. Informed consent for this procedure was obtained from all patients or their relatives. The localisation of the esophageal defect was

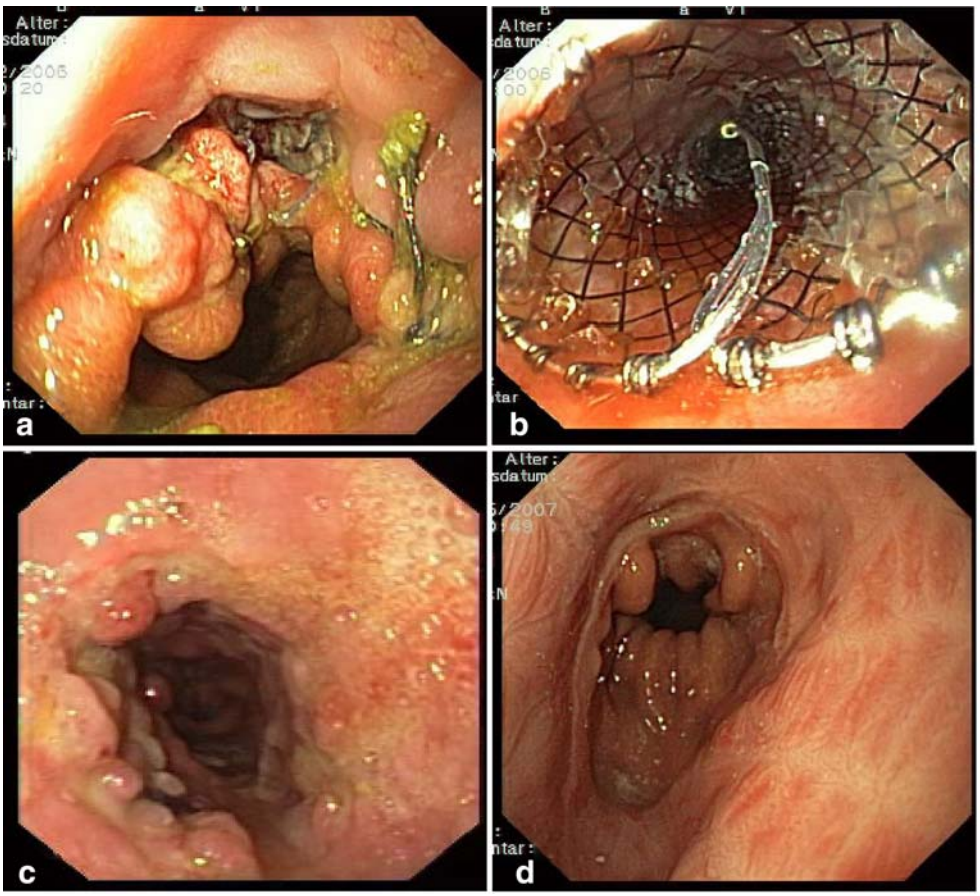

Fig. 1 Example of endoscopic stent treatment in a patient with anastomotic leakage after abdomino-thoracic esophageal resection with gastric tube reconstruction (hand-sutured anastomosis). **a** The leak within the anastomotic line after endoscopic rinsing with saline appears at 12:00. **b** Endoscopic view after stent implantation (10 cm, Ultraflex©, 28/23 mm). The loop for extraction appears at 6:00. **c** The anastomosis after stent extraction 2 months after implantation. The former leak is entirely closed. Granulomatous tissue indicates the uncovered part of the stent. **d** The esophago-gastric anastomosis on control endoscopy 3 months after stent extraction. There are no signs of stenosis.

indicated on the skin surface with an opaque marker for consecutive fluoroscopy. A stiff guide wire (Eder Puestow wire, MTW Endoscopy, Wesel, Germany) was then inserted into the duodenum and a 10-cm long (7 cm covered), 23-mm-(shaft) and 28-mm-wide (proximal throat) nitinol stent (Ultraflex® Boston Scientific Corp., Natick, MA, USA) was released under fluoroscopic control, having the leakage localized in the middle of the stent. In case of incomplete stent expansion, spontaneous expansion was awaited and control endoscopy was performed the next day. Perianastomotic and pleural drainage was obtained by existing chest drains or by insertion of drains operatively or under CT guidance. All patients received broad spectrum antibiotics. Enteral nutrition was initiated after stent implantation using a gastric probe or a triluminal probe (Fresenius Kabi, Bad Homburg, Germany) in patients with upper intestinal paralysis after having controlled successful sealing of the leak. Oral feeding was started after weaning and extubation as long as the patients showed sufficient vigilance and ability to swallow. Stent extraction was performed after 4–6 weeks in all patients with sufficient healing process. This was defined as a lack of clinical symptoms of residual infection with normalization of serum markers and regular results in endoscopic and radiological control examinations.

During the observation period, 32 consecutive patients (22 men and 10 women) were treated with an endoluminal stent (Tables 1 and 2). No patients treated with endoluminal stents were excluded from this study. There were 22 anastomotic leakages after esophagectomy (n=19) or transhiatal gastrectomy (n=3) and ten perforations (laparoscopic fundoplication, n=2; four Boerhaave syndrome; or four iatrogenic ruptures). Nine patients (fundoplication, n=2; iatrogenic rupture, n=3; Boerhaave syndrome, n=4) were transferred to our department for further treatment. The underlying disease was malignant in 23 patients (esophageal adenocarcinoma, n=13; esophageal squamous carcinoma (n=7); gastric MALT-lymphoma (n=1); breast cancer (n=1); or bronchial carcinoma, n=1), and 19 patients of those were treated with curative intention. Five patients had neoadjuvant radiation and/or chemotherapy. Mean age was 61.4±9.4 years (44–81). Median interval between operation and diagnosis of anastomotic leakage was 10 (2–49) days. Only 7 of 24 anastomotic leakages were diagnosed within the first postoperative week. In patients with esophageal perforation, median time interval before diagnosis in our department was 4 (0–24) days. Median time interval between diagnosis of leakage and stent treatment was 3 days (0–611) in patients with anastomotic leakages and 5 days (0–33) in patients with esophageal perforations. One patient had a fistula between the esophagus and the bronchial system for approximately 2 years (611 days) after cancer-related esophagectomy without any signs of recurrent disease. However, in this patient, the stent did not succeed in closing the fistula, and the patient died approximately 1 year after stent implantation due to chronic bronchopneumonia.

At the time of first endoscopy, the mean leakage diameter was 7.3±5.5 mm (1–22 mm, median 5 mm) as measured with a spread biopsy forceps as reference, showing a necrotic mucosa with purulent secretion surrounding the borders of the leakage and into the wound cavity in nearly all patients. Contrast dye application over the endoscope showed a paravasation in all patients, pouring into the mediastinum (n=18), the pleural cavity (n=10), the abdomen (n=2), or into the tracheo-bronchial system (n=2).

In 18 patients (56%), a futile surgical closure of the defect was performed before stent therapy, consisting of oversewing and drainage (n=12), anastomotic resection and redoing of the anastomosis (n=5), or esophageal resection with construction of a gastric tube (n=1). In 14 patients, endoscopic stent placement was the primary treatment to seal the leakage. In ten of these patients, no further treatment was necessary, whereas in the remaining four, surgical or interventional thoracal drainage was performed before stenting.

All clinical parameters were documented prospectively using Microsoft Excel and analyzed descriptively. The main parameters were hospital lethality and morbidity, successful sealing of the esophageal leak, method-related complications such as stent migration or development of stenoses, onset of oral nutrition, and length of hospital stay. Patients with a benign underlying disease had clinical and endoscopic follow-up examinations until they were clinically asymptomatic. Those patients with esophageal carcinoma were followed in our oncological unit and received clinical and endoscopic examinations following a routine schedule.

Results

Stent placement was technically correct in all patients, resulting in a complete bridging of the defect at the time of endoscopic control examination. Complete functional sealing of the lesion was achieved in 25 patients (78%) but was delayed in seven patients by penetrating drains (n=3), strong reflux of gastric fluids (n=1), early stent dislocation (n=1), or incomplete stent expansion (n=2). After prompt retraction of the drains, decompression of the stomach, or stent correction, these patients showed no further extravasation upon subsequent radiological control examination.

In seven patients (five anastomotic leakages, two perforations), a definitive functional closure of the defect could not be achieved by stent application. However, in five of these patients, a definitive closure of the defect was

Table 1 Patient Demographics

Pat.	Age/sex	Underlying disease	Etiology[a]	Operative procedure[a]	Fistula location[b]
Demographics of patients with anastomotic leakages					
1	50-m	pT2N0 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
2	50-m	ypT2N0 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
3	67-m	pT3N1 adenocarcinoma		Abdomino-thoracic esophagectomy	Bronchus
4	66-m	pT2N0 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
5	52-m	pT1N0 squamous carcinoma		Abdomino-thoracic esophagectomy	Mediastinum
6	64-m	pT3N0 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
7	50-m	ypT2N1 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
8	53-m	pT3N1 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
9	59-f	pT2N0 adenocarcinoma		Abdomino-thoracic esophagectomy	Pleura
10	63-m	pT2N1 adenocarcinoma		Abdomino-thoracic esophagectomy	Pleura
11	67-m	ypT1N0 squamous carcinoma		Abdomino-thoracic esophagectomy	Mediastinum
12	49-f	pT1N0 adenocarcinoma		Abdomino-thoracic esophagectomy	Mediastinum
13	58-m	ypT3N1 squamous carcinoma		Abdomino-thoracic esophagectomy	Mediastinum
14	50-f	ypT1N0 squamous carcinoma		Abdomino-thoracic esophagectomy	Trachea
15	62-f	pT1N0 squamous carcinoma		Abdomino-thoracic esophagectomy	Pleura
16	52-m	ypT1N0 squamous carcinoma		Abdomino-thoracic esophagectomy	Pleura
17	77-f	pT3N1 squamous carcinoma		Abdomino-thoracic esophagectomy	Pleura
18	71-f	pT3N1 adenocarcinoma		Transhiatal esophagectomy	Pleura
19	52-m	Esophageal diverticulum		Transhiatal esophagectomy	Pleura
20	69-m	Perforated MALT-lymphoma after HTX		Transhiatal gastrectomy	Abdomen
21	73-m	pT2N1 adenocarcinoma		Transhiatal gastrectomy	Mediastinum
22	63-m	pT4N1 adenocarcinoma		Transhiatal gastrectomy	Mediastinum
Demographics of patients with esophageal perforations					
23	44-f	GERD	Lap. fundoplication		Abdomen
24	65-f	GERD	Lap. fundoplication		Mediastinum
25	60-m	-	Boerhaave		Mediastinum
26	81-m	-	Boerhaave		Mediastinum
27	76-f	-	Boerhaave		Pleura
28	66-m	-	Boerhaave		Mediastinum
29	73-f	Cardiac (TEE), breast cancer	Iatrogenic		Mediastinum
30	65-m	Cardiac (TEE)	Iatrogenic		Pleura
31	60-m	pT3N1 bronchial ca.	Iatrogenic		Pleura
32	58-m	Thoracoscopic decortication after lung abscess after NTX	Iatrogenic		Pleura

Lap. fundoplication laparoscopic fundoplication, *TEE transesophageal echocardiography*, *GERD* gastroesophageal reflux disease, *HTX* orthotopic heart transplantation, *NTX* heterotopic kidney transplantation

[a] Event leading to leakage or perforation

[b] Cavity to which the esophageal leak had contact to

Table 2 Patient Therapeutic Outcomes

Pat.	Interval to stent treatment (d)[a]	Stent-type	Primary sealing[b]	Further treatment	Hospital stay (d)[c]	Interval to stent-extraction (d)[d]
Results of patients with anastomotic leakages						
1	19	Nitinol	Pos.	–	37	219
2	14	Nitinol	Pos.	Esophago-jejunostomy	44	13
3	27	Nitinol	Pos.	Bronchial and aortic stent	102	94
4	16	Nitinol	Neg.	Fibrin glue and clipping	*	6
5	611	Nitinol	Neg.	Stent exchange	124	86
6	28	Nitinol	Pos.	–	46	-
7	8	Nitinol	Pos.	–	69	62
8	10	Nitinol	Pos.	–	13	-
9	11	Nitinol	Pos.	–	22	144
10	9	Nitinol	Pos.	–	34	41
11	13	Nitinol	Pos.	Interventional drainage	21	37
12	8	Nitinol	Neg.	Reanastomosis	70	4
13	24	Nitinol	Pos.	Fibrin glue	39	25
14	27	Nitinol	Neg.	Rethoracotomy and fistula closure	15	-
15	14	Flex-stent	Pos.	–	43	35
16	5	Nitinol	Pos.	–	63	426
17	27	Nitinol	Pos.	Stent in stent	80	-
18	127	Nitinol	Pos.	–	19	-
19	11	Nitinol	Pos.	Rethoracotomy, pneumolysis, drainage	59	52
20	20	Choo	Neg.	–	*	-
21	4	Nitinol	Pos.	Fibrin clue and clipping after stent extraction	31	64
22	14	Nitinol	Pos.	–	98	59
Results of patients with esophageal perforations						
23	12	Nitinol	Pos.	–	7	51
24	57	Nitinol	Neg.	Colonic interponate	196	8
25	33	Nitinol	Pos.	–	108	21
26	2	Nitinol	Pos.	–	20	-
27	6	Nitinol	Neg.	Abdomino-thoracic esophagectomy	48	13
28	5	Nitinol	Pos.	Thoracotomy and drainage	37	45
29	2	Flex-stent	Pos.	Thoracotomy and drainage	*	–
30	36	Nitinol	Pos.	–	*	–
31	0	Nitinol	Pos.	–	50	–
32	12	Nitinol	Pos.	–	115	–

Neg. negative, *Pos*. positive, *asterisk* death in ICU

[a] Interval from diagnosis of leakage until stent implantation in days

[b] Primary sealing of the leakage or perforation after stent implantation as detected by radiological control examination

[c] Hospital stay after stent implantation in days

[d] Interval between endoscopic stent implantation and stent extraction in days

achieved either by consecutive operation (two esophagectomies with colonic interponate or gastric conduit, one resection and redoing of the anastomosis, one oversewing of the defect) or ongoing conservative treatment on an outpatient basis (one patient with a stable fistula), and two patients received stent in stent placement.

Total mortality in our patients with esophageal leakage or perforation was 15.6% (five of 32 patients) despite successful closure of the esophageal leakage in three of the five. Two of the non-surviving patients developed perpetuating sepsis (one with successful closure and one with persistent leakage; Table 3), and in two patients with advanced metastatic disease intensive care, therapy was discontinued. Another patient died after a fulminant pulmonary embolism resulting from thrombosis of the subclavian vein as a complication of long-term parenteral nutrition. The fifth patient died approximately 1 year after futile stent treatment due to chronic bronchopneumonia as described above. Bleeding did not occur in this study. The stent dislocation rate was 6% (one Choo-Stent, one Nitinol;

Table 3 Complications After Esophageal Stent Implantation

Complication	Number of patients (%)
Leak persistence	7 (22%)
Stent migration	2 (6%)
Enduring Sepsis	2 (6%)
Pulmonary embolism	1 (3%)
Mucosal tear after extraction	4 (12.5%)
Stenosis	3 (9%)

In total, in nine of 32 patients different stent-related complications occurred during the entire treatment period. The overall method-related complication rate was 28.1%.

Table 3). Mean duration of intensive care treatment was 18.5±22.6 (1–102) days, with 10.3±12.9 (1–52) days of invasive mechanical ventilation. This was followed by a mean stay on the observation ward of 17.7±16.8 (1–82) days before patients could be transferred to the regular surgical ward. Twenty-six of 32 (81%) patients stayed on the intensive care unit for at least 1 week or at least 2 weeks on the observation ward.

Enteral feeding using gastric or enteral probes was started in median 1 day after stenting (range, 0–21 days). Oral feeding with regular solid food was started in median after 22 days (range, 3–107 days).

In the 27 surviving patients, 19 individuals (70%) experienced stent extraction in our institution. Median time interval until stent extraction was 46 (range, 4–426) days. During stent extraction mucosal tears and collar emphysema occurred in three and one patients, respectively. In 1 of these patients, the mucosal tear resulted in a severe stenosis. Four patients had additional endoscopic fibrin glue application or clipping after stent extraction. In seven patients (five with anastomotic leakage and two with esophageal perforation), the stent was not removed due to fistula persistence or recurrence (n=3), extensive stent ingrowth (n=2), or severe stenosis (n=2) that was treated by stent in stent. At the last time of follow-up, in a median of 1.4 years (range, 92–1,319 days) after stent implantation, six of them had regular oral feeding, but one patient with a neurogenic swallowing disorder was still dependent on parenteral nutrition despite successful fistula closure. However, two of these patients died due to pneumonia, and one complained of strong esophageal reflux, while in two others, metastatic disease developed. One patient, who was transferred to another department 3 weeks after stenting, was lost to follow-up; thus, it is not known whether the stent was extracted. During the entire treatment, in nine patients (28.1%) stent-related complications occurred (Table 3). During the entire hospital course, 9.3±6.8 endoscopic examinations were performed. These endoscopies included, besides diagnostic and control purposes, further endoscopic interventions such as fibrin glue applications, implantations of enteral feeding tubes, APC coagulations of overgrowing granulation tissue to prepare stent extraction, and stent extraction itself. The 27 surviving patients were discharged 58 (19–253) days after primary operation or esophageal perforation.

Endoscopic follow-up was achieved in 23 patients, while four patients were lost to follow-up. Mean follow up time was 2.0 years (0.2–7.3 years). In two patients, both with esophageal perforation, stenosis occurred requiring repetitive endoscopic balloon dilatation, whereas in the remaining patients endoscopy was regular. With regard to patients with underlying malignant disease, follow-up was achieved in 16 patients, of whom ten died in a median of 1.4 years (range, 0.6–3.1 years) after stent implantation, 80% of those due to tumor progress. Six patients were still alive at the time of last follow-up, in a median 4.9 years (range, 1.2–7.3 years) after stent implantation.

Discussion

The spectrum of manifestations of intra-thoracic leakages due to anastomotic leakages or perforations ranges from clinically silent to fulminant sepsis. Therefore, appropriate treatment must be matched to the individual patient. Due to disappointing results after reoperation, management of esophageal leaks have shifted increasingly toward a more conservative approach, including endoscopic procedures such as fibrin-glue injections, clip application, and covered self-expanding metallic or plastic stents.[16–18,24,28–34] As there is still no consensus for optimal treatment, it is not surprising that, for endoscopic stent therapy, only case reports and small series with different underlying diseases have been published.[18,20,24,27,28,30,35] Our study is also limited, as it was not randomized and not conducted after a strict treatment protocol. Moreover, different causes of esophageal leakages or underlying diseases were included. However, to our knowledge, our study presents not only one of the largest series so far; we also included patients with intra-thoracic esophageal leakages only, and all stent applications were performed by a single experienced endoscopist. This may explain why, besides our extensive experience with this difficult group of patients as a centre for esophageal surgery, the technical success rate was high and the mortality rate was acceptable compared to other published stent series (Table 4). However, the comparability of patient series will unquestionably always be problematic for several reasons including infrequent occurrence of these cases and the fact that neither the extent of the leaks nor the health status was standardized in most of the studies. The mortality rate after endoscopic stent treatment was considerably lower than the mortality rates of up to 60% in patients with sole surgical reintervention as reported in the literature, although the diagnosis of the leak or perforation

Table 4 Comparison of Other Published Series

Author	Roy Choudry[20] 2001	Doniec[18] 2003	Siersema[24] 2003	Gelbmann[19] 2004	Huenerbein[17] 2004	Langer[23] 2005	Schubert[21] 2005	Johnson[22] 2005	Freeman[26] 2007	Own results 2007	Total
Patients (n)	14	21	11	9	9	24	12	22	21	32	175
Leakage (n)	14	18	3	5	9	24	12	2	21	24	132
Perforation (n)	0	3	8	4	0	0	0	20	–	10	45
Abdominal (n)	0	12	0	0	0	0	0	0	NS	0	12
Thoracic (n)	14	9	11	9	9	18	12	22	NS	32	136
Cervical (n)	0	0	0	0	0	6	0	0	NS	0	6
Sepsis[a] (%)	100	52	72	NS	56	33	66	NS	NS	81	
Time until stenting[b] (days)	19.5 (9–34)	6 (3–63)	3 (1–28)	22 (1–65)	7.7 (2–10)	19 (4–65)	15 (10–45)	11<1	12 (3–31)	14 (0–611)	
Stent type[c]	Mixed	Ultraflex©	Flamingo©/ Ultraflex©	Polyflex©	Polyflex©	Polyflex©	Polyflex©	Ultraflex©	Polyflex©	Ultraflex©	
Technical success (%)	100	100	100	100	100	92	100	95	100	100	98
Sealing rate (%)	84	90	91	78	89	89	100	95	95	78	88
Complication rate (%)	7	76	NS	33	22	46	17	12,5	24	28	29
Stent migration (%)	NS	NS	9	30	22	37	17	14	24	6	20
Healing (%)	93	81	82	66	100	89	92	77	95	81	85
Mortality (%)	7	28	0	33	0	25	0	23	5	15	15
Enteral nutrition[d] (days)	NS	NS	7–18	NS	11	1	5–43	NS	NS	1/22	
Stent extraction (%)[e]	7	57	64	67	100	50	100	77	95	70	69
Stent treatment[f] (days)	NS	55 (9–122)	49 (42–98)	135 (32–242)	29	NS	28 (14–56)	21	51 (15–175)	45 (4–426)	
Hospital stay[g] (days)	17 (4–117)	67 (14–158)	NS	NS	35	8 (3–24)	25 (5–78)	18 (4–97)	12 (4–44)	58 (19–253)	

The comparison to other series emphasizes the heterogeneity of patient collectives published so far and the wide variety of stent-types and therapies used. These differences should be considered when assessing the effectiveness of stenting procedures.

[a] Percentage of patients with a septic course of disease

[b] Interval between operation or perforation, respectively, and stent implantation

[c] *Mixed* Three different types of metal stents; *Flamingo*© Flamingo Wallstent, Boston Scientific Corp., Natick, MA, USA; *Ultraflex*© Ultraflex Wallstent Boston Scientific Corp., Natick, MA, USA; *Polyflex*© Polyflex Wallstent, Rusch Corp., Wiesbaden, Germany

[d] Interval from stent implantation until oral nutrition in days

[e] Percentage of patients in which stent extraction was successfully completed

[f] Interval of stent implantation until stent extraction in days

[g] Time of stent implantation until discharge from in hospital treatment in days

and stent application was delayed and the majority of our patients were in a septic condition.[15,18,19,22,23,36] This delayed stent treatment can be partly explained as stent implantation was assumed to be a last-choice procedure for anastomotic leakage, and therefore, 19 of 32 patients underwent futile attempts of surgical closure before stenting. Earlier stenting might further decrease mortality and morbidity of this life-threatening condition in the future. For this reason, endoscopy should be performed as soon as a patient's postoperative development after esophageal resection differs from the normal postoperative course, for example, by occurrence of weaning problems, fever, or atrial fibrillation.

In patients with esophageal perforation, time from perforation to diagnosis has also been considered to be of crucial importance to morbidity and mortality rates.[6–9,25,37] For example, Johnsson et al.[22] described a mortality rate of nearly 50% in patients when time of perforation to diagnosis and stent treatment was >24 h compared to 0% if stent treatment occurred within 24 h. In our series, only one esophageal perforation was treated by stent implantation on the same day, and this patient was discharged without any further complications. All other patients were transferred secondarily from other hospitals, and stent treatment was performed a median of 6 days after perforation.

Endoscopic treatment of esophageal leaks is elaborate and potentially cost-intensive, as stent implantation is not the only endoscopic procedure during the treatment. Repeated endoscopies are performed until a correct diagnosis is achieved once the suspicion of leakage is raised. Besides stent implantation or extraction, several endoscopies can be performed for lavage of the necrotic cavity, placement of nutrition probes, preparation of stent extraction, or control purposes. It has been shown that mortality can be reduced by repeated endoscopic lavage and debridement together with adequate drainage until clean granulation tissue is observed before stent treatment.[14,21] Endoscopy is an important component in the treatment of esophageal leakages and therefore should be available in all surgical units when performing esopheageal surgery.

Whether self-expanding covered metal or plastic (silastic) stents are favorable in sealing esophageal leakages is still under discussion. Covered metal stents have been used in the treatment of esophageal cancer, malignant fistulae, and iatrogenic esophageal injury, with significant success in poor-risk patients.[38,39] However, doubts have been raised about the long-term effectiveness of covered metal stents because of their complications, such as hemorrhage, strictures, and fistulization.[40] In contrast to silastic stents, most metallic stents become strongly embedded in the esophagus wall, making endoscopic retrieval extremely difficult.[40–42] In our study, seven patients had their stents never removed for different reasons, and most of them had normal food intake, putting into question whether the stents must be removed at all. Nonetheless, stent extraction should be aimed for, especially as reflux and aspiration problems can occur. In this regard it has become clear from our series and the literature that currently used covered metal stents can be removed safely in most patients with a low complication rate. Moreover, self-expanding metal stents are available with a larger diameter than silastic stents, allowing quite a tight connection and a large contact area with the esophageal wall, thus reducing fluid migration between stent and mucosa. On the other hand, reintervention rate due to stent dislocation is remarkably high in series using self-expanding silastic stents, occurring up to 37.5%,[17,19,23] whereas in our series, stent dislocation occurred in only 6%. However, as both stent types have their disadvantages, other stent types should be made available in the near future. Indeed, preliminary data using a new covered mushroom-shaped metallic stent are encouraging. These stents completely sealed the fistula in all patients with a zero 30-day mortality and stents being removed in all patients after approximately 18 to 48 days.[43] Moreover, follow-ups at seven to approximately 30 months showed that all leaks were healed without stent-related complications.

In summary, endoscopic placement of self-expanding stents is safe and effective in patients with anastomotic leakage or perforation of the esophagus. Limiting factors might be the extent of the defect, the delay in treatment, the septic condition of the patient, cardiac disease or immunosuppression, and underlying malignant disease. Every disturbance of the normal postoperative or postinterventional course should trigger physicians to initiate endoscopic inspection with the possibility of early stent placement to avoid systemical sepsis combined with adequate surgical or interventional drainage of fluid collections.

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Diagnostic Laparoscopy for Patients with Potentially Resectable Pancreatic Adenocarcinoma: Is It Cost-Effective in the Current Era?

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Abstract
Introduction For patients with potentially resectable pancreatic cancer, diagnostic laparoscopy may identify liver and peritoneal metastases that are difficult to detect with other staging modalities. The aim of this study was to utilize a population-based pancreatic cancer database to assess the cost effectiveness of preoperative laparoscopy.
Material and Methods Data from a state cancer registry were linked with primary medical record data for years 1996–2003. De-identified patient records were reviewed to determine the role and findings of laparoscopic exploration. Average hospital and physician charges for laparotomy, biliary bypass, pancreaticoduodenectomy, and laparoscopy were determined by review of billing data from our institution and Medicare data for fiscal years 2005–2006. Cost-effectiveness was determined by comparing three methods of utilization of laparoscopy: (1) routine (all patients), (2) case-specific, and (3) no utilization.
Results and Discussion Of 298 potentially resectable patients, 86 underwent laparoscopy. The prevalence of unresectable disease was 14.1% diagnosed at either laparotomy or laparoscopy. The mean charge per patient for routine, case-specific, and no utilization of laparoscopy was $91,805, $90,888, and $93,134, respectively.
Conclusion Cost analysis indicates that the case-specific or routine use of laparoscopy in pancreatic cancer does not add significantly to the overall expense of treatment and supports the use of laparoscopy in patients with known or suspected pancreatic adenocarcinoma.

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This study was approved by the Institutional Review Board of Oregon Health and Science University and the Research Committee at the Oregon State Cancer Registry.

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Introduction

Pancreatic cancer continues to be a major source of cancer mortality. There were 33,700 new cases diagnosed in 2006, with mortality nearly equaling incidence.[1] The economic impact of pancreatic cancer is substantial.[2] Cost estimates in 1999–2000 for treatment ranged from $7,279 to $15,143 monthly per patient depending on the extent of disease progression.[3] The majority of these costs are accrued by in-hospital treatments, including surgical procedures and chemotherapy.

For patients with pancreatic cancer, the only chance for cure is surgical resection, with best-reported 2- and 5-year actuarial survival 36% and 20%, respectively, after resection and adjuvant therapy.[4] Unfortunately, only 10–15% of patients present with resectable disease at the time of diagnosis.[5] The accurate and cost-effective identification of patients that are surgical candidates remains a significant clinical challenge.

Multi-detector helical computed tomography (CT) serves as the primary imaging study for most patients with potentially resectable pancreatic cancer. In recent years, the utilization of endoscopic ultrasound (EUS) with biopsy has increased, which may improve accuracy in assessing resectability.[6] Many surgeons also routinely employ diagnostic laparoscopy (DL) before proceeding to laparotomy. Laparoscopy is the only technique that allows direct visualization of peritoneal surfaces and the liver capsule and offers the possibility of minimally invasive diagnosis of small volume metastatic disease in these areas.[7–10] Patients diagnosed with metastatic disease at laparoscopy can be spared a non-resectional laparotomy. In recent years, however, developments in CT technology have led to a decreased yield from laparoscopy.[10] These advances have prompted some to assert that routine preoperative DL is not necessary and may not be cost-effective.[10,11] The benefits to those with metastatic disease diagnosed at laparoscopy who subsequently avoid a non-resectional laparotomy (NRL) include shorter hospital stay and lower morbidity. Most importantly, patients who are spared non-resectional laparotomy have a shorter interval to other, non-surgical treatments for pancreatic cancer including chemotherapy and radiation therapy. While multiple authors have examined the utility of incorporating DL in various staging methods, few have investigated the cost effectiveness of DL in pancreatic cancer.

The aim of this study was to utilize the clinical outcomes observed in a large population-based analysis of surgically treated pancreatic cancer patients to evaluate the cost effectiveness of diagnostic laparoscopy in patients with potentially resectable known or suspected pancreatic adenocarcinoma (PAC).

Material and Methods

Patients

Data from the Oregon State Cancer Registry (OSCaR) were linked with primary medical record data for years 1996–2003. According to Oregon statute, all cases of cancer must be reported to the registry. All patients with surgically treated PAC were identified using International Classification of Diseases, Version 9 (ICD-9) diagnosis codes and Current Procedure Terminology (CPT) codes.[12,13] Only patients with confirmed pathologic diagnosis of pancreatic ductal adenocarcinoma were included; excluded were proximal cholangiocarcinoma, any cancer of unknown primary, intraductal papillary mucinous neoplasms, mucinous cystadenocarcinoma, lymphomas, sarcomas, oncocytomas, giant papillary carcinomas, and neuroendocrine tumors of the pancreas. All patients with disease considered potentially resectable and who underwent procedures in any of the following categories were included in the analysis: DL, laparotomy, pancreaticduodenectomy, biliary and/or enteric bypass (a complete list of ICD-9 and CPT codes used is included in Appendix). The study period included the years 1996–2003. After study, candidates were identified in the registry, and their records were obtained from the treating institution. Records from 27 hospitals were submitted to OSCaR. The records were de-identified and then made available for review.

For each patient, we reviewed the admission history and physical, operative note, pathology report, imaging data, and discharge summary. Preoperative workup was determined and included multi-detector CT for the majority of patients (96%). CT findings were categorized as either predicting resectability or unresectability. A subset of scans demonstrated findings suspicious for metastases or locally advanced disease, but the findings were not definitive. These scans were described as “equivocal.”

Operative notes and pathology reports were reviewed to determine the role and findings of laparoscopic exploration as well as the extent and type of resection performed. Demographic information, tumor characteristics, and presenting signs and symptoms were also recorded. Patients were excluded from the study if they had pancreatic neuroendocrine tumors, cystic neoplasms, or pathology other than pancreatic adenocarcinoma. This study was reviewed and approved by the institutional review board of the Oregon Health and Science University (OHSU) and the OHSU Cancer Institute.

Development of the Cost-Analytic Measure

Because cost accounting data were not available for all procedures or all study hospitals examined in this study, hospital charges from our institution (OHSU) were used to develop a uniform cost-analytic measure applied across all patients in the study. Because the measure is derived from charges rather than cost, the absolute monetary numbers are not broadly applicable and are not the primary outcome measure of the study. Instead, this methodology allowed us to formulate a single metric to compare the relative economic impact of different utilization strategies of laparoscopy across different hospital systems. Hospital length-of-stay, all pathology charges, and other hospital-based clinical service charges are included in the charge data. Not included in the analysis are charges for subsequent pancreatic cancer-related procedures including reoperation or endoscopic interventions such as stent placement for biliary or enteric obstruction.

To develop the cost-analytic tool, mean hospital charges for laparotomy, biliary bypass, enteric bypass, pancreaticoduodenectomy, and DL were determined by review of billing data from OHSU for fiscal years 2005–2006 using CPT codes and diagnosis-related group codes.[14] Physician charges were calculated from the Centers for Medicare and Medicaid Services regional physician fee schedule according to CPT code.[15] The charge for DL as an additional procedure (DL+) when combined with either pancreaticoduodenectomy or laparotomy was determined based on charge per minute of operative time, equipment, and OR processing charges. Upon review of the operative notes, we determined that the vast majority of surgeons, when they used DL, performed an examination of the peritoneum with little dissection in the lesser sac and no laparoscopic ultrasound. The time to perform this procedure is typically 30 min or less. Because a higher charge is ascribed to the first hour of operating room time, the contribution of OR time to the total cost of DL+ was determined from charges incurred for time beyond the first hour. This charge was added to the mean charge for each patient in each of the treatment arms employing DL.

Cost Analysis

Cost effectiveness was modeled for three different utilization strategies for diagnostic laparoscopy: (1) routine (all patients), (2) case-specific, and (3) no utilization. Case-specific utilization refers to the practice of using laparoscopy in some patients but not others. In this approach, the decision to perform laparoscopy was driven by clinical suspicion for metastatic disease from radiographic or clinical findings. We analyzed the outcomes from our clinical study to create an outcome model for each of the three utilization strategies for DL. We then applied the aggregate charge data to each arm of the model and determined an average charge per patient for each method of employing DL. For example, for the routine model in which laparoscopy would be utilized in all cases of known or suspected PAC, the charge for laparoscopy was added to each patient regardless of ultimate resectability. However, a subset of patients in this group avoided the expense associated with non-resectional laparotomy when metastatic disease was diagnosed at laparoscopy. To account for the false negatives inherent with laparoscopy, the same rate (26%) was applied to the NRL group so that ultimately, five patients that would undergo DL in this group were incorrectly deemed resectable. On laparotomy, these patients were unresectable but incurred the charge for both DL and laparotomy. We modeled the case-specific laparoscopy approach based on the observed practice in our clinical study. This included the charge of laparoscopy in a subset of patients, but also included the savings for the group of patients that were diagnosed with metastatic disease at laparoscopy where the expense of non-resectional laparotomy was avoided. To model the approach of non-utilization of laparoscopy, all patients avoided the additional charge of laparoscopy, but all patients with metastatic disease underwent laparotomy for diagnosis and incurred the charges associated with that procedure.

An additional subset analysis was performed based on lesion location. We focused this analysis on those tumors located only in the periampullary region of the gland (head and uncinate process). The one-way analysis of variance test was used to compare mean charges between the three approaches.

Results

A total of 298 patients with potentially resectable pancreatic adenocarcinoma were identified as surgical candidates during the study period (Table 1). Median age was 64.6 years (range 26–90). There was a nearly even distribution of the study population by gender (male, 52%). Most of the lesions were periampullary in location (79%), and the majority were clinical stage T3 based on preoperative imaging (59%). Presenting symptoms included but were not limited to jaundice, epigastric pain, and weight loss (63%, 62%, and 57%, respectively).

Preoperative imaging is depicted in Table 2 and included CT in 96% of patients and EUS in 34%. Of those who had EUS, the majority also had CT (96%). Four of the patients who had no record of CT had EUS as their primary preoperative imaging modality. In the 229 patients who had both a CT scan and a resection, CT scan accurately

Table 1 Patient Demographics and Clinical Outcome

	Number	Percentage
Median age, years (range)	64.6 (26–90)	NA
Gender		
Male	154	51.7
Female	144	48.3
Tumor location		
Periampullary	236	79.2
Distal	62	20.1
Tumor size (pre-op imaging)		
≤2 cm	31	10.4
>2 cm	124	41.6
Unknown	143	48.0
T stage[a]		
T1	16	5.4
T2	51	17.1
T3	175	58.7
T4	16	5.4
Unknown	40	13.4
Presenting symptoms/signs[b]		
Jaundice	187	62.8
Epigastric pain	184	61.7
Weight loss	170	57.1
Back pain	70	23.5
Pruritis	59	19.8
Anorexia	57	19.1

[a] AJCC Manual, 6th ed
[b] Patients may have more than one

predicted resection in 192 (84%). Another 32 patients with CT scan results deemed "equivocal" were also successfully resected despite apparent concerns for unresectability on CT. Of 231 patients deemed resectable after staging by CT scan, 39 (17%) were ultimately unresectable due to peritoneal or locally advanced disease. Endoscopic ultrasound correctly predicted resectability in 63 of 85 patients (74%), with 17 equivocal reports. Of the 74 patients who had EUS suggesting resectability, 11 (15%) had unresectable disease at either laparotomy or DL.

Patient characteristics and outcome were examined by the utilization of DL (Table 3). Laparoscopy was used in 86 patients (28.9%), of which, 73 had tumors located in the periampullary region and 13 had distal pancreatic tumors. In this group, laparotomy was avoided in 24 patients (28%) who had metastatic disease discovered at laparoscopy. Two of these patients underwent laparoscopic bypass procedures—one biliary and the other enteric bypass. Of the remaining 62 in whom laparotomy was performed, 46 (74%) were resected and 16 (26%) had a NRL. In the NRL group, nine were found to be unresectable due to vascular invasion, two had metastatic disease in lymph nodes that were in regions outside the planned resection, and five had distant disease precluding resection.

In the non-DL group, 212 patients were taken directly to laparotomy without laparoscopy. Of these, 194 (92%) were resected and 18 (8%) had a NRL due to either metastatic disease or local invasion precluding resection. Specifically, three patients had vascular involvement, 14 had metastatic disease in the liver or peritoneum, and one patient had positive regional lymph nodes that were considered to be outside the resection field.

Charge data are depicted in Table 4. Based on an operating room charge for 30 min of operative time and laparoscopic equipment charges, the additional charge for DL performed in the same operative session as pancreaticoduodenectomy or laparotomy was $3,529. Alternative procedures performed for unresectable disease in the NRL group included diagnostic laparotomy, biliary and/or enteric bypass.

When each of the treatment strategies is modeled using our analytic charge measure, the three strategies for DL are very similar in resource utilization (Table 5). Case-specific use of DL proves to be the least expensive at $90,888 per patient (Fig. 1). Next is routine use at $91,805 (Fig. 2). Non-utilization of laparoscopy is the most expensive at $93,134 per patient (Fig. 3). There was not a significant difference between these three values (p=0.9626).

In our study, it appears that 16 of 52 (26%) patients deemed resectable at laparoscopy had local or metastatic disease precluding resection. However, it should be noted that a number of these patients had M1 disease identified at DL, but went on to open palliative bypass.

When examining the subset of patients with only head and uncinate process lesions (n=236, 79.1%), we observed similar results. The mean charges for this group were $92,453, $93,889, and $93,928 in the case-specific, routine, and non-utilization arms, respectively. The difference between each group was not statistically significant (p=0.9882).

Table 2 Surgical Resectability by Preoperative Imaging Findings

Assessment of Resectability	Resection		Total
	Yes	No	
CT			285
Resectable	192 (84)	39 (17)	231
Equivocal	32 (65)	17 (35)	49
Unknown	5	0	5
No CT	11	2	13
EUS			100
Resectable	63 (85)	11 (15)	74
Equivocal	17 (85)	3 (15)	20
Unknown	5	1	6
No EUS	155	42	198

Numbers in parenthesis are percentages.

Table 3 Surgical Outcome for 298 Patients with Potentially Resectable Pancreatic Cancer

Course	Resected	NRL	M1 disease[a]	Total
Directly to laparotomy	194 (91.5%)	18 (8.5%)	NA	212 (71.1%)
Diagnostic laparoscopy	46 (74.2%)	16 (25.8%)	24 (27.9%)	86 (28.9%)
Total	240 (80.5%)	34 (11.4%)	24 (27.9%)	298

NRL non-resectional laparotomy, *M1* metastatic disease
[a] Identified at laparoscopy

Discussion

This study represents a statewide, population-based audit of the surgical practices utilized in the treatment of patients with potentially resectable pancreatic adenocarcinoma. We found that surgeons used diagnostic laparoscopy in 29% of the study patients. Laparoscopy contributed significantly to the staging in this subset of patients, with metastatic disease identified in 28% who were subsequently spared laparotomy. However, even the addition of laparoscopy did not allow completely accurate identification of resectable patients. Twenty-six percent of patients that underwent laparoscopy and had no laparoscopic indication of unresectability were eventually assessed as unresectable at laparotomy. The overall resectability rate (74%) was actually lower in the group of patients undergoing laparoscopy than the larger group of patients taken directly to laparotomy.

We suspect that the more favorable resectability rate for patients taken directly to laparotomy without laparoscopy relates to bias inherent in the selection of patients for staging laparoscopy that are high risk for metastatic disease. Unfortunately, the data available in this study do not allow us to determine with accuracy the criteria that surgeons used to select patients for laparoscopy. Such preoperative findings are likely to include suspicious, but not diagnostic, findings on CT scan and elevated preoperative CA 19-9. Some of these criteria may be difficult to measure even with the clinical data reviewed for this study.

Table 4 Estimated Charges for Pancreatic Cancer Procedures

Procedure	Charge ($)	SD ($)
DL[a]	3,529	NA
DL only	16,900	3,789
NRL	54,730	23,253
NRL + DL	58,575	21,710
PD	102,415	42,555
PD + DL	106,261	55,159

Charges for pancreatic cancer procedure include hospital charges, physician fees, equipment, and operating room costs
DL diagnostic laparoscopy, *NRL* non-resectional laparotomy (including biliary or enteric bypass), *NRL + DL* non-resectional laparotomy with diagnostic laparoscopy, *PD* pancreaticoduodenectomy, *PD +DL* pancreaticoduodenectomy with diagnostic laparoscopy, *SD* standard deviation
[a] Charge for DL as an additional procedure; does not include physician fees

Our data indicate that by using a uniform charge structure as a measurement of the relative differences between utilization strategies, laparoscopy may be performed routinely or on a case-specific basis without increasing the charges for care provided. We found that the average charge per patient was quite similar regardless of whether patients would have received laparoscopy routinely, on a case-specific basis, or not at all. In fact, the average per patient charge for groups in which DL was used either on a case-specific basis or routinely had a lower mean charge than those in whom DL was not used (Table 5).

The false negative rate for DL observed in this study (26%) was high compared to reported rates of 2–9%.[16–18] However, this group likely represents the appropriate use of DL—an additional staging method in patients who likely have occult metastatic disease. Thus, it is not surprising that many of these patients did in fact harbor locally advanced or distant disease undetectable by CT and DL despite a high index of suspicion on the part of the surgeon. It is notable that many of these procedures were performed in an era before durable endoscopic stents were widely available and surgical bypass was more commonly used for palliation. Thus, a portion of the patients with metastatic disease identified on DL ultimately underwent laparotomy with palliative bypass. More recent experience has demonstrated that patients diagnosed with metastatic disease at laparoscopy only rarely require operative intervention for palliation.[19] Even with the more liberal utilization of surgical bypass that was practiced in the early years of this series, the use of routine or case-specific DL was still economically neutral when compared to non-utilization of laparos-

Table 5 Projected Mean Charge Per Patient Based on Surgical Method of Employing DL

Approach to DL	Mean charge per patient—all lesions* ±SD	Mean charge per patient—Head and uncinate lesions** ±SD
Case-specific	$90,888±29,042	$92,453±29,360
Routine	$91,805±44,452	$93,889±45,381
No DL	$93,134±34,570	$93,928±35,226

SD standard deviation
*p=0.9626; **p=0.9882

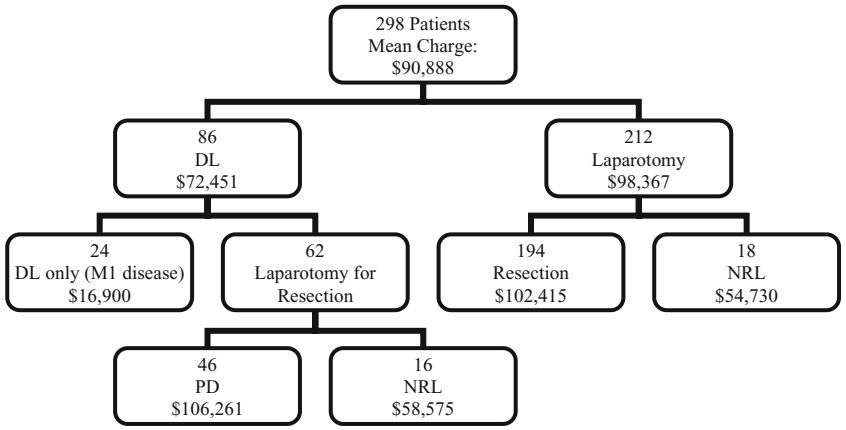

Figure 1 Mean charges in cost-analytic model for DL on a case-specific basis. All charges represent mean charge per patient in each associated subgroup. *DL* diagnostic laparotomy, *NRL* non-resectional laparotomy.

copy when modeled both for all lesions and those limited to the periampullary region.

The liberal utilization of laparoscopy has sound clinical rationale. Pancreatic cancer frequently spreads to the peritoneal surfaces and liver. CT alone rarely identifies small volume peritoneal and hepatic disease, with limited capability for detecting lesions <1 cm. In our study, 17% of patients with a CT scan predicting resectability were unresectable at laparotomy. In a study of patients with locally advanced disease, Liu and Traverso[20] demonstrated that as many as 34% of patients with no evidence of M1 disease on CT actually harbor occult disease. Among those who have examined the use of DL in patients with potentially resectable disease, the utility of DL varies widely for preventing unnecessary laparotomy 19–38%.[8,16–18,21] In our study, DL prevented an unnecessary laparotomy in a large percentage of patients (27.9%). Improvements in CT imaging have greatly enhanced the ability to determine resectability. However, CT alone is often unable to predict *unresectability* in a subset of patients. It is this group who benefit from the addition of staging laparoscopy. When used together, CT and DL have a reported sensitivity of 87% and a positive predictive value for unresectability as high as 100%.[22] The additive value of using these tools together enhances the diagnostic capability of either alone.

Few studies have directly assessed the role of staging laparoscopy in PAC, and there has been a diminishing yield of DL in those that have.[16–18,21,23] In publications that have addressed cost effectiveness, theoretical models have been created, and intervention/benefit ratios have been postulated, but neither cost nor charge data have been applied to actual clinical outcomes.[10,24] In a detailed cost analysis model, Tierney and colleagues[24] demonstrated that the combination of laparoscopy and EUS yielded the most cost-effective staging strategy and that laparoscopy alone led to the highest resection rate. Friess et al.[10] have suggested that laparoscopy must be seven times cheaper than laparotomy to offset the cost of "unnecessary" laparoscopy in patients who are ultimately resected. This group demonstrated relatively low rates of unresectability after CT (14%), but none of the patients actually underwent laparoscopy. Their analysis compared the cost of DL as a stand-alone procedure to diagnostic laparotomy, but did not include cost data, nor did they consider the cost of DL as a perioperative procedure. While our analysis demonstrates that the charge for DL as a stand-alone procedure was one third the cost of laparotomy, when the economic impact of laparoscopy is considered across a large cohort, the expense of DL is essentially neutral in resource utilization. Further, while the authors do continue to strongly recommend DL

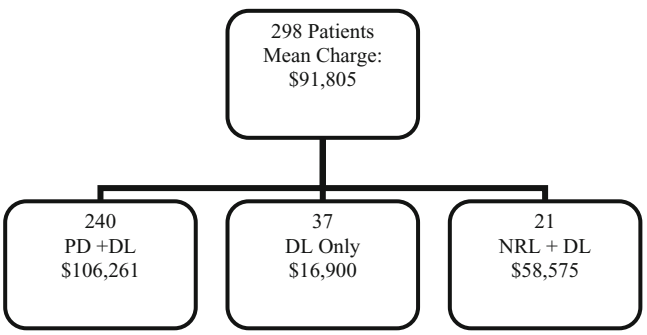

Figure 2 Mean charges in cost-analytic model for the routine use of DL. All charges represent mean charge per patient in each associated subgroup. *DL* diagnostic laparotomy, *PD* pancreaticoduodenectomy, *NRL* non-resectional laparotomy.

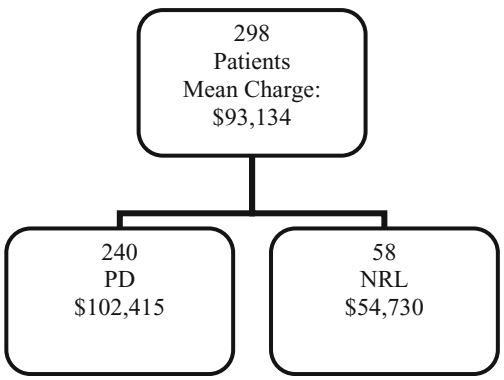

Figure 3 Mean charges in cost-analytic model for not utilizing DL. All charges represent mean charge per patient in each associated sub-group. *PD* pancreaticoduodenectomy, *NRL* non-resectional laparotomy.

for those patients in whom metastases cannot be excluded, they do not speculate on the cost benefit of this approach. We have shown that in these patients, a case-specific approach to DL is not cost-prohibitive.

Several limitations of our analysis must be acknowledged. This study extrapolates from hospital charges at a single institution to construct an analytic tool for the comparison of different strategies for the utilization of DL. Hospital charges represent neither incurred costs (direct or indirect) nor reimbursed costs, leading some to argue that hospital charge data are inadequate for cost analysis.[25] As the aim of this study was to survey practices and outcomes in a wide variety of facilities, it was necessary to construct a single analytic tool to apply to the entire study population. In this study, hospital charges are not designed to be an absolute measure of pancreatic cancer cost but rather serve as a tool to compare the relative costs of different utilization strategies for preoperative laparoscopy.

The most robust argument against the use of hospital charge analyses is that they tend to underestimate the financial impact of additional interventions or procedures. This has indeed been problematic in studies where laparoscopic procedures are shown to be more expensive than their open counterparts.[26,27] In those instances, however, laparoscopy led to a *higher* charge or a *higher* cost, or both. In fact, our study showed the opposite: that the addition of laparoscopy was cost neutral or possibly associated with a modest reduction in mean hospital charge per patient treated. Other authors have demonstrated similar cost effectiveness when analyzing cost and charge data for laparoscopy across numerous procedures in pediatric surgery.[28]

In this study, we have excluded patients with neuroendocrine tumors, duodenal cancer, and ampullary tumors—all disease sites in which preoperative laparoscopy may play a role. However, as the study uses the pathologic data from a variety of hospitals and there was not a central pathologic review, it is possible that there is some heterogeneity in the study group. In particular, it is possible that some of the patients had cancer arising in the distal bile duct rather than the pancreas. We do not believe, however, that this compromises the conclusions or clinical applicability of the study findings.

Conclusion

In summary, we found that DL may be performed either on a case-specific basis or routinely in all cases of suspected PAC. Neither of these approaches appears to significantly increase the economic burden of PAC care. When used as a preoperative technique, DL remains an important adjunct for identifying M1 disease that is missed on CT.

Acknowledgments The authors wish to thank Dr. Charles Vollmer for his generous assistance in the preparation of this manuscript.

Appendix

Table 6 A-CPT and ICD-9 Codes (Not Intended for Inclusion in Published Manuscript Unless Requested by Reviewers)

Diagnosis/Procedure	ICD-9	CPT
Pancreatic adenocarcinoma	157.0	
	157.1	
	157.2	
	157.3	
	157.4	
	157.8	
	157.9	
Pancreatic resections	52.51	48140
	52.52	48145
	52.53	48150
	52.59	48152
	52.6	48153
	52.7	48154
		48155
Laparoscopy–1999		56310
		56300
		56305
		56399
Laparoscopy–2004	54.51	44200
	52.21	49320
	54.21	49321
	54.23	49329
	54.24	
	65.11	
	65.13	
	68.15	
Other		
Extra-hepatic biliary cancer	156.1	
Ampulla of vater cancer	156.2	
Laparotomy		49000
Laparotomy/Exploration		47015
Hepatico-jejunostomy		47780
Gastro-jejunostomy		43820
Laparoscopic ultrasound		76986

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Prospective Nonrandomized Comparison Between Pylorus-Preserving and Subtotal Stomach-Preserving Pancreaticoduodenectomy from the Perspectives of DGE Occurrence and Postoperative Digestive Functions

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Abstract
Background To determine the influence of pylorus preservation after pancreaticoduodenectomy, we compared the postoperative course of subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) and pylorus-preserving pancreaticoduodenectomy (PPPD).
Methods A prospective, nonrandomized comparison of 77 consecutive patients undergoing PPPD (n=37) or SSPPD (n=40) between January 2003 and March 2007 was planned. The early postoperative course, dietary intake, and the incidence of delayed gastric emptying (DGE) were evaluated.
Results SSPPD included significantly more cases of regional lymph node dissection (D2, PPPD 53% vs. SSPPD 80%) and portal vein resection. The median duration of surgery (457 vs. 520 min) was significantly shorter, and blood loss (619 vs. 1,235 ml) was significantly less in PPPD. Regarding postoperative clinical factors, the duration of nasogastric tube intubation (1 vs.1 day), days until solid diet (7 vs. 7 days), and the incidence of DGE (9% vs.10%) were similar in PPPD and SSPPD. However, the postoperative/preoperative body weight ratio (95% vs. 93%) was significantly higher, and the postoperative hospital stay (31 vs. 38 days) was significantly shorter in PPPD (p<0.05).
Conclusions Despite the bias of the operative factors, the incidence of DGE and postoperative dietary intake after SSPPD was comparable with PPPD, and therefore, pylorus preservation seemed to have no impact on postoperative dietary intake or DGE.

Keywords Pylorus-preserving pancreaticoduodenectomy · Subtotal stomach-preserving pancreaticoduodenectomy · Delayed gastric emptying

Introduction

Pancreaticoduodenectomy (PD) and pylorus-preserving pancreaticoduodenectomy (PPPD) are considered as the standard surgical treatment for pancreatic and periampullary malignancies.[1–5] Recently, several large-volume randomized control studies[6–10] and meta-analysis[11,12] comparing PD and PPPD have been reported with a conclusion that there is no significant difference in the oncologic outcome and quality of life between the two operative methods. However, the occurrence of delayed gastric emptying (DGE) in the postoperative course after PDs is a controversial object.[13–15] The mechanism of DGE is still unclear, and several causal mechanisms for DGE, such as interrupted gastrointestinal neural connection, local ischemia, loss of gastrointestinal hormone production, anatomical position, intra-abdominal infection, undetected anastomotic leakage or pancreatitis, and pylorus preservation have been proposed and discussed.[4]

Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) has been performed in Japan since the 1990s. In standard PD, usually 30–40% of the distal stomach is

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resected, while in SSPPD, the stomach is separated at the 2- to 3-cm proximal side of the pylorus ring and most part of the stomach is preserved. This method was intended to maintain the pooling ability of the stomach and avoid the occurrence of DGE by the resection of the pylorus ring.[16] However, the superiority of SSPPD has not been validated in any clinical study. Therefore, we investigated the outcome of the early postoperative period of PPPD and SSPPD, and examined the postoperative course, dietary intake, and incidence of DGE.

Material and Methods

Patients and Methods

Between January 2003 and March 2007, 77 consecutive patients received PPPD (PP, n=37) or SSPPD (SS, n=40) at the Sapporo Medical University Hospital. The following patients were excluded from the study because the cited factors would have strongly influenced the postoperative course: cases with hepatectomy (more than one hepatic segment; PP 1, SS 2), cases with extended retroperitoneal lymph node dissection (SS 2), cases with hepatic artery resection/reconstruction (SS 1), cases in which the preoperative performance status was remarkably poor (PP 1), and cases that individuals experienced severe non-surgery-related complications (PP 1, SS 5). The diseases indicated for surgery included periampullary adenocarcinoma (including gall bladder carcinoma with peripancreatic lymph node metastasis) and metastatic tumors, benign tumors and inflammatory diseases. A total of 64 cases (PP 34, SS 30) were retrieved for analysis.

A single team specializing in biliary and pancreatic surgery performed the operation and postoperative patients care. The specialty of the team chief was biliary and pancreatic surgery, and the other attending surgeons were rotating senior residencies. The operating surgeon was selected from the members of the surgical group on the basis of the case type. A standardized operative maneuver was performed in every operation.

Indications for Operation

A strict criterion for the selection between PPPD and SSPPD was not used. To determine a baseline, we selected PPPD as the standard procedure, and SSPPD was undertaken in the following situation: (1) Perigastric lymph nodes were macroscopically suspicious for tumor metastasis, (2) pancreatic serosal invasion was suspicious, (3) dense adhesion or inflammatory change around the peripyloric region existed, and pylorus preservation seemed to be difficult. Our intent is to ensure a certain tumor-free margin and to maintain a sufficient blood flow of the duodenal cuff. Such a decision is usually made during operation depending on the difficulty of the maneuvers.

Standardized Operative Maneuvers

When dividing the gastrointestinal tract in PPPD, the duodenum was divided 3–5 cm below the pylorus ring. In SSPPD, the stomach was divided 2–3 cm above the pylorus ring, at the pyloric region of the stomach. The pancreas was transected at the level of the portal vein or superior mesenteric artery.

For lymph node dissection in patients with a malignant disease, the common-to-proper hepatic artery and portal-to-superior mesenteric vein were skeletonized. In SSPPD, lymph nodes of the inferior and superior pylorus ring were also dissected. According to a classification developed by the Japan Pancreas Society,[17] this lymph node dissection was identified as "D2." In patients with a benign disease, only the regional lymph nodes around the pancreatic head were removed, and this lymph node dissection was identified as "D1." Furthermore, some patients with pancreatic cancer required an additional dissection of the nerve plexus around the superior mesenteric artery at a maximum of the right half circumference or superior mesenteric-to-portal vein resection when necessary to achieve a certain tumor-free margin and curative resection.

After resection, a modified Child's reconstruction was performed. First, the proximal jejunal stump was brought posterior through the mesenterium, and pancreaticojejunostomy was carried out in an end-to-side fashion using a duct-to-mucosal anastomosis. The hepaticojejunostomy was performed in an end-to-side fashion using single-layer suture. An end duodenal (or stomach)-to-side jejunal anastomosis was made after transposing the stomach posterior to the transverse colon through a newly constructed hole in the transverse colon mesenterium, and the distal stomach was stretched to the infracolic space. Furthermore, a Braun anastomosis was made. An enteral feeding tube was placed in the jejunum. Two closed-system drainages were placed in the Winslow foramen and around the pancreatico-jejunal anastomosis.

Postoperative Management

From April 2004, we have followed a prescribed protocol of postoperative clinical management of patients: The nasogastric tube is removed if the discharge is below 500 ml, usually on the first day after surgery. Water drinking is allowed after the nasogastric tube is removed, usually on the first day after surgery. Enteral feeding through the jejunal tube is started on the second day after

surgery. Usually, a patient's diet starts on the fifth day after surgery. It starts with liquefied rice, water-rich rice gruel, rice-rich gruel, and regular rice. The dietary form is modulated appropriately, depending on the digestive symptoms. In this study, the last two types of diet (rice-rich gruel and regular rice) were considered to be solid diets.

Laxatives were given through the enteral feeding tube in the jejunum for peristalsis acceleration. After the start of the oral diet, patients received erythromycin stearate and mosapride citrate orally as a prokinetic agent. For postoperative gastric-acid-secretion suppression, histamine 2 receptor antagonist was used intravenously, and after starting the liquid diet, the patients took a proton pump inhibitor orally.

The dietary intake for every meal was recorded. The amount of dietary intake was defined as the ratio between the actual intake of food and the food provided. Fractions of one sixth from 0 to 1 were used, and the whole volume intake became 1. The record started from the first postoperative day until the day of discharge. Dietary intake for the whole day was calculated from the largest meal that the patient ate during the day.

Patients were considered for discharge or start of adjuvant chemotherapy, when one could eat satisfactorily and the performance status recovered about the same as the preoperative level. This implicates basically the ability to eat at least half of the provided meal routinely and no longer required any supplemental nutrition.

DGE was defined as (1) requiring a nasogastric tube for ≧10 days or (2) the inability to tolerate a solid diet for ≧14 days after surgery, according to the definition of Van Berge Henegouwen et al.[18]

Data Collection

All patients were followed prospectively with special emphasis on the occurrence of postoperative oral intake and digestive symptoms.

The significance of this clinical study and the purpose of the methodology were explained to all patients, and their informed written consent for this as well as for the handling of blood samples and other laboratory results were obtained.

Statistical Analysis

The results reported are the median obtained. The comparability of the PPPD and SSPPD groups was verified with the Mann–Whitney *U* test and Fisher exact probability test. Significance was accepted at the 5% level.

Results

Characteristics of Patients

From January 2003 to March 2007, 77 patients received PDs, and 64 patients (PP 34, SS 30) were retrived for analysis according to the exclusion criteria. Age, gender, and details of the background diseases are listed in Table 1. There were no differences in background with regard to age and gender between the two groups. However, as this was a non-randomized study, the SSPPD group had significantly more cases of periampullary adenocarcinoma (PP 18, SS 24, $p=0.003$), especially pancreatic cancer (PP 1, SS 15, $p=0.00002$).

Table 1 Characteristics of Patients

	Total ($n=64$)	PPPD ($n=34$)	SSPPD ($n=30$)	*p* Value
Age (years)	66 (28–79)	66 (28–78)	65 (39–79)	*0.56*
Gender men/women	38/26	20/14	18/12	*0.56*
Disease periampullary adenocarcinoma/other	42/22	18/16	24/6	*0.021*
Periampullary adenocarcinoma				
Pancreatic	16	1	15	*
Ampullary	11	10	1	
Distal bile duct	11	7	4	
Gall bladder (lymph node metastasis)	4	0	4	
Other				
Chronic pancreatitis	2	1	1	
Duodenal diverticulitis	1	0	1	
RCC metastasis	3	1	2	
IPMN	11	9	2	
Endocrine tumor	3	3	0	
Solid pseudopapillary tumor	2	2	0	

RCC renal cell carcinoma, *IPMN* intraductal papillary mucinous neoplasms
*$p=0.00001$

Table 2 Operative Factors

	Total (n=64)	PPPD (n=34)	SSPPD (n=30)	p Value
Lymph node dissection D1/D2	22/42	16/18	6/24	0.021
Portal vein resection	9	2	7	0.049
Operating time (min)	485 (275–768)	457 (275–670)	520 (305–768)	0.006
Blood loss (ml)	890 (180–3300)	619 (180–2080)	1235 (230–3300)	0.0004
Blood transfusion (units)	1 (0–14)	0 (0–4)	0 (0–14)	0.028

Operative Factors

Operative factors are listed in Table 2. As the indication for surgery was different between the two groups, there were more D2 lymph node dissection cases and portal vein resection cases (PP 2, SS 7) in the SSPPD group, and the difference was statistically significant. The median duration of surgery (PP 457 min, SS 520 min), median blood loss (PP 610 ml, SS 1235 ml), and perioperative blood transfusion [PP 0 (range 0–4) units, SS 0 (range 0–14) units] were all significantly lower in the PPPD group.

Complications After Surgery

Surgical morbidity, relaparotomy, and mortality are listed in Table 3. There were no significant differences in the occurrence of each complication between the two groups.

The overall incidence of DGE was 9.4% (six of 64 patients), 9% (three of 34patients) in PPPD, and 10% (three of 30 patients) in SSPPD. There were four patients with other surgical complications, three patients (PP 1, SS 2) with pancreaticojejunostomy leakage, and two with aspiration pneumonia (PP 1, SS 1).

Pancreaticojejunostomy leakage was defined as a case in which the main pancreatic duct or jejunal limb was identified by radiological study, and inquiry as to the amylase level of the drainage fluid was not made. Pancreaticojejunostomy leakage occurred in 15% of PPPD patients (n=5) and 17% of SSPPD patients (n=5). All cases were treated conservatively. Other leakage was diagnosed by fistulology: 6% in PPPD (n=2) and 3% in SSPPD (n=1), and all three cases had a fistula of the proximal jejunal limb.

There were two reoperation cases in SSPPD. One had a leakage in the proximal jejunal limb and required reoperation (resection and re-suture of the jejunal neo-stump) 2 months after the initial surgery. The other had an idiopathic perforation of the jejunal limb on the tenth day after surgery. There was one death in the SSPPD group. The individual developed postoperative cholangitis on the 16th postoperative day, which led to multiple organ failure and death on the 21st postoperative day despite various intensive treatments.

Postoperative Course

Factors affecting dietary intake during the short-term postoperative course are listed in Table 4. The median duration of nasogastric tube intubation was 1 day after surgery regardless of the operative method. Reinsertion of the nasogastric tube was done in 12% of PPPD patients (n=4) and 10% of SSPPD patients (n=3).

The median duration before water drinking was 1 day in the PPPD group and 2 days in the SSPPD group, and the median duration before the commencement of an oral diet was 5 days in both groups. A solid diet in both groups was started at a median of the seventh postoperative day. There was no significant difference in any of the factors analyzed.

It took a median of 20 days in the PPPD group and 23 days in the SSPPD group until patients were able to

Table 3 Morbidity and Mortality

	Total (n=64)	PPPD (n=34)	SSPPD (n=30)	p Value
Surgical morbidity	23 (36%)	11 (32%)	12 (40%)	0.35
Delayed gastric emptying	6 (9%)	3 (9%)	3 (10%)	0.60
Pancreaticojejunostomy leakage	10 (16%)	5 (15%)	5 (17%)	0.55
Other leakage	3(5%)	2 (6%)	1 (3%)	0.55
Intra-abdominal hemorrhage	1 (2%)	0	1 (3%)	0.47
Intra-abdominal abscess	4 (6%)	2 (6%)	2 (7%)	0.64
Wound infection	6 (9%)	2 (6%)	4 (13%)	0.28
Severe cholangitis	1 (2%)	0	1 (3%)	0.47
Aspiration pneumonia	2 (3%)	1 (3%)	1 (3%)	0.72
Relaparotomy	2 (3%)	0	2 (7%)	0.22
Mortality	1 (2%)	0	1 (3%)	0.47

Table 4 Post-operative Course

	Total (n=64)	PPPD (n=34)	SSPPD (n=30)	p Value
Interval for removal of nasogastric tube (days)	1 day (0–7)	1 (1–2)	1 (0–7)	0.61
Reinsertion of nasogastric tube (%)	7 (11%)	4 (12%)	3 (10%)	0.57
Start of water drinking (days)	1 day (1–6)	1 (1–5)	2 (1–6)	0.24
Start of liquid diet (days)	5 days (3–16)	5 (3–16)	5 (3–13)	0.58
Start of solid diet (days)	7 days (4–39)	7 (4–35)	7 (4–39)	0.77
Eat one half of the provided meal routinely (days)	22.5 days (3–50)	20 (5–50)	23 (3–50)	0.25
Postoperative weight (1 month)/preoperative weight (%)	94.2% (81–102)	94.9 (87–100)	93.0 (81–102)	0.026
Postoperative hospital stay (days)	35 days (19–90)	31 (19–67)	38 (22–90)	0.017
Postoperative hospital stay or start of adjuvant chemotherapy (days)	31.5 days (19–90)	29 (19–69)	34 (19–90)	0.14

routinely eat more than one half of the meal provided, and there was no significant difference between operative methods. Discharge from the hospital was considered possible if the patient was able to consume more than one half a meal for approximately five continuous days; however, when a patient could not eat more than one half until the discharge day, we counted this as 50 days as a matter of convenience.

The weight ratio (%), assessed by comparing the weight at 1 month postoperatively with the preoperative weight was 95% in the PPPD and 93% in the SSPPD group, and the weight recovery was significantly better in the PPPD group (p=0.026).

The postoperative hospital stay was 31 days for the PPPD group and 38 days for the SSPPD group, being 7 days shorter for the PPPD group (P=0.017). It is noteworthy, however, that postoperative adjuvant chemotherapies were introduced in 9% of the PPPD patients (n=3) and 30% of the SSPPD patients (n=9) during the same hospitalization. This represented a significantly greater number in the SSPPD group (p=0.031). Additionally, the "postoperative hospitalization days or days until initiation of adjuvant chemotherapy" were 31.5 days in total, and 29 days in PPPD patients and 34 days in SSPPD patients, with no significant difference between two operative methods.

In addition, we separately analyzed the perioperative data and hospital course in cases of D1 and D2 lymph node dissection. In D1 lymph node dissection cases (Table 5), there was no difference in the background disease, operation time, or perioperative blood transfusion. However, there was a significantly higher volume of intraoperative bleeding in SSPPD (p=0.008). The postoperative outcomes showed no significant difference. In D2 lymph node dissection cases (Table 6), SSPPD included significantly more pancreatic cancer cases, and SSPPD resulted in significantly longer operation time, much blood loss, and perioperative blood transfusion. However, the postoperative outcomes were similar in both operative methods, except that pre- and postoperative weight ratio showed a significant difference.

Discussion

PD causes many postoperative complications. In particular, after a distal gastrectomy, the stomach pooling ability decreases, which impairs postoperative dietary intake. PPPD and SSPPD are an operative method to avoid distal gastrectomy and maintain the stomach pooling ability. In SSPPD, the gastrectomy line is set 2–3 cm proximal to the pylorus ring and is more distal than the gastrectomy line in

Table 5 D1 Lymph Node Dissection

	Total (n=22)	PPPD (n=16)	SSPPD (n=6)	p Value
Periampullary adenocarcinoma/other (n)	2/20	1/15	1/5	0.48
Operating time (min)	436 min (275–580)	436 (275–580)	437 (305–532)	0.76
Blood loss (ml)	730 ml (180–2700)	550 (180–2050)	1500 (730–2700)	0.008
Blood transfusion (units)	1 units (0–8)	0 (0–4)	1 (0–8)	0.23
Delayed gastric emptying (n)	4 (18%)	2 (13%)	2 (33%)	0.29
Start of solid diet (days)	7 days (5–12)	7 (5–35)	11 (5–12)	0.51
Eat one half of the provided meal routinely (days)	20 days (9–50)	19 (9–50)	23 (12–24)	0.63
Postoperative weight (1 month)/preoperative weight (%)	95% (89–100)	95 (89–100)	98 (93–99)	0.36
Postoperative hospital stay (days)	29 days (21–78)	27 (21–67)	33 (30–78)	0.066

Table 6 D2 Lymph Node Dissection

	Total (n=42)	PPPD (n=18)	SSPPD (n=24)	p Value
Periampullary adenocarcinoma/other (n)	40/2	17/1	23/1	0.68
Pancreatic cancer	16 (38%)	1 (6%)	15 (63%)	0.0001
Operating time (min)	500 min (322–768)	459 (322–670)	539 (415–768)	0.022
Blood loss (ml)	905 ml (180–3,300)	810 (180–2,080)	1085 (230–3,300)	0.019
Blood transfusion (units)	0 unit (0–14)	0 (0–4)	0 (0–14)	0.047
Delayed gastric emptying (n)	2 (5%)	1 (6%)	1 (4%)	0.68
Start of solid diet (days)	7 days (4–39)	7 (4–21)	7 (4–39)	0.90
Eat one half of the provided meal routinely (days)	24 days (3–50)	24 (5–50)	25 (3–50)	0.29
Postoperative weight (1 month)/preoperative weight (%)	94% (81–102)	95 (87–100)	92 (81–102)	0.034
Postoperative hospital stay (days)	38 days (19–90)	35 (19–62)	39 (22–90)	0.13

standard PD. This helps preserve almost the full capacity of the stomach and improves many of the postoperative symptoms of a gastrectomy. Compared with PPPD, as the pylorus ring is cut in SSPPD, there is no postoperative edema and paresis of the pylorus ring, and the passage of food through the stomach may be easier, which is expected to reduce DGE occurrence.[16]

Recent randomized control trials[6–10] have indicated that there is no difference in the curability and postoperative survival between PD and PPPD patients, and more surgeons are choosing PPPD as the preferred method for pancreatic cancer surgery. However, in our opinion, for cases of pancreatic cancer with invasion suspicious to the anterior serosa of the pancreas or around the pylorus ring, SSPPD rather than PPPD seems to be suitable from the oncologic viewpoint; SSPPD reduces the need for manipulation of the pancreas head, which leads to a reduction in tumor seeding and facilitates the dissection of the peripargastric lymph node around the pylorus ring because the gastroepiploic and infrapyloric arteries do not need to be preserved. There is no definite evidence for the tumor seeding during SSPPD,[19,20] and the necessity of peripargastric lymph node dissection in pancreatic cancer is controversial. However, in patients with pancreatic head cancer, it is known that lymph node metastases in 6% to 8% of the peripyloric lymph nodes and 0% to 1% of the lesser and greater curvature lymph nodes.[21,22] The procedure for an SSPPD is not particularly difficult, and the postoperative outcome is as good as that obtained with PPPD; our indication for the so-called standard PD, which involves removing 30–40% of the stomach, is extremely limited at Sapporo Medical University Hospital. Recently, the standard PD is only being performed on patients who have previously undergone a distal gastrectomy.

Regarding reports comparing PPPD with SSPPD, a collective case study was reported by Hayashibe et al.,[16] in which 12 patients underwent PPPD and 21 SSPPD. There was no significant difference regarding the operation time, bleeding, or length of hospitalization. However, nasogastric tube intubation lasted 11 days for PPPD and 6 days for SSPPD, and the number of days until the start of liquid diet was 15 days for PPPD and 10 days for SSPPD, both factors being significantly shorter in SSPPD. The occurrence of DGE was also significantly less in SSPPD (PPPD 50% vs. SSPPD 14%).

In our study, the results on postoperative dietary intake were almost equal between PPPD and SSPPD. The occurrence of DGE was low as well (PP 9%, SS 10%). The operation time was significantly long, and the amount of intraoperative bleeding and rate of perioperative transfusion were significant in SSPPD. The postoperative/preoperative weight ratio was significantly poor, and postoperative hospitalization was significantly long in SSPPD. We assume that the results in postoperative factors attribute to the fact that (1) SSPPD patients included more individuals with pancreatic cancer, requiring more aggressive surgery and D2 lymph node dissection, and (2) we tend to perform SSPPD in cases that we found difficulty in the maneuver around the pancreatic head during operation, regardless of the background disease. Even though the probability is very small, the resection of the antrum may have some influence on the postoperative body weight loss in SSPPD, and further study of the postoperative digestive function of SSPPD may be necessary. However, our conclusion is that postoperative digestive function in PPPD and SSPPD is almost equal, and pylorus preservation does not influence the postoperative dietary intake and the outbreak of DGE.

Recently, several reports have been published, indicating a lower incidence of DGE after specific reconstruction methods in PPPD.[23–28] One particular reconstruction method, the so-called “vertical stomach reconstruction”, was reported by Murakami et al.[23], and “antecolic duodenojejunostomy” was reported by Sugiyama et al.[24] In their method, the right gastric artery is divided, and the duodenum is antecolically anastomosed to the jejunum and placed below the mesocolon in a straight line. These researchers have reported the incidence of DGE as 10% and

8%, respectively. Tani et al.[25] reported a randomized control study of antecolic vs. retrocolic duodenojejunostomy in patients undergoing PPPD. DGE was 5% in the former and 50% in the latter, i.e., significantly smaller in the antecolic reconstruction. However, in our preliminary results, no significant differences between antecolic (n=18) and retrocolic patients (n=46) were found.

We have used a method for vertical and retrocolic stomach reconstruction in both PPPD and SSPPD as the standard since 2002. The stomach is stretched, and the duodenal cut off or the distal stomach is anastomosed below the mesocolon to set the stomach-to-jejunal loop vertically in the left abdomen. We sort the retrocolic route from the perspective to layout the stomach-to-jejunal loop straight in the ventral–dorsal direction as well. This vertically straight reconstruction may contribute to an alimentary downward movement as a result of the force of gravity.

Additionally, it has been reported that DGE is avoidable by appropriate postoperative management as well.[29] Our prescribed protocol of postoperative clinical management of patients included enteral tube-feeding from postoperative day 1 with laxative and cyclic enteral nutrition to promote early recovery of bowel peristalsis and the use of prokinetic agents such as erythromycin. Several randomized controlled trials have investigated that erythromycin decreases the incidence of DGE. [30,31] Previous studies gave erythromycin intravenously; however, we used erythromycin orally, and patients with DGE were not able to take the drug. Therefore, from our preliminary analysis (data not shown), oral intake of erythromycin seemed to have no correlation with the occurrence of DGE or oral intake.

The occurrence of DGE and patients postoperative oral intake ability are impacted by various matters; however, our reconstruction method and postoperative management resulted in a low incidence of DGE and good oral intake, whether PPPD or SSPPD was performed.

Conclusion

In this study, the dietary intake during the early postoperative period was approximately equal in the PPPD and SSPPD groups, and this outcome indicated that pylorus preservation is not a great risk for the outbreak of DGE.

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Cachexia Worsens Prognosis in Patients with Resectable Pancreatic Cancer

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Abstract
Introduction Pancreatic cancer is the fourth leading cause of cancer-related death in Western countries with a poor prognosis (5-year survival rates, 25% in patients after tumor resection with adjuvant treatment; overall, the 5-year survival rate is about 4%; Jemal et al., CA Cancer J Clin, 55:10–30, 2005). Many patients develop a cachectic status during the progression of the disease, and this syndrome accounts for up to 80% of deaths in patients with advanced pancreatic cancer. Remarkably, there are only a few data available on the impact of cachexia in patients with pancreatic cancer scheduled for tumor resection.
Material and Methods Therefore, in this study, 227 consecutive patients with ductal adenocarcinoma of the pancreas were documented over an 18-month period regarding the prevalence of cachexia and its influence on perioperative morbidity and mortality with a special interest to postoperative weight gain and survival in a prospectively designed database and followed up.
Results In 40.5% of the patients, cachexia was already present at the time of operation. The cachectic patients did present in a worse nutritional status, represented by lower protein, albumins, and hemoglobin levels. Despite no significant differences in tumor size, lymph node status, and CA19-9 levels, the resection rate in patients with cachexia was reduced (77.8% vs. 48.9%) due to a higher rate of metastatic disease in patients with cachexia. The morbidity and in-hospital mortality revealed no significant difference. However, patients with and without cachexia lost weight after operation, and the weight gain started not until 6 months after operation. The survival in patients with cachexia was significantly reduced in patients undergoing tumor resection as well as in palliative treated patients.
Conclusion Cachexia has a significant impact on survival and performance status in palliative patients as well as in patients operated for pancreatic cancer. But tumor-related cachexia is not necessarily dependent on tumor size or load and that metastatic dedifferentiation of the tumor might be a critical step in the development of tumor-associated cachexia.

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Keywords Cachexia · Pancreatic cancer · Nutritional status · Survival

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in Western countries, and in 2006, there were about 32,000 deaths related to pancreatic cancer in the USA.[1] Ductal pancreatic adenocarcinoma is characterized by retroperitoneal and perineural infiltration, early formation of multiple distant metastases, and resistance to most

adjuvant treatment regimes.[2–7] Surgical resection is the patient's only hope for cure and offers a significantly improved prognosis, with a median survival after resection of 14–20 months and 5-year survival rates up to 25%.[6,8–12] According to recent publications, the standard treatment regime in resectable pancreatic cancer should be a potentially curative resection followed by adjuvant systemic chemotherapy.[7,13,14] However, most patients develop local or distant tumor recurrence within 2 years after resection,[2,15–17] often associated with rapid development of a cachexia syndrome.

Today, there is no definitive and consistent definition of cachexia in cancer patients. However, most authors define cachexia in tumor patients as a weight loss of 10% or more within 6 months. Severe wasting accounts for approximately 30–50% of deaths in patients with gastrointestinal cancer and up to 80% of deaths in patients with advanced pancreatic cancer.[18–21] The main physical changes in cachexia are anorexia and malnutrition resulting from changes in gastrointestinal function and loss of appetite as well as massive loss of adipose and muscle tissue because of changes in lipid and protein metabolism.[20,22–26] Increased energy expenditure in combination with decreased energy intake exacerbates the progressive disturbance of nutritional status.[26–28] In particular, because of skeletal muscle loss, many cachexia patients develop pulmonary insufficiency with dyspnea as a frequent symptom (up to 80%).[29]

Different pathways of proteolysis in cancer cachexia have been proposed, but in spite of intensive research, most of the pathophysiological mechanisms remain poorly understood.[24] The underlying mechanisms of muscle depletion also are largely unknown, but several studies have shown that an ATP/ubiquitin-dependent pathway is responsible for muscle protein catabolism.[30] Reduced oral food intake and/or increased energy expenditure can lead to a negative protein balance and weight loss in pancreatic cancer patients.[31,32] In addition, pro-inflammatory cytokines are associated with altered host energy metabolism, leading to an acute-phase reaction that results in protein degradation.[32]

Although there has been some progress in elucidating the molecular mechanisms underlying the development of cancer cachexia, our knowledge of related clinical features, courses, and therapy is still limited. Physicians and surgeons often judge the cachexia syndrome as a one-way street of no return, yet to date, no detailed data on the progression of weight loss, especially in muscle or fat tissue, are available. In most cases, only the weight of the patient at the beginning of the disease is recorded; however, in cachectic patients with unresectable pancreatic cancer, nutritional interventions over an 8-week period could achieve weight stabilization and improve survival and quality of life.[18] For these reasons and to obtain more reliable data on the development and progression of cachexia in pancreatic cancer, we assessed over a period of 18 months (June 2004 through November 2005) the prevalence of cachexia in pancreatic cancer patients scheduled for tumor resection. Furthermore, the influence of cachexia on perioperative morbidity and mortality as well its impact on survival was examined in resectable pancreatic cancer patients.

Material and Methods

Patients

From June 2004 to November 2005, 227 patients with histologically confirmed ductal adenocarcinoma of the pancreas were operated in the Department of General Surgery, University of Heidelberg. Table 1 shows the characteristics of all patients in detail. Each patient was asked to give informed consent for data collection. For each patient, we performed a precise evaluation of the clinical course of the disease and the treatment until admission to our department. All data of patients who were referred for an operation were collected in a prospectively designed database. In 150 patients (66.1%), a tumor resection was performed, and in 77 patients (33.9%), a palliative operation was done because of local advanced disease or the intraoperative diagnosis of distant metastases.

Weight and Body Composition

Pre-illness stable weight, actual weight at operation, height, and duration of weight loss were registered. The body mass index for each participant was calculated [height[m]/(weight[kg] × weight[kg])]. The patients were assessed as being cachectic in cases of unintended weight loss greater than 10% of the pre-illness stable body weight. In addition, the occurrence of diabetes mellitus and related treatment were registered.

Histological Diagnosis

The histological diagnosis of ductal pancreatic cancer in each patient was established by two independent pathologists of the Department of Pathology, University of Heidelberg. In case of tumor resection, histopathological classification was made according to the TNM classification, version 2005, including examination of the resection margin and grading. Tumor staging was determined according to the Union Internationale Contre le Cancer (UICC) classification.[33,34]

Postoperative Nutritional Management

On the first postoperative day, patients were allowed to drink tea and/or water up to 500 ml/day; on the second

Table 1 Characteristics of Pancreatic Cancer Patients with and without Cachexia Scheduled for Tumor Resection

Patients with PDAC *N*=227		∅ Cachexia *N*=135 (59.5%)	Cachexia *N*=92 (40.5%)	*p* value
Gender	Male	69 (51.1)	60 (65.2)	0.036
	Female	66 (48.9)	32 (34.8)	
Age		64 (57/70)	65 (57/70)	0.380
Body mass index		24.2 (22.57/27.2)	23.01 (20.76/25.47)	0.003
Weight loss (kg)		2 (0/5)	12 (10/15)	<0.001
Weight loss (%)		2.1 (0/6.5)	14.9 (11.5/19.2)	0.001
CA19-9 (U/ml)		161 (43.25/588.65)	262.20 (46.9/1,367.0)	0.199
ASA classification	I	2 (1.5)	1 (1.1)	0.007
	II	63 (46.7)	27 (29.3)	
	III	69 (51.1)	62 (67.4)	
	IV	1 (0.7)	2 (2.2)	
Tumor resection	yes	105 (77.8)	45 (48.9)	<0.001
	no	30 (22.2)	47 (51.1)	
Distant metastases		37 (27.4)	39 (42.4)	0.019
Tumor stage	UICC II	92 (68.1)	45 (48.9)	0.005
	UICC III	6 (4.4)	8 (8.7)	
	UICC IV	37 (27.4)	39 (42.4)	
30 days mortality		5 (3.7)	6 (6.5)	0.333
Morbidity		56 (41.5)	40 (43.5)	0.765
Diabetes mellitus	Yes	27 (20)	43 (46.7)	<0.001
	No	108 (80)	49 (53.3)	

postoperative day, the patients were allowed to drink as much as they wanted, and oral food intake was routinely started on the third postoperative day. In patients with delayed gastric emptying (nausea, repeated vomiting) or patients with delayed oral food intake, we started a parenteral nutrition on the fifth postoperative day. After resection, every patient was given enzyme supplementation orally.

Morbidity

For in-hospital morbidity, every sign or symptom that prolonged the in-hospital stay and/or had to be treated by surgical therapy, interventional drainage, or non-invasive therapy was registered. The prevalence of wound infection, postoperative bleeding, and cholangitis, pancreatic fistula, intra-abdominal abscesses, delayed gastric emptying, pneumonia, urinary tract infection, myocardial infarction, and pulmonary embolism were evaluated.[35,36]

Follow-up

For follow-up, we saw patients every 6 months in our outpatient clinic or performed a telephone interview. Patients were asked if any treatments were necessary after discharge from the Department of Surgery. In addition, we asked whether they had developed diabetes, whether body weight was stable after the operation, and whether they had completed planned adjuvant or palliative oncological treatment.

Statistical Analysis

Statistical analysis, including multivariate analysis, was performed using SPSS software, version 14 (SPSS Inc., Chicago, IL., USA). Survival curves were calculated using Kaplan–Meier analysis and the log-rank test. For testing significant differences between the examined groups, we

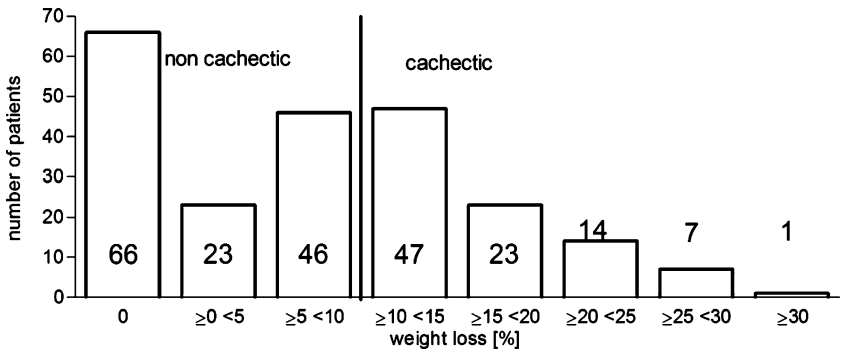


Figure 1 Preoperative weight loss in 227 consecutive patients scheduled for tumor resection: shows the distribution of weight loss (%) in patients divided in patients with and without cachexia.

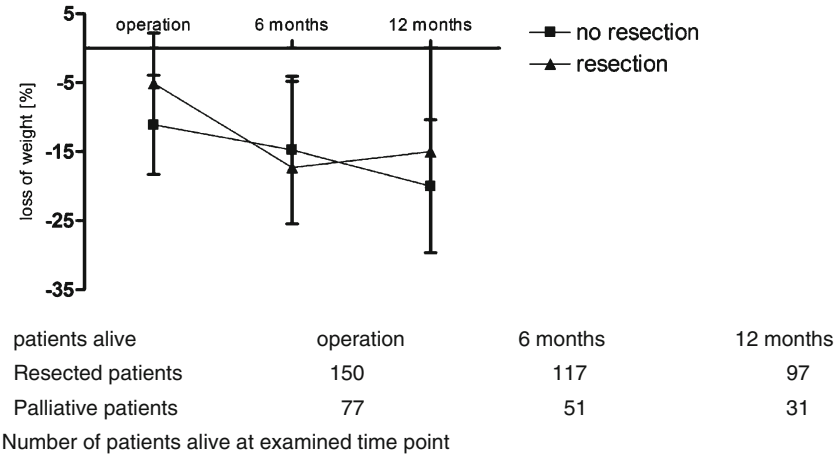


Figure 2 Postoperative weight course of pancreatic cancer patients with tumor resection or with palliative operations.

used the Student's *t* test and the Mann–Whitney *U* test. Significance level was defined as $p<0.05$. Results are reported as median [lower/upper quartile].

Results

All Patients

Of the 227 patients with histologically proven ductal adenocarcinoma, 40.5% ($N=92$) were cachectic and 59.5% ($N=135$) were non-cachectic (Table 1). Figure 1 presents the distribution of weight loss in the patients who presented in the department of surgery for an operative treatment. Regarding the body mass index, there was a significant difference between cachectic and non-cachectic patients ($p=0.003$, Table 1). Median weight loss in cachectic patients was 12 kg (10/15 kg); median relative weight loss was 14.9% (11.5/19.2). In the non-cachectic patients, median weight loss and relative weight loss was 2 kg (0/5) and 2.1% (0/6.5), respectively ($p<0.001$). Figure 2 shows the postoperative course of weight loss and weight gain in patients with pancreatic cancer after tumor resection or palliative operation. There was no significant difference in preoperative CA19-9 levels as a marker of tumor load [non-cachectic: median=161 U/l (43.25/588.65) vs. 262.20 (46.9/1367.0) in cachectic patients] ($p=0.199$).

We identified a significant difference in resection rate between patients with and without cachexia: in 77.8% of patients without cachexia and in only 48.9% of patients with cachexia, tumor resection was possible ($p=<0.001$). In 150 patients, the tumor could be resected, and in 77 patients, a palliative bypass operation or an exploratory laparotomy was performed. Stage UICC II was diagnosed in 68.1% ($N=92$) of patients without cachexia versus 48.9% ($N=45$) of patients with cachexia. During the operation, significantly more UICC IV stages (metastatic disease) were diagnosed in patients with cachexia (42.4%, $N=39$) than in patients without cachexia (27.4%, $N=37$; $p=0.005$). In regard to perioperative morbidity and in-hospital mortality, there was no significant difference between patients with and without cachexia (perioperative morbidity $p=0.765$, in hospital mortality $p=0.333$). In contrast, there was a significant difference in endocrine pancreatic function between the groups. A total of 20% ($N=27$) of patients without cachexia had diabetes mellitus, but in the group of patients with cachexia, 46.7%, ($N=43$) were diabetic ($p=<0.001$). There was no significant difference in the treatment of diabetes mellitus between patients with and without cachexia ($p=0.557$) regarding the need of insulin, oral medication, or a glucose-reduced diet. Table 2 shows

Table 2 Laboratory Tests of Pancreatic Cancer Patients with and without Cachexia Scheduled for Tumor Resection

Patients with PDAC $N=227$	∅ Cachexia $N=135$ (59.5%)	Cachexia $N=92$ (40.5%)	p value
CrP (g/l)	4.4 (1.0/10.1)	8.3 (2.3/30.9)	0.003
Protein (g/l)	73.9 (71.15/77.2)	71.9 (68.18/75.6)	0.007
Albumin (g/l)	44.1 (41.3/46.1)	41.35 (39.43/43.9)	<0.001
Glucose (mg/dl)	111.5 (98.0/141.0)	141.0 (104.25/175.25)	0.002
Haemoglobin (g/dl)	13.1 (12.15/14.3)	12.6 (11.53/13.7)	0.019
Bilirubin (mg/dl)	0.8 (0.45/2.05)	0.9 (0.5/3.7)	0.301

Table 3 Characteristics of Patients with and without Cachexia Undergoing Tumor Resection

Resected patients N=150		∅ Cachexia N=105 (70%)	Cachexia N=45 (30%)	p value
Gender	Male	52 (49.5)	29 (64.4)	0.094
	Female	53 (50.5)	16 (35.6)	
Age		64 (57/ 70)	66 (61/72)	0.245
Body mass index		24.22 (22.54/27.37)	23.67 (21.88/26.16)	0.189
Weight loss (kg)		0 (0/ 4.5)	12 (10.0/16.5)	<0.001
Weight loss (%)		0 (0/ 5.7)	15.3 (12.3/20)	<0.001
CA19-9 (U/ml)		148.85 (36.39/419.5)	137.45 (20.73/658.93)	0.980
ASA classification	I	2 (1.9)	0 (0)	0.198
	II	49 (46.7)	17 (37.8)	
	III	54 (51.4)	28 (62.2)	
Tumor size	T1	1 (1.0)	0 (0)	0.508
	T2	0 (0)	0 (0)	
	T3	101 (96.2)	45 (100)	
	T4	3 (2.8)	0 (0)	
Lymph node status	Negative	23 (21.9)	9 (20)	0.795
	Positive	82 (78.1)	36 (80)	
Distant metastases		11 (10.5)	1 (2.2)	0.089
Grading	G1	4 (3.9)	6 (14.3)	0.076
	G2	64 (62.7)	26 (61.9)	
	G3	34 (33.3)	10 (23.8)	
Resection margin	R0	58 (55.8)	18 (40)	0.062
	R1	43 (41.3)	24 (53.3)	
	R2	3 (2.9)	3 (6.7)	
Tumor stage	UICC II	91 (86.6)	44 (97.8)	0.040
	UICC III	3 (2.9)	0 (0)	
	UICC IV	11 (10.5)	1 (2.2)	
Type of resection	Whipple	78 (74.3)	39 (86.7)	0.076
	Total DP	8 (7.6)	4 (8.9)	
	Left res.	19 (18.1)	2 (4.4)	
30 days mortality		3 (2.9)	2 (4.4)	0.621
Morbidity		45 (42.9)	25 (55.6)	0.155
Diabetes mellitus	Yes	22 (21)	22 (48.9)	0.001
	No	83 (79)	23 (51.1)	

DP duodenopancreatectomy, *Left res* left resection

the differences in laboratory results between patients with and without cachexia. In patients with cachexia, total protein (p=0.007), albumin (p=<0.001), and hemoglobin levels (p=0.019) were significantly reduced. In contrast, C-reactive protein (CrP; p=0.003) and glucose levels (p= 0.002) were significantly elevated in these patients. There was no difference in bilirubin levels between the patients with and without cachexia (p=0.301).

To evaluate the impact of cachexia on the postoperative course, patients were separated into a resected and a palliative-operated group.

Patients Undergoing Tumor Resection

In patients undergoing tumor resection (N=150), there was no significant difference in age, gender, body mass index or American Society of Anesthesiologists (ASA) classification. Table 3 highlights that the distribution of the type of resections is not significantly different between patients with and without cachexia. Furthermore, a difference in tumor location between patients with and without was not present, and the preoperative documented weight loss was independent of the tumor location. The CA19-9 levels were

Table 4 Laboratory Results in Patients with and without Cachexia Undergoing Tumor Resection

Patients with PDAC N=150	∅ Cachexia N=105 (70%)	Cachexia N=45 (30%)	p value
CrP (g/l)	4.1 (1.0/9.2)	6.3 (1.0/11.7)	0.317
Protein (g/l)	73.5 (70.73/77.2)	70.85 (68.33/75.8)	0.040
Albumin (g/l)	43.9 (40.98/45.90)	41.7 (39.6/43.9)	0.016
Glucose (mg/dl)	113.0 (98.75/142.5)	124.0 (98.0/169.5)	0.252
Haemoglobin (g/dl)	13.0 (12.05/14.25)	13 (11.7/13.7)	0.316
Bilirubin (mg/dl)	0.8 (0.4/1.85)	1.45 (0.6/6.28)	0.078

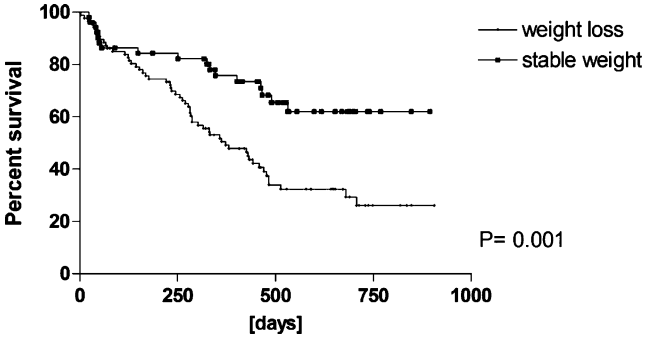


Figure 3 Kaplan–Meier survival curves in resectable pancreatic cancer patients with preoperative weight loss and resectable pancreatic cancer patients with stable weight.

not significantly different between patients, in whom a tumor resection was performed, with and without cachexia as well as tumor size and lymph node metastases as an index for similar tumor load in these groups. The median relative weight loss in patients after tumor resection at the time of operation was 0% (0/5.7) in patients without cachexia and 15.3% (12.3/20) in patients with cachexia (p=<0.001). However, although CA 19-9 levels, tumor size, lymph node invasion, and tumor stage were comparable, patients with cachexia had a tendency to a higher rate of R1 resections than patients without cachexia (p=0.062). Furthermore, more patients with cachexia and pancreatic cancer developed diabetes mellitus (p=0.001, Table 3); patients undergoing tumor resection with cachexia had significantly reduced protein (p=0.040) and albumin levels (p=0.016, Table 4). There was a non-significant tendency to longer survival in patients without cachexia (p=0.240). Median survival was 483 days for patients without cachexia compared to 426 days for patients with cachexia.

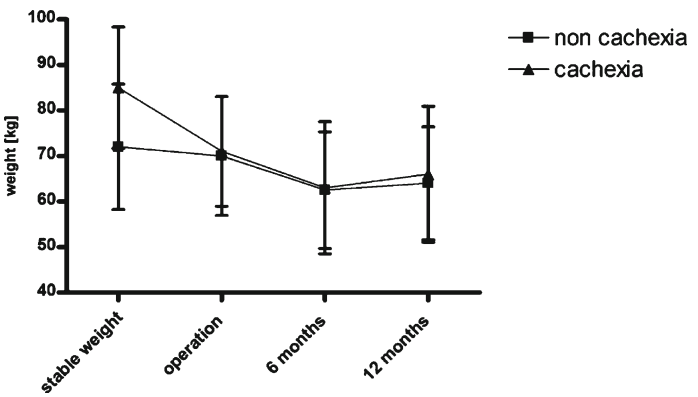
In contrast, when patients are divided into groups with and without weight loss, a significant survival difference was found. Patients without weight loss had a mean survival of 654 days, whereas survival for patients with weight loss was 451 days after resection (p=0.001, Fig. 3). Furthermore, in the multivariate analysis, weight loss emerged as an independent prognostic factor. At the end of the follow-up period [median follow-up 406 days (221/; 532)] 59.3% (N=80) of patients without cachexia were still alive; 44.4% (N=40) of patients with cachexia were alive.

In this study, the natural course of postoperative weight loss/gain of the patients was evaluated every 6 months. Figure 4 shows the pre-illness stable weight as well as the median body weight at operation and the postoperative course at 6 and 12 months after the operation. Interestingly, patients with and without cachexia exhibited weight loss after tumor resection. At 6 months after the operation, patients with cachexia had lost 23.4% of their pre-illness stable weight, and patients without cachexia had lost 14.8%. Weight gain began at the earliest at 6–12 months after the operation (Fig. 4).

Palliative Surgery

In 77 patients, a palliative surgical procedure—either exploratory laparotomy, gastrojejunostomy, and/or a choledochojejunostomy—was performed. A total of 38.9% (N=30) of the palliative operated patients had no cachexia; the remaining 61.03% (N=47) did. Between the two groups, there were no significant differences in age, gender, ASA classification, occurrence of distant metastases, or tumor stage (Table 5).

Survival did not differ between the two groups. Median survival was 287 days in patients without cachexia compared to 227 days for patients with cachexia (Fig. 5). After the palliative surgery, patients continued to lose body



patients alive	operation	6 months	12 months
Non cachexia	105	74	51
Cachexia	45	32	22

Number of patients alive at examined time points

Figure 4 Median weight in patients with resectable pancreatic cancer patients: 6 months before tumor diagnosis (stable weight), 1 day before tumor resection (operation), 6 months postoperatively, and 12 months postoperatively.

Table 5 Characteristics of Patients with and without Cachexia Undergoing Palliative Surgery

Palliative surgery N=77		∅ Cachexia N=30 (38.9%)	Cachexia N=47 (61.03%)	p value
Gender	Male	17 (56.7)	31 (66.0)	0.415
	Female	13 (43.3)	16 (34.0)	
Age		63 (55/70)	64 (55/70)	0.597
Body mass index		24.81(22.55/27.29)	22.59 (19.93/24.93)	0.017
Weight loss (kg)		3.5 (1.5/6)	12 (10/15)	<0.001
Weight loss (%)		5.8 (1.7/7.9)	14.9 (11.4/18.6)	<0.001
Ca19-9 (U/l)		435.00 (66.1/2711.0)	359.0 (79.9/2483.0)	0.771
ASA classification	I	0 (0)	1 (2.1)	0.055
	II	14 (46.7)	10 (21.3)	
	III	15 (50.0)	34 (72.3)	
	IV	1 (3.3)	2 (4.3)	
Distant metastases		26 (86.7)	38 (80.8)	0.509
Tumor stage	UICC II	1 (3.3)	1 (2.1)	0.536
	UICC III	3 (10.0)	8 (17.0)	
	UICC IV	26 (86.7)	38 (80.9)	
30 days mortality		21 (6.7)	4 (8.5)	0.770
Morbidity		11 (36.7)	15 (31.9)	0.669
Diabetes mellitus	Yes	5 (16.7)	21 (44.7)	0.012
	No	25 (83.3)	26 (55.3)	

weight regardless of their preoperative weight loss (Fig. 6). In the lab work results, there were significant differences between patients with and without cachexia. The CrP levels were doubled in patients with cachexia (p=0.019) compared to patients without cachexia. Albumin (p=<0.001) and protein levels (p=0.051) were reduced in patients with cachexia. The glucose levels were significantly elevated in patients with cachexia (p=0.003); hemoglobin was also significantly reduced in patients with cachexia (p=0.007). In bilirubin levels, there was no significant difference between the examined groups (Table 6).

Discussion

This study examined 227 consecutive patients, 150 of these underwent resection for ductal adenocarcinoma of the pancreas. The prevalence of cachexia in this study was 40.5%, demonstrating that even in selected patients with an early stage of pancreatic cancer who are scheduled for pancreatic cancer resection, almost half of the patients had significant preoperative weight loss. We can assume that the occurrence of a dramatic weight loss is a symptom of a progressed tumor stage (Table 1). Additionally, the weight loss of patients with cachexia had significant impact on the nutritional status, with reduced protein, albumin, and hemoglobin levels. Furthermore, patients with cachexia had significantly higher CrP levels, which underlines the chronic and systemic inflammatory reaction of these patients and supports the proposal of Fearon et al.[32] to include CrP values in the diagnosis of cachexia (Table 2). This emphasizes that pancreatic cancer even in non-metastatic stages causes a systemic process, and there are hints that pro-inflammatory reactions can induce hypermetabolism resulting in weight loss and cachexia.[37] In addition, it is well known that pancreatic cancer can induce diabetes, and this is especially true in patients with cachexia which had a significant higher rate of diabetes with an altered glucose metabolism represented by higher glucose levels, which may highlight the underestimated systemic effects of the tumor.[38]

For further analysis, the patients were separated into a resected and a palliative-treated group. In patients with

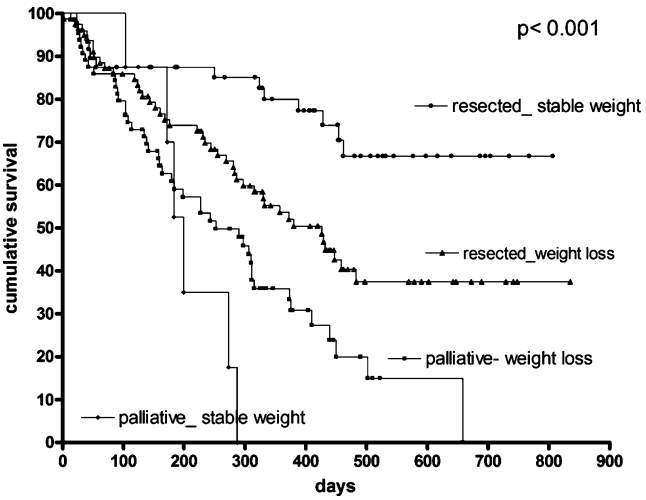
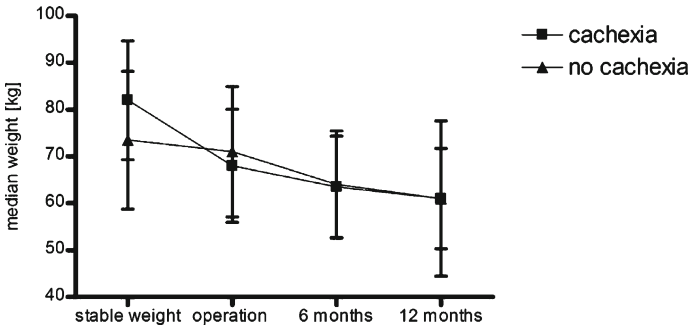


Figure 5 Kaplan–Meier survival curves in pancreatic cancer patients with tumor resection and preoperative weight loss, pancreatic cancer patients with tumor resection and preoperative stable weight, pancreatic cancer patients with palliative surgery and preoperative weight loss and stable weight, and pancreatic cancer patients with palliative surgery with stable weight.



patients alive	operation	6 months	12 months
Non cachexia	30	18	10
Cachexia	47	25	9

Number of patients alive at examined time points

Figure 6 Median weight in patients with non-resectable pancreatic cancer patients: 6 months before tumor diagnosis (stable weight), 1 day before tumor resection (operation), 6 months postoperatively, and 12 months postoperatively.

tumor resection, no differences in tumor size, resection margins, or lymph node invasion were present between patients with and without cachexia. These results agree with those of recent studies which found that tumor-related cachexia is not necessarily dependent on tumor size or load.[39–41] Further support comes from the finding that preoperative CA 19-9 levels in patients with and without cachexia (in the resection as well as in the palliative groups) was not significantly different. Moreover, the occurrence of distant metastasis was significantly higher in patients with cachexia, leading to a reduced resection rate and a worse UICC Stadium in these patients. The earlier metastatic occurrence in patients with cachexia suggest that dedifferentiation of the tumor is a critical step in the development of tumor-associated cachexia. A recent study has found that certain tumors may create an environment that predetermines metastasis by tumor-mediated upregulation of chemoattractants; thus, metastatic dedifferentiation of the tumor might play a key role in the systemic effects of malignant diseases.[38]

We also found that weight loss in the context of cachexia is an important factor in the prognosis of patients with pancreatic cancer. In this study, survival was significantly better in patients who exhibited no weight loss compared to patients who did, especially in the resected group. Additionally, this observation was verified by multivariate analysis in which weight loss was identified as an independent prognostic factor for survival in patients with pancreatic cancer. Davidson et al.[18] demonstrated recently a longer survival in weight-stable pancreatic cancer with palliative treatment. The current study has now shown that this is also the case for patients who undergo resection for pancreatic cancer.

In addition, there was no difference in the preoperative performance status of the patients. Remarkably, all patients, regardless of group, lost up to 23% of their stable weight as far as 6 months after the operation. Quite surprisingly, initial weight gain started no earlier than 6–12 months after resection, and no differences in the postoperative course of weight gain between patients after tumor resection with and without cachexia were found, whereas the postoperative course of weight in palliative patients is difficult to explain because only very few patients survived for 12 months in this group. This outcome may mean that progressive weight loss of patients with cachexia could be moderated by tumor resection, thereby removing the trigger for wasting in tumor-associated cachexia.

Conclusion

In conclusion, patients with cachexia undergoing tumor resection do not exhibit a worse preoperative performance condition and do not have larger tumors or a worse tumor

Table 6 Differences in Laboratory Tests in Palliative Operated Patients with and without Cachexia

Patients with PDAC *N*=77	∅ Cachexia *N*=30 (38.9%)	Cachexia *N*=47 (61.03%)	*p* value
CrP (g/l)	7.2 (1.8/11.6)	14.7 (5.1/37.9)	0.019
Protein (g/l)	75.1 (71.93/77.23)	72.2 (67.85/75.58)	0.051
Albumin (g/l)	44.7 (42.75/47.1)	41.15 (38.53/ 43.55)	<0.001
Glucose (mg/ dl)	105.5 (97,25/135.25)	149.0 (107.0/191.0)	0.003
Haemoglobin (g/ dl)	13.75 (12.65/14.58)	12.60 (11.2/13.6)	0.007
Bilirubin (mg/dl)	1.0 (0.5/3.0)	0.8 (0.5/2.45)	0.705

grade; however, preoperative weight loss may predict a shorter survival. Because more cachectic patients are in a metastasized tumor stage, this status is associated with more progressed tumor disease. Therefore, weight loss may indicate a switch of pancreatic cancer to systemic disease. More efforts should target minimizing pre- and postoperative weight loss because even stabilization of weight can prolong survival.[18] We suggest that in further studies of pancreatic cancer treatment, more attention should be focused on the development of cachexia and ongoing weight loss.

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Open and Laparoscopic Spleen-preserving, Splenic Vessel-preserving Distal Pancreatectomy: Indications and Outcomes

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Abstract
Background Spleen-preserving distal pancreatectomy has been described lately in order to reduce the risks associated with splenectomy. The aim of this study is to report a series of open and laparoscopic distal pancreatectomies with splenic vessel preservation.
Methods From June 2001 to April 2007, 11 spleen-preserving distal pancreatectomies were performed, utilizing open and laparoscopic techniques. The main variables recorded were demographics, intra- and postoperative complications, and final pathology results.
Results All 11 spleen-preserving distal pancreatectomies were performed successfully. Laparoscopic resection was possible in seven patients. Postoperative morbidity consisted of one pancreatic fluid collection. The overall incidence of pancreatic leak was 18%. The final pathology revealed serous cystadenoma in 36% of the cases, neuroendocrine tumor in two cases, three mucinous cystadenomas, one carcinoid tumor, and one intrapancreatic spleen. With a median follow-up of 26 months, no splenic vein thrombosis was detected.
Conclusions Open or laparoscopic spleen-preserving distal pancreatectomy with splenic vessel preservation is a feasible and safe procedure. In selected cases of cystic lesions and low grade neoplasms, distal pancreatectomy with splenic preservation is possible.

Keywords Laparoscopy · Pancreatic resection · Splenic preservation

Introduction

Historically, distal pancreatectomy included removing the spleen due to the anatomical proximity of the body and tail of the pancreas to the splenic artery and vein. Several authors have described spleen-preserving distal pancreatectomy in order to reduce the changes and risks associated with splenectomy.[1–4] Complications following splenectomy include leukocytosis, thrombocytosis, overwhelming postsplenectomy sepsis, and some degree of immunodeficiency. There are few reports of spleen-preserving distal pancreatectomy: in the setting of pancreatic trauma, chronic or acute pancreatitis and for benign pancreatic tumors. Technically, the spleen can be preserved in three different ways when performing a distal pancreatectomy.[4] First, the operation can be performed by preserving the splenic vessels, assuring excellent blood supply to the spleen. Second, it can be achieved by sacrificing the splenic vessels but with the preservation of both the short gastric and left gastroepiploic arteries and veins. Finally, spleen-preserving distal pancreatectomy can be performed with the ligation of the splenic, short gastric, and gastro-epiploic arteries and veins. In these last two operations, the blood supply to the spleen postoperatively remains uncertain.

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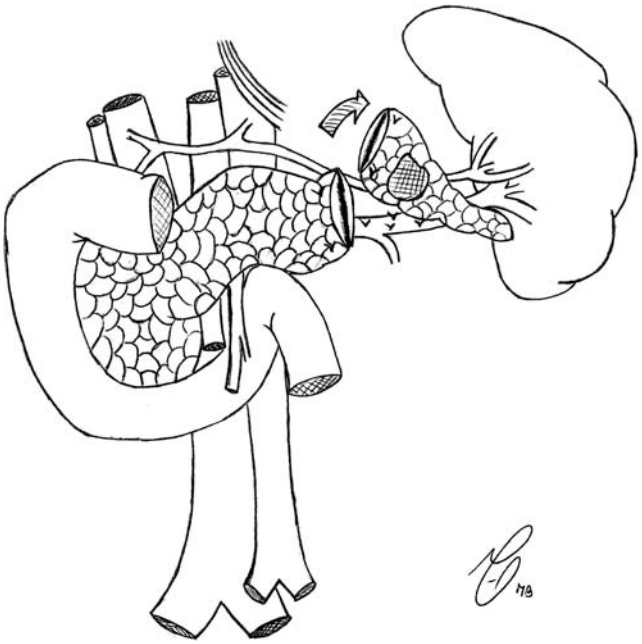

Figure 1 Open splenic vessel preserving distal pancreatectomy technique.

By preserving the splenic artery and vein, there is good blood supply to the spleen, and the danger of splenic necrosis and abscess formation is reduced.[5] In attempt to mitigate the sequelae following the splenectomy, we have been interested in preserving the spleen during distal pancreatectomy. The aim of this study is to report a series of open and laparoscopic distal pancreatectomies with spleen and splenic vessel preservation, its indications, and the outcomes.

Material and Methods

We retrospectively reviewed a series of distal pancreatectomies performed from June 2001 to April 2007 at the University of Nebraska Medical Center. Only those operations where spleen and splenic vessel preservations were possible were included in our analysis. Both open and laparoscopic approaches were performed. The main variables recorded were demographic data, intra- and postoperative complications, operative time, estimated blood loss, length of stay, final pathology results, and the incidence of pancreatic leak. A closed suction drain close to the pancreatic stump was placed in every patient. Postoperative pancreatic fistula was defined as the drain amylase level three times the serum level after postoperative day 3, in accordance with the International Study Group on Pancreatic Fistula Definition.[6] Follow-up was recorded from the outpatient clinic visits. This was a study approved by the Institutional Review Board at the University of Nebraska Medical Center at Omaha, NE, USA.

Operative Techniques

Open Approach

Following a midline incision, the patient's abdomen is explored. The gastrocolic ligament is divided exposing the lesser sac. The inferior border of the pancreas body is then mobilized along its entire length, starting from the left of the superior mesenteric vein proceeding to the splenic hilum. With the exception of lesions in the very distal aspect of the pancreas tail, all resections are performed in an antegrade fashion. The pancreatic body is transected after the splenic vein is dissected free from the under surface of the pancreas. Following this, small branches from the splenic vein and the splenic artery are individually ligated. The dissection proceeds toward the splenic hilum until the distal aspect of the pancreas has been completely mobilized. The pancreatic stump is oversewn, and the omentum mobilized and sutured to the pancreatic stump. An external close suction drain is placed near the pancreatic cut surface (Figs. 1 and 2).

Laparoscopic Approach

The patient is placed in the supine position. In selected patients who have lesions in the distal most aspect of the pancreatic tail, the patient is placed in a modified left lateral decubitus position (30°). A 10-mm supraumbilical port is placed as well as a 10-mm port in the left upper abdomen, along the left midclavicular line. A 5-mm port is placed in the left anterior axillary line just below the costal margin. An additional 5-mm port is typically placed in the epigastric region. Following the survey of the abdomen, the gastrocolic ligament is then divided using a Ligasure (Valleylab, Boulder, CO, USA). Occasionally, this is carried out to

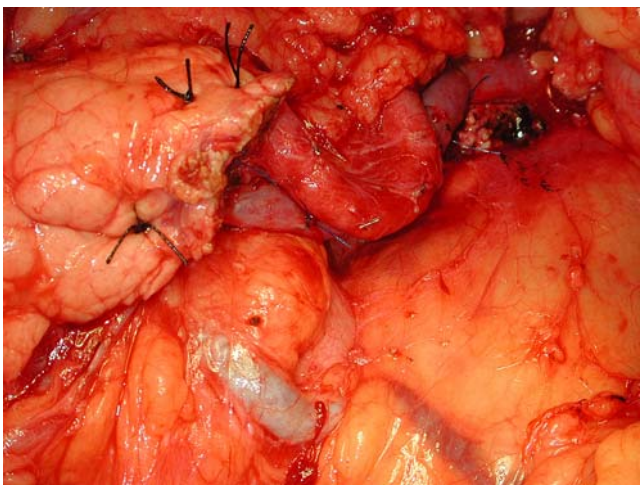

Figure 2 Splenic artery and vein (*arrows*) after open distal pancreatectomy.

mobilize the splenic flexure. This allows us to expose the inferior aspect of the pancreas body. The pancreas body is then dissected from the retroperitoneum exposing the splenic vein. The neck of the pancreas is then transected using the Ligasure at the splenic vein/superior mesenteric vein confluence. Using either a 5-mm Ligasure or small clips, venous branches to the pancreatic body are occluded and divided. This proceeds in an antegrade fashion towards the splenic hilum. Once this is complete, the splenic artery is identified at the superior border of the pancreas and the dissection proceeds in a retrograde fashion with similar techniques used to divide the arterial branches. The specimen is placed into a specimen bag and brought out through the umbilical port site. The pancreatic stump is then cauterized and a looped suture is applied around the pancreatic stump to constrict it circumferentially. A close suction drain is placed near the pancreatic cut surface and brought out through one of the trocar sites.

Results

From June 2001 to April 2007, a total of 30 distal pancreatectomies were performed. Spleen and splenic vessel preservation was possible in 11 patients (36%). All 11 spleen-preserving pancreatectomies were performed successfully. Laparoscopic resection was possible in the seven patients and there were no conversions to open. The patient demographics and results are outlined in Table 1. The mean tumor size was 2.9 cm, ranging between 0.7 and 7.5 cm. Only one patient suffered an intraoperative splenic artery injury, which was repaired without consequence. Postoperative morbidity consisted of one amylase rich pancreatic fluid collection, which was drained percutaneously by the interventional radiology. The mean operative time was 152 min for the open group and 182 min for the laparoscopic group. The estimated blood loss was 214 and 362 ml in the laparoscopic and open group, respectively. The median length of stay for the open and laparoscopic approach was 9 and 6.2 days, respectively. The mean length of the pancreatic specimen resected was 6 cm (3.4–12). Pathologic examination revealed serous cystadenoma in four patients (36%), three mucinous cystadenomas, neuroendocrine tumor of the pancreas in two cases, one carcinoid tumor, and one intrapancreatic spleen (Table 1). Seven patients (63%) had elevated drain amylase levels (greater than three times serum level) on postoperative day 2. In all but one patient, the drain amylase level normalized when it was reevaluated on the postoperative day 5. Overall, the incidence of pancreatic leak was 18%. With a median follow-up of 26 months, no splenic vein thrombosis was detected.

Discussion

Preserving the spleen during distal pancreatectomy can be technically challenging, however, given the risk of the infectious complications of a splenectomy, several authors believe that it is worth it.[7–11] Postsplenectomy patients are immunocompromised hosts. A quantitative reduction in T-helper2 cells count and interleukin-12 concentrations has been documented.[12, 13] These abnormalities may be of clinical relevance in terms of host protection against invading organisms, especially the pneumococcal infections. In a review of over 12,000 patients, it was demonstrated that removal of the spleen in the nonmalignant disease in adults was not associated with the increased frequency of infection.[14] However, the authors stated that the severity of the infection is worse in the postsplenectomy patients. In addition, it is also well-documented that the incidence of overwhelming postsplenectomy sepsis is increased in splenectomy for malignant disease.[15] Despite the immunologic

Table 1 Open and Laparoscopic Approach Results

	Open	Laparoscopic
n	4	7
Age—mean (range)	63.2 (37–81)	63.8 (34–78)
BMI—mean (range)	29	29.5
Intraoperative complications	1	–
Size (cm)—mean (range)	3.8 (2–7.5)	2.3 (0.7–5.5)
Operative time (min)—mean (range)	152 (145–185)	182 (120–300)
EBL (ml)—mean (range)	362 (200–450)	214 (20–950)
Postoperative complications	–	1[a]
Length of stay (days)—mean (range)	9 (6–15)	6.2 (2–21)
Pathology	1 serous cystadenoma	3 serous cystadenoma
	1 mucinous cystadenoma	2 mucinous cystadenoma
	1 carcinoid	1 neuroendocrine
	1 insulinoma	1 intrapancreatic spleen

[a] Postoperative fluid collection

consequences of splenectomy, preserving the spleen during distal pancreatectomy is still controversial. Benoist and colleagues reported that the spleen preservation was associated with more morbidity when compared to splenectomy when performing a distal pancreatectomy.[16] On the other hand, in a retrospective review from Memorial Sloan-Kettering Cancer Center, after comparing the distal pancreatectomy with and without splenectomy, the authors concluded that preserving the spleen was associated with a reduction in perioperative infectious complications, severe complications, and length of hospital stay.[9] Another advantage of spleen preservation is that an increase in the white cell or platelet count does not occur.[1]

A common complication after distal pancreatectomy is pancreatic leak. Several authors have proposed different techniques to reduce its incidence. These include various ways of transecting the pancreas (ultrasonic dissector, harmonic scalpel, bipolar cautery, etc.), fibrin glue sealing of the pancreatic stump, and octreotide administration. Lately, a group from Japan published satisfactory results with the use of prophylactic preoperative pancreatic stents.[17] The International Study Group on Pancreatic Fistula Definition published in 2005 the new guidelines to characterize a pancreatic leak.[6] Another issue discussed in this meeting was the amylase content in operative placed drains. Fluid amylase is well recognized as an integral and unavoidable biochemical definition of postoperative pancreatic fistula (POPF), but the amylase activity can range from hundreds to thousands of international units depending on the pancreatic glandular function and dilution by the inflammatory serous fluid. The consensus agreed to a value of more than three times the normal serum value on a postoperative day 3 to denote when the POPF is first suspected. Strasberg et al.[18] and DeOliveira et al.[19] also suggested a new grading classification (grade 1 to grade 5) of postoperative pancreatic–enteric anastomosis failure based on the clinically relevant definitions, which we think might also apply to our study.

In our patient population, the drain amylase was measured in the postoperative days 2 and 5 in order to suspect the development of pancreatic leaks. Sixty-three percent of the patients presented high drain amylase levels on postoperative day 2 and only one patient persisted with the elevated drain amylase levels on postoperative day 5. In addition, one patient presented with a postoperative fluid collection requiring percutaneous drainage, which gives us an 18% incidence of pancreatic leak.

Two rare complications that may occur after this procedure are bleeding from the splenic vessels or splenic vein thrombosis. Bleeding can be due to digestion of the wall of the splenic vein or artery by the pancreatic juice originating from the cut end of the pancreas. Injury to the splenic vein intraoperatively can result in thrombus formation also. None of these complications were seen in our group of patients.

During the last decade, laparoscopic splenic vessel preserving distal pancreatectomy has been described, mainly for benign lesions of the distal pancreas.[10,20–24] All authors came to the conclusion that laparoscopic splenic vessel preserving distal pancreatectomy is as safe and feasible as the open technique. Our series included seven laparoscopic approaches. There was no need to convert to an open operation and there was one postoperative complication consisting of a fluid collection that was drained percutaneously. The laparoscopic approach resulted in a shorter hospital stay.

There is consensus in the literature that this procedure should be reserved for benign disease of the distal pancreas. All tumors were resected with negative margins. However, the lymph node dissection performed was limited. Only three patients showed presence of lymph nodes in the final pathology report. Even though they were all negative, the number of lymph nodes would have been inadequate for malignant tumor resections.

Conclusion

Open or laparoscopic spleen-preserving distal pancreatectomy (with splenic vessel preservation) appears to be a feasible and safe procedure. In selected cases of cystic lesions and low-grade neoplasms, distal pancreatectomy with splenic preservation is possible.

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Epidural Analgesia for Pancreatoduodenectomy: A Critical Appraisal

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Abstract
Introduction Epidural analgesia has emerged as a commonly applied method to improve pain management and reduce perioperative complications in major abdominal surgery. However, there is no detailed analysis of its efficacy for pancreatic operations. This study compares clinical and economic outcomes after epidural and intravenous analgesia for pancreatoduodenectomy.
Material and methods Data for 233 consecutive patients, who underwent pancreatoduodenectomy, were prospectively acquired and retrospectively reviewed at a single institution, pancreato-biliary specialty practice. From October 2001 to February 2007, all patients were offered thoracic epidural analgesia, and those who declined received intravenous analgesia. Perioperative pain management was dictated as an element of a standardized clinical pathway for pancreatic resections. Clinical and economic outcomes were analyzed and compared for epidural analgesia and intravenous analgesia groups.
Results One hundred eighty-five patients received epidural analgesia, and 48 received intravenous analgesia, with equivalent baseline patient demographics between the groups. Patients administered epidural analgesia had lower pain scores but significantly higher rates of major complications. Pancreatic fistulae and postoperative ileus occurred more frequently, and patients with epidural analgesia more often required discharge to rehabilitation facilities. A trend towards longer hospitalizations was observed among epidural analgesia patients, but total costs were statistically equivalent between the groups. Further analysis demonstrates that 31% of epidural infusions were aborted before anticipated (fourth postoperative day) because of hemodynamic compromise and/or inadequate analgesia. These select patients required more transfusions, aggressive fluid resuscitation, and subsequently suffered even higher rates of gastrointestinal and respiratory complications, all attributing to higher costs. Multivariate analysis demonstrates that preoperative hematocrit concentration less than 36%, elderly age (>75 years), and chronic pancreatitis predict failure of epidural infusions.
Conclusion Thoracic epidural analgesia after pancreatic resections is associated with hemodynamic instability, which may compromise enteric anastomoses, gastrointestinal recovery, and respiratory function. These outcomes are exacerbated in poorly functioning epidurals and suggest that epidural analgesia may not be the optimal method for perioperative pain control when pancreatoduodenectomy is performed.

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Keywords Epidural analgesia · Whipple resection · Pancreaticoduodenectomy · Complications · Hospital costs · Pain

Introduction

Pain is a pivotal symptom in most pancreatic disease processes. It afflicts 90% of patients with the various tumors of the periampullary region and is an underappreciated presenting symptom for these diseases.[1–2] Furthermore, debilitating abdominal or back pain ultimately represents

the most common indication for surgical intervention in patients with chronic pancreatitis.[3–4] However, pain is not only regarded as a significant preoperative problem but is also considered a critical parameter in optimal postoperative recovery. Its clinical impact has been previously described and shown to contribute to severe postoperative morbidity.[5] Furthermore, several prospective trials demonstrate that postoperative pain is a key factor in poor quality of life after pancreatic resection surgery.[6–9] Strategies to optimize perioperative analgesia must, therefore, be adopted to effectively improve surgical recovery.

In recent years, epidural analgesia has emerged as an acceptable method to improve perioperative pain management among patients undergoing major abdominal surgery.[10–14] Epidural analgesia works through blockade of nociceptive afferent nerve signaling, as well as through suppression of the physiologic surgical stress response. Its putative benefit is the provision of regional analgesia, while preserving gastrointestinal motility and blood flow. Concomitant blockade of sympathetic efferent nerves reduces coronary vasoconstriction and decreases the incidence of vasoocclusive episodes and thromboembolic events.[14–15] Most randomized trials demonstrate that epidural analgesia not only provides superior pain control to that provided by intravenous analgesia but also contributes to better surgical outcomes. Foremost among these benefits are lower rates of complications, early bowel recovery, shorter hospital stays, and reduced hospital costs.[12,16–21]

Although epidural analgesia is commonly applied, there is, to date, insufficient evidence to support its use in pancreatic operations. In fact, no single study has independently examined outcomes of epidural analgesia after pancreatic surgery, and there lacks any data to suggest lower rates of complications or earlier bowel recovery occur in this domain. Hypotension and bradycardia, two common adverse effects of epidural analgesia, are poorly tolerated in high-acuity operations such as pancreatoduodenectomy, which has a high propensity for excessive blood loss and rapid fluid shifts.[12] In addition, epidural analgesia may compromise pancreatico-enteric anastomotic healing. Although the early return of bowel function observed with epidural analgesia is thought to benefit patients undergoing colorectal resections, it has been suggested that forceful intestinal contractions and inadequate bowel perfusion might actually increase the risk of anastomotic breakdown and predispose patients to anastomotic leaks.[22–24]

The presumed benefits of epidural analgesia in pancreatic surgery remain unclear and are poorly understood. Thus, the objective of this study is to examine the efficacy of epidural analgesia in a contemporary series of patients undergoing pancreatoduodenectomy at a single, high-volume pancreato-biliary surgical specialty center.

Material and Methods

Data Collection

In accordance with guidelines for human subject research, approval was obtained from our institutional review board. Data on preoperative, intraoperative, and postoperative care were prospectively collected. Preoperative parameters include patient demographics (i.e., age, gender, and medical history), presenting symptoms (i.e., jaundice, weight loss, diarrhea, pain, etc), laboratory tests, prior imaging studies, and preoperative therapies (i.e., endoscopic ductal stenting or sphincterotomy). The American Society of Anesthesiologists (ASA) physical status was determined for all patients.[25] Intraoperative parameters include total blood loss, operative time, fluid resuscitation, application of vasoactive agents and blood transfusions, and gland characteristics, as well as the use of drains, stents, or somatostatin analogues.

For each patient, the Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM)[26] was calculated to evaluate the severity of surgical disease at the completion of pancreatic resection. This measure of patient acuity is a reliable scoring system for estimating preoperative morbidity. It reflects the risk of developing a postoperative complication (from 0 to 100%) for each individual patient undergoing a high-acuity operation. Details of its use have been previously described in a separate analysis consisting of more than 300 pancreatic resections.[27]

Postoperative events and clinical outcomes were recorded and include therapeutic and diagnostic strategies, nutritional support, lab and imaging studies, patient-reported pain severity, recovery of gastrointestinal function, incidence and type of complications, intensive care unit (ICU) transfers and duration, reoperations, postoperative duration of stay, discharge disposition, hospital readmissions, and death within 30 days postoperatively. The incidence of postoperative complications was defined according to the Clavien complication scheme.[28] This system describes complications based on escalating levels of therapeutic interventions required to treat adverse events and has been analyzed and validated in a large international series of more than 6,000 patients spanning a variety of operations and in a series of more than 600 pancreatic resections.[29] Clinically relevant pancreatic fistula were defined as Grade B or C fistulae according to the International Study Group of Pancreatic Fistula classification scheme.[30] All economic data were collected and analyzed using our institution's Casemix TSI data system. Total hospitals costs are defined as costs from the initial operation to hospital discharge, plus any costs accrued during hospital readmissions within 30 days postoperatively. Data were stored on a secured prospectively collected database and analyzed independently by a data manager.

Surgical Technique

From October 2001 to February 2007, 233 patients underwent pancreatoduodenectomy, with either a classical resection (n=37) or the pylorus-preserving modification (n=196). All patients received intraoperative general anesthesia. After proximal resection of the pancreas, a pancreatico-jejunal anastomosis was constructed in a duct-to-mucosa, end-to-side fashion, with either a single- or two-layer interrupted anastomosis. Ductal stents across the anastomosis were seldom used (n=36), usually in the setting of a pancreatic duct less than 3 mm in diameter. No pancreaticogastrostomies were performed. Prophylactic octreotide was given subcutaneously (dose 150 μg every 8 h) and continued postoperatively in 128 patients considered high risk for pancreatic fistula based on soft gland texture and/or small duct size. A single drain was routinely placed anterior to both the pancreatico-jejunal and biliary anastomoses and exteriorized through the right lateral abdominal wall. Drain output was measured for amylase content consistently after tolerance of a soft diet, which usually occurred on postoperative day 6.

Analgesic Management

Perioperative pain management followed a standardized protocol as part of our institutional carepath for pancreatic resections.[31] On the morning of surgery, all patients were initially offered thoracic epidural analgesia, unless they had any of the following contraindications: preoperative international normalized ratio greater than or equal to 1.5, spinal surgery involving hardware of the thoracic spine less than 6 months before the operation, or infection at epidural insertion site. Eligible patients who chose epidural analgesia had thoracic epidural catheters placed within a T5–T9 interspace level according to standard procedures. An initial dose of 1.5% lidocaine with epinephrine was infused to test the efficacy of analgesia and to ensure proper catheter placement. Continuous epidural infusion was initiated at least 30 min before surgical incision, usually at a rate of 8 ml/h, and consisted of either combined hydromorphone 10 mcg/ml+bupivacaine 0.1% 1 mg/ml (n=105), or hydromorphone 20 mcg/ml+bupivacaine 0.1% 1 mg/ml (n=69), chosen at the discretion of the attending anesthesiologist. Eleven patients received local bupivacaine 0.1% 1 mg/ml alone without additional narcotic. Epidural infusions were employed during the operative case and were continued up to 96 h (approximately 4 days) postoperatively. All epidural and patient-controlled analgesia (PCA) solutions were adjusted at the discretion of the attending surgeon, in consultation with the institution's Acute Pain Service, when patients reported poor pain control or when hemodynamic parameters failed to improve. Epidural catheters were usually removed on postoperative day 4 but were occasionally aborted earlier for these same reasons (hemodynamic compromise and/or inadequate analgesia). Patients were then transitioned to intravenous PCA and/or oral pain medication (Percocet or acetaminophen/codeine) for the remainder of the postoperative period.

Those patients who declined epidural analgesia or in whom preoperative epidural placement was not successful received intravenous fentanyl during the operation and were administered intravenous PCA postoperatively, until they could tolerate oral pain medication. Ketorolac was administered for breakthrough pain. Nurses routinely conducted neurological testing every 1 to 2 h for all patients. Excessive anesthetic depth was treated by decreasing the epidural infusion rate or by holding PCA infusions. Our generalized algorithm for analgesic management after pancreatoduodenectomy is illustrated in Fig. 1.

Postoperative Course

All other aspects of care were dictated by an institutionally derived standardized clinical pathway for pancreatic resections.[31] Postoperative fluid therapy was standardized for all patients, which included lactated Ringer's (LR) and/or D5$^1/_2$ normal saline, and was administered at a rate of 125 ml/h immediately after leaving the operating room. The rate was decreased to 75 ml/h on postoperative day 1 and maintained until the patient tolerated a clear liquid diet or required parenteral supplemental nutrition. Fluid boluses of LR or D5$^1/_2$ normal saline were administered to treat hypotension or low urine output. If hemodynamic parameters or urine output did not improve with additional fluid boluses, the epidural infusion rate was slowed or discontinued, and vasoactive agents were applied whenever necessary. This general management scheme is summarized in Fig. 1.

Pain Assessment

Pain at rest and with movement was assessed every 2 h whenever possible from entrance to the recovery room until postoperative day 4. Patients were asked to report the severity of pain using a verbal ranking scale from 0 to 10, with 0 indicating no pain was present and 10 corresponding to severe, intolerable pain.

Clinical Analysis of Postoperative Analgesia

A detailed analysis of epidural and intravenous analgesia ensued, with a particular emphasis on clinical and economic outcomes. The following clinically relevant outcomes were scrutinized: recovery of gastrointestinal function, duration of stay, minor and major complications, ICU transfers and duration, discharge disposition, hospital readmission, reoperation, and 30-day mortality. Furthermore, the incidence of

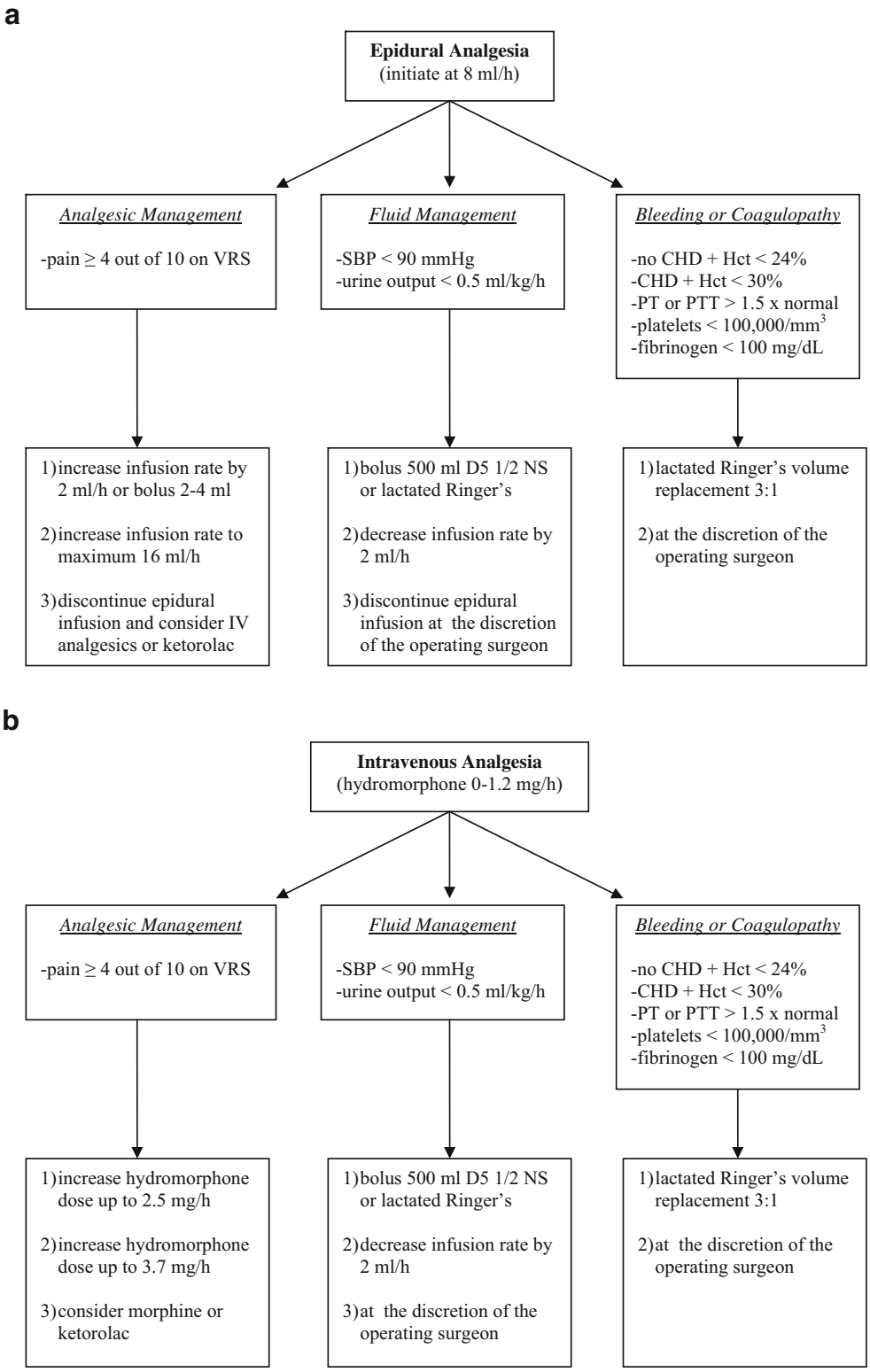


Figure 1 **a** General algorithm for analgesic and fluid management of patients administered epidural analgesia. **b** General algorithm for analgesic and fluid management of patients administered intravenous analgesia.

hemodynamic compromise, as well as the need for aggressive fluid resuscitation and/or blood transfusion, was explored and compared for each treatment modality. Table 1 defines these clinical parameters. Descriptions of specific postoperative complications are listed in Table 2.

Observed-to-Expected Morbidity Analysis

A separate analysis was performed to reveal further the variance in surgical quality between patients who receive epidural and intravenous analgesia. Specifically, we corre-

Table 1 Clinical Parameters for Analysis of Perioperative Analgesic Modalities

Clinical Parameters	Definition
Recovery of gastrointestinal function	Days from the initial operation until passage of flatus and/or bowel movement
Duration of stay (LOS)	Days from the initial operation to hospital discharge
ICU transfer	Treatment in intensive care setting on or after postoperative day 1, excluding admissions to the ICU directly from the operating room
Patient discharge disposition	Hospital discharge to one of three options after the initial operation: to home, to home with arrangements for visiting nurse assistance, or to a rehabilitation facility
Hospital readmission	Readmission for management of postoperative complications within 30 days of hospital discharge
Reoperation	Surgical exploration during initial hospitalization or within 30 days of hospital discharge, exclusive of the index procedure
Blood transfusion	Units of packed red blood cells required postoperatively, excluding blood products received during the initial operation
Hemodynamic compromise	Systolic blood pressure <90 mmHg and/or urinary output <0.5 ml/kg/h for 2 h

lated the actual number of complications with the predicted number of complications—the observed-to-expected (O/E) morbidity ratio. Expected morbidity was predicted for each of the 233 patients in accordance with the POSSUM. The expected morbidity for our practice overall, as well that for epidural and intravenous groups, was then estimated by calculating the mean POSSUM score for the cohort assessed. The actual incidence of postoperative complica-

Table 2 Definitions of Postoperative Complications

Postoperative Complications[a]	Definition
Ileus	Absence of bowel sounds, failure to pass flatus or bowel movement by postoperative day 5, and the need for total parenteral nutrition (TPN)
Delayed gastric emptying	Failure to resume oral liquid intake by postoperative day 10, and/or emesis >500 ml on or after postoperative day 5, and/or continued nasogastric drainage >500 ml on after postoperative day 5
Pancreatic fistula[b]	Any measurable drainage from an operatively placed drain with an amylase content at least three times normal serum amylase level on or after postoperative day 3, with at least one of the following parameters: fistula requiring supplemental nutrition, antibiotics, and/or somatostatin analogue, sepsis or other signs of infection, persistent drainage longer than 3 weeks, radiographic evidence of a peripancreatic fluid collection, fistula requiring percutaneous drainage, hospital readmission, or surgical exploration, fistula resulting in death of patient
Biliary leak	Bilious drainage from intraoperatively placed drains, and/or radiographically confirmed fluid collection, requiring surgical, endoscopic, or radiographic intervention
Gastrointestinal bleed	Guaiac-positive hematemesis, hematochezia, or melena and no other source of ongoing blood loss or the sudden appearance of frank blood either on NG lavage or per rectum, with subsequent fall in hemoglobin of 2 gm/dl, and requiring blood product transfusion or reoperation
Abscess	Culture-positive purulent drainage from intra-abdominal fluid collection obtained percutaneously or operatively and/or radiographically confirmed fluid collection with systemic or localized signs of infection (i.e., elevated WBC, body temperature >38°C, purulent drainage)
Myocardial infarction	Increase in serum concentration of CK-MB and Troponin and/or the following EKG changes: new Q-waves at least 0.04 s duration, new persistent ST elevation/depression
Acute renal failure	Serum creatinine greater than 3.0 mg/dl or doubling of baseline value and/or need for dialysis
Pulmonary embolism	Acute onset of dyspnea or tachypnea, hypotension, or increased CVP, positive V/Q scan, and/or chest CTA, and requiring pharmacologic therapy
Respiratory distress	$PaCO_2$>60 mmHg and requiring pharmacologic therapy or intubation or the need for intubation or mechanical ventilation for more than 24 h postoperatively
Pneumonia	Presence of new infiltrate on CXR, and the following: body temperature >38°C, abnormal elevation of WBC, or positive sputum Gram stain or culture, and requiring IV antibiotic treatment
Wound complications	Any evidence of infection (i.e., eyrthema, purulent discharge, induration) and requiring antibiotic treatment or evidence of dehiscence
Urinary tract infection	Culture-positive urine, pyuria and bacteriuria on urinalysis, and requiring antibiotic treatment
Neurological complications	Cerebral hypoxia, cerebral vascular accidents, or intracranial hemorrhage, with the onset of hemiplegia, hemianesthesia, hemianopia, aphasia, or unconsciousness

[a] Severity of postoperative complications (i.e., minor and major complications) graded according to the Clavien complication scheme[28]
[b] Pancreatic fistulae were defined according to the International Study Group of Pancreatic Fistula (ISGPF) classification scheme[30]

tions (observed morbidity) was also determined for all patients undergoing pancreatic resection within our practice and by analgesic type, employing the Clavien framework.

Using the actual incidence of postoperative complications and the mean POSSUM, O/E morbidity ratios were calculated for the epidural and intravenous cohorts. Surgical quality was evaluated through analysis of variance in O/E morbidity. A ratio equal to 1.00 demonstrates the expected performance. Ratios greater than 1.00 suggest that outcomes are worse than expected. Conversely, ratios less than 1.00 suggest outcomes achieved are better than expected.

Economic Analysis of Postoperative Analgesia

An economic analysis was performed to determine which treatment modality was more cost effective. Total hospital costs were compared for epidural and intravenous analgesia. Furthermore, itemized costs (pharmacy, radiology, transfusion, laboratory, ICU, room, and operating costs) were examined individually to evaluate and compare resource utilization associated with each pain regimen. Table 3 defines these economic parameters.

Aborted Epidurals

Similar analyses were performed on a subset of patients whose epidural catheters were removed before anticipated (postoperative day 4) because of hemodynamic compromise and/or inadequate pain control. This select group of patients with "aborted" epidurals was delineated to determine the incidence and impact of poorly functioning epidurals. Furthermore, outcomes after administration of intravenous analgesia and both functional and aborted epidurals were effectively compared. Patient demographics and preoperative parameters were also examined to identify predictive risk factors for nonfunctional epidurals.

Statistical Analysis

Treatment modalities were compared using the Chi-squared statistic, analysis of variance, and the Student's t tests. Factors associated with complications were calculated based on cross-tabulations using the Chi-squared statistic and the Pearson correlation test. Statistical significance was accepted at a p value less than 0.050. Factors contributing to early removal of epidural catheters were analyzed with univariate and multivariate analysis using the stepwise logistic regression model. Factors with $p \leq 0.250$ were retained for multivariate analysis. Only those factors demonstrating $p < 0.050$ on the final multivariate analysis were considered significant. All statistical computations were performed using Statistical Package for the Social Sciences 14.0 for Windows (SPSS, Chicago, IL).

Results

Patients

Two surgeons (Callery and Vollmer) performed 233 consecutive pancreatoduodenectomies. The most common presenting symptoms included obstructive jaundice (50%), abdominal pain (37%), and weight loss (29%). Three fourths of all patients underwent preoperative evaluation or therapeutic biliary ductal drainage using endoscopic retrograde cholangiopancreatography. All patients were taken to the operating room with intent for curative or palliative resection of suspected periampullary tumors, pancreatitis, intraductal papillary mucinous neoplasms, or

Table 3 Economic Parameters for Comparison of Epidural and Intravenous Analgesia

Economic Parameters	Definition
Total hospital costs	Costs from the initial operation to hospital discharge plus any costs incurred during hospital readmissions
Itemized costs	
Pharmacy costs	Costs for all medications, fluid management, and nutritional support, including parenteral and enteral nutrition received postoperatively
Radiology costs	Costs for all imaging studies (i.e., chest radiographs, computed tomography scans, ultrasound) and interventional radiology procedures (i.e., percutaneous drainage, endoscopy) obtained postoperatively
Transfusion costs	Costs for all blood products (i.e., packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets) received postoperatively
Laboratory costs	Costs for all laboratory studies, including serum chemisty panel, complete blood count, and drain amylase levels obtained postoperatively
ICU costs	Costs attibutable to management in the postanesthesia or intensive care units
Room costs	Costs for postoperative hospital accomodations and routine nursing care
Operating costs	Costs for the initial operation and for any reoperations 30 days postoperatively

cystic disease. Final pathology revealed that patients had pancreatic ductal adenocarcinoma (n=93) most often. Other pathologies encountered included other periampullary malignancies (n=41), chronic pancreatitis (n=33), cystic disease (n=27), neuroendocrine tumors (n=8), and other benign (n=25) or malignant lesions (n=6).

Baseline Characteristics

All patients were eligible for administration of epidural analgesia. Overall, 185 (79%) received perioperative pain management by epidural infusion; the remainder (48 patients) declined this option and were instead administered intravenous and PCA. Baseline preoperative characteristics were similar between the groups, with no statistically significant difference in the age, gender, body mass index, or previous medical history of the patient cohorts (Table 4). Comparisons of ASA physical status and POSSUM indicated that the two treatment groups were indeed similar at both the beginning and at the completion of surgical resection. Analysis of final pathology also revealed no statistically significant difference in disease entities between the groups.

Intraoperative Outcomes

In addition to an examination of preoperative characteristics, operative outcomes were compared between patients who received intravenous and epidural analgesia (Table 5). Although the pylorus-preserving pancreatoduodenectomy technique was performed more often than the classical Whipple's resection in this series, they were not applied differently between the epidural analgesia and intravenous analgesia analgesic cohorts (p=0.526). The median operating time, defined as the time from skin incision to skin closure, was 91 min longer for patients who received intravenous analgesia (p<0.001). This discrepancy is largely explained by differences in rates of staging laparoscopy employed in each cohort (27 intravenous vs 8% epidural, p=0.001). In our practice, intravenous analgesia is the analgesic modality more often chosen

Table 4 Preoperative Patient Characteristics According to Analgesic Modality

Preoperative Parameters	Intravenous	Epidural	p Value[b]
Patients (% of total)	48 (21)	185 (79)	–
Age (years)	60 [35–84]	65 [23–90]	0.542
Gender (%)			0.100
Male	30 (62)	91 (49)	
Female	18 (38)	94 (51)	
BMI (kg/m^2)	24.4 [18.0–42.0]	25.7 [17.5–48.9]	0.736
ASA Classification (%)			0.088
I	1 (2)	2 (1)	
II	12 (25)	83 (45)	
III	33 (69)	96 (52)	
IV	2 (4)	4 (2)	
POSSUM[a] (median)	69.2%	56.7%	0.122
Coronary heart disease (%)	10 (21)	20 (11)	0.065
Hypertension (%)	25 (52)	88 (48)	0.577
COPD (%)	8 (17)	17 (9)	0.136
Diabetes mellitus (%)	15 (31)	43 (23)	0.253
Smoking history (%)	24 (50)	89 (48)	0.815
Final pathology (%)			0.472
Pancreatic adenocarcinoma	21 (44)	72 (39)	
Periampullary malignancy	8 (17)	33 (18)	
Chronic pancreatitis	8 (17)	25 (14)	
Cystic neoplasm	2 (4)	25 (14)	
Other lesions	9 (19)	30 (16)	
TNM stage—pancreatic adenocarcinoma (%)			0.412
Stage 0	0 (0)	1 (1)	
Stage IA	0 (0)	6 (8)	
Stage IB	1 (5)	5 (7)	
Stage IIA	7 (33)	13 (18)	
Stage IIB	13 (62)	47 (65)	
Stage III	0 (0)	0 (0)	
Stage IV	0 (0)	0 (0)	

All continuous variables reflect the median value; values in brackets denote the range. *BMI* Body mass index, *ASA* American Society of Anesthesiologists, *COPD* chronic obstructive pulmonary disease

[a] Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity [26]

[b] All p values for comparison between groups

Table 5 Operative Outcomes for Each Perioperative Analgesic Modality

Operative Outcomes	Intravenous	Epidural	*p* Value[a]
Patients (% of total)	48 (21)	185 (79)	–
Type of resection (%)			0.526
Classic	6 (12)	30 (16)	
Pylorus-preserving	42 (88)	155 (84)	
Operative time (min)	478 [268–685]	387 [189–780]	<0.001
Staging laparoscopy (%)	13 (27)	15 (8)	0.001
Operative blood loss (ml)	325 [60–2,000]	350 [100–15,000]	0.692
Fluid administration (l)			
Crystalloid	5.0 [3.0–11.5]	4.8 [1.1–4.2]	0.479
Total	5.0 [3.0–11.5]	4.8 [1.5–4.2]	0.461
Intraoperative blood transfusions (%)	12 (25)	36 (20)	0.398
Octreotide administration (%)	21 (44)	107 (58)	0.103
Vasoactive agents employed (%)	11 (23)	30 (16)	0.277

All continuous variables reflect the median value; values in brackets denote the range.
[a] All *p* values for comparison between groups

when staging laparoscopy is performed. The rationale is that patients who may harbor unresectable lesions avoid the risks and costs associated with epidural catheter placement, particularly if the operating surgeon forgoes a definitive pancreatoduodenectomy. The practice of staging laparoscopy adds nearly 80 min to the total operative time: median 469 min for cases employing staging laparoscopy (range=339–685) and 391 min for those without (range=139–780). However, despite a longer operation, intraoperative blood loss was no greater (p=0.692) in the intravenous cohort, and the intraoperative administration of intravenous fluid, blood products, and vasoactive agents was similar between the two groups.

Pain Control

After surgical resection, pain management by epidural infusion was marginally better than that provided by intravenous analgesia (Fig. 2). The mean verbal ranking pain scores was lower when epidural infusion was applied (2.4 vs 3.1), but this did not reach statistical significance (p=0.080). However, pain during the first 2 postoperative days was significantly better controlled using epidural analgesia. Thereafter, the efficacy of pain control was equivalent between the groups.

Postoperative Outcomes

Clinical Analysis

Clinical outcomes were considered for patients who received either intravenous or epidural analgesia (Table 6). Although the overall incidence of postoperative complications was equivalent between the groups, patients administered epidural analgesia remained in the hospital 1 day longer (median 9 vs 8 days; mean 10.4 vs 8.6 days; p=0.061).

Deeper scrutiny reveals that this is due in large part to slower recovery of bowel function in the postoperative course (median 6 vs 5 days, p=0.030) and significantly more respiratory, gastrointestinal, and infectious complica-

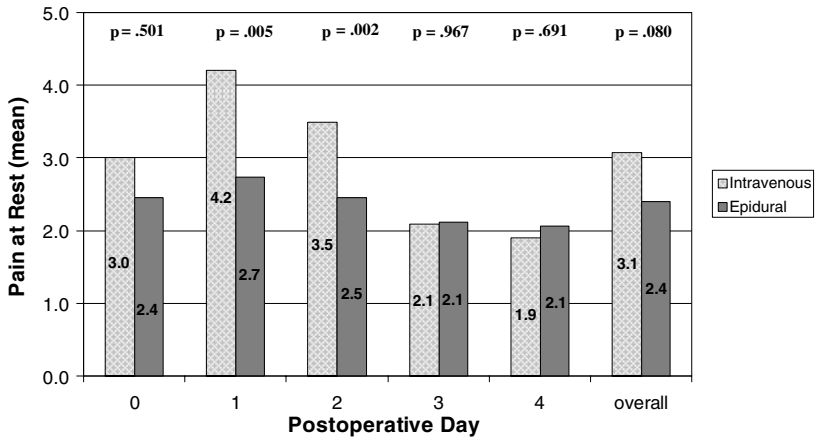


Figure 2 Verbal ranking pain scores for patients undergoing pancreatoduodenectomy.

Pain at Rest (mean ± SD)	Day 0	Day 1	Day 2	Day 3	Day 4	Overall
Intravenous	3.0 ± 2.6	4.2 ± 2.4	3.5 ± 2.2	2.1 ± 2.1	1.9 ± 1.7	3.1 ± 1.9
Epidural	2.4 ± 2.4	2.7 ± 2.5	2.5 ± 2.3	2.1 ± 1.9	2.1 ± 1.8	2.4 ± 1.8

Table 6 Clinical Outcomes for Intravenous and Epidural Analgesia

Postoperative Outcomes	Intravenous	Epidural	*p* Value[a]
Recovery of bowel function (days)	5 [2–7]	6 [2–15]	0.030
Overall morbidity (%)	21 (44)	99 (54)	0.228
Respiratory complications (%)	0 (0)	14 (8)	0.049
Gastrointestinal complications (%)			
Ileus	1 (2)	21 (11)	0.050
Delayed gastric emptying	4 (8)	16 (9)	0.945
Pancreatic fistula	2 (4)	29 (16)	0.036
Biliary leak	2 (4)	11 (6)	0.632
Gastrointestinal bleed	2 (4)	11 (6)	0.632
Overall	9 (19)	62 (34)	0.048
Infectious complications (%)			
Pneumonia	2 (4)	11 (6)	0.632
Urinary tract infection	2 (4)	15 (8)	0.349
Wound infection	5 (10)	35 (19)	0.164
Abscess	1 (2)	15 (8)	0.141
Sepsis	0 (0)	7 (4)	0.171
Overall	9 (19)	63 (34)	0.041
Other complications (%)			
Cardiovascular	1 (2)	5 (3)	0.809
Neurological	1 (2)	3 (2)	0.826
Renal	1 (2)	5 (3)	0.809
Overall	2 (4)	10 (5)	0.729
Hemodynamic compromise (%)	11 (23)	72 (39)	0.039
Therapeutic interventions (%)			
Antibiotics	6 (12)	68 (37)	0.001
Hyperalimentation	2 (4)	31 (17)	0.026
Blood transfusion	9 (19)	34 (18)	0.953
Invasive intervention (%)			
CT-guided percutaneous drainage	1 (2)	7 (4)	0.564
Reoperation	0 (0)	12 (6)	0.070
ICU utilization (%)	1 (2)	11 (6)	0.281
Duration of stay (days)	8 [4–27]	9 [6–48]	0.061
Patient discharge disposition			
Home	30 (64)	89 (49)	0.111
Home with nursing assistance	13 (28)	59 (32)	
Rehabilitation facility	4 (8)	35 (19)	
Hospital readmission (%)	8 (17)	14 (8)	0.055
Mortality (%)	1 (2)	2 (1)	0.583

All continuous variables reflect the median value; values in brackets denote the range.
ICU Intensive care unit
[a] All *p* values for comparison between the intravenous and epidural groups

tions among patients within the epidural cohort. Overall, pancreatic fistulae and postoperative ileus represented the most common intra-abdominal complications and occurred more frequently when epidural analgesia was administered. As a result, these patients were more likely to require parenteral nutrition than those who received intravenous analgesia (17 vs 4%, $p=0.026$). Similarly, patients in the epidural group were more than twice as likely to develop any type of infectious complication (odds ratio [OR] 2.23, 95% confidence interval [CI] 1.02 to 4.91, $p=0.041$) and subsequently received more intravenous antibiotics for definitive management of pneumonia, urinary tract infection, wound infection, abscess, or sepsis.

Invasive interventions, including computed tomography-guided percutaneous drainage and reoperation, were seldom employed overall during the postoperative period (3 and 5%, respectively) but were used more often when epidural analgesia was the applied method of pain control. Of the 16 patients who required invasive intervention for drainage of purulent fluid collections, control of intra-abdominal bleeding, and repair of dehisced wounds or anastomoses, 15 (94%) were managed by epidural analgesia, and only one received intravenous analgesia. Because invasive interventions were more frequently employed among patients in the epidural cohort, these patients often required placement in rehabilitation facilities at the time of hospital discharge, although not statistically different (19 vs 8%, $p=0.080$). The overall rate of mortality was 1.3% and was unchanged across the epidural and intravenous groups (1.1 and 2.1%, respectively).

Observed-to-Expected Morbidity Analysis

In addition to differential clinical outcomes, deeper analysis demonstrates considerable variance in the quality of surgical care among patients who receive epidural and intravenous analgesia. The expected morbidity (mean POSSUM) for patients undergoing pancreatic resection within our practice equaled 58.0%. Therefore, preoperative risk assessment predicted that 135 patients would develop at least one postoperative complication. This morbidity analysis demonstrates that postoperative outcomes achieved were better than expected, as only 120 patients actually developed a complication, for a global O/E ratio of 0.89.

This ratio was higher for patients administered epidural infusions when compared to patients who received intravenous analgesia—0.94 vs 0.70, respectively—and approached statistical significance (χ^2 3.04; *df* 1; p=0.081). Although morbidity outcomes for both epidural and intravenous cohorts exceeded benchmark standards for pancreatic resection, this analysis demonstrates that the quality of surgical care is markedly improved when intravenous analgesia—not epidural analgesia—is employed.

Economic Analysis

An analysis of fiscal outcomes further compared the differential impacts of epidural and intravenous analgesia in patients undergoing pancreatoduodenectomy (Table 7). Because operating times were significantly shorter among epidural patients, these patients had significantly lower operating room costs (median) compared to intravenous patients ($4,637 epidural analgesia vs $5,171 intravenous analgesia, p=0.025). However, this $500 difference was offset by greater hospital room costs, reflective of the longer duration of stay by 1 day. All other itemized cost centers demonstrated no significant differences between the groups, with a trend to greater pharmacy and room costs among patients administered epidural analgesia. Total hospital costs (median) were less than $20,000 per patient and were nearly identical between the groups (p=0.652).

Aborted Epidurals

A separate analysis was performed for those patients whose epidural catheters were removed before postoperative day 4, to determine the contribution of a poorly functioning epidural. Overall, 58 patients had epidurals aborted for early and persistent hemodynamic compromise (33 patients—18% of the epidural cohort) or inadequate pain control (25 patients—14% of the epidural cohort). This distinct group of patients represented 25% of all patients undergoing pancreatoduodenectomy and, more importantly, just under one third of all patients managed by epidural infusion.

Postoperative Pain Control

Significant differences were observed in the efficacy of pain control among this select group of "aborted" epidurals (Fig. 3). When this scenario occurred, less effective pain management resulted. Compared to patients who received functional epidurals, verbal ranking pain scores were significantly higher overall when aborted epidurals were administered (median 3 vs 2; mean 3.0 vs 2.1, p=0.008); yet, pain scores of the aborted epidural group mirrored those of the intravenous group, both overall (3.0 vs 3.1, p= 0.920) and on a daily basis.

Clinical Outcomes

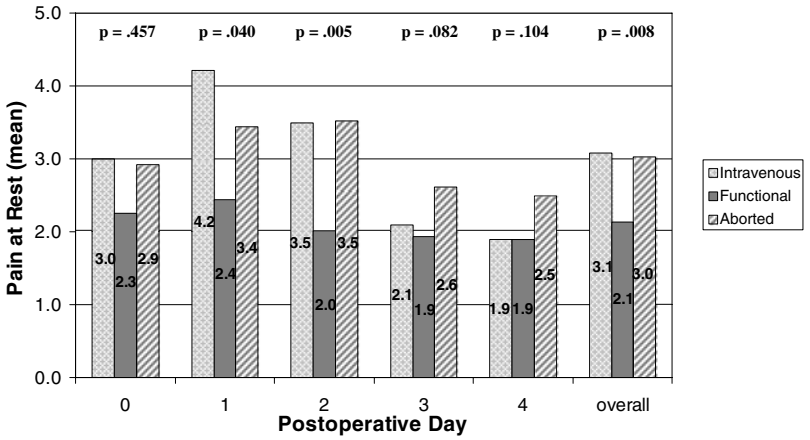
Clinical and economic outcomes for this group of aborted epidurals were also compared to those of well-functioning epidurals, as well as with those patients receiving intravenous analgesia (Table 8). Compared to patients with functional epidurals, those with aborted epidurals suffered more severe clinical and economic outcomes.

The overall incidence of postoperative complications was significantly increased among the aborted epidural cohort (67 vs 47% in the functional epidural cohort, p= 0.011). Furthermore, these patients more often required aggressive fluid resuscitation (74 vs 50%, p=0.002) and postoperative blood transfusions (26 vs 15%, p=0.076). Consequently, patients with aborted epidurals were more

Table 7 Economic Outcomes for Intravenous and Epidural Analgesia

Outcomes[a]	Intravenous ($)	Epidural ($)	p Value[b]
Operating costs	5,170 [3,434–7,941]	4,637 [2,684–9,445]	0.025
Pharmacy costs	858 [229–3,247]	955 [249–26,614]	0.232
Radiology costs	339 [76–5,012]	361 [76–12,205]	0.524
Transfusion costs	115 [0–5,769]	153 [0–24,241]	0.423
Laboratory costs	534 [271–1,390]	552 [186–6,792]	0.302
Room costs	6,628 [1,894–19,159]	7,186 [4,260–21,137]	0.836
ICU costs	924 [403–8,737]	937 [44–89,945]	0.258
Total hospital costs	19,798 [13,366–88,870]	19,962 [4,108–178,124]	0.652

ICU Intensive care unit
[a] All cost metrics reflect median values; values in brackets denote the range.
[b] All p values for comparison between groups



Pain at Rest (mean ± SD)	Day 0	Day 1	Day 2	Day 3	Day 4	Overall
Intravenous	3.0 ± 2.6	4.2 ± 2.4	3.5 ± 2.2	2.1 ± 2.1	1.9 ± 1.7	3.1 ± 1.9
Functional Epidural	2.3 ± 2.3	2.4 ± 2.3	2.0 ± 2.0	1.9 ± 1.9	1.9 ± 1.7	2.1 ± 1.8
Aborted Epidural	2.9 ± 2.5	3.4 ± 2.7	3.5 ± 2.5	2.6 ± 2.1	2.5 ± 2.1	3.0 ± 1.7

Figure 3 Comparison of verbal ranking pain scores when epidurals are aborted.

than three times as likely to develop respiratory complications (OR 3.23, 95% CI 1.06 to 9.78, p=0.031), and the incidence of clinically relevant pancreatic fistulae was significantly higher (25 vs 12%, p=0.024). Rates of hospital readmission were similarly increased among patients with aborted epidurals (14 vs 5%, p=0.030). In addition to these outcomes, O/E morbidity analyses revealed that outcomes were worse than expected when epidural infusions were aborted (O/E=1.11) and better than expected when functional epidurals were achieved (O/E=0.86).

Clinical outcomes were most severe for patients whose aborted epidurals were attributed to hemodynamic compromise rather than to poor pain control. Respiratory complications occurred in 28% of patients with hemodynamic compromise and only 3% of patients with poor pain control (p=0.006). Gastrointestinal complications occurred with 80 and 48% frequency, respectively (p=0.014). Clinically relevant pancreatic fistulae were similarly more common among patients whose epidurals were aborted due to hemodynamic compromise (36 vs 9%, p=0.012), indicating a strong association between these two events. O/E morbidity ratios were also higher—1.25 for patients with hemodynamic compromise and 0.93 for patients with poor pain control.

Economic Outcomes

Aborted epidurals incurred total hospital cost equaling $23,956—approximately 20% higher than that of patients

Table 8 Comparison of Intravenous Analgesia, Functional and Aborted Epidurals

Postoperative Outcomes	Intravenous	Functional Epidural	Aborted Epidural	p Value[a]
Patients (% of total)	48 (21)	127 (54)	58 (25)	–
Recovery of bowel function (days)	5 [2–7]	5 [2–15]	6 [3–12]	0.091
Complications (%)				
Respiratory	0 (0)	6 (5)	8 (14)	0.008
Gastrointestinal	9 (19)	26 (20)	36 (62)	<0.001
Infectious	9 (19)	40 (32)	23 (40)	0.066
Other	2 (4)	5 (4)	5 (9)	0.385
Overall	21 (44)	60 (47)	39 (67)	0.020
Hemodynamic compromise (%)	11 (23)	39 (31)	33 (57)	<0.001
Duration of Stay (days)	8 [4–27]	9 [6–43]	10 [6–48]	0.063
Patient discharge disposition				
Home	30 (64)	58 (46)	31 (54)	0.046
Home with nursing assistance	13 (28)	47 (37)	12 (21)	
Rehabilitation facility	4 (8)	21 (17)	14 (25)	
Hospital readmission (%)	8 (17)	6 (5)	8 (14)	0.023
Mortality (%)	1 (2.1)	1 (0.8)	1 (1.7)	0.750
Total hospital costs	19,798	19,681	23,956	0.107

All continuous variables reflect the median value; values in brackets denote the range.
[a] All p values for comparison between the single groups

receiving either a functional epidural or intravenous analgesia. A detailed cost analysis was further performed to more effectively compare intravenous and epidural analgesia. Using the incidence of functional and aborted epidurals and the median hospital cost for each cohort, the weighted average was calculated to determine the expected total hospital cost for a patient undergoing pancreatoduodenectomy when pain is managed by epidural infusion. This weighted average hospital cost ($21,021) equates to an additional cost of $1,223 per patient when epidural—rather than intravenous—analgesia is offered.

Risk Factors for Aborted Epidurals

A stepwise regression analysis was performed to identify risk factors for nonfunctional epidurals. Univariate analysis demonstrated that elderly age (>75 years; $p=0.047$), low preoperative hematocrit concentration (<36%; $p=0.011$), and the use of somatostatin analogues (octreotide; $p=0.040$) contributed to a poorly functioning epidural. However, only a low preoperative hematocrit level was associated with aborted epidurals overall on multivariate analysis ($p=0.048$); elderly age ($p=0.092$) and the use of somatostatin analogues ($p=0.200$) were not significant predictors of aborted epidurals. Epidural infusions administered to patients with hematocrit levels below 36% were twice as likely to fail (OR 2.12, 95% CI 1.03 to 4.35, $p=0.025$) as patients with normal hematocrit levels (greater than 36%).

Epidurals aborted in the setting of hemodynamic compromise were associated with elderly age (>75 years), preoperative jaundice, hypertension, low hematocrit concentration, low creatinine clearance (<60 ml/min), and the use of octreotide intraoperatively. Multivariate analysis, however, demonstrates that elderly age and low hematocrit level alone predispose patients to hemodynamic compromise and therefore increase the risk of aborted epidurals. Poor pain control was similarly associated with elderly age, pancreatitis, a history of excessive alcohol use, low hematocrit level, and intraoperative blood loss. Of these factors, only pancreatitis and hematocrit level were associated with the early removal of epidural infusions because of poor fanalgesia. In fact, of the 25 patients that had pancreatitis and received epidural analgesia, eight (32%) registered failed infusions, and all eight (100%) were due to poor pain control.

Discussion

For major abdominal operations, thoracic epidural analgesia is now widely regarded as a suitable, if not superior, alternative to intravenous analgesia. In fact, at many institutions, perioperative epidural analgesia is the preferred option for optimizing postoperative recovery. Although the efficacy of this modality has been debated in the past 20 years, arguments for its generalized use have been strengthened by numerous prospective, randomized clinical trials comparing epidural to intravenous analgesia.[12,16–21,32–33]

The first randomized clinical trial assessing epidural analgesia for high-acuity operations was reported in 1987, by Yeager et al.[32] Patients administered epidural infusions during intra-abdominal, intrathoracic, and noncerebral vascular surgery had significantly lower rates of complications than the control group (32 vs 76%, $p=0.002$), particularly cardiovascular and infectious complications. In addition, postoperative duration of stay was shorter, and the average hospital cost was more than $9,000 lower. Although the small number of patients in this study is often criticized (28 epidural and 25 intravenous), the trial's findings were the first to suggest that postoperative outcomes and costs could be improved by employing perioperative epidural analgesia.

Subsequently, one of the largest randomized trials, conducted by Park et al.,[17] compared the impact of perioperative epidural analgesia and parenteral opioids in 1,021 patients undergoing major abdominal operations. Although there were no significant differences in rates of morbidity or mortality, the authors concluded that epidural analgesia provides better postoperative pain relief but that the effect on postoperative outcomes varies with the type of operation performed. Among vascular, gastric, biliary, and colonic operations performed, only abdominal aortic operations demonstrated statistically significant differences in the rates of cardiovascular and respiratory complications in favor of epidural analgesia.

The generalizability of these results, as well as those of other studies, has often been called into question. Many have suggested the effects of thoracic epidural analgesia are less beneficial in operations involving the upper abdomen than they are in the lower abdomen. In fact, some authors contend that continuous epidural infusions have no positive impact in upper abdominal operations.[10,14,33–34] Others have raised concern about the safety of this analgesic modality, particularly when employed for liver resections, which harbor an inherent risk of coagulopathy and hepatotoxicity.[35–37] These uncertainties are further compounded by a paucity of randomized trials examining the efficacy of epidural analgesia in upper abdominal operations specifically, particularly in terms of pancreatic operations. Although a frequently cited study—reported by Rigg et al. in 2002[16]—did include 35 pancreatic operations (of 915 total), no pancreatic morbidity endpoints were evaluated. Given the lack of a detailed analysis of epidural analgesia in this domain, we retrospectively examined our experience with the efficacy of this analgesic technique in a large, consecutive, contemporary series of patients undergoing pancreatoduodenectomy.

In that epidural analgesia is currently accepted as the standard of care at our hospital, as well as at many other

institutions, all patients were initially considered for this modality of perioperative pain control. None were found to have distinct contraindications for this technique (coagulopathy, recent back surgery, infected site). Accordingly, the majority of patients were administered perioperative analgesia by epidural infusion, while those who refused received intravenous and PCA. These distinct cohorts had equivalent preoperative characteristics, while the severity of comorbid illnesses and the complexity of the operation were also similar. Only ASA physical status distinguished the patient groups preoperatively, as patients who received intravenous analgesia, in fact, presented with higher acuity (class III/IV).

In this series of pancreatoduodenectomies, the generally described benefits of epidural infusion were limited only to better postoperative pain scores than their intravenous counterparts. However, this significance was limited to the first 2 postoperative days. Despite better immediate postoperative analgesia, return of gastrointestinal function was significantly delayed by a day among epidural patients, and more importantly, they suffered from minor and major postoperative complications more often. Duration of stay was subsequently longer, and hospital costs were substantially higher. These findings suggest that epidural analgesia is more often associated with deleterious outcomes and confers, at the very least, no financial benefit for patients undergoing pancreatoduodenectomy.

This first-pass analysis of the data assumes that all epidural infusions function adequately. Further examination of the epidural cohort, however, indicates that this is not the case. Poorly functioning epidurals, defined as any condition that requires epidural catheter removal and the conversion to an alternative pain control modality, occurred in 31% of patients and was most often the consequence of perioperative hemodynamic instability. This underappreciated failure rate is consistent with previously reported failure rates in large retrospective and prospective series on epidural use.[16,38]

Hemodynamic instability frequently occurs during and after pancreatoduodenectomy, irrespective of the analgesic modality. However, previous reports demonstrate that this phenomenon is also a common adverse effect of perioperative epidural analgesia, particularly when local anesthetics are used, and is a common indication for early termination of epidural infusions.[14,38–39] The overall effect of reduced catecholamine release and decreased vascular resistance results in the redistribution of blood flow away from healing anastomoses. This vascular "steal" phenomenon may cause a significant decrease in anastomotic perfusion and has been suggested to compromise anastomotic integrity. Furthermore, management of hypotension or oliguria frequently requires aggressive fluid resuscitation, an approach that may contribute to significant pulmonary or bowel wall edema. These physiologic effects may explain higher pancreaticojejunostomy-related fistulous complications.[22–24] Correspondingly, our findings demonstrate that among patients whose epidurals are aborted because of hemodynamic instability, rates of respiratory, gastrointestinal, and fistulous complications are significantly increased.

While the current study is the largest to specifically examine the efficacy of epidural analgesia for pancreatoduodenectomy, there are certainly inherent limitations of this analysis. First, this study was conducted within a single, specialty practice at a high-volume institution that employs a standardized approach to care of these high-acuity patients and does not allow for comparative assessment across multiple practices, which may or may not have better success with epidural analgesia or surgical outcomes. Second, continuous epidural infusion regimens were restricted to hydromorphone and bupivacaine analgesics. Therefore, it remains unclear whether other medications or anesthetic approaches are more effective for patients undergoing pancreatoduodenectomy. Finally, although there is remarkable equivalence between the study groups, the findings of this study are derived from a retrospective analysis with uneven group assignment. Therefore, all conclusions on the efficacy of epidural analgesia must be tempered by these study limitations. A blinded, randomized controlled study is certainly warranted to provide definitive answers to the provocative findings raised here.

Conclusion

The results of this study indicate that although it may provide more effective initial pain control, epidural analgesia does not necessarily improve other critical outcomes after pancreatoduodenectomy. This may be explained by the high propensity for rapid fluid shifts and excessive blood loss during this operation, which may negate the proposed benefits of administering analgesic medications by epidural infusion. These results are reinforced by the frequent need to terminate epidural infusions because of hemodynamic compromise or inadequate analgesia. Patients in this select group—usually very elderly and anemic—will often encounter more severe clinical and economic outcomes. For these reasons, the prevalent use of epidural analgesic techniques should be reconsidered in patients undergoing pancreatoduodenectomy.

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Proctocolectomy–Ileal Pouch-Anal Anastomosis for Ulcerative Colitis After Liver Transplantation for Primary Sclerosing Cholangitis: A Multi-institutional Analysis

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Abstract
Background The association between primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) often mandates their contemporaneous management. Orthotopic liver transplantation (OLTX) has emerged as the only curative therapy for PSC, and total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the definitive treatment for refractory UC. The published experience to date describing IPAA after OLTX has been limited; we sought to examine outcomes associated with proctocolectomy-IPAA after OLTX.
Materials and Methods We reviewed our multi-institutional experience performing proctocolectomy-IPAA for UC after OLTX for PSC.
Results Twenty-two patients underwent proctocolectomy-IPAA for UC after OLTX for PSC at four academic medical centers between 1989 and 2006. No perioperative complications or allograft dysfunction were observed. During a median follow-up of 52 months, complications have included transient dehydration (n=6), chronic pouchitis (n=2), recurrent PSC (n=2), small bowel obstruction (n=2), and pouch-anal anastomotic stricture (n=1). Median 24-h stool frequency was 5, and fecal continence was reported as satisfactory by all patients.
Conclusions This multi-institutional experience suggests that proctocolectomy-IPAA can be performed safely after OLTX. Management strategies should include optimization of small bowel length during pouch and ileostomy construction, vigorous postoperative hydration, early ileostomy closure, and careful monitoring for pouchitis.

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Keywords Proctocolectomy · Liver transplantation · Ileal pouch-anal anastomosis · Ulcerative colitis · Primary sclerosing cholangitis

Abbreviations

PSC	primary sclerosing cholangitis
UC	ulcerative colitis
OLTX	orthotopic liver transplantation
IPAA	ileal pouch-anal anastomosis
PTLD	post-transplantation lymphoproliferative disorder

Introduction

Primary sclerosing cholangitis (PSC) is a disorder of progressive intrahepatic and extrahepatic biliary tract

Table 1 Patient Data

Demographics	Values
Gender	14 male, 8 female
Age, mean (range)	45 years (29–67)
Indication for proctocolectomy (number)	refractory ulcerative colitis (15) UC, T2 adenocarcinoma (3) UC, colonic dysplasia (3) UC, PTLD (1)
Interval from OLTX to proctocolectomy, median (range)	45 months (7–168)

PTLD Post-transplant lymphoproliferative disorder

fibrosis that can ultimately result in biliary cirrhosis and/or cholangiocarcinoma. The only definitive management for PSC is orthotopic liver transplantation (OLTX); indeed, PSC currently accounts for about 5% of all OLTX procedures performed in the USA.[1] Approximately 70% of PSC patients develop inflammatory bowel disease, most commonly ulcerative colitis (UC).[2] This high degree of association between these diseases often necessitates their combined management.

Restorative proctocolectomy with ileal-pouch anal anastomosis (IPAA) has been established as a safe and definitive treatment for refractory UC. A subset of PSC patients who have undergone prior OLTX may eventually manifest UC disease activity or complications that will require colectomy with IPAA. With continuing refinements in perioperative management and immunosuppression, the life expectancy of PSC patients treated with OLTX will probably continue to improve, increasing the likelihood that progressive UC may necessitate therapeutic intervention in these patients. Unfortunately, limited data are available to guide the management of UC with IPAA after OLTX. One published series of four patients undergoing IPAA for symptomatic UC after OLTX for PSC described significant operative and postoperative morbidity, including hemorrhage, hepatic artery thrombosis, bowel obstruction, chronic rejection, chronic pouchitis, and recurrent PSC.[3] In this report, we describe the largest multi-institutional experience to date of 22 patients who underwent restorative proctocolectomy with IPAA for UC after OLTX for PSC, with acceptable operative and postoperative morbidity.

Materials and Methods

We retrospectively identified patients who underwent IPAA for symptoms or complications referable to UC after previous OLTX for PSC between 1987 and 2006; due to the relative rarity of this clinical scenario, we combined the collective experience of four major tertiary referral centers (University of Wisconsin School of Medicine and Public Health, University of Utah Health Sciences Center, University of Nebraska Medical Center, and Penn State College of Medicine) and collected relevant data by chart review and patient follow-up.

OLTX for PSC was performed through a bilateral subcostal incision and included construction of a 25–40 cm antecolic or retrocolic Roux-en-Y choledochojejunostomy for biliary drainage (to permit complete excision of native biliary epithelium). Proctocolectomy-IPAA was performed in two stages. In the initial procedure, proctocolectomy was performed through a lower midline incision beginning below and not incorporating the previous OLTX incision, with construction of an ileal reservoir using a 35- to 40-cm segment of distal ileum to fashion a J, S, or W pouch. Whenever feasible, a complete rectal mucosectomy was performed, and the ileal pouch was anastomosed to the anal canal. A covering loop ileostomy was created in all cases and subsequently taken down in a second procedure performed after an interval of at least 1 month.

Results

Patient characteristics are outlined in Table 1. Twenty-two patients (14 male and 8 female, mean age of 45 years) underwent proctocolectomy with IPAA for UC after OLTX at the University of Wisconsin Hospital and Clinics (n=8), the University of Nebraska Medical Center (n=7), the University of Utah Health Sciences Center (n=4), and the Penn State College of Medicine (n=3) between 1987 and 2006. Indications for colectomy were severe and refractory UC (n=15), UC with colonic adenocarcinoma (n=3), UC with colonic dysplasia (n=3), and UC with focal post-transplant lymphoproliferative disorder (n=1). The median interval from OLTX to proctocolectomy with IPAA was 45 months (range, 7–168 months).

Operative and hospitalization data are outlined in Table 2. Median operative time for proctocolectomy and IPAA was 6.1 h (range, 2.5–8.6 h), with a median estimated blood loss

Table 2 Hospitalization Data

	Values
Operative time, median (range)	6.1 h (2.5–8.7)
Estimated blood loss, median (range)	400 cc (100–1,400)
Pouch type (number)	S-IPAA (14) J-IPAA (7) W-IPAA (1) Rectal mucosectomy (17)
Length of hospitalization, median (range)	11 days (4–18)

of 400 cc (range, 100–1,400 cc). Fourteen S-IPAA, seven J-IPAA, and one W-IPAA pouches were constructed. In 17 of the 22 patients reviewed, a complete rectal mucosectomy was performed. No operative mortalities or intraoperative complications were encountered. The median length of hospitalization was 11 days (range, 4–18 days).

Postoperative outcome data are outlined in Table 3. Median follow-up after proctocolectomy was 52 months (range, 11–163 months). The median interval from proctocolectomy to ileostomy reversal was 2 months (range, 1–12 months). No postoperative mortality or allograft loss was encountered. Thirteen patients (62%) developed at least one episode of pouchitis during the follow-up period. Of these, six patients had single episodes without recurrence, and two experienced chronic, recurring symptoms requiring long-term suppressive therapy. Six patients (27%) developed episodes of dehydration requiring intravenous fluid replacement; all of these episodes occurred before ileostomy closure. One patient required outpatient intravenous supplementation via a peripherally inserted central venous catheter to maintain adequate fluid balance until ileostomy reversal. Four patients who developed dehydration problems had undergone S-pouch construction, and two had undergone J-pouch construction. Two patients developed elevated liver enzymes with cholangiographic evidence of recurrent PSC. Two patients developed small bowel obstructions during follow-up, with one patient requiring operative adhesiolysis. One patient developed a pouch-anal anastomotic stricture refractory to dilatational therapy that required operative revision. All patients reported satisfactory stool frequency and fecal continence, with a median maximal 24-h stool frequency of 5 (range, 4–10).

Discussion

The association between PSC and UC often necessitates their contemporaneous management. Fortunately, these diseases are effectively treated with OLTX and total proctocolectomy with IPAA, respectively. The interrelationships between these disease processes and their treatments have received a fair amount of scientific scrutiny, and several intriguing issues have emerged. Although colectomy for UC does not appear to affect the severity of coexisting PSC,[4] it has been suggested that the use of steroids and other immunosuppressive agents given to patients after OLTX should improve the severity of coexisting UC. Among 47 patients with PSC and UC in Sweden, UC symptoms improved in 65% and worsened in only 6% after OLTX.[5] Analysis of 29 similar patients at the University of Chicago demonstrated that 49% had quiescent UC after OLTX, while 20% experienced symptomatic flares. No patients in this series required proctocolectomy after OLTX, leading the authors to conclude that UC can usually be managed medically in patients after OLTX.[6] In a similar review of 23 patients with PSC and UC who underwent OLTX at the University of Pittsburgh, six patients with quiescent UC before OLTX continued to be asymptomatic after transplantation. Of the remaining 17 patients who had symptomatic UC before OLTX, 88.2% reported improvement in UC symptom severity after transplantation.[7]

In contrast, seven of 14 patients with symptomatic UC at UCLA continued to suffer active UC after OLTX, and three of 13 with asymptomatic UC developed active UC after OLTX.[8] The potential for UC to worsen despite immunosuppression is also illustrated in a report from the University of Pittsburgh describing 14 cases of de novo inflammatory bowel disease developing after solid organ transplantation.[9] Complicating this matter is the current trend in OLTX immunosuppression directed at minimizing or altogether eliminating chronic prednisone therapy. Experience with this immunosuppressive strategy at the Royal Free Hospital in London revealed that four of 12 patients with pre-OLTX quiescent UC began developing symptoms after transplantation, and four of four patients with pre-OLTX active UC developed worsening symptoms.[10] In previously reported data, seven of 33 patients with PSC and UC at the University of Wisconsin who underwent OLTX without prior colectomy experienced reactivation of their UC symptoms despite their immunosuppression.[11] Clearly, whether the clinical course of UC is generally exacerbated or improved by OLTX remains uncertain. In 14 of the 22 cases in the present series, the indication for proctocolectomy and IPAA after OLTX was symptomatic UC that was no longer amenable to medical management. However, the retrospective nature of our study precludes any meaningful assessment of the impact of post-transplantation immunosuppression on UC severity.

Another clinical concern is whether immunosuppression can accelerate the development of dysplasia or malignancy

Table 3 Postoperative Outcomes

	Values
Follow-up, median (range)	51.5 months (10–163)
Interval to ileostomy closure, median (range)	2 months (1–12)
Complications (number)	Pouchitis (13) Dehydration (6) Recurrent PSC (2) Small bowel obstruction (2) Anastomotic stricture (1)
Maximal daily stool frequency, median (range)	5 (4–10)

that can arise in the setting of UC. This issue is complicated by the observation that PSC alone may increase the likelihood of dysplastic or malignant degeneration in UC. In a retrospective review from the Cleveland Clinic, 25% of patients with both UC and PSC developed colonic dysplasia or cancer, compared to 5.6% of patients with UC alone. Furthermore, cancer arising in patients with UC and PSC tended to present with more advanced, proximally located, and ultimately fatal lesions.[12] Notably, this relationship appears to be bidirectional, as concurrent UC and PSC results in a twofold increase of both colonic and biliary malignancies.[13] Interestingly, three of 27 patients with UC and PSC at the New England Deaconess Hospital with no endoscopic evidence of colonic neoplasm before OLTX developed new colonic neoplasms 9, 12, and 13 months after OLTX, demonstrating that colon dysplasia or cancer can arise very quickly after transplantation.[14] The University of Pittsburgh experience identified colon cancer arising in 6.5% of patients with UC and PSC after OLTX.[15] Three patients in the present series underwent proctocolectomy and IPAA for histologically confirmed adenocarcinoma, diagnosed between 30 and 91 months after OLTX, and three others underwent proctocolectomy and IPAA for UC with evidence of colonic dysplasia.

The high risk of performing a proctocolectomy and ileostomy with or without ileal pouch reconstruction in patients with active PSC liver disease has been well-documented.[16–18] However, the published experience with proctocolectomy and IPAA after OLTX for PSC to date has been limited.[3,19] One report described four patients treated in this manner at the Queen Elizabeth Hospital in Birmingham, England.[3] Three patients developed early postoperative hemorrhage, complicated in one patient by hepatic artery thrombosis and transient liver dysfunction. One patient developed a small bowel obstruction and enteroenteric fistula requiring operative repair; this patient also developed chronic allograft rejection and recurrent PSC and subsequently expired. One patient developed recurring episodes of pouchitis requiring chronic metronidazole therapy. The present report represents the largest series to date of patients who have undergone proctocolectomy with IPAA after OLTX for UC and PSC, respectively. In contrast to the aforementioned report, we observed comparatively fewer postoperative complications. No patient in our series developed early postoperative hemorrhage or graft dysfunction as a result of post-colectomy complications. Only one patient required reoperative intervention, performed for a chronic bowel obstruction that failed to respond to conservative management. Other complications included pouchitis, postoperative dehydration, and a pouch-anal anastomotic stricture.

There may be an increased likelihood of pouchitis after proctocolectomy-IPAA in patients with coexisting PSC. A comparison of 1,097 patients with UC alone to 54 patients with both UC and PSC at the Mayo Clinic identified a 10-year cumulative risk of pouchitis of 45.5% among patients with UC and 79% among patients with both UC and PSC (without OLTX).[20] A smaller study from the same institution examining patients with UC and PSC who had undergone OLTX after IPAA confirmed the high prevalence of pouchitis in this population; furthermore, their data suggested that undergoing OLTX did not improve or exacerbate the clinical course of a patient's pouchitis.[21] In contrast, a review of a large series of 1,005 patients undergoing IPAA at the Cleveland Clinic (not limited to those with UC and PSC) identified a overall pouchitis incidence of 23.5%.[22] Indeed, 13 of the 22 patients in our experience have had at least one episode of pouchitis. To date, all cases have been effectively controlled with metronidazole or ciprofloxacin treatment, and only two patients have experienced chronic, recurring pouchitis symptoms.

Several management lessons may be inferred from our collective experience. First, IPAA after OLTX must be undertaken with the awareness of an enhanced potential for postoperative dehydration. Six patients required some form of therapeutic intervention for dehydration after IPAA. This was primarily observed during the period between colectomy and ileostomy closure. Dehydration and electrolyte imbalance is a common problem often requiring readmission for patients with functional ileostomies, but these are typically corrected after ileostomy closure.[23–25] Nevertheless, our observation that 27% of patients developed problems of dehydration suggests that this cohort of patients might be at a higher risk of this complication. The reason for this possible risk is not clear. Theoretically, these patients may be susceptible to functional compromise in small bowel absorptive mucosa; total small bowel length is foreshortened due to the 30- to 40-cm segment used to construct the Roux-en-Y choledochojejunostomy, the 30- to 40-cm of terminal ileum used to construct the IPAA and the variable length of distal ileum taken out of alimentary continuity by the temporary diverting ileostomy. In our series, the development of dehydration did not appear to be associated with the type of IPAA (S, J, etc.) constructed. Fortunately, no patient in our experience suffered complications in liver allograft function as a result of transient dehydration or hypovolemia. Nevertheless, the potential for this worrisome outcome should encourage close hemodynamic and graft monitoring and vigorous fluid replacement while the patient has an ileostomy. Furthermore, ileostomy reversal should not be unnecessarily delayed when demonstration of normal pouch healing has been confirmed. There is evidence to suggest that omission of a loop ileostomy may be safe in selected patients.[26] However, the potential ramifications of pouch-anal complications in this immunocompromised cohort of patients may mandate inclusion of a temporary diverting ileostomy.

In this series, proctocolectomy and IPAA were performed through a lower midline incision, with special care taken to avoid the previous OLTX incision. In this manner, one may minimize wound complications and the likelihood of injuring the Roux limb or other bowel, which may have become adherent to the anterior abdominal wall at the previous incision. Another critical step in the operative procedure involves the dissection of the Roux limb and removal of the transverse colon. Due to their close proximity, meticulous operative technique is necessary to avoid injury to small bowel and mesentery. This is particularly important in patients with antecolic Roux limbs, as the mesentery to the Roux limb can be damaged during removal of the transverse colon. Furthermore, the potential inability to fully advance the ileal pouch into the anal canal must be anticipated in this cohort of patients. This may require either an incomplete endoanal mucosectomy or careful tailoring of pouch design to permit a tension-free endorectal anastomosis. One patient in this series developed a pouch-anal anastomotic stricture that may have been induced by tension on this anastomosis at the time of pouch construction. Of course, presence of retained rectal mucosa will mandate careful follow-up evaluation for early inflammatory or dysplastic changes.

Conclusion

In this report, we describe our collective multi-institutional experience with performing restorative proctocolectomy with IPAA for UC after OLTX for associated PSC. In contrast to previous case series, we have observed that IPAA may be performed safely and with reasonable outcomes for those who have previously undergone OLTX. Our experience also highlights a number of operative and postoperative clinical considerations that should be incorporated into the management of this cohort of patients.

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Routine Contrast Imaging of Low Pelvic Anastomosis Prior to Closure of Defunctioning Ileostomy: is it Necessary?

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Abstract
Purpose The purpose of the study was to determine the utility of routine contrast enema prior to ileostomy closure and its impact on patient management in patients with a low pelvic anastomosis.
Material and Methods Two hundred eleven patients had a temporary loop ileostomy constructed to protect a low colorectal or coloanal anastomosis following low anterior resection for cancer (57%) or other disease (12%) or to protect an ileal pouch–anal anastomosis following restorative proctocolectomy (31%). All patients were evaluated by physical examination, proctoscopy, and water-soluble contrast enema prior to ileostomy closure. Imaging results were correlated with the clinical situation to determine the effects on patient management.
Results The mean time from ileostomy creation to closure was 15.6 weeks. Overall, 203 patients (96%) had an uncomplicated course. Eight patients (4%) developed an anastomotic leak, seven of which were diagnosed clinically and confirmed radiographically before planned ileostomy closure. Resolution of the leak was confirmed by follow-up contrast enema. One patient, whose pouchogram revealed a normal anastomosis, clinically developed a leak after ileostomy closure. It is important to note that routine contrast enema examination did not reveal an anastomotic leak or stricture that was not already suspected clinically.
Conclusions All patients who developed an anastomotic leak in this study were diagnosed clinically, and the diagnosis was confirmed by selective use of radiographic tests. Routine contrast enema evaluation of low pelvic anastomoses before loop ileostomy closure did not provide any additional information that changed patient management. The utility of this routine practice should be questioned.

Keywords Defunctioning ileostomy · Loop ileostomy · Coloanal anastomosis · Colorectal anastomosis · Anastomotic leak · Gastrograffin enema · Pelvic surgery · Rectal cancer

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Introduction

Low pelvic anastomotic leaks after colorectal surgery are associated with a higher incidence of pelvic sepsis, poor functional outcome, and decreased cancer survival.[1–5] In an effort to decrease the severity of complications if an anastomotic leak occurs, colorectal surgeons frequently create a temporary defunctioning loop ileostomy.[4,6,7] The ileostomy is routinely surgically closed approximately 3 months postoperatively after maturation of the distal anastomosis. Prior to takedown of the temporary ileostomy, the distal anastomosis is routinely evaluated for integrity and patency by physical examination, proctoscopy, and radiographically by contrast enema.

Despite these routine practices, little data exist to support the routine use of contrast enema prior to ileostomy closure.

It has been our experience that patients who develop an anastomotic leak present with clinical symptoms long before scheduled ileostomy closure. In addition, contrast enema rarely reveals an occult leak or a stricture that is not identified by digital rectal examination or proctoscopy. Therefore, we hypothesized that routine contrast enema does not provide adjunctive clinical information that changes patient management. This study reports the experience of a single institution in the evaluation of low pelvic anastomoses prior to defunctioning loop ileostomy closure.

Material and Methods

A retrospective review of a prospectively maintained database was performed to select patients who had a defunctioning loop ileostomy between 1997 and 2004 from a single institution. Patient demographics, clinical examination, radiographic imaging, and clinical course were reviewed and analyzed.

Routine postoperative follow-up entailed a clinic visit 4–6 weeks after surgery at which time patients underwent clinical evaluation including a digital rectal examination and proctoscopy by a staff colorectal surgeon. Patients were then seen again approximately 3 to 4 months postoperatively at which time they were again evaluated by digital rectal examination and proctoscopy. Prior to this clinic visit, each patient underwent radiographic evaluation of the distal anastomosis by water-soluble contrast enema. If the anastomosis appeared intact and patent on examination, the patient was scheduled for ileostomy closure. Any patient with clinical suspicion of anastomotic complications was evaluated further and treated accordingly at the time of symptoms. All patients underwent contrast evaluation prior to final closure.

Contrast enema was performed by an experienced radiologist at a single tertiary care center. A 24-Fr Foley catheter was inserted via the patient's anus, and water-soluble contrast was instilled to create a column of contrast back to the loop ileostomy. Adequate distention to evaluate potential leaks was determined by the radiologist. Post-evacuation views were obtained for every patient.

Contrast enema results were reviewed and compared with the information gained from patient symptoms and clinical examination. The comparison was made to determine if routine contrast enema prior to ileostomy closure affected patient management.

Results

Two hundred eleven patients underwent construction of a temporary defunctioning loop ileostomy to protect a low colorectal, coloanal, or ileal pouch–anal anastomosis between 1997 and 2004. There were 126 men and 85 women with a mean age of 53.2 years (range 16–89 years). One hundred forty-six patients underwent low anterior resection for cancer (N=121) or other diseases (N=25) with a low colorectal or coloanal anastomosis. Diagnoses other then cancer included Crohn's disease, radiation proctitis, diverticulitis, and toxic colitis. Sixty-five patients underwent a total proctocolectomy with an ileal pouch–anal anastomosis. The majority of these patients (N=56) had ulcerative colitis. The remaining patients had familial adenomatous polyposis (FAP) or total colonic aganglionosis. A summary of patient demographics and surgical characteristics is presented in Table 1. Of note, only one patient in the rectal cancer group was treated with adjuvant or postoperative radiation. This patient had no anastomotic trouble. Eleven patients in the rectal cancer group were operated directly, without any neoadjuvant treatment. The majority (109 of 121 patients) of the rectal cancer patients were treated with neoadjuvant chemotherapy and radiation.

The mean time from ileostomy creation to closure was 15.8 weeks (range 5–47 weeks). Of the 211 patients evaluated in this study, 203 (96%) had no anastomotic complications following the initial operation including ileostomy creation as well as after the ileostomy closure. Prior to stoma closure, contrast enema confirmed a patent intact anastomosis.

Eight patients developed an anastomotic leak. These patients are summarized in Table 2. Of the patients who had an anastomotic leak, one had a heavily irradiated pelvis with radiation proctitis being the indication for surgery, and

Table 1 Description of Patient Population and Surgical Procedures

Characteristics	Description
Gender	126 men, 85 women
Mean age (years)	53
Median time to ileostomy closure (weeks)	15.8
Diagnosis (N)	
Rectal cancer	121
Ulcerative colitis	56
Other[a]	34
Procedure (N)	
LAR with low CRA or CAA	121
TPC with IPAA	65
Other[b]	25

LAR Low anterior resection, *CRA* colorectal anastomosis, *CAA* coloanal anastomosis, *TPC* total proctocolectomy, *IPAA* ileal pouch–anal anastomosis

[a] Coloanal anastomoses for rectal cancer were constructed with a colonic J pouch (70), coloplasty (13), straight coloanal anastomosis (30)

[b] Other diseases included diverticulitis, FAP, total colonic aganglionosis, radiation proctitis, and Crohn's disease

Table 2 Patients with an Anastomotic Leak

Diagnosis	Anastomosis	Detection method	Symptoms	Leak (POD)
Adenocarcinoma	Coloplasty–anal	Clinical/CT	Blood per anus	21
Adenocarcinoma	Straight coloanal	Clinical/CT	Pelvic pressure	40
Ulcerative Colitis	Ileal pouch–anal	Clinical/CT	Fever, pain	38
Adenocarcinoma	Straight coloanal	Clinical/CT	Fever, nausea	11
Ulcerative Colitis	Ileal pouch–anal	Clinical/CT	Fever, pain	23
Radiation Proctitis	Straight coloanal	None, normal contrast enema	None	16 weeks postclosure
Adenocarcinoma	Colonic J pouch–anal	Clinical/digital exam/CT	Blood per anus	29
Ulcerative Colitis	Ileal pouch–anal	Clinical/proctoscopy/CT	Pelvic pain	32

CT Computed tomography, *POD* postoperative day

in all four of the rectal cancer patients who leaked, treatment included neoadjuvant chemotherapy and radiation.

Seven of the eight patients developed anastomotic complications prior to ileostomy closure. All seven patients had clinical characteristics and physical examination findings that prompted imaging evaluation and further management well before planned closure of the ileostomy. Common signs and symptoms included fever, pelvic pain or pressure, and blood per anus. None of these anastomotic leaks were occult findings discovered only by contrast enema. Resolution of leak was confirmed by contrast enema prior to ileostomy closure in seven patients. One patient had a persistent radiographic leak for 6 months without clinical consequences. It was felt that the leak was contained and that closure of the ileostomy would not affect the clinical situation. Therefore, this patient was closed despite radiographic detection of leak. He did well after closure.

One patient had an anastomotic breakdown 16 weeks after loop ileostomy closure. This patient had a normal physical examination and appeared clinically well prior to ileostomy closure. Contrast enema evaluation prior to closure revealed an intact patent anastomosis.

Discussion

Clinical management decisions should be based on clinical or scientific evidence. As pressure increases to provide more streamlined and cost-effective medicine, the utility of common traditional practices must be questioned. Routine evaluation of low pelvic anastomoses prior to temporary ileostomy closure is one such practice. This study reviewed a large series of patients who underwent creation and closure of a defunctioning loop ileostomy and analyzed the clinical usefulness of contrast imaging of the distal anastomosis prior to closure. Our results suggest that selective rather than routine contrast imaging evaluation is appropriate.

Reported incidence of anastomotic leaks for coloanal and ileoanal anastomoses range from approximately 3% to 12%.[8–12] The true incidence, however, is unknown as the presence of a defunctioning ileostomy often attenuates or completely conceals symptoms of anastomotic complications. It is our practice to divert all patients who undergo a low anterior resection for rectal cancer when the tumor is located at or beneath the anterior peritoneal reflection. These are mid-rectal or low rectal cancers, and surgical treatment involves a total mesorectal excision with an anastomosis constructed either at or within 2 cm of the dentate line. This is a high-risk anastomosis with a significant leak rate reported in the literature. These patients make up the majority of the cases we examined. Another large number of cases are total proctocolectomies with an ileal pouch anal anastomosis. At our institution, this anastomosis is always diverted as well. The rest of the cases we examined include low anastomoses that were considered by the surgeon to be high risk (redo surgery, radiation, Crohn's disease) for a variety of reasons. The common thread is that all of these anastomoses were within reach of the surgeon's examining finger and proctoscope such that they could be clearly examined in the office.

Despite the indication for the diverting loop ileostomy, it is common practice to routinely evaluate the anastomosis with a contrast enema just before loop ileostomy closure to identify occult problems that might preclude closure. In our experience, the overall anastomotic complication rate is low, but more importantly, these data indicate that complications are detected clinically in the postoperative state as a result of investigating pelvic symptoms, and they can be managed nonoperatively. No strictures were identified by contrast enema. However, this is not to say that no patients were found to have anastomotic narrowing by digital exam before ileostomy closure. Based on clinical experience, a small percentage of patients will have some anastomotic narrowing detected at their first postoperative visit. However, this is easily managed by digital dilatation. Just prior to closure, the water-soluble contrast enema demonstrated

widely patent anastomoses, and no patients had clinical outlet obstruction after closure of their ileostomy.

Secondly, the anastomotic leak rate in this series was 4%, and all leaks were detected by clinical acumen and confirmed radiographically. If a leak was suspected, a pelvic computed tomography (CT) scan was the initial radiographic test utilized as is the preference of the senior author. CT can not only detect a leak but can accurately delineate the presence and extent of pelvic abscess, which may potentially be drained percutaneously with radiographic guidance. Detection of an anastomotic leak by water-soluble contrast enema is often utilized based on clinician preference and is a reasonable option, despite not being used in this study. In direct comparison of pelvic CT scan and contrast enema to detect suspected leaks from an ileal pouch–anal anastomosis, CT scans have been shown to have a higher sensitivity.[13,14]

Although this is a relatively large study for this topic, one must consider the effect of not detecting occult leaks in this study due to an inadequate number of anastomoses evaluated. The confidence intervals for the leak rates were computed based on exact probabilities from a binomial distribution. Based on our study numbers and statistical analysis, we can say with 95% certainty that there is less than a 1.5% chance that an occult leak could exist but would not be detected in our study based on the number of patients examined. If we look at the subset of only coloanal anastomoses, the 95% upper confidence bound is 2.5%. If we look at only ileal pouch–anal anastomoses, the upper confidence bound is 4.5%. We feel that this number is substantially low enough to consider not routinely (i.e., without symptoms) using contrast enema evaluation before closure.

We believe that an aggressive early approach to diagnosis and treatment of an anastomotic leak low in the pelvis more often leads to an acceptable outcome. When leaks are detected at 12–14 weeks after surgery by routine contrast enema, tracts are well developed, and well-formed abscess walls are fibrotic. Achieving closure of these spaces prior to loop ileostomy closure can be quite troublesome. It is more advantageous to detect and treat the leaks early based on clinical suspicion or by digital or proctoscopic exam 4–6 weeks after surgery. A normal exam at this time reliably predicts a normal contrast enema months later, before ileostomy closure. Therefore, we support early clinical examination as the key in determining the need for imaging evaluation.

We did selectively employ contrast enema on the seven patients with an anastomotic leak to confirm healing prior to ileostomy closure. It accurately identified healing in six of six patients and a persistent leak in one patient. The one patient who manifested symptoms of leak after closure of his ileostomy did not have evidence of leak on his contrast enema.

Literature on this subject is sparse, but our results are consistent with those published for the use of routine pouchogram of colonic J-pouch–anal anastomosis prior to closure of a defunctioning ileostomy.[15] Of the 84 patients evaluated, patient management was changed in only one case as a result of information gained by contrast enema. In this series, three patients were found to have a stricture by digital rectal examination and three anastomotic leaks were confirmed radiographically after clinical suspicion. Looking at the accuracy of the routine pouchogram results, three of four strictures and the one leak that was identified radiographically were false positives. One occult pouch–vaginal fistula was identified. Of the three occult leaks that became apparent after ileostomy closure, none were detected by pouchogram before closure. This data suggest that even if studying the anastomosis prior to closure is warranted, a contrast enema has limited accuracy.

Several points can be extrapolated from our study regarding anastomotic leaks. Although the true leak rate may be higher than reported because of the protective effect of a defunctioning ileostomy, occult leaks likely do not impact management. Small occult leaks that heal prior to ileostomy closure without clinical consequence will not change patient management. Significant leaks will become evident clinically regardless of the presence of a diverting ileostomy, and they can be managed appropriately. We can assume that the leaks that are clinically undetected are small and have healed by the time the ileostomy is to be closed. This assumption has implications for groups that suggest not using a defunctioning ileostomy and for those who advocate a brief interval between ileostomy creation and closure. The utility of detecting occult anastomotic complications by contrast enema within the first month after surgery is unknown, and possible detection of yet-unhealed occult leaks in this situation may have a role. This information applies to the variety of low pelvic anastomoses that were created and defunctioned for different diseases in this study. Regardless of the disease process, the same principle of using diagnostic tests based on clinical acumen remains true.

Based on our study, we propose the following approach to closing a defunctioning stoma. Without any clinical signs or symptoms, the patient returns to the clinic 4–6 weeks after surgery for clinical evaluation including inspection of the anastomosis by digital rectal examination and proctoscopy. If this evaluation is normal, the patient returns to the clinic approximately 2 months later for the same evaluation and plans for closure of the ileostomy without contrast enema evaluation. If, at any time, there is suspicion for anastomotic complication either by evaluation in clinic or by symptoms, radiographic evaluation is warranted. Although not specifically evaluated in this study, adoption of this strategy would theoretically save time, money, and patient discomfort.

Conclusion

Within the context of an adequate history, clinical vigilance and suspicion, physical examination, and proctoscopy, routine evaluation of low pelvic colorectal or coloanal anastomoses prior to closure of a temporary defunctioning ileostomy does not influence clinical management. Water-soluble contrast enema evaluation should be utilized selectively, and the necessity of this routine practice should be questioned.

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Radical Redo Surgery for Local Rectal Cancer Recurrence Improves Overall Survival: A Single Center Experience

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Abstract
Background To date, the survival benefit of redo surgery in locally recurrent rectal adenocarcinoma remains unclear.
Study Design In an institutional study, operations for recurrence were retrospectively analyzed. Survival was calculated using the Kaplan–Meier plot and Cox regression analysis.
Results A total of 72 patients with local recurrence were explored or resected. In 38 patients, there was synchronous distant organ recurrence. Forty-five of 72 were re-resected and in 37 of 45 cases, R0 situations were achieved. In 11 of 38 metastasized patients, both local and distant organ recurrence were successfully removed. For obtaining tumor control, resections of inner genitals, bladder, and sacral bone were necessary in 10, 4, and 11 patients, respectively. Survival was better for patients re-resected with a median overall survival of 54.9 months, as compared with 31.1 months among non-resected patients (p=0.0047, log-rank test). Subgroup analysis revealed that a benefit of re-resection was observed to a lesser extent in synchronous local and in distant disease. Cox analysis showed that initial Dukes stage and complete resections of local recurrences were independently determining prognosis (relative risk 1.762 and 0.689, p=0.008 and p=0.002, respectively).
Conclusions Radical surgery for local recurrence can improve survival if complete tumor clearance is achieved, and concomitant distant tumor load should not principally preclude re-resection.

Keywords Rectal cancer · Adenocarcinoma · Recurrence · Total mesorectal excision · Metastases

Introduction

Local recurrence of rectal adenocarcinoma may represent treatment failure and lead to death despite the absence of distant organ disease.[1] Its risk may be partly reduced by an improved multidisciplinary therapy including neo-adjuvant and adjuvant radiochemotherapy.[2] Local recurrence is believed to be partly dependent on radicality of primary surgery.[3] Total mesorectal excision is the gold standard in primary rectal surgery and has lead to a notable reduction of recurrent pelvic tumor manifestation.[4,5] Much effort is currently put into assessing the role of the circumferential rather than the distal resection margin in the development of local recurrence, but its impact has not been definitely defined.[6] As for the distal margin, a minimal tumor distance of 1 cm is considered sufficient, at least for T1,2 tumors.[7] Furthermore, some current recommendation postulates a circumferential clearance into the perirectal connective tissue of at least 2 mm to minimize the risk of recurrence.[8,9] In contrast, no standard treatment exists for local recurrence.[10,11] Often, radiochemotherapeutic measures of rescue and palliation are rendered impossible due to a previous radiochemotherapy. In these cases, redo surgery may be the only remaining therapeutic option. Here, the reasons for redo

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surgery are both functional and oncological.[12] Some uncertainty remains concerning the long-term survival benefit of patients with local recurrence undergoing redo resections including pelvic exenterations with sacral bone resections or cystectomies.[13] Recently, the feasibility and safety of pelvic rescue surgery by sacral bone resection has been strongly advocated, but its benefit in long-term survival has not been completely clarified.[14]

Patients and Methods

A total of 72 patients with histopathologically proven local recurrence of rectal adenocarcinoma, including patients with synchronous distant organ recurrences (n=38), underwent surgery at our institution. Primary operations had been performed either at the University Medical Center Hamburg (UMCH) or in a referring center. Patient charts were analyzed retrospectively. For follow-up, either the general practitioners were interviewed, or the patients themselves were contacted on the phone and seen in our out-patient department. Clinical data on stage, primary and subsequent surgeries, type of recurrence, and time and causes of death were available in all patients. Patients who did not undergo total mesorectal excision at primary surgery were excluded. Patients with peritoneal carcinomatosis undergoing palliative surgery were also excluded from the study. Patients with distant organ metastases principally amenable to surgery, e.g., liver metastases, were included. The decision to operate was made after accurate patient counseling. All patients had given informed consent to detailed clinicopathological data acquisition by the Hamburg Cancer Registry. Two patients with a positive history of non-rectal malignancy were also excluded.

Data on age, sex, pTNM stages, and the types of surgeries were compared using cross tables and association between categorical variables was estimated using the χ^2 test or Fisher's exact test. The Dukes classification was applied for staging.

Independent samples were compared with the Student t test. Survival was estimated from date of primary surgery to

Table 1 Patient Characteristics of Rectal Cancer who Developed Local Recurrence: Sex, Age, Stages, Types of Rectal Resection, and Primary pM1 Resections

	Re-resection not performed upon local recurrence, n (%)	Re-resections performed upon local recurrence, n (%)	Total, n (%)	p value[a,b]
Total	27	45	72	
Gender				
Male	16 (59.3)	28 (62.2)	44 (61.1)	0.808[a]
Female	11 (40.7)	17 (37.8)	28 (38.9)	
Age at the time of primary surgery				
≤65 years	20 (74.1)	28 (62.2)	48 (66.7)	0.439[a]
>65 years	7 (25.9)	17 (37.8)	24 (33.3)	
Initial resection				1.000[a]
Anterior resection (sphincter-preserving)	20 (74.1)	32 (71.1)	52 (72.2)	
Abdomino-perineal resection	7 (25.9)	13 (28.9)	20 (27.8)	
Dukes stage				
A	0	8 (17.8)	8 (11.1)	0.144[b]
B	9 (33.3)	12 (26.7)	21 (29.2)	
C	13 (48.1)	18 (40.0)	31 (43.1)	
D	5 (18.5)	7 (15.6)	12 (16.7)	
pT1	0	2 (4.4)	2 (2.8)	0.553[b]
pT2	4 (14.8)	8 (17.8)	12 (16.7)	
pT3	20 (74.1)	32 (71.1)	52 (72.2)	
pT4	3 (11.1)	3 (6.7)	6 (8.3)	
pN0	9 (33.3)	22 (48.9)	31 (43.1)	0.397[b]
pN1	9 (33.3)	13 (28.9)	22 (30.6)	
pN2	9 (33.3)	10 (22.2)	19 (26.4)	
pM(liver) 0	25 (92.6)	38 (84.4)	63 (87.5)	0.468[a]
pM(liver) 1	2 (7.4)	7 (15.6)	9 (12.5)	
Initial pM1 surgery				
No	1 (3.7)	2 (4.4)	3 (4.2)	
Yes	4 (14.8)	5 (11)	9 (12.5)	
Not applicable (M0)	22 (81.5)	38 (84.4)	60 (83.3)	

[a] Fisher's exact test
[b] χ^2 test

Table 2 Patients Developing Local and Distant Recurrences Within a Median Observation Time of 42.2 Months (95% confidence interval, 37.7–46.7) and Re-Resections

	Only local recurrence, *n* (%)	Local recurrence first, distant later, *n* (%)	Synchronous local and distant recurrences, *n* (%)	Total, *n* (%)
No re-resection:	12 (35.3)	4 (22.2)	11 (55.0)	27 (37.5)
Local re-resections:	22 (64.7)	9 (50.0)	3 (15.0)	34 (47.2)
Both local recurrence and distant metastases resections[a]	0	5 (27.8)	6 (30.0)	11 (15.3)
Total	34	18	20	72

[a] Includes hepatic, distant lymphatic and pulmonary resections, partly as multistage procedures

date of death or censoring and displayed with the Kaplan–Meier method. Predictors were determined using univariate (log-rank test, figures) and multivariate (Cox regression, Table 4) analysis. A p value <0.05 was considered statistically significant. Data analysis was performed with SPSS (Chicago, IL, USA) software, version 11.5.

Results

Patient characteristics are depicted in Table 1. Sex, age, stage, and different surgical operations, including sphincter-preserving anterior resections and abdomino-perineal resections, are compared with resectability of recurrence. Among 72 patients, re-resections were carried out in a total of 45 patients. In the remaining 27 patients, although indicated by the interdisciplinary tumor board, re-resection was not carried out for the following reasons: refusal of the patient to undergo pelvic exenteration (n=7), bad general condition (n=4), irresectable circular pelvic infiltration (n=5), lumbar vertebral fixation (n=3), hydronephrosis due to retroperitoneal lymph node metastases (n=1), lymphogenic affection of the root of the superior mesenteric artery (n=1), intraoperatively detected bilobar hepatic metastases (n=5), and infiltration of preexisting urostomy (n=1). These tumors were partly palliated by diverting ileostomy. Table 1 reveals no significant correlation between primary tumor characteristics and the decision to resect. Rather, initial Dukes stage, pT stage, and pN stage are equally distributed. pM1 stages were defined by either distant lymph node metastases or distant organ metastases according to UICC. Among all Dukes D stages (n=12), initial pM1 liver disease could be initially resected in 9 of 12 patients by concomitant liver resection. Three patients had extrahepatic distant pM1 disease. In three patients who did not undergo initial pM1 surgery, excellent tumor control was achieved by subsequent chemo-(radio)-therapy. At recurrence, an interdisciplinary tumor board decided on the order in which to proceed on an individual basis. Among all 72 patients with local recurrence, 50 had been treated with adjuvant (radio-)chemotherapy after their first operation. The regimens were not uniform. However, mostly 5-fluorouracil and leucovorin were given. Out of 45 re-resections, 34 had been pretreated with radiochemotherapy. At recurrence, four of the non-treated 11 were given chemotherapy and seven were given radiochemotherapy before re-resection. After re-resection, 8 of 45 patients with R2 resections were given chemotherapy. The remaining 27 non-resected recurrences were also given chemotherapy (n=17), radiation (n=5), or both (n=5) depending on preceding therapies.

Re-resections of recurrences A compilation of redo surgeries for local and distant organ recurrences is shown in Table 2. In total, 45 of 72 histologically proven local recurrences

Table 3 Management of Local Recurrence

	No re-resection[a], *n* (%)	Debulking, *n* (%)	Curative resection, *n* (%)	Total, *n* (%)	p value
	27	8	37	72	
Exploration, deviation enterostomy	27	0	0	27 (37.5%)	
Anterior resection of neo-rectum	0	7 (87.5%)	10 (27.0%)	17 (23.6%)	
Abdomino-perineal redo resection	0	0	3 (8.1%)	3 (4.2%)	
Abdomino-perineal redo resection including resection of vagina, uterus, seminal vesicles, prostate	0	0	10 (27.0%)	10 (13.9%)	<0.001[b]
Multivisceral resection: total pelvic exenteration including cystectomy	0	1 (12.5%)	3 (8.1%)	4 (5.6%)	
Multivisceral resection: total pelvic exenteration including lower sacrectomy	0	0	11 (29.7%)	11 (15.3%)	

[a] Conditions precluding re-resection of recurrence are mentioned in the text.
[b] χ^2 test

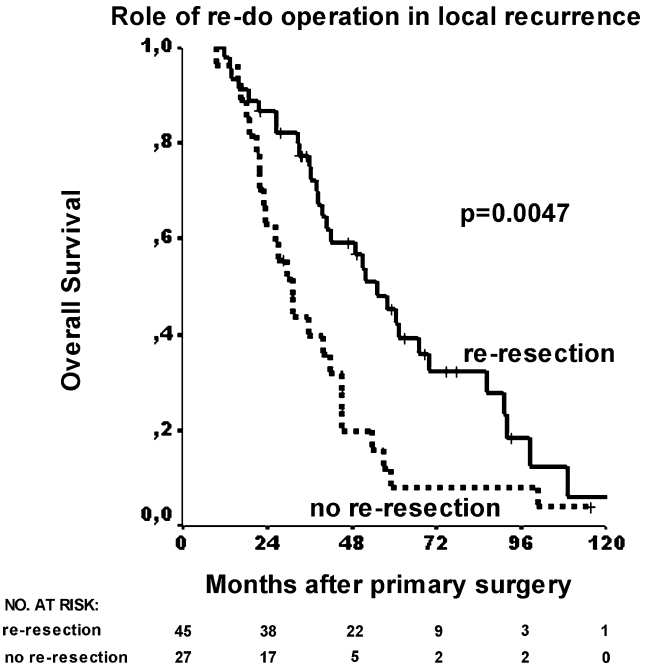

Figure 1 Re-resections (n=45) in 72 local recurrences. The time axis is given in months after first rectal resection.

were re-resected during a median observation time of 42.2 months (Table 2). Thirty-four of 72 patients only developed local recurrences and were partly re-resected (22/34, 64.7%). Thirty-eight patients additionally developed distant organ recurrences. Eighteen of 38 patients developed these recurrences consecutively. Re-resections were performed in these patients as nine local re-resections and five combined local and distant operations (14/18, 77.8%). Patients with synchronous onset of local and distant recurrence were amenable to surgery in 9 of 20 cases (three local re-resections, six combined local and distant recurrence operations, 45%). Mostly, tumor control was achieved by a multistage surgical concept, which lead to two or more follow-up operations.

Operative procedures in local recurrences Table 3 depicts local re-resections. Complete removal with clear microscopic resection margins could be achieved in 37 of 72 patients. Tumor debulking was carried out in 8 of 72 patients. Twenty-seven of 72 patients were not re-resected. Details of redo surgeries are given in Table 3. In summary, extended resections including multi-visceral resections, cystectomies, and sacrectomies obtained tumor freedom (n=37) more often in the post-surgical situation than in standard rectum resections (p<0.001, chi-square test, Table 3).

Perioperative mortality and morbidity Mean postoperative hospitalization time was 19 days (range, 6 to 45) for surgery of recurrence versus 15 days (range, 8 to 23) for primary surgery in the same patients (data available in n=38, p=0.020, Student's t test). Sixty-day mortality was 9% (5/45 re-resections), and morbidity included different surgical and non-surgical complications. Serious complications (n=11) extending hospitalization and leading to repeated surgery or death include respiratory and cardiac insufficiency (n=2), cerebral stroke (n=1), postoperative bleeding (n=1), anastomotic insufficiency and peritonitis (n=3), urinary conduit dysfunction and ureter leakage (n=2), urinary incontinence (n=1), and lower extremity numbness (n=1).

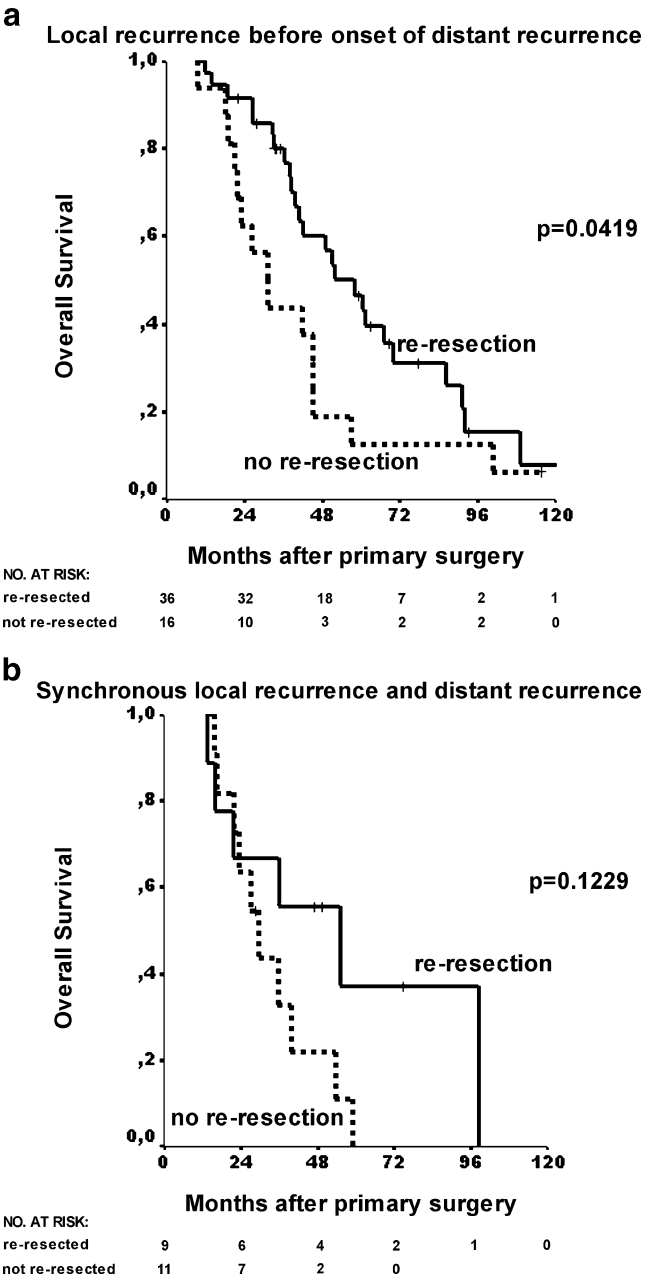

Figure 2 **A** and **B** Survival curves for re-resections versus no resections for local recurrence before onset of distant recurrence (n=52) and in synchronous local and distant recurrence (n=20).

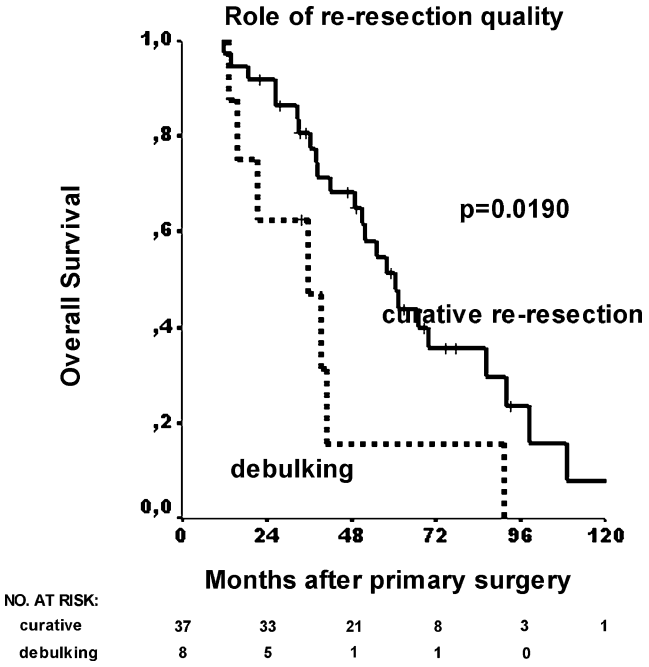

Figure 3 Curative re-resections and debulking for local recurrence (n=45).

Survival after local re-resections At onset of local recurrence, survival was better for re-resected patients, with 31 of 45 death events (median overall survival 54.9 months, range 42.6–67.2 months, 95% confidence interval) as compared with 25 of 27 death events (31.1 months, range 24.1–38.1 months, p=0.0047, log-rank test, Fig. 1) among non-resected patients. In the absence of distant organ recurrence at the time point of first redo surgery (n=52) and at synchronous metastases (n=20), an improved survival was observed for those re-resected. We compared 36 of 52 and 9 of 20 re-resections, respectively (Fig. 2A and B), and found the univariate analysis to be statistically significant. Twenty-five of 36 re-resected patients in Fig. 2A suffered death events (median 57.9 months, range 43.3–72.4), whereas 15 of 16 non-resected patients died (median 31.1 months, range 21.2–41.0, p=0.0419, log-rank test). There were nine local recurrences in the presence of distant disease (Fig. 2B), which were concomitantly re-resected if possible. The latter survived better with six of nine events (median 54.9, range 16.9–92.9) as compared with non-resected patients with 10 of 11 events (median 29.8, range 20.1–39, p=0.1229, log-rank test). A different survival rate was observed in complete and debulking resections (p=0.0190, log-rank test, Fig. 3)., with a median overall survival of 60.2 months (95% confidence interval 48.3–72.1 months) in 27 of 45 patients and 35.7 months (95% confidence interval 14.8–56.7 months) in 8 of 45 patients, respectively.

Multivariate analysis To analyze the independent risk factors for overall survival after developing local recurrence, we performed a Cox regression analysis for 72 local recurrences (Table 4). We found that a higher Dukes stage at primary presentation and local resectability at local recurrence were significant independent risk factors, whereas additional onset of distant disease was not.

Discussion

The principal intention in the interdisciplinary management of rectal cancer is the prevention of any form of recurrence. To achieve this goal, neo-adjuvant and adjuvant (chemo) radiotherapy have been compared recently in a few randomized trials by Norwegian, Swedish, Dutch, and German research groups.[15–19] A large Swedish trial demonstrated that 11% of curatively resected patients receiving preoperative radiotherapy had developed local recurrence after a 5-year follow-up period. Preoperative radiochemotherapy, in contrast to postoperative radiochemotherapy, seems to improve local control and is associated with reduced toxicity, although it could not be shown to improve overall survival.[20] In addition, the surgeon has been recognized to have an important role in treatment outcome. For example, in the Netherlands, national training programs for colorectal surgeons have been implemented.[21–25]

Local recurrence displays multiple phenotypes and requires individual therapeutic concepts. In a recent study by a leading institution, excellent survival results with a multimodality therapy including intraoperative radiation have been described.[26] In another study on sacral bone resection for locally recurrent rectal cancer, a benefit of

Table 4 Cox regression Analysis for Overall Survival After Developing Local Recurrence (n=72)

	p value	Relative risk	95% Confidence interval
Overall survival			
More than 65 years vs. 65 years or less	0.482	1.289	0.636–2.610
Female vs. male	0.873	0.950	0.509–1.773
Higher Duke's stage	0.008	1.762	1.163–2.668
Resection of local recurrence/no re-resection	0.002	0.689	0.546–0.870
Onset of Distant metastases/no distant metastases	0.597	1.208	0.600–2.432

these highly traumatizing procedures could be shown: A total of 62% of patients could be completely resected (R0), and 30% remained tumor-free after a median time of 26 months after onset of recurrence.[27] However, long-term survival data calculated from the time point of *primary* manifestation of rectal cancer are frequently missing. Moreover, information about concomitant distant organ disease are not mentioned. Hence, in our institutional study, we focused on the benefit of surgery in both isolated pelvic and concomitant distant organ recurrence and calculated survival from the time point of first diagnosis. Our study shows that surgery of local cancer recurrence results in better overall survival and that this survival benefit also exists in patients with concomitant distant organ metastases. Remarkably, this significant survival benefit can be observed in a patient cohort like ours that has fewer patients as compared with the high volume studies mentioned above. Our resectability rate of local recurrences was about 65%. The resection rates were lower for patients with concomitant distant organ disease where resections were performed in about 45%. From these 45%, two thirds were resected for both local and distant tumor recurrence. Thus, we can verify that surgery was an indication in a representative amount of cases with both local and distant disease.

Furthermore, we tried to determine whether our highly traumatizing pelvic surgical procedures are associated with better tumor control as well as improved survival. The first point is linked to a common key observation at *primary* tumor manifestation, whereas initial Dukes D stage affects overall survival expectedly much more than any local control.[28,29] In contrast, *after* onset of local recurrence, concomitant distant disease might not be as important for survival, but rather the local recurrence itself might be a life-limiting process (Table 4). Based on these preliminary observations, we would like to suggest that surgery may be an indication in cases of local recurrence in the absence as well as in the presence of distant tumor disease.

Important limitations of the present study are as follows: Patients presenting with recurrence were inhomogeneous with respect to size and site of recurrence, types and duration of previous chemotherapy or radiotherapy, and time until recurrence. The aim of this retrospective study therefore was to include all patients who presented for resection of rectal cancer recurrence and were deemed resectable. The authors did not discriminate between different previous therapies that the patients had previously undergone. Subgrouping with respect to preceding radio-chemotherapies would have lowered patient numbers significantly and would have not allowed for statistical analysis. We are aware that our survival results have to be interpreted carefully due to the inhomogeneity of our study population.

Obviously, complete resection of both local and distant recurrence was superior in prolonging overall survival as compared with debulking procedures (Fig. 3). However, serious complications that may occur as a result of pelvic exenterations and sacral bone resections have to be considered, and their oncological benefit needs to be put into perspective.

As displayed in Table 3, different surgical strategies were chosen depending on the topography of recurrence. Operations performed encompassed simple neo-rectum excisions, abdomino-perineal resections, and resections of neighboring organs and extensions to the sacral bone. We found that a higher radicality of local re-resection corresponded with complete R0 resections. Curative R0 re-resectability lowered the overall risk to die to 0.689 in the Cox regression analysis of overall survival.

In conclusion, an aggressive surgical strategy for local recurrence seems to be justified to achieve local control particularly in tumors refractory to (radio)chemotherapy. We recommend that concomitant distant disease should not exclude surgical intervention especially when a total resection of both local and distant manifestations is likely to be accomplished.

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Adhesions are Common and Costly after Open Pouch Surgery

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Abstract
Purpose Open ileal pouch surgery leads to high rates of adhesive small-bowel obstruction (SBO). A laparoscopic approach may reduce these complications. We aimed to review the incidence of adhesive SBO-related complications after open pouch surgery and to model the potential financial impact of a laparoscopic approach purely as an adhesion prevention strategy.
Materials and Methods We reviewed cases of open ileal pouch patients kept on a database and examined annually. Case notes were studied for episodes of adhesive SBO requiring admission or reoperation. Similar parameters were studied in a small series undergoing laparoscopic pouch surgery. The financial burden of the open access complications was estimated and potential financial impact of a laparoscopic approach modeled.
Results Two hundred seventy-six patients were followed up after open surgery (median, 6.3; range, 0.2–20.1 years). There were 76 (28%) readmissions (median length of stay, 7.4 days) in 53 patients (19%) and 28 (10%) reoperations (43% within 1 year). Laparoscopic patients required less adhesiolysis at second-stage surgery (0% vs 36%, $p<0.0001$) and had less SBO episodes within 12 months of surgery (0% vs 14%, $p<0.0001$) than open patients. Modeling a laparoscopic approach cost \$1,450 and saved \$3,282, thus netting \$1,832 per pouch constructed.
Conclusion Open ileal pouch surgery results in significant cumulative long-term access-related complications, particularly adhesions. These impose a large medical burden on patients and financial burden on health-care systems, all of which may be recouped by a laparoscopic approach, despite higher theater costs.

Keywords Ulcerative colitis · Adhesions · Small-bowel obstruction · Ileal pouch surgery · Laparoscopy

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Background

In the last two decades, proctocolectomy and ileal pouch has become the gold standard surgical treatment for ulcerative colitis.[1,2] Functional results and quality of life are good, although short-term complications are frequent and well described.[3] However, longer-term complications such as adhesive small-bowel obstruction (SBO) are common, problematic, and often overlooked.

Adhesions of some degree are present in virtually every patient after abdominal or pelvic surgery. A proportion will develop adhesive SBO requiring admission, some frequent costly multiple readmissions, and some will require reoperation with or without small bowel resection, incurring risk of further postoperative morbidity and mortality.[4–6]

Colorectal surgery has a recognized high risk of developing such adhesive SBO.

Patients undergoing total colectomy pose the highest risk. This is probably due to a combination of factors including long incisions, multiple quadrant surgery, retraction and packing, bleeding, and long duration of surgery. After ileal pouch surgery, adhesive SBO has been reported between 13% and 35%.[7] Most of these studies are small retrospective series with short or incomplete follow-up.

Because ileal pouch surgery is performed in young patients with benign disease, the recognition of the risk of adhesive SBO and the long-term medical and financial implication is essential. Consequently, this should prompt consideration of appropriate adhesion prevention strategies, and ileal pouch represents an excellent model for assessment of such strategies.

We aimed to evaluate adhesions and adhesive SBO in a cohort of patients undergoing open ileal pouch surgery over a 20-year period. We also aimed to compare these to a group of patients undergoing laparoscopic ileal pouch surgery and to model the potential financial impact of a laparoscopic approach as an adhesion prevention strategy.

Materials and Methods

Data of patients undergoing ileal pouch surgery at the John Radcliffe Hospital (Oxford, UK) were entered on a prospective pouch database and followed up annually in clinic. Patients with diagnosis of ulcerative colitis were included (patients with familial adenomatous polyposis, indeterminate colitis or Crohn's disease were excluded). We interrogated the database and analyzed the notes of all patients undergoing open ileal pouch between January 1984 and December 2003. Adhesive SBOs were documented from clinic notes and letters, local doctor correspondence, and inpatient and operation notes.

The diagnosis of SBO was defined by a combination of clinical criteria (pain, nausea, vomiting, cessation of stools, distension, and abnormal bowel sounds) and imaging (dilated loops of small bowel and air-fluid levels). All admissions for SBO with or without surgery were recorded. Data recorded included time interval of SBO since surgery, staging of ulcerative colitis surgery (single-stage, proctocolectomy and ileal pouch; two-stage, colectomy then subsequent proctectomy and ileal pouch), presence and severity of adhesions at second-stage surgery, length of readmission, and findings at adhesiolysis surgery.

We also assessed a small cohort of patients undergoing laparoscopic ileal pouch surgery between August 2003 and December 2004. Because of short follow-up in this cohort, the only two adhesion parameters chosen to be comparable with open surgery were presence and severity of adhesions at second-stage surgery and readmissions and reoperations for SBO in the first year after surgery (as about half of adhesive SBO episodes occurred within the first year after total colectomy).

Data were analyzed using Fisher's exact test, and the Kaplan–Meier curve was used to calculate the cumulative probability of developing SBO and needing surgery. We assumed costs of readmission (mean hospital stay, 7 days) and reoperation (mean hospital stay, 14 days) for adhesive SBO as estimated by Ellis.[5]

For economic modeling, we assumed the use of simple rather than ultrasonic dissection instruments (as we use). For infertility modeling, we assumed a reduction in fertility of 50%[8] for open pouch surgery, and that half of the female patient below the median patient age (36 years) were potentially affected.

Results

Patient Demographics

During this period, 404 patients underwent open ileal pouch surgery, and 276 satisfied the inclusion criteria for the study. Median follow up was 6.3±4.5 years (range 0.2–20.1 years). Patient characteristics are shown in Table 1.

Readmission for SBO after Open Surgery

Sixty-five patients (24%) developed 123 episodes of SBO (1.9 episodes per patient). Fifty-three patients (19%) developed 76 episodes of SBO (28%; 1.4 episodes per patient; range, 1–15) that required readmission (Table 1). The median length of stay for readmissions was 7.4 days. There were a further 47 episodes involving 13 patients of similar symptoms characteristic but not severe enough to warrant admission and were managed by their local doctor. Many of these non-admitted patients subsequently developed more severe episodes requiring admission.

Table 1 Patient Characteristics and Summary of Late Access-Related Episodes

Characteristics and Summary	Values
Total patients	276
Mean age at surgery (years)	36.3±12.1
Female/male ratio	1:1.3
Surgery: 1st vs 2nd stage	1:1.8
Mean follow-up (years)	6.3±4.5
Not readmitted (patients/episodes)	65/123
Adhesive SBO readmission (episodes, %)	76 (28%)
Wound complications (episodes, %)	
Incisional hernia	18 (7%)
Keloid scar	11 (4%)

Timing of Readmission for SBO after Open Surgery

Almost half of all readmissions for SBO (45%) occurred in the first year after pouch surgery. The remaining were fairly evenly distributed annually thereafter but continued to occur even up to 10 years postsurgery. Six patients (3%) developed seven episodes of SBO between stages 1 (colectomy) and 2 (proctectomy and ileal pouch; 9% of all SBO episodes). The annual cumulative risk of readmission for SBO post-ileal pouch surgery is illustrated in Fig. 1.

Reoperation for SBO after Open Surgery

Twenty-eight patients (10%) required reoperation and adhesiolysis (Table 2), including two patients needing small bowel resection for ischemia. The median length of stay for reoperation was 14.4 days. Of these 28 patients, 3 (11%) required reoperation for SBO between surgical stages 1 and 2.

Timing of Reoperation for SBO after Open Surgery

Twelve (43%) reoperations were performed within 1 year of ileal pouch surgery, six (21%) between 1 and 5 years, five (18%) between 6 and 10 years, and two (7%) over 10 years after ileal pouch surgery. The risk of reoperation for SBO was greatest in the first year after ileal pouch surgery, and the cumulative risk steadily rises every year thereafter (Fig. 1). The risk of reoperation is related to the number of readmissions for SBO, doubling after the fist episode and reaching 80% after the third.

Staging, Adhesions, and SBO after Open Surgery

A number of 100 patients (36%) had single-stage surgery, while 176 patients (64%) had two-stage surgery. At second-stage surgery, preliminary adhesiolysis was undertaken in 64 patients (36%). The adhesions were graded as severe in 20 patients (11%) and moderate in 44 (25%). A relationship between the degree of adhesions scored at the second-stage surgery, and the need of readmission was observed. Two thirds of SBO episodes requiring readmission (31 out of 51) occurred in these patients (66.6% vs 17.8%, $p=0.04$) without significant difference between adhesiolysis for adhesions scored as moderate or severe. There was no significant difference in the number of readmission episodes (25% vs 29%, $p=0.47$) nor the number of patients readmitted (18% vs 20%, $p=0.67$) for adhesive SBO between those who had undergone single- or two-stage surgery, respectively (Table 2). There was no significant difference in the proportion of patients who required adhesiolysis for SBO between those undergoing single-stage (9%) and two-stage surgery (11%; $p=0.59$).

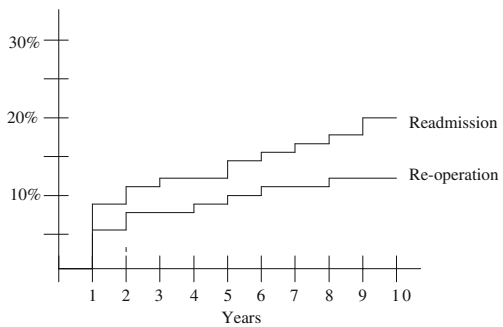

Figure 1 Cumulative risk of readmission and reoperation for adhesive SBO.

Table 2 Adhesive SBO: Single vs Two-stage Surgery

Severity	Single-Stage (%)	Two-Stage (%)	p value
Readmitted			
Episodes	25 (25%)	51 (29%)	0.47
Patients	18 (18%)	35 (20%)	0.67
Reoperated	9 (9%)	19 (11%)	0.59

Adhesions and SBO after Laparoscopic Surgery

Fourteen patients underwent urgent totally laparoscopic subtotal colectomy for acute severe ulcerative colitis between August 2003 and December 2004 (75% male; mean age, 42.0 years). There were no conversions. Median follow up was shorter than for open cases (2.0 vs 6.3 years). Nine patients came with proctectomy with or without ileal pouch. Abdominopelvic adhesions were virtually absent in all cases, with significantly fewer patients undergoing preliminary adhesiolysis for moderate or severe adhesions at second-stage surgery in the laparoscopic (0%) compared to the open group (36%; $p<0.0001$).

Significantly fewer patients developed 'early' SBO requiring readmission (before and in the first year after pouch formation) in the laparoscopic group (0%) compared to open patients (14%; $p<0.0001$). Significantly fewer patients developed SBO requiring reoperation (before and in the first year after pouch formation) in the laparoscopic group (0%) compared to open patients (4%; $p=0.001$).

Costs of Open Surgery: SBO

Assuming Ellis's costs for our population ($2,740 per readmission for mean hospital stay 7 days; $8,462 per reoperation for mean hospital stay 14 days), 76 readmissions would cost an estimated $208,240 (or $754 per pouch constructed) and 28 reoperations $236,936 (or $858 per pouch constructed), a total cost of $445,176 (or $1,612 per pouch constructed).

Costs of Open Surgery: Infertility

For infertility economic modeling, we assumed a reduction in fertility of 50% for open pouch surgery.[8] The success rate of in vitro fertilization (IVF) is mainly dependent on female age (the age of the oocytes) rather than cause of infertility. For women up to their mid-1930s, the live birth rate per IVF cycle is in the region of 25–30%, decreasing to <10% for women over 40.[9] Consequently, multiple treatment cycles are usually needed. The National Health Service funding for IVF is limited, meaning that most couples are forced to self-fund at a cost of $6,000–8,000 each cycle. We conservatively assumed half of women below the median patient age (36 years) were potentially affected.

Economic Modeling: Laparoscopic vs Open Approach

To examine the cost-effectiveness of laparoscopic approach as an adhesion prevention strategy, we calculated the extra cost of a laparoscopic approach and modeled the potential offset savings of a reduction in adhesions and adhesive complications (SBO and infertility; Table 3; this assessment ignores the additional potential savings from less incisional hernias and potentially earlier discharge if pouch surgery can be performed through a small Pfannensteil incision, as we do, after initial laparoscopic total colectomy). Modeling was undertaken assuming adhesion reduction of 25%, 50% and 100%, but 50% reduction was considered a reasonable estimate.

A laparoscopic pouch costs an extra $1,450 in disposables and extra theater time. A reduction in adhesive events of 50% would save an estimated $1,286 per pouch constructed in adhesive SBO costs and $1,996 per pouch constructed in infertility costs. This would provide a cost savings of $3,282 per pouch constructed, easily recouping the outlay costs of a laparoscopic approach, yielding a net surplus of $1,832 per pouch.

Table 3 Potential Costs and Savings of a Laparoscopic Approach ($ Per Pouch)

	Costs	Savings[a]		
		25%	50%	100%
Extra theater time (£ 250/h)	1,000			
Disposable ports	250			
Disposable clip applicator	200			
Reduction in adhesions				
Fewer readmission		378	566	754
Fewer reoperations		430	644	858
Faster stage 2 surgery		38	76	58
Less infertility		1,332	1,996	2,662
Earlier discharge stage 2 surgery			?	
Reduced incisional hernia			?	
Total	1,450	2,178	3,282	4,332

[a] Assuming reduction in adhesions by 25%, 50%, and 100%

Discussion

Adhesions formation after laparotomy occurs virtually in every patient as a response to peritoneal injury. This is an adaptive and protective process leading to subsequent repair of the peritoneal surface.[5] Based on autopsy and prospective clinical studies, the incidence of adhesion formation after abdominal surgery has been shown to range from 67% to 93%.[4,10] Similarly, adhesion formation after pelvic surgery has been reported to range from 51% to as high as 100%.[11,12]

Apart from the beneficial effects of the development of adhesions, the negative clinical consequences are very well documented.[13] Adhesions are the most common cause of SBO, contributing between 49 and 74% of cases of SBO.[14–16] Of all hospital admissions, up to 3% are due to adhesions.[13,17] Approximately 2–3% of all surgeries performed in major hospitals are for adhesive SBO with a morbidity rate that exceeds 50% and a mortality rate as high as 10%.[4,14,18] Furthermore one third of the patients who require adhesiolysis for SBO will be readmitted with further adhesive SBO.[19] The incidence of SBO ranges widely, from as low as 0.3% for gynecologic procedures without hysterectomy performed for benign disease to as high as 35% after total colectomy and ileal pouch formation.[7,20] The majority of the SBO episodes occur early within a year of index surgery, but the risk continues to increase with time steadily thereafter, SBO sometimes occurring decades after the original surgery.[6,21–23]

After colorectal surgery, particularly, the risk of development of adhesive SBO is high.[24,25] Parker et al. reported a readmission rate due to adhesions after colorectal surgery of 16%, with two thirds requiring adhesiolysis. In the longer-term, 50% of all patients were readmitted with adhesion-related problems at least twice in the 10-year study period.[21] Nieuwenhuijzen et al.[6] reported adhesive SBO overall in 18% of patients after total or subtotal colectomy with a mean follow up of 5 years. The incidence increased with length of follow-up, from 11% at 1 year rising to 30% at 10 years postsurgery.

Of all colorectal surgery, proctocolectomy and ileal pouch is associated with the highest incidence of adhesive SBO (Table 4). These patients require an abdominal and pelvic dissection, often with multiple-staged surgery. The mean risk of readmission for SBO after ileal-pouch-pooled reported patients is 18% (range 12 to 35%) and of reoperation, 6% (range, 3 to 19%).[3,7,22–38] However, many of these are small studies with limited follow-up. Studies with longer follow-up demonstrate a higher cumulative

Table 4 Incidence of SBO after Total Colectomy/Ileal Pouch Surgery

Author	Patients	Mean follow-up (Months)	Incidence SBO (%)	Incidence Reoperation (%)
Poppen	69	51	23	10
McMullen	73	38	16	10
Skarsgard	75	15	13	3
Becker	92	3	12	n/s
Oresland	100	20	n/s	6
Young	100	68	27	8
Vasilevsky	116	28	35	19
Nicholls	152	44	n/s	13
Fonkalsrud	184	n/s	n/s	9
Nyam	187	60	13	3
Marcello	460	36	20	7
Francois	626	28	17	8
Galandiuk	851	n/s	13	n/s
Fazio	1,005	35	25	7
McLean	1,178	104	23	7
Present study	276	75	19	10
Range (mean)	–	3–104 (45)	12–35 (18)	3–19 (6)

incidence of SBO. After ileal pouch, Fazio et al.[3] found early SBO in 15%, rising to 25% with longer follow-up, with adhesiolysis in 7%. At the Mayo Clinic, Francois et al.[37] observed SBO in 17% of patients and adhesiolysis in 8% at mean follow-up of 28 months after ileal pouch. Similarly, at the Lahey Clinic, Marcello reported an incidence of SBO of 20% with adhesiolysis in 7% at mean follow-up of 36 months.[38] The largest study from MacLean from Toronto prospectively analyzed 1,178 patients undergoing ileal pouch for mean follow-up of 8.3 years. They observed adhesive SBO in 23% and adhesiolysis in 7%.[7] In our study, almost 45% of SBO episodes occurred the first year after ileal pouch surgery.

Due to the frequency of adhesive SBO and the subsequent complications and costs, several preventive strategies have been developed and proposed to reduce their incidence and severity. Some of these are site-specific to prevent localized adhesive disease, while others work in a more generalized fashion to prevent adhesions throughout the peritoneal cavity.

Pharmacological agents that reduce the peritoneal inflammatory reaction and cytokine release or products, which stimulate the peritoneal fibrinolytic activity to enhance lysis of adhesions in their fibrinous stage, have been developed with variable degree of success on animal models and sparse successes after clinical application.[39–41] Recently, there has been an increasing interest in barrier adhesions prevention products (such as liquid/gel or absorbable/non-absorbable membranes), which work separating damaged peritoneal surfaces, some with encouraging clinical efficacy.[29,39]

However, follow-up are still short and many of these product are still under development, and further studies are need to prove a significantly decrease in adhesions formations and clinical effectiveness. The simplest, most practical prevention strategy is meticulous surgical technique. To reduce adhesion formations, the surgeons should minimize peritoneal injury, proceed with gentle tissue handling, recognize and respect surgical planes, minimize blood loss, and bacterial contamination. Because these principles are intrinsic to minimally invasive surgery, the use of this approach might, aside from the known pain and short-term recovery benefits, reduce the incidence of adhesions and adhesive SBO. Recent randomized animal studies have shown a reduction of up to 50% in adhesion formation in laparoscopy vs laparotomy.[42,43] Similar findings have been observed in human trials in gynecologic surgery[44] and after transperitoneal urologic laparoscopy.[11]

Potential shortcomings of our economic modeling are the time horizon and small number of laparoscopic surgeries performed with short follow-up. Most patients that undergo pouch surgery are relatively young and have a normal life expectancy. As a consequence, the ideal time horizon would be much longer. Furthermore, other potential cost savings might be taken into consideration. Reduced adhesions might allow safer, quicker second-stage surgery by avoiding or minimizing preliminary adhesiolysis with less operative time. The risk of incisional hernia development is significantly reduced with laparoscopic compared to open surgery.[45] We believe that these results are generalizable to centers with treatment strategies, probabilities of events, and costs that are similar to those incorporated into our analysis.

Adhesions affect female fertility through disruption of the relationship between the ovaries and fimbrial ends of the fallopian tubes, thus reducing gamete transport. The degree to which fertility is affected will depend on the degree of disruption. Dense pelvic adhesions affecting the adnexae will reduce the monthly chance of conception (fecundity) to almost zero, whereas flimsy adhesions leaving healthy fimbriae will have less effect. For women with dense adhesions, IVF, an expensive and invasive treatment, may be the only realistic option. When the degree of adhesions are less, then surgery to improve fertility may be appropriate. Adhesiolysis of adnexal adhesions has been shown to improve the conception rate after 24 months from 16% (untreated) to 45% (treated).[46]

Conclusion

Open ileal pouch surgery results in significant cumulative long-term access-related complications, particularly adhesions. These impose a large medical burden on patients and

financial burden on health-care systems, all of which may be recouped by a laparoscopic approach, despite higher theater costs.

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Selective Surgical Treatment of Patients with Rectal Carcinoma and Unresectable Synchronous Metastases Based on Response to Preoperative Chemotherapy

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Abstract
Background The time schedule for chemotherapy and primary tumor resection in patients with rectal carcinoma (RC) and unresectable synchronous metastases (USM) is not well defined. We evaluated whether response to chemotherapy is an appropriate criterion for deciding to perform surgery.
Methods We treated 22 patients with RC and USM who received chemotherapy and were regularly evaluated. After documentation of a partial remission (PR) or stable disease (SD), patients were offered resection of the primary tumor. Results were compared with those of a historical control group of 42 patients who underwent immediate surgery.
Results Seven patients had a PR, four showed SD, and 11 progressed under chemotherapy. Seven patients underwent resection of the primary tumor (no perioperative mortality). The median survival for all 22 patients was 20.2 months. Patients with primary tumor resection survived 27.2 months, whereas patients without resection survived only 12.4 months (p=0.017). The median survival in the control group was 13.5 months (perioperative mortality, 9.5%).
Conclusion Chemotherapy and response-dependent resection of the primary tumor results in the same survival time as that attained with immediate surgery. Patients who face a poor prognosis due to progressive disease are thereby spared the risks of major rectal surgery.

Keywords Rectal cancer · Synchronous metastases · Chemotherapy · Surgery · Palliative treatment

Introduction

Recent advances in the chemotherapy of metastatic colorectal cancer (CRC) and radiofrequency ablation of metastases have extended therapeutic options for stage IV disease.[1–5] The traditional view is that resection of the primary tumor is the first-line treatment even in patients with unresectable metastases.[6–8] However, there is growing evidence that patients do equally well without an operation, thereby avoiding the morbidity and mortality of major tumor surgery.[9–13] We recently reviewed our stage IV CRC patients with unresectable metastatic disease in a multivariate analysis, which showed that the resection of the primary tumor was a predictor of prolonged survival in a subgroup of asymptomatic patients only in cases in whom perioperative mortality was excluded. Applied chemotherapy was the only treatment-related factor associated with prolonged survival on an intention-to-treat basis. We therefore concluded that chemotherapy should be the first treatment step in these patients, selecting a group of patients who might benefit from a deferred resection of the primary tumor.[14] In this study, we demonstrate the feasibility of this concept in patients with resectable rectal carcinoma and unresectable metastases.

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Material and Methods

From January 2001 until December 2006, we treated 58 patients with histologically proven adenocarcinoma of the rectum and distant metastases. Thirty-six patients were excluded from the study: 16 patients underwent a complete resection of the primary tumor and the metastases, only one of these patients had a histopathologically positive resection margin at the metastatic site. Another eight patients underwent immediate primary tumor resection on the basis of an initially curative concept. This failed because of progressive metastatic growth after restaging. Ten patients were unsuitable for chemotherapy for various reasons, and two patients were not considered because they had a far advanced primary tumor. Metastases in the remaining 22 patients were judged unresectable by a senior surgeon (K. L.). Criteria for unresectability of liver metastases were multiple bilobar hepatic metastases, hepatic metastases with infiltration of the liver pedicle or the liver veins, or concomitant unresectable extrahepatic disease. None of these patients was amenable to radiofrequency ablation. The criterion for unresectability of extrahepatic metastases was advanced metastatic disease that precluded complete resection of all metastatic tissue. The patients were offered initial chemotherapy, which was administered by their local medical oncologist. Six out of these 22 patients received chemoradiotherapy in a situation when a curative approach initially appeared to be possible. Chemotherapy alone was continued when the unresectability of the metastases became clear in these six patients after restaging. Otherwise, radiation therapy was not used due to the increased toxicity of simultaneously given intensified chemotherapy. If patients showed symptoms of tumor stenosis, a diverting colostomy was performed. Response to chemotherapy was regularly evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). Patients with stable disease or partial remission were considered for primary tumor resection. All patients gave informed consent and were regularly followed up in our colorectal tumor clinic until death or December 2006. The data was prospectively collected in our tumor database. The primary end point of this retrospective analysis was survival, and secondary endpoints were tumor complications, necessary operations, and perioperative mortality. To rule out hidden survival disadvantages, we compared the total study population with the best group from our previous study (42 asymptomatic patients with rectal cancer and unresectable metastases who had primary tumor resection.)[14]

Comparisons between the study group and the historical group were performed by means of the Mann–Whitney *U* test, the chi-square test, and Fisher's exact test where appropriate. Survival was calculated with the Kaplan–Meier method and survival differences tested with the log rank test. The Statistical Package for Social Sciences (SPSS ® 8.0; Chicago, IL, USA) was used for statistical analysis.

Results

The patient population comprised 20 males and two females with a median age of 67.5 years (range, 41–76 years). Details are given in Table 1. Fourteen patients had liver metastases only, the other eight patients had metastases at multiple sites. Of these, five patients had both metastases in the liver and at other sites, and another three patients had metastases at multiple extrahepatic locations (see Table 2). All patients initially received chemotherapy, 13 of them oxaliplatin/5-fluorouracil(FU)/folinic acid (including one patient with bevacizumab), two patients received capecitabine/oxaliplatin, four patients received 5-FU/folinic acid in various regimes, one patient received irinotecan and oxaliplatin within a study protocol, another one received irinotecan/5-FU/folinic acid, and in one patient, the chemotherapy regimen was not known. In the initial course, a median of four cycles of chemotherapy was given (range, 1–12 cycles). Seven patients achieved a

Table 1 Characteristics of the Study Population and the Historical Control Group

	Study population, n=22	Control group, n=42	p Value
Age, median (range)	67.5 (41–76)	64.5 (40–84)	NS
Male/female	20:2	27:15	0.02
CEA>5 ng/ml	4.5%	28.6%	0.02
Performance status, ECOG/WHO[a] (average)	1.0	1.1	NS
Only liver involvement	63.6%	66.6%	NS
Diffuse liver spreading	59.1%	46.4%	NS
Proportion T4	31.8%	23.8%	NS
Grading G1/2 vs. G3	18:4	32:10	NS
Chemotherapy	All	57.1%	–
Mortality	0	9.5%	–

[a] Eastern Cooperative Oncology Group/World Health Organization

Table 2 Pattern of Metastases

Site	Number of patients	Percent
Liver only	14	63.7
Diffuse	11	
Invasion of vascular structures	3	
Liver and other sites	5	22.7
Liver and lungs	3	
Liver and peritoneum	1	
Liver and distant lymph nodes	1	
Extrahepatic sites	3	13.6
Lungs only	1	
Lungs and distant lymph nodes	1	
Bone and distant lymph nodes	1	

partial remission and four patients a stable disease (see Table 3). In nine patients who presented with tumor stenosis, a diverting colostomy was created to avoid the complications of complete obstruction. Five of these operations were performed laparoscopically. Two patients who initially underwent colostomy could be resected in the course of the disease, and their normal bowel passage was restored. Overall, five patients with partial remission and two patients with stable disease had their primary tumor resected, five with anterior resection and two with abdomino-perineal excision. The operation was done after a median interval of 6 months (range, 5–16 months). One patient with partial remission had no detectable primary tumor at the time of reevaluation and was not operated on. The other patient with initially partial remission had a second carcinoma treated first but progressed after 3 months. The two non-resected patients with stable disease died soon after the first reevaluation. In the non-resection group, one operation was necessary due to obstruction in the course of the disease. There was no mortality in any of the operations.

The overall median survival for all 22 patients was 20.2 (range, 1.5–30.8) months. Patients who had their primary tumor resected showed a median survival of 27.2 (range, 20.2–30.8) months as compared to patients without resection who had a median survival of 12.4 (range, 1.5–27.2) months (p=0.017; Fig. 1). Comparing all patients with a positively selected historical control group, survival was similar with our new concept (20.2 vs. 13.5 months, including perioperative mortality; p=0.37, Fig. 2). The striking difference between the two populations was the lower percentage of patients who received chemotherapy and the perioperative mortality of 9.5% in the historical group (Table 1).

Discussion

There is an ongoing discussion on whether or not to resect the primary tumor in stage IV CRC patients with unresectable metastatic burden. Authors who favor an aggressive surgical approach do so because of possible downstream complications such as obstruction, bleeding, and perforation.[6,7]

The study by Scoggins et al. is the harbinger of a new approach that focuses on an immediate application of chemotherapy, leaving the primary tumor in situ.[9] The authors of this study compared 23 patients who received chemotherapy with 66 patients who had their primary tumor resected. The need to operate on non-resected patients due to complications arose only in two patients (8.7%), while they found a 4.6% mortality rate (3:66) in the resection group. Survival was not different in the two groups (median survival of 16.6 months in the non-resection group vs. 14.5 months in the resection group). Similar results were reported by Michel et al., who compared 23 CRC patients without resection with 31 resected patients.[12] The non-resection group was slightly biased toward more patients with rectal cancer and fewer patients with less than four liver metastases. Seven patients without primary tumor resection (21.7%) underwent surgery for obstruction, all of them suffering from colonic carcinoma. Median survival was not significantly different, amounting to 14 months for non-resected patients and 21 months for resected patients. Notably, there were four complete resections of both the primary and the secondary tumor in the latter group and two in the first group in the course of the disease. A third study presented a matched control design between resected and non-resected patients.[13] Again, there was no difference in survival

Table 3 Chemotherapy Regimen and Tumor Response

State of disease	FOLFOX	CAP/OX	5-FU/FOL	IRI OX	FOLFIRI	not known
Complete response	–	–	–	–	–	–
Partial response	6	–	1	–	–	–
Stable disease	–	–	3	–	1	–
Progressive disease	7[a]	2		1	–	1

FOLFOX oxaliplatin/5-fluorouracil (FU)/folinic acid, *CAP/OX* capecitabine/oxaliplatin, *5-FU/FOL* 5-FU/folinic acid, *IRI OX irinotecan and oxaliplatin*, *FOLFIRI* irinotecan/5-FU/folinic acid

[a] One patient was treated in combination with bevacizumab.

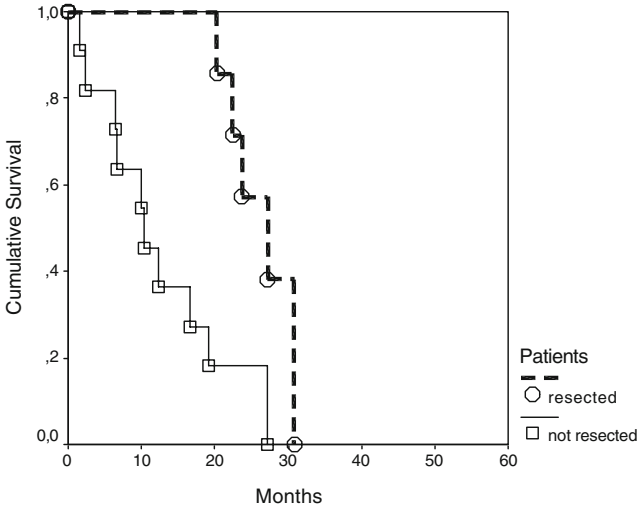

Figure 1 Kaplan–Meier survival curves for patients without primary tumor resection (n=15) and with primary tumor resection (n=7). Median survival for patients with primary tumor resection was 27.2 (range, 20.2–30.8) months and for patients without primary tumor resection 12.4 (range, 1.5–27.2) months (p=0.017).

between the two groups with a median survival of 23 months for 32 resected patients and 22 months for 27 non-resected patients. Each group comprised six patients who ultimately attained a complete resection. Intestinal obstruction occurred in four out of 27 non-resected patients. The problem of primary tumor complications was addressed by Tebbutt et al. who found a similar complication rate in 82 patients without initial primary tumor resection as compared to that in 280 patients who had their primary tumor removed.[11]

There is growing evidence that the strategy of leaving the primary tumor in place is equally acceptable and results in a comparable survival period with the advantage that it avoids the morbidity and mortality of major surgery. However, a stage IV rectal cancer may become more complex with passage of time. There are rapidly deteriorating patients in whom chemotherapy is ineffective, and there are patients with good tumor response who become candidates for curative surgery at the primary and the distant tumor site.[15–17] But even in responders who remain in a situation of unresectable distant disease, survival for 2 years or longer is common.[13] In a previous study, we found a subgroup of asymptomatic patients with colorectal cancer in whom primary tumor resection was an independent factor for predicting longer survival (11.7 vs. 5.2 months in unresected asymptomatic patients; HR, 0.5; p=0.021, Cox regression analysis).[14] The positive effect of primary tumor resection was cancelled out by a mortality of 8.5%, as confirmed by others.[18] We concluded that a selected group of patients might benefit from a deferred resection. Response to chemotherapy is a reliable selection criterion according to our previous data. The present study shows that a consecutive series of patients does equally well, tending toward an even better result than in a favorably selected historical group. Both responders and nonresponders to chemotherapy benefit from deferred resection. The former get a good local tumor control with an acceptable mortality rate (which was zero in this series), the latter are spared a long stay in the hospital and unnecessary surgical complications. As far as liver metastases are concerned, this approach is consistent with the chemotherapy-first concept of a recent study comprising patients with advanced but potentially resectable synchronous liver metastases from CRC. If reevaluation of metastatic disease reveals resectability after chemotherapy—which was not the case in our group—an attempt should be made to resect the metastases and to deal with the primary tumor afterward.[19]

Our study has some clear limitations. The study design is retrospective in nature, and the number of patients included is only small. That is because we focused on a relatively narrow subset of stage IV rectal cancer patients that remained unresectable after the exclusion of any possible curative approach. In this respect, only 22 out of 58 patients (37.9%) with distant metastases were eligible for our concept. To further validate this approach, it would be necessary to organize a multicenter observational trial. The design of this trial would have to address many challenges like standardization of resectability criteria of distant metastases, standardization of the use of chemotherapy, immunotherapy, radiation therapy, or radiofrequency ablation in a palliative setting.

Our concept did not consider endoscopic stenting for obstructing lesions. The insertion of self-expanding metallic stents was first reported by Itabashi et al. in 1993[20] to

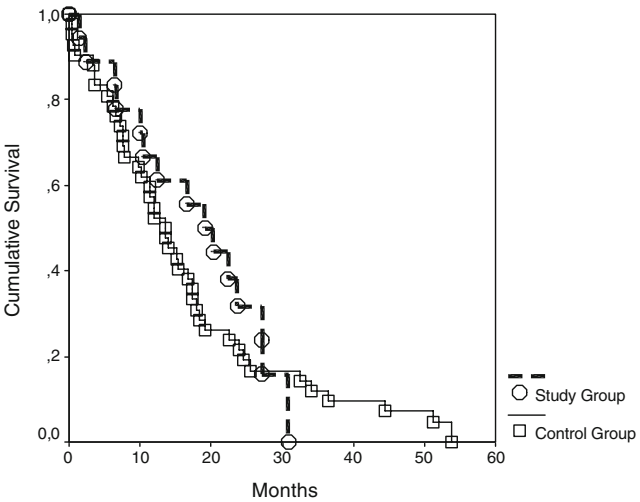

Figure 2 Kaplan–Meier survival curves for the study group with initial chemotherapy (n=22) and the historical control group with initial surgery (n=42). Median survival for the study group was 20.2 (range, 1.5–30.8) months and for the control group 13.5 (range, 0.3–53.8) months (including perioperative mortality; p=0.37).

relieve acute obstruction of the colon or rectum. Since then, it has gained growing acceptance as a palliative means or a bridging to elective surgery.[21,22] The clinical success rate for palliative stenting ranges from 72% to 90%, and the procedure is associated with only a low morbidity.[22,23] However, severe complications like bowel perforation, bleeding, and dislocation, and a long term failure rate of 21% to 67% have been described.[23,24] We were cautious to use endoscopic stenting due to an only limited experience with this technique.

Conclusion

Our study provides data that the management of patients with stage IV rectal cancer and unresectable distant disease with initial chemotherapy and response-dependent resection of primary tumor results in an equivalent or longer survival time and fewer surgical complications than those following an immediate approach. Patients who respond to chemotherapy may profit from the potential benefits of local tumor control by surgery.

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Atopy is a Risk Factor for Acute Appendicitis? A Prospective Clinical Study

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Abstract
Purpose The purpose of the study was to assess the role of atopy on the development of appendicitis. Acute appendicitis is the most common indication for emergent laparotomy especially in the late teens and early 20s. The pathogenesis generally begins with luminal obstruction caused by fecal mass, seeds, stricture, and bacterial, parasitic, or viral infections. The present study was designed to evaluate whether allergic reaction is indeed an undefined leading factor for luminal obstruction.
Material and Methods Mix inhalant and food prick tests were performed in 111 patients who underwent appendectomy for acute appendicitis and in 100 control patients. The material of appendectomy was examined, acute appendicitis was verified and graded according to the severity of inflammation and eosinophilic infiltration rate in the wall of appendix by a pathologist. Demographic data were recorded, and peripheral eosinophil count was also performed.
Results Mix prick test of 33 patients (29.7%) and food prick test of 14 patients (12.6%) were positive in study group when compared with 7 patients (7%) and 1 patient (1%) in control group ($p<0.001$). A total of 38 patients (34.2%) in the study group were reactive with mix or food prick test when compared with 8 patients (8%) in control group. There was no significant difference between eosinophilic infiltration rate, peripheral eosinophil count, severity of inflammation, and Alvarado score of mix prick test positive and negative patients in study group.
Conclusion Atopy incidence in patients with acute appendicitis was significantly higher when compared with control group. However, eosinophilic infiltration rate, inflammation grade, and peripheral eosinophil count were not able to explain the relationship between the two conditions. Atopy is a risk factor for acute appendicitis.

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Keywords Atopy · Allergy · Appendicitis · Eosinophilic infiltration

Background

Appendicitis is a life-threatening disorder, which occurs more commonly in men than in women, with a peak incidence in the late teens and early 20s. It is a common cause of surgical emergency with approximately 280,000 appendectomies performed each year in the USA.[1] Patients with this condition usually underwent an emergent appendectomy because of high mortality and the assumption that acute appendicitis evolved to perforated disease.

A negative appendectomy rate was reported 4–27% in different series.[2] This means that one of every four patients underwent general anesthesia and surgery without appen-

dicitis. Despite all advances in the medical technology and laboratory tests, diagnosis of acute appendicitis is not always easy and clear. History and physical examination are still the key factors in the detection of appendicitis. The surgeon should decide in a relatively short time whether to operate the patient or not. Description of new risk factors or development of new diagnostic tests may prevent patients from unnecessary surgical interventions and avoid surgeons from medico-legal responsibility.

Appendicitis results from an obstruction of the appendiceal lumen most commonly caused by a fecal mass. Stricture, barium ingestion, bacterial, parasitic, or viral infections are the other responsible factors. The obstruction sets off an inflammatory process that can lead to infection, thrombosis, necrosis, and perforation. Infections in the digestive tract can lead to lymphoid hyperplasia, which squeeze the appendix and cause obstruction.[3]

Human appendix, at least in children, has the characteristics of a well-developed lymphoid organ. It contains about 200 lymph follicles in the submucosa. The highest number of lymph follicles occurs in the 10- to 20-year-old age group, with a decline in number after age 30. Lymph follicles are totally absent after age 60.[3] These age groups are similar with the age distribution of patients with acute appendicitis. Lymphoid hyperplasia seems to be the main cause of luminal obstruction rather than the fecal or foreign masses.

Allergic reactions to medication in some patients with acute appendicitis have captured our attention, and we thought that allergic reactions may cause lymphoid hyperplasia in appendix that goes to obstruction of lumen and appendicitis. Seasonal variations of acute appendicitis incidence have also been observed in many studies. In view of this idea and observations, we designed this study to evaluate the role of atopy on the etiology of acute appendicitis and to find a new risk factor for this disease.

Material and Methods

The study was approved by the ethical committee of Gulhane Military Medical Academy (GATA) (Ankara-Turkey) and has been performed in the same institution between October 2005 and March 2006.

Patient Selection Patients who underwent an appendectomy operation and agree to participate in this study were included. All patients were 14 years or older. The initial diagnosis of appendicitis was made on the following criteria: history of abdominal, especially right lower quadrant pain with nausea and/or vomiting, fever of more than 38°C and/or leukocytosis above 10,000 cells/ml, right lower quadrant guarding, and tenderness on physical examination. The surgeon verified appendicitis at the operation. If the appendix looked normal and did not explain the clinical findings, this patient was not included in the study. If the histopathological diagnosis was not acute appendicitis, this patient was excluded from the study. Patients with the following conditions were also excluded: rejection to participate the study, history of using antihistaminic, antiallergic, and tricyclic antidepressant drugs for last the 1 week, presence of intraabdominal abscess, generalized peritonitis, shock on admission, history of cirrhosis and coagulation disorders, contraindication to general anesthesia (severe cardiac and/or pulmonary disease), inability to give informed consent due to mental disability, and pregnancy. History of allergic disease was not used as an inclusion or exclusion criteria.

Eligible patients were informed for the risk and benefits of additional tests (mix inhalant and food prick tests) and asked to sign a detailed informed consent, which has been approved by the institutional review board.

Selection of Control Patients Age- and sex-matched healthy individuals or ASA 1 patients who were admitted to the Department of General Surgery for other diseases were included into the control group. They were informed for the study and signed a consent form for the additional allergy tests. History of allergic disease was not investigated.

Surgery and Postoperative Course All operations have been performed by the residents under the supervision of an attending surgeon with open technique. A McBurney muscle-splitting incision of 4–5 cm in the right lower quadrant was used. A double ligation of the stump was performed with a non-absorbable suture. Patients received 1 g of cephazolin every 12 h intravenously from the time of diagnosis until the surgery. Patients in whom a complication (gangrenous or perforated appendicitis) was observed during the surgery were treated with double antibiotic coverage (cephazolin and metranidazole) until the white blood cell count was within the normal limits and the temperature was below the 37.9°C for 24 h. Other patients did not receive any antibiotic postoperatively. Bowel sounds were checked every 12 h. Once present, the patients were started on a clear liquid diet and advanced to regular diet when the liquid diet was tolerated and flatus was observed. Patients were discharged when they tolerated a regular diet, had a normal white blood cell count under 10,000/ml, and were afebrile for 24 h.

Blinding Attending surgeons decided to operate the patients according the signs and symptoms. They also noted whether the appendix was really inflamed or not according to the intraoperative findings. Residents informed the patients about the study and planned further tests. All allergy tests were performed and interpreted by a specialist

from the Department of Allergy. All surgical specimens underwent routine histopathologic examination at the Department of Pathology. Microscopic slides were re-examined for the grade of inflammation and eosinophilic infiltration rate by the same pathologist. The pathologist was not aware of the results of allergy tests.

Allergic Tests Mix inhalant and food prick tests were performed in the Department of Allergy usually in postoperative 2–4 day before patient is discharged. Every patient reviewed and signed an informed consent form, which explains the study and test procedures. The eosinophil count from peripheral capillary blood was also performed and recorded. Mix inhalant prick test (MPT; Allergopharma; grass mix, weed mix, tree mix, mold mix, mixed epidermal, cockroach, Der. Farinea, Der. Pteronyssinus, latex) and food prick test (Allergopharma) including 40 food antigen were used. Small drops of the "allergen" were placed onto the forearm; then, the skin was pricked to allow a tiny amount of the allergen into the skin. Reactions were measured 10 min later and recorded by the same allergist. Histamine hydrochloride as a positive control and 0.9% sodium chloride as a negative control were used in skin prick test (SPT). Positive control was reactive and negative control was non-reactive in every patient.

Pathologic Examination Initial examination of appendix was made during the routine program of the Department of Pathology. The pathologists reported their diagnosis without any information whether the specimen was from the study or not. After the last operation, a total of 111 cases were retrieved from the archive material of the Pathology Department of GATA. All cases were initially checked by hematoxylin and eosin (H&E)-stained sections to confirm acute appendicitis. Polymorphous leukocytic infiltration in the muscle wall of appendix was sufficient to meet the criteria of acute appendicitis. Then, H&E-stained sections were used for the evaluation of inflammation on the wall and eosinophilic leukocyte infiltration. Initially, the sections were scanned at low-power field to detect the maximum areas of inflammatory infiltrate containing eosinophilic leukocytes. Then, the sections were scanned at high power field to quantify the eosinophilic leukocytes. The number of high-power field areas analyzed for the evaluation of eosinophilic leukocyte infiltration varied from 5 to 15 areas per sample. The intensity of eosinophilic leukocyte infiltration was assessed semi-quantitatively. The intensity of eosinophilic leukocyte infiltration was graded using a three-stage grading scale: negative (−), weak positive (1+), moderate positive (2+), and strong positive (3+). During this examination, the severity of appendicitis is also graded in four stages according to the advancement of inflammation on the wall as acute appendicitis (limited at mucosa), supurative appendicitis (limited on the wall), periappendicitis, and perforation and/or local peritonitis.

Outcome Parameters Name, age, sex of the patient, date of operation, and signs and symptoms at the admission (right lower quadrant pain, nausea and/or vomiting, body temperature, WBC, right lower quadrant guarding, and tenderness) and Alvarado score[4] on physical examination, allergy tests (MPT, latex, and food), total eosinophil count, history for allergic disease, histopathological examination reports [acute appendicitis (limited at mucosa), supurative appendicitis (limited on the wall), periappendicitis and perforation and/or local peritonitis], and eosinophil infiltration rate are recorded.

Statistical Methods SPSS for Windows V.11.5 was used for statistical analysis. We used frequencies and percentages for nominal data and mean+standard deviation for continuous data as descriptive statistics. Chi-square test and *t* test were used to compare the groups. Statistical significance level was 0.05.

Results

A total of 111 patients who underwent an appendectomy for acute appendicitis [study group (SG)] and 100 volunteer patients [control group (CG)] were evaluated at the Department of Surgery, GATA between October 2005 and March 2006. Patient characteristics were similar in booth groups. In the SG, 15 female and 96 male patients were presented, and in CG, 25 female and 75 male patients were included. The mean age was 23.12 (ranged between 14 and 57) in SG and 25.35 (ranged between 14 and 65) in CG.

Routine histological examination of the appendectomy specimen confirmed the diagnosis of acute appendicitis in every patient. Seven patients in SG (6.3%) and eight patients in CG (8%) described allergic complaints (unproven with allergic tests).

MPT was positive among 33 (29.7%) patients of SG when compared with 7 patients (7%) in CG, and the difference was statistically significant ($p<0.001$; Table 1). MPT was negative among 78 (70.3%) patients of SG and 93 (93%) patients of CG. Fourteen patients (12.6%) in SG and one patient (1%) in CG were reactive for food prick test. The difference was statistically significant ($p<0.001$; Table 1). Latex-positive patients existed in both groups. Five of 14 patients in whom the food allergy test was positive were not reactive for MPT. A total of 38 patients (34.2%) in SG were reactive for MPT or food test when compared with 8 (8%) patients from the CG.

Table 1 Comparison of MPT and Food Test Results Between Two Groups

	Study Group		Control Group		*p* value
	Positive Number (%)	Negative Number (%)	Positive Number (%)	Negative Number (%)	
MPT	33 (29.7)	78 (70.3)	7 (7.0)	93 (93.0)	<0.001
Food	14 (12.6)	97 (87.4)	1 (1)	99 (99)	<0.001
Food or MPT	38 (34.2)		8 (8)		<0.001

MPT Mix prick test, *Food* Allergy test for food

Eosinophilic infiltration rate was (−) in 53 patients, (1+) in 45 patients, (2+) in 6 patients and (3+) in 7 patients. Eosinophilic infiltration rate score was compared in MPT (+) SG (n=33) and MPT (−) SG (n=78), but the difference was not statistically significant (p=0.664; Table 2). Mean Alvarado score in MPT (+) SG (n=33) was 8.09 (SD, 0.31190), and it was 7.78 (SD, 0.17753) in MPT (−) SG (n=78). There was no statistically significant difference between Alvarado scores of both groups (p=0.366; Table 2).

The hystopathologic grade (severity) of appendicitis is also compared among atopic and non-atopic groups. The advancement of inflammation in the wall was not significantly different between MPT(+) and (−) patients (Table 2), between food allergy test (+) and (−) patients, and any allergy test (+) and (−) patients.

Total eosinophil count was compared between the study and control groups, between the MPT (+) and MPT (−) SG, and between the MPT (+) SG and CG. The differences were not statistically significant. (p=0.180, p=0.565 and p=0.194, respectively; Table 3) Correlation between the total eosinophil count and eosinophilic infiltration rate were not statistically significant in SG, in MPT (−) SG and in MPT (+) SG (p=0.484, p=0.756, and p=0.096, respectively)

Discussion

The cause of appendicitis relates to blockage of the lumen of the appendix. The blockage leads to increased pressure, impaired blood flow, and inflammation. Most commonly, feces blocks the inside of appendix. Bacterial or viral infections in the digestive tract can also lead to swelling of lymph nodes, which squeeze the appendix and cause obstruction. Swelling of lymph nodes is known as lymphoid hyperplasia. The aim of this study was to evaluate the role of atopy in the development of lymphoid hyperplasia, obstruction of the lumen, and acute appendicitis.

Gastrointestinal system (GIS) is one of the main entrances into the body for allergens during whole life. Gastrointestinal tract usually (95%) develops immune tolerance to the allergen, which is taken mostly by foods. Allergic reaction or intolerance may occur in few patients. Approximately 1 ton of food passes through gastrointestinal tract in an adult person and confronts the intestinal immune system with a large quantity of diverse antigens.[5] Mucosal and cellular immune systems are active in GIS in which immune tolerance mechanism is evolving since childhood age.

The term “atopy” is used for a predisposition toward the development of immediate hypersensitivity reactions against common environmental antigens and defined as the presence of at least one positive SPT with or without clinical manifestation. The prevalence of atopy is about 30–40% in Western population.[6] Exposure to the allergen and after allergic inflammation produce clinical signs and symptoms in main target organs, such as skin, eyes, nose, and airway, and usually, it can cause subclinical manifestation in other organs as gastrointestinal system, bone marrow, etc.

Eosinophils are present intensively in cecum and in all gastrointestinal tissue except esophagus.[5] Previous studies showed Th2 type allergic inflammation affected by eosinophils in GIS.[7] Increases of eosinophilic infiltration is

Table 2 Comparison of Eosinophilic Infiltration Rate and Alvarado Score and Grade of Inflammation (Severity of Appendicitis) in MPT (+) and MPT (−) Patients of Study Group

	MPT (+) (n=33)	MPT (-) (n=78)	p
Eosinophilic infiltration rate, number (%)			
0	13 (39.4)	40 (51.3)	0.664
1	15 (45.2)	30 (38.5)	
2	2 (6.1)	4 (5.1)	
3	3 (9.1)	4 (5.1)	
Alvarado score			
Mean (SD)	8.09 (1.79)	7.78 (1.56)	0.366
Grade of inflammation, number (%)			
Acute	12 (36.4)	37 (47.4)	
Supurative	6 (18.2)	21 (26.9)	0,221
Periappendicitis	14 (42.4)	18 (23.1)	
Perforation/peritonitis	1 (3.0)	2 (2.6)	

MPT Mix prick test, *SD* standard deviation

Table 3 Total Eosinophil Count

	TEC (/mm^3)	SD	*p* value
SG	100	71.66843	
CG	86.5	74.14666	
MPT(+) SG	106.06	75.78503	
MPT (−) CG	97.43	70.20260	
SG compared with CG			0.180
MPT (+) SG compared with MPT (−) SG			0.565
MPT (+) SG compared with CG			0.194

TEC Total eosinophil count, *SD* standard deviation, *SG* study group, *CG* control group, *MPT* Mix prick test

demonstrated in gastroduodenal biopsies of atopic patients even when macroscopic appearance of gastroduodenal mucosa is normal.[8] Subclinical eosinophilic inflammation in atopic patients may assist thickening at appendicular mucosa, facilitate the luminal obstruction, and predispose appendicitis. Some diseases and conditions accompanied by eosinophilic infiltration such as eosinophilic gastroenteritis[9–11] or some parasitic infections[12,13] may figure acute abdomen. Despite the large lumen, intensity of inflammation may be as much as leading a bowel obstruction in patient with focal eosinophilic infiltration at intestinal mucosa.[14] Relatively narrow lumen of the appendix is predisposed to obstruction in patient with eosinophylic infiltration, and acute appendicitis can occur in these patient groups.

Previous studies have shown that the intestinal mucosa of patients with food allergy contains not only an increased amount of activated eosinophils but also show an enhanced immunologic responsiveness of these cells when exposed to anti-IgE-dependent stimuli or other of-feeding allergens.[15] Cross-reaction between pollen and fresh food may also create immunologic responsiveness.[16] Pollen allergy may suggest itself by oral intake of fruits, such as apple, pear, peach, and potatoes, in consequence of food-pollen cross reactivity, and induce subclinical eosinophilic infiltration in GIS.[7–17]

Eosinophilic gastroenteritis (EG) is characterized by eosinophilic infiltration of any gastrointestinal segment. Clinical manifestations range from non-specific gastrointestinal complaints to more specific symptoms such as luminal obstruction, protein-losing enteropathy, malabsorption, and eosinophilic ascites. Approximately 50% of patients with EG have a history of atopy.[18] While the most commonly seen allergic disease with EG is food allergy, sometimes, asthma may accompany EG. Asthmatic patients who have peripheral eosinophilia and gastrointestinal symptoms must be evaluated for EG.[19]

A previous study demonstrated that eotaxinin provides eosinophil accumulation in bowel wall of atopic patients.[15] Clinical and experimental studies showed that reaction to food allergen increases when gastric motility decreases like after using antacid drugs.[20] Decreases of intestinal motility may facilitate the clinical appearance of acute appendicitis. Seasonal variation of frequency is also interesting. Appendicitis varies by season but peaks in the summer, July to be exact. Many studies demonstrated this variations, but the cause is not clear.[21] Food allergy, especially fruit-related allergies, may affect the increased incidence in July.

The most rapid and accurate way of identifying atopic individuals and causative allergens is the SPT.[22] It is fast, relatively non-invasive, and significantly better than specific IgE measurement. Once a positive value or reactivity is determined with SPT, it persists during a long time even in treated patients. In a follow-up study, SPT results are found positive after 12 years in patients that underwent immunotherapy for pollen allergy.[23] New sensitization may occur any time in patients and may be detect with SPT, but previous positive results are persistent.[23,24]

Because the sensitivity and specificity of skin testing requires withholding medication that could change the skin reactivity, it seems important to take into account the possible influence of some drugs. These drugs are well known. H_2-receptor antagonists, some tricyclic antidepressants (Desipramine and Doxepin), and antihistamines are the most likely drugs to interfere with skin tests.[24–26] They have a suppressive effect on the wheal, flare, and itching sensation in SPT. In this study, patients who take such medications are excluded.

To the best of our knowledge, there is no other study in the English literature evaluating the effect of atopy in the pathophysiology of acute appendicitis. According to our findings, significantly more patients in SG have atopy compared with controls. The difference was significant for even MPT, food prick test, and both. These results support our hypothesis, and we suggest that atopy is a risk factor for acute appendicitis. The correlation between the atopy and eosinophilic infiltration and the relationship between the clinical severity of acute appendicitis and atopic status has been interrogated. However, histopathological examination of appendectomy specimen did not confirm the expected increase of eosinophilic infiltration in atopic patients. Even eosinophilic infiltration rate was slightly high in SG, the difference was not statistically significant. Findings from histopathological examination in this study revealed that the tissue eosinophilia is not sufficient to explain the relation between atopy and appendicitis.

Mean eosinophil count in peripheral blood was higher among MPT (+) SG patients than MPT (−) SG and CG patients but the difference was not statistically significant. A correlation between peripheral eosinophil count and eosinophilic infiltration in appendix could not be demonstrated. Recent studies showed that the skin tests, eosino-

philic infiltration, and IgE level are not correlated with each other.[27] Blood IgE level is also not correlated with those in fecal and jejunal fluid.[27]

This study was performed between October and March, which is a time period out of pollen season. Of 33 patients, 30 with atopy had sensitivity to in-house allergens (mite, cockroach, and fungus). Sensitivity to in-house allergens that occurs during winter season seems to be a risk factor for acute appendicitis. Our results will be more meaningful if further similar studies are performed in pollen season to reveal the relationship between the pollen allergy and acute appendicitis.

Conclusion

Atopy incidence in acute appendicitis was significantly higher when compared with control patients. However, eosinophilic infiltration in the wall of appendix, severity of inflammation, and peripheral eosinophil count were not able to explain the relationship between the two conditions. Atopy is a risk factor for acute appendicitis. Notification of any previous allergic conditions may be used as a supportive finding in the diagnosis of acute appendicitis.

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Early Relaparoscopy for Management of Suspected Postoperative Complications

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Abstract
Background Diagnosis of complications after laparoscopic surgery is difficult and sometimes late.
Methods We compared the outcome of patients who had early (<48 h) relaparoscopy for suspected postoperative complication to those where relaparoscopy was delayed (>48 h).
Results During the study period, 7726 patients underwent laparoscopic surgery on our service. Of these, 57 (0.7%) patients had relaparoscopy for suspected complication. The primary operations were elective in 48 patients and emergent in nine. Thirty-seven patients had early, 20 had delayed, secondary operations. The most common indication in the early group was excessive pain (46%) followed by peritoneal signs in 35%. In the delayed group, the most common indication was signs of systemic inflammatory response syndrome in 30% and peritoneal signs in 25%. Relaparoscopy was negative in 16 (28%) patients with no difference between groups. The identified complication was treated laparoscopically in 37(65%) patients, and the rest were converted. The patients in the delayed group had a significantly longer hospital stay ($p<0.003$) and had a higher rate of complications ($p<0.05$). They also had a higher mortality rate (10% vs. 2.7%), but the difference was not statistically significant.
Conclusions A policy of early relaparoscopy in patients with suspected complications enables timely management of identified complications with expedient resolution.

Keywords Laparoscopy · Complications · Diagnosis · Management · Relaparoscopy

Introduction

The main advantage of minimally invasive over open surgery is the shorter and more benign postoperative course. Following elective or emergency laparoscopic procedures, most patients are discharged the next day and suffer minimal postoperative pain and discomfort. However, minimally invasive surgery is not without risk. The reported incidence of complications varies with the particular operation and ranges between 0.05% and 8%.[1, 2] A delay in diagnosis of these complications is common (40–77%)[1,3–5] and is associated with significant morbidity and mortality.[6–8]

When complications are suspected, most surgeons rely on imaging studies for diagnosis; however, at least early on, the radiological findings are nonspecific. Residual fluids or free gas in the peritoneal cavity are common after laparoscopic surgery and are often misinterpreted as normal postoperative findings.[1, 9]

Most surgeons are reluctant to take patients back to the operating theater, and the aphorism that the operating surgeon is the last one to recognize a complication is well known. However, early relaparoscopy is usually easy and safe, as the old port sites can be used for blunt entry and may be the most efficient route to diagnosis and management.

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Table 1 Patient Data

	Early	Delayed	Total
Mean age (range)	49.9 (22–77)	56.0 (24–86)	53(22–86)
Sex (% female)	68	85	74
Mean ASA score	2.0	2.1	2.1
Elective operation (%)	84	60	75

In this study, we retrospectively compared the outcomes of patients who had early (less than 48 h from the original operation) relaparoscopy to the outcomes of those where the intervention was delayed. We hypothesized that early relaparoscopy would lead to improved outcomes as well as be cost effective.

Material and Methods

General

We reviewed the records of all patients who had relaparoscopy for suspected complications between January 2000 and July 2006. The patients were identified by manual review of the operating room registry. All patients had primary and repeated surgery in our department at Soroka Medical Center tertiary 1100 beds hospital providing medical care to more than one million residents in Southern Israel. One of the principles of our hospital, which is readmission of all patients, is performing to primary service where surgery was done. All patients were instructed before discharge and, in case of any postoperative problem, they may call or return directly to our department. On our knowledge, all patients that had postoperative complications after primary laparoscopic surgery included in this series.

The patients were divided into early (<48 h) or delayed (>48 h) groups based on the interval between the primary operation and the relaparoscopy. Data collected included age, sex, American Society of Anesthesiologists (ASA) score, type of primary surgery, use of imaging studies, indications for reoperation, operative findings, duration of relaparoscopy and rate of conversion, morbidity related to the relaparoscopy, final disposition, and overall length of stay.

Epiinfo v3.3 (Centers for Disease Control and Prevention, Atlanta, GA, USA) was used for data entry and analysis. Nonparametric statistics were used for comparing length of stay and Fisher's exact test for frequencies; $p < 0.05$ was considered significant.

Surgical Considerations

Repeated laparoscopy was attempted in all patients when complication was suspected after laparoscopic procedure. There were no cases when reexploration was performed by open manner from the beginning.

Reentry into the abdomen was done through one of the previous port sites, using a bluntly inserted 11-mm cannula. Following the establishment of pneumoperitoneum, other cannulas were inserted via the old port sites under vision.

In cases of bile leaks from the cystic duct stump, the stump was closed with an endoloop (Surgitie, Auto Suture, United States Surgical Corporation, Norwalk, CT, USA). When the source of the leak was not readily identified, an intraoperative cholangiogram was performed via the stump. In cases for suspected gastric perforation where the hole was not readily seen, the stomach was filled with methylene blue dye to localize the injury.

Other complications were managed by either conversion to a formal laparotomy, a small target incision, or laparoscopically at the discretion of the operating surgeon.

Results

During the study period, 7726 patients had laparoscopic surgery on our service. Of these, 57 patients (0.7%) had relaparoscopy for suspected complications and were included in the present series. Of these, 37 had early (48 h or less) relaparoscopy, and in 20, the secondary operation was delayed. Three patients in early (8%) and ten in late group (50%) were discharged after surgery and readmitted to our department. The distribution of age, sex, and ASA score was similar between the groups, but there were slightly more emergency operation in the delayed group (Table 1).

The distribution of primary operations is listed in Table 2. All patients with suspected complications after either primary or revisional laparoscopic banding for morbid obesity were reoperated on early. Two thirds of the 27 relaparoscopies following cholecystectomy were in the

Table 2 Primary Laparoscopic Procedure

Surgery type	Early all/ negative (*n*)	Delayed all/negative (*n*)	Total/ negative (*n*)
Cholecystectomy	19/8	8/2	27/10
Bariatric procedure	11/1		11/1
Incisional hernia repair	3/1	6/2	9/3
Perforated viscus	2/0	2/2	4/2
Appendectomy	1/0	2/0	3/0
Kidney biopsy	–	1/0	1/0
Drainage of urachal abscess	1/0		1/0
Ovarian cystectomy		1/0	1/0
Overall	37/10	20/6	57/16

Table 3 Indications for Relaparoscopy

Indication	Early all/negative (*n*)	Delayed all/negative (*n*)	Total/negative (*n*)
Postoperative pain	17/10	4/1	21/11
Peritoneal signs	13/1	5/3	18/4
SIRS	2/0	6/2	8/2
Intestinal obstruction	1/0	3/0	4/0
Bile leak	3/0	–	3/0
Overt shock	–	2/0	2/0
Bleeding	1/0	–	1/0

SIRS Systemic Inflammatory Response Syndrome

early group. Other primary operations were more or less evenly distributed between the groups.

The decision to perform relaparoscopy was made by the attending surgeon involved in the case; however, input from other group members, including residents, was often influential. The indications for relaparoscopy are listed in Table 3. The most common indication in the early group was excessive pain and increased demand for narcotics (46%) followed by peritoneal signs (tenderness, guarding) in 35%. In the delayed group, the most common indication was signs of systemic inflammatory response syndrome in 30% and peritoneal signs in 25%. Excessive pain was the indication in only 20% of the patients in the delayed group.

Although 30% of patients had some sort of imaging study, the studies had little influence on the decision to operate. In the early group, 18% of the patients had an imaging study, all of which were negative (with a false negative rate of 67%). In the delayed group, 55% of the patients had an imaging study. This includes four patients with intestinal obstruction evident on plain films. One patient had a US examination which was a true negative, and six patients had an abdominal computed tomography (CT) with five true positives and one false negative.

The findings at relaparoscopy by timing group are summarized in Table 4 and described according to primary procedure in Table 5. Bile leaks and bleeding were the most common identified complications after laparoscopic cholecystectomy, followed by gastric perforation after bariatric surgery and small bowel obstruction and adhesions after incisional hernia repair. Gastric perforations were all in the early group, while the rest were more or less evenly distributed between the groups. The rate of negative reexplorations was similar in both groups (10/37 and 6/20, or 27% and 30%, respectively). All 16 patients with negative explorations had no further complications and were discharged uneventfully after 2 or 3 days. In both groups, negative explorations were more common when the primary operation was cholecystectomy and when the only indication was excessive pain.

In both groups, the majority (85%) of the complications could be handled laparoscopically. In particular, early diagnosis of hollow viscus injury enabled successful laparoscopic suturing in six out of ten patients where it was identified. One patient with cecal injury following laparoscopic appendectomy was managed by tube cecostomy. Laparoscopic release was possible in all five cases of small bowel obstruction.

The outcome of relaparoscopy is summarized in Table 6. The patients in the delayed group had a significantly longer hospital stay ($p<0.003$ by the Wilcoxon rank sum test) and had a higher rate of complications ($p<0.05$ by Fisher's exact test). They also had a higher mortality rate (10% vs. 2.7%), although the difference was not statistically significant.

There were three deaths in this series. One was a 57-year-old woman who had a bile leak from the gallbladder bed following cholecystectomy for acute cholecystitis. The indication for relaparoscopy was septic shock and acute renal failure; the source of the leak could not be identified, and leak was drained initially. She failed to improve, and we attempted to drain the biliary tree via a tube in the cystic duct. She was found to harbor invasive gallbladder carcinoma in the resected specimen.

The second death was a young man with a congenital immune deficiency disorder who also went into septic shock following a rather minor bile leak from an accessory cystic duct. He actually went home following the original cholecystectomy and was readmitted 3 weeks later in severe sepsis. He died despite successful closure of the leak and adequate drainage.

Table 4 Intraoperative Findings at Diagnostic Relaparoscopy

Postoperative complications	Early (*n*)	Delayed (*n*)	Total (*n*)
Bile leak	5	3	8
Hematoma and bleeding	5	3	8
Gastric tear	6	0	6
Intra-abdominal abscess	2	2	4
Infected intra-abdominal fluid	5	–	5
Small bowel incarceration above the mesh	1	2	3
Small bowel tear	1	1	2
Adhesions	–	2	2
Colonic tear	2	–	2
Urinoma	–	1	1
Without findings	10	6	16

Table 5 Most Frequent Complications According to Primary Surgical Procedure

	Bile leak		Hematoma/bleeding		Abscess/infected fluid		Tears		SBO/adhesions	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
Cholecystectomy	5	3	3	3	1	1	1			
Bariatric			1		2		7			
Hernia repair			1						1	4
Other					4	2	1	1		

The third death was a woman who had a gastric injury following laboratory-measured blood gases. She had a water soluble contrast study, which failed to identify the leak but led to a significant delay in diagnosis. She had multiple operations and a stormy course in the intensive care unit and died of multiple organ failure.

Discussion

Dealing with complications is part and parcel of the practice of surgery. Laparoscopic surgery is no exception. Following laparoscopic surgery, complications occur in between 0.05% to 8% of patients.[1,2,10,11] The key to obtaining a favorable outcome despite the complications is early recognition and prompt attention.

When injuries are recognized during the procedure, the outcome is usually favorable, as they can be primarily repaired. However, delayed diagnosis is often associated with increased morbidity and mortality. From one half to two thirds of injuries[5,12] are discovered belatedly, and it stands to reason that earlier diagnosis may improve outcome.

Following laparoscopic surgery, the postoperative course is usually smooth and is characterized by minimal pain and early mobilization. Whenever the postoperative course does not follow the usual pattern and recovery is delayed, a complication should be suspected.[6] Lee[4] argues, and we agree, that suspicion should be raised when a patient is not doing well after a cholecystectomy and exhibits extraordinary abdominal pain, anorexia, or fever. He suggested that such findings require appropriate diagnostic studies.

Diagnostic studies can be some sort of imaging or laboratory tests. Laboratory tests are rather nonspecific and have a poor diagnostic yield,[1] so most surgeons rely on imaging studies. The results of the present study suggest that these, too, are often misleading and can cause an unnecessary delay in diagnosis.

In the present series, imaging studies had a high false negative rate and led to a delay in diagnosis, with at least one death. Similar findings were also reported by Schrenk,[1] who emphasized that negative investigations do not exclude a serious complication. Even positive findings are not always conclusive. For instance, Dexter[9] showed that following laparoscopic cholecystectomy, as many as 43% of patients have free fluid in the abdominal cavity by CT scan or ultrasonic examination and that this finding is nonspecific and usually meaningless.

A formal laparotomy is overkill for diagnostic purposes. Most surgeons resort to a formal laparotomy when a bowel injury is identified.[12] However, a formal laparotomy is associated with pain, ileus, and increased risk of abdominal infection. Consequently, it is only employed after a definitive diagnosis or clear indications that the patient is in trouble.

In contrast, relaparoscopy is simple and, if negative, does not increase morbidity. When done early, the old port sites are still open and access and pneumoperitoneum can be achieved bluntly (even when the Veress needle was used during the initial laparoscopic operation); consequently, its use as the primary diagnostic modality in suspected complications can be justified.

In the present series, we were able to make the correct diagnosis by relaparoscopy in all cases. Our findings are supported by similar results in other recent series.[9,13–15] Laparoscopy allows visualization of entire abdominal cavity, recognition of a complication, and its treatment. Often, an identified complication can be handled laparos-

Table 6 Surgery Results

Outcome	Early	Delayed	Total
Mean operative time (min)	37.8±20.4	36.0±16.3	37.2±19.0
Conversions (%)	13.5	10	12.3
Mean number of relaparoscopies, *n* (range)	1.1(1–2)	1.25(1–3)	1.2 (1–3)
Mean postoperative hospital stay, days*	11.6±11.4	19.4±12.9	14.4±11.1
Postoperative complications (%)*	5	25	12.3
Mortality (%)	2.7	10	5.3

*$p<0.05$

copically, and a formal laparotomy can be avoided. In this series, as many as 80% of the complications were handled laparoscopically. This enhances patients' (and surgeons') satisfaction with the overall process despite the complication and shortens hospital stay.

The range of laparoscopic procedure-associated complications including Veress needle and trocar injuries, iatrogenic tears of distended and inflamed bowel wall, and tears during dissection of adhered bowel loops after previous abdominal surgery, injuries following use of cautery for dissection. In our series, gastric tears occurred following perigastric dissection during laparoscopic gastric banding placement. During relaparoscopy, small bowel and colonic tears were found after cholecystectomy, appendectomy, and revision bariatric procedure. Small bowel obstruction was the most frequent complication following laparoscopic incisional hernia repair.

Twenty-seven of 57 patients underwent relaparoscopy following suspected complications of laparoscopic cholecystectomy. In this group, eight patients (30%) had bile leaks, all were successfully managed during relaparoscopy. Alternative management options for bile leaks include percutaneous drainage and endoscopic retrograde cholangiopancreatography (ERCP) with stenting or sphincterotomy. Percutaneous drainage alone requires prolonged hospitalization, as the drain may remain in situ for a while until drainage stops, or must be supplemented by ERCP if the leak persists.

ERCP is not a benign procedure. Its morbidity and mortality is usually underestimated. Most series report "ERCP-related mortality" or "Procedure-specific mortality" or other similar terms, which are vague and open to obvious biases. In series that report overall or 30-day mortality, the mortality rate ranges from 1.4–4%*****. Deaths are more common with interventions, such as sphincterotomy and repeat procedures.

In addition, a stent, if placed, must be removed 1–3 months later. Removing the stent involves additional exposure to the risk of ERCP and increases costs. The data presented here suggest that the mortality and morbidity of early relaparoscopy is lower than that of ERCP.

In the present series, 28% of the relaparoscopies were negative. Negative relaparoscopies were not associated with any complications and had minimal impact on patient's hospital stay. These patients were not doing well and so were not candidates for next day discharge. The negative reexplorations eliminated the need for multiple imaging studies and reassured both patient and surgeon that all was well.

One argument against early relaparoscopy is that it may increase overall costs. Although we did not calculate costs directly (mainly because public hospital care in Israel is free), the mean hospital stay in the delayed group was almost twice as long as the stay in the early group. This represents a potential saving which should far outweigh the added costs of the negative reexplorations.

The morbidity in the early group was also lower than in the delayed group. This result was not due to a higher rate of negative relaparoscopies or to the nature of complications discovered. Both groups had similar rates of negative explorations, and the incidence of hollow viscus injuries was also similar between the two groups

As a matter of departmental policy, the relaparoscopy was almost always done by the attending surgeon who supervised the primary procedure and assisted by a second experienced laparoscopic surgeon who was not involved in the original operation. We feel that this policy enhances both the diagnostic accuracy and the ability to handle most complications laparoscopically.

Conclusions

Although our conclusions are limited by the retrospective nature of this study, we can conclude that clinical findings are highly suspicious for the presence of complications and that in experienced hands, early relaparoscopy is a fast and safe method of identifying and often solving the problem.

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The Effect of Perineural Invasion on Overall Survival in Patients with Gastric Carcinoma

Luo Tianhang · Fang Guoen · Bi Jianwei · Ma Liye

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Abstract
Aims The availability of different treatment options for gastric carcinoma has reopened the question of correct definition of high-risk categories, which may help in identifying patients with high risk for poor prognosis who would benefit more from adjuvant therapy after operation. Perineural invasion (PNI) seems to provide useful information for management. Therefore, we examined the effect of PNI on overall survival (OS) in patients with gastric carcinoma and the association between PNI and other clinical and pathological factors.
Patients and Methods A total of 1,632 patients with gastric carcinoma from 2000 to 2005 were analyzed retrospectively. Paraffin sections of surgical specimens from all patients who underwent gastric resection were stained with laminin. If carcinoma cells infiltrated into the perineurium or neural fascicles, PNI was assessed as positive. Survival analysis was done in 1,372 patients with T1–T4 tumors who underwent curative resection.
Result PNI was positive in 518 of the 1,632 patients (31.7%). The size of tumors, T stage, differentiation of tumor, and clinical stage were significantly related to PNI positivity. The proportion of large tumors was significantly higher in PNI-positive patients than in PNI-negative patients ($P<0.01$). As the depth of gastric mural invasion or clinical stage increased, the positive rate of PNI also increased. The OS of the PNI-positive patients was significantly shorter than that of the PNI-negative patients in the univariate analysis ($P<0.01$). At multivariate Cox proportional hazards model of OS analysis, the positivity of PNI appeared to be an independent prognostic factor for OS (hazards ratio [HR]=3.23, 95%CI=2.6–8.11, $P<0.01$), which was also influenced by tumor differentiation, T stage, and clinical stage ($P<0.01$).
Conclusion Our results suggested that the incidence of PNI was high in gastric carcinoma and that it corresponded to the progression of disease. It could provide additional information for identifying patients who are at high risk for poor prognosis. PNI can be a candidate for a new kind of prognostic parameters.

Keywords Gastric carcinoma · Overall survival · Perineural invasion

Introduction

Gastric carcinoma is endemic in many countries around the world with more than 800,000 new cases each year.[1] Until the 2000s, gastric carcinoma was still one of the most frequent tumors and the leading cause of cancer death in the world.[1] In recent decades, the incidence rate has declined, but the prognosis of gastric carcinoma in China as well as most Western countries has not improved much, and the cumulative 5-year survival rates of all patients with gastric carcinoma have changed only slightly over the past four decades but remain under 20%.[1,2] Trying to find the cause turns out to be the most important question that every practitioner would attempt to answer. During the development of the clinical treatment in operable gastric carcinoma, the extent of surgery and the value of adjuvant treatment remain as matters of scientific debate. Surgery still represents the cornerstone of any curative procedure,[2,3] but the availability of various and different treatment

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options has reintroduced the crucial question that a correct definition of high risk for poor prognosis categories may help these patients to get benefits from additional medical treatments after operation.[4,5] So it is urgent to find other biological or pathological factors which can be indicated as possible prognostic indicators together with classic variables, which are well-known to have a definite prognostic value (i.e., TMN and clinical stage categories).

Perineural invasion (PNI) is a process by which cancer cells invade the perineurium or neural fascicles and wrap around nerves. PNI is reported to be a common route of spread in carcinomas of the pancreas and biliary tract, but is relatively rare in rectal carcinoma. It is a crucial route for the local spread of tumor associated with poor prognosis. The prognostic significance of PNI in gastric carcinoma had been investigated in a few studies,[6,7] but they had not reached consensus.

The objective of our study was to investigate the role of PNI as prognostic factor in the group of patients who underwent surgical resection for gastric carcinoma with the aim to serve as a tool for a more accurate and rational treatment selection.

Patients and Methods

Patients

Patients were eligible if they were naive to chemotherapy before operation and had histologically or cytologically proven, locally or advanced primary gastric adenocarcinoma who underwent curative gastric resection or palliative operation between January 2000 and December 2005 in Shanghai Changhai Hospital, China, which is a tertiary teaching hospital with more than 1,700 beds serving 25,000 inpatients and 1,200,000 outpatients and emergencies each year. The case volumes for gastric carcinoma reach more than 600 per year.

Additional inclusion criteria were age 18 to 85 years, life expectancy >3 months, and adequate organ functions (leukocyte count >3,500/μl, platelet count >100,000/μl, hemoglobin >10.0 g/dl, serum creatinine <1.25 times upper limit of normal [ULN], transaminases and alkaline phosphatase <2.5 times ULN or <5 times ULN in patients with liver metastasis, bilirubin <1.5 times ULN, and prothrombin time <12.0 s). Patients with central nervous system involvement or other significant medical conditions were excluded. Data were collected retrospectively.

All the patients were given standard operation and chemotherapy according to the NCCN Clinical Practice Guidelines in Oncology Gastric Cancer (V.1.2000); and the follow-up data of the patients were collected by telephoning the patients or outpatients service. Following-up of patients occurred at 28-day interval for half a year, then at 3-month interval for 2 years, at 6-month interval for 3 years, and yearly thereafter. Following-up consisted of physical examination, a complete blood count, chest radiography, and ultrasound of the abdomen as clinically indicated. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) would be performed if necessary.

Histopathological Evaluation

Surgical specimens were processed 30 min after being resected. The specimens were fixed in 10% formalin and embedded in paraffin. Then the paraffin-embedded blocks were cut into 5-μm-thick sections and stained with laminin; the endoneurium of nerve fibers and perineurium around the nerve fasciculi were strongly stained. If cancer cells infiltrated into the perineurium or neural fasciculus, PNI was assessed as positive.

The histologic type of gastric carcinoma was grouped according to the histological classification for gastric carcinoma by the WHO (2000);[8] the depth of tumor infiltration (T), regional lymph nodes (N), distant metastasis (M), stage grouping, and histologic grade were grouped according to the UICC TNM staging classification for malignant gastric carcinoma (fifth edition, 1997).[9]

Data Management and Statistical Analysis

The association between PNI positivity and other clinical or pathological features was analyzed by the Pearson chi-squared test or Fisher's exact test when appropriate. Survival distribution and curves were calculated by the Kaplan–Meier method, and the differences of survival curves were estimated by log-rank test.

Cox multiple regression analysis was used to assess the role of PNI as prognostic factor adjusted for those variables that had significant results at multivariate analysis. Tested variables included sex (male or female), age (≤60 or >60 years), grade of tumor differentiation (well-differentiated, moderately differentiated, poorly differentiated, or undifferentiated), pT stage (Tis–T4), pN stage (N0, N1, N2, or N3), location (upper 1/3, middle 1/3, lower 1/3, more than 1/3, or whole), hepatic metastasis (negative or positive), peritoneal metastasis (negative or positive), clinical stage (stage 0, stage I, stage II, stage III, or stage IV), and PNI (presence or absence of PNI). Relative risk was defined as the ratio of the probability that an event (recurrence or death) would occur to the probability that it would not occur. The prognostic power of covariates was expressed by calculation of a relative risk with a 95% confidence interval (95%CI). For statistical analysis, overall survival (OS) was defined as the interval between surgery to death or last visit.

All tests were two-sided, and P values less than 0.05 were considered to be statistically significant. Analysis was performed by the statistical package SPSS (SPSS, Chicago, IL, USA).

Results

Enrollment and Patient Characteristics

Between January 2000 and December 2005, a total of 1,726 patients were enrolled. A total of 94 patients were considered ineligible at inclusion. Reasons for ineligibility were death before operation (two patients), neuroendocrine tumor (five patients), high bilirubin level (six patients), high serum creatinine level (seven patients), hemoglobin level (nine patients), and missing in the follow-up (65 patients).

Therefore, the subjects of this study included 1,632 patients. The patients eligible to this research consisted of 1,133 men and 499 women with the mean age of 56.2± 10.61 years (range 18–85 years). The mean time of follow-up was 47.42±12.36 months (25–84 months).

Association between PNI Positivity and Clinicopathological Features

A total of 518 of the 1,632 patients (31.7%) were PNI positive. The size of tumors, pT stage, differentiation of tumor, and clinical stage were closely related to the PNI positivity, but there was no significant association between PNI positivity and sex, age, tumor location, lymph node metastasis, and hepatic metastasis (Table 1). The ratio of large tumors was significantly higher in the PNI-positive patients than in the PNI-negative patients ($P<0.01$); the positivity of PNI also increased as the differentiation of tumors worsened, the depth of gastric mural invaded, and clinical stage increased (as calculated from Table 1, PNI positivity appeared 11.63% in well-differentiated tumors, 29.93% in moderately differentiated tumors, 34.32% in poorly differentiated tumors, 70.83% in undifferentiated tumors; 0% in Tis tumors, 8.64% in T1 tumors, 17.7% in T2 tumors, 36.01% in T3 tumors, 90.08% in T4 tumors, $P<0.01$; 0% in stage 0 tumors, 13.45% in stage I, 17.3% in stage II, 30.52% in stage III, 66.35% in stage IV, $P<0.01$). The proportion of tumors with peritoneal metastasis was significantly higher in the PNI-positive patients than in the PNI-negative patients ($P<0.05$).

Prognostic Significance of PNI in Patients who Underwent Potentially Curative Resection

The type of operation (palliative operation or curative operation) is one of the most important prognostic factors of gastric carcinoma, so we had only chosen the patients who underwent potentially curative resection for survival analysis. And as there was no PNI in the patients with Tis tumors or clinical stage 0, they were excluded from the survival analysis. Thus, overall survival analysis was performed in the remaining 1,372 patients.

As shown in the OS curves (Fig. 1), the mean survival of the PNI-positive patients (mean=20.95 months) was significantly shorter than that of the PNI-negative patients

Table 1 Association between PNI and Clinicopathological Features

Clinicopathological features	PNI (+) Number	PNI (−) Number	P values
Sex			0.59[a]
Male	355	778	
Female	163	336	
Age			0.14[a]
≤60 years	286	571	
>60 years	232	543	
Location			0.46[b]
Upper 1/3	56	151	
Middle 1/3	183	372	
Lower 1/3	241	508	
More than 1/3 or whole	38	83	
Tumor differentiation			<0.01[b]
Well-differentiated	10	76	
Moderately differentiated	214	501	
Poorly differentiated	277	530	
Undifferentiated	17	7	
Tumor size			<0.01[a]
≤5 cm	322	821	
>5 cm	196	293	
pT stage			<0.01[b]
Tis	0	62	
T1	23	148	
T2	77	358	
T3	300	533	
T4	118	13	
pN stage			0.09[b]
N0	199	476	
N1	204	444	
N2	95	166	
N3	20	28	
Hepatic metastasis			0.07[a]
Negative	443	912	
Positive	75	202	
Peritoneal metastasis			0.02[a]
Negative	481	1065	
Positive	37	49	
Clinical stage			<0.01[b]
Stage 0	0	53	
Stage I	28	296	
Stage II	55	263	
Stage III	159	362	
Stage IV	276	140	

[a] P values are based on the Fisher's exact test.
[b] P values are based on the Pearson chi-squared test.

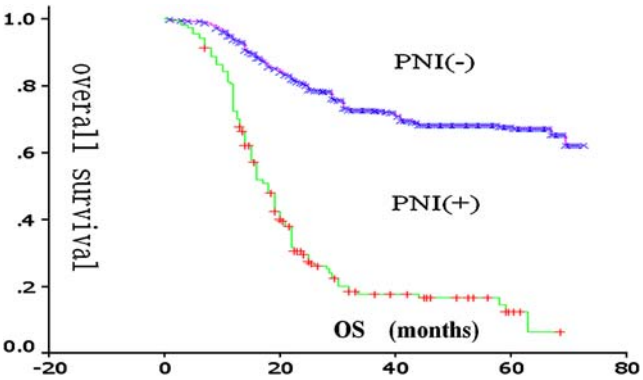

Figure 1 Overall survival curves (Kaplan–Meier) of the PNI-positive patients (median=20.95 months) was significantly shorter than that of the PNI-negative patients (median=57.86 months; $P<0.01$, log-rank test).

(mean=36.86 months; $P<0.01$), which was also influenced by tumor differentiation, pT stage, and clinical stage ($P<0.01$). And as shown in the multivariate Cox proportional hazards model analysis, tumor size, pN stage, hepatic metastasis, and peritoneal metastasis also had independent prognostic significance to OS ($P<0.05$; Table 2).

Discussion

PNI seemed to possess the necessary potential to provide useful information for the clinical management of patients with gastric carcinoma. During our research, we stained specimens with laminin to assess the positivity of PNI and found that 518 of the 1,632 patients (31.7%) were PNI positive, and PNI was not found in the tumors only confined to the mucosa (Tis). The size of tumors, pT stage, differentiation of tumor, and clinical stage were closely related to the PNI positivity. The positive rate of PNI increased as the differentiation of tumors worsened, the depth of gastric mural invaded, and clinical stage increased. Our findings suggest that the presence or absence of PNI is an important factor influencing the clinical outcome of gastric carcinoma patients who underwent radical surgery and, more interestingly, it appears an independent prognostic factor effecting on OS ($P<0.01$), which is also influenced by variables already known to represent important prognostic factors such as tumor differentiation, pT stage, and clinical stage.

PNI was reported as a crucial route of spread for carcinoma and it had been reported that the rate of positivity for PNI was approximately 20% in colonic and rectal carcinoma,[10,11] but much higher 50–80% in pancreatic carcinomas and 85–88% in carcinomas of the biliary tract.[12–14] There were only a few studies which had investigated on the presence and prognostic significance of PNI in gastric carcinoma and had not reached a consensus.[4,5,11] Duraker et al.[6] found that PNI was positive in 211 of the 354 patients (59.6%) and the incidence of PNI increased with the progression of gastric carcinoma, but PNI did not provide any additional information to the classical prognostic parameters. Tanaka et al.[7] conducted two studies examining PNI and found that advanced gastric carcinomas with the presence of PNI revealed poor prognosis.

In the present analysis, we emphasized the effect of PNI on OS in patients with gastric carcinoma and found a statistically significant difference on OS between patients with PNI and patients without PNI. The median OS for patients with PNI is 20.95 months, which was significantly worse than that of the patients without PNI (57.86 months).

Table 2 Cox Proportional Hazards Model Analysis of the Prognostic Factors in Overall Survival Patients

Factor	Relative risk	95%CI	*P* values
Sex			
Male	0.21	0.69–0.96	0.87
Female			
Age			
≤60 years	1.58	1.00–1.12	0.63
>60 years			
Location			
Upper, middle, or lower 1/3	0.65	0.91–1.08	0.06
More than 1/3 or whole			
Tumor differentiation			
Well-differentiated	1.12	0.71–1.21	<0.01
Moderately differentiated	0.34	0.54–0.92	
Poorly differentiated	1.25	1.02–2.29	
Undifferentiated	4.12	1.98–5.89	
Tumor size			
≤5 cm	2.31	0.87–2.09	0.03
>5 cm			
pT stage			<0.01
T1	0.27	0.45–1.13	
T2	0.98	0.76–1.69	
T3	1.29	0.92–3.01	
T4	3.96	4.62–11. 21	
pN stage			0.04
N0	0.46	0.45–1.13	
N1	0.44	0.28–1.10	
N2	1.29	0.92–3.01	
N3	3.09	1.62–5. 01	
Hepatic metastasis			
Negative	1.69	0.52–2.99	0.07
Positive			
Peritoneal metastasis			
Negative	4.40	3.21–9.92	0.01
Positive			
Clinical stage			<0.01
Stage I	0.22	0.55–0.93	
Stage II	0.51	0.13–1.56	
Stage III	3.49	2.92–6.87	
Stage IV	6.23	4.55–11. 62	
Perineural invasion			
Negative	3.23	2.6–8.11	<0.01
Positive			

At multivariate analysis, the presence of PNI appeared as an independent prognostic factor for OS. Our observations seem to identify well what has been already suggested by other studies hypothesizing that PNI may represent a prognostic factor in gastric carcinoma. It can be an independent prognostic factor which is not influenced by tumor stage, tumor differentiation, lymph node involvement, and other classical factors. Our data in gastric carcinoma patients are of particular relevance. PNI is, in fact, able to identify subgroups of gastric carcinoma patients with worse clinical outcome who need to be offered more effective postoperative treatment.

Compared with other studies that investigated on PNI, the case volumes of this research were the largest and the clinicopathological features investigated were relatively comprehensive. The results could be considered authentic because the percentage of missing follow-up was very low. But the retrospective nature of this study could be considered an important limitation, and the data should be reconfirmed by prospective studies. This study was based on the experience of limiting patient numbers and patient selection to local practice. A further limitation was the time of follow-up (25–84 months with mean 47.42±12.36 months); our research was not long enough to make full observations, and the 5-year survival could not be estimated clearly because more than 50% of the patients had not been observed for more than 60 months. So we would make further research on the follow-up of the patients and we would investigate on the pathogenesis of PNI in the next step.

The pathogenesis of PNI has not yet been sufficiently clarified yet. Dai et al.[15] and Nagakawa et al.[13] reported that cancer cells infiltrated the perineural space directly through the perineurium from the cancer nest or via vessels penetrating the perineurium. It is thought that cancer cells could invade into the perineurium and infiltrate the perineural space and interstitium with little resistance. Kameda et al.[12] reported that the number of layers of the perineurium at the terminals of the nerves had decreased, although the number of layers increased at the central nerve and tumor cells invaded the perineurium through that site causing PNI. Murakawa et al.[16] stated that the mechanism of neural invasion could be partly explained by the close anatomical relationship between the pancreas and celiac neural plexus. Nagakawa et al.[13] claimed that the high incidence of PNI in carcinomas of the pancreas and biliary tract was because of the rich autonomic innervation of these organs, but they also reported that the mechanisms of entry of cancer cells into the nerves remained unelucidated. As seen in our series, the frequency of PNI is high in gastric carcinoma in which the proximity of the stomach and celiac nerve plexus may play a role in this phenomenon. Whether gastric carcinoma "neurotropism" is present or not would be a subject of research in the future.

In conclusion, the incidence of PNI is high in gastric carcinoma and increases with the progression of disease. PNI provides important additional information to classical prognostic parameters. Although prospective studies are needed, taken together, our findings underline the importance of a careful search for PNI in gastric carcinoma patients as it may provide additional useful information for identifying patients who are at high risk for poor prognosis and may be candidates for more effective postoperative medical treatment.

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Improved Survival Following Right Trisectionectomy with Caudate Lobectomy without Operative Mortality: Surgical Treatment for Hilar Cholangiocarcinoma

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Abstract
Background We conducted this study to assess the safety of performing right trisectionectomy with caudate lobectomy for hilar cholangiocarcinoma by analyzing postoperative mortality and morbidity, and to evaluate the effect of such procedure on pathological curability and long-term overall survival.
Methods A retrospective clinicopathological analysis was performed for 16 hilar cholangiocarcinoma patients who underwent right trisectionectomy with caudate lobectomy from June 1999 to April 2003. The median follow-up period was 36.9 months. The preoperative Bismuth–Corlette type was type II in four patients, type III_A in 10 patients, and type IV in two patients.
Results The median liver volume after hepatic resection was 21.9% of the total liver volume. Postoperative complications including one chronic liver failure developed in 12 patients, but no in-hospital deaths occurred. A postoperative pathological examination showed a cancer free margin in all of the proximal resection sites, although three cases had carcinoma *in situ* (CIS) lesions in the distal margin that were confirmed during surgery. The 1-, 3-, and 5-year overall survival rates were 94.1%, 64.2%, and 64.2%, respectively.
Conclusion We obtained excellent survival rates without any in-hospital deaths following right trisectionectomy with caudate lobectomy. This procedure may be an effective surgical procedure that can be executed to achieve low mortality rate and high pathological curability for hilar cholangiocarcinomas, except for Bismuth type III_B.

Keywords Right trisectionectomy · Caudate lobectomy · Hilar cholangiocarcinoma

Introduction

In 1973, Longmire published the first report on the use of combined hepatic resection for hilar cholangiocarcinoma with high mortality **rates** and poor survival.[1] At that time, hepatic resection was not **recommended** for the treatment of hilar cholangiocarcinoma because of high mortality and morbidity.[2,3] Since the 1990s, more aggressive approach including the use of extensive liver resections have been performed.[4–7] The use of major hepatectomy as a surgical treatment of hilar cholangiocarcinoma has increased the resectability and improvement in the long-term results were evident.[8–10]

Recently, the 5-year survival rate for hilar cholangiocarcinoma has been reported as 18–41%.[7,10–18] In-hospital deaths from postoperative hepatic failure has been the biggest attribute to this poor survival rates.[19–23] A negative resection margin is a significant prognostic factor for long-

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term survival.[10,14] A more extensive hepatic resection may result in the curability of hilar cholangiocarcinoma. However, a more extensive hepatic resection would be limited because of the possibility of postoperative hepatic failure. Although appropriate procedures are not agreed on, major hepatectomy has been advocated for complete tumor clearance, and the resectability and long-term survival rates have been improving. We have performed right trisectionectomy with caudate lobectomy for the curative resection of hilar cholangiocarcinoma. The aim of this study was to assess the safety of right trisectionectomy with caudate lobectomy for hilar cholangiocarcinoma by analyzing of the postoperative mortality and morbidity, and to evaluate the effectiveness of this procedure by assessing the pathological curability and overall survival.

Patients and Methods

Between June 1999 and April 2003, 30 patients with hilar cholangiocarcinoma underwent surgical resections with intent to cure by a single surgeon (DW Choi). This study analyzed 16 patients with hilar cholangiocarcinoma who underwent right trisectionectomy with caudate lobectomy during this period. The age of the patient involved in this study ranged from 48 to 71 with the median age was 59.6 years. The gender distribution was 12 men and four women. Preoperative computed tomography (CT) and cholangiogram were used to determine the resectability and the extent of hepatic resection. The absolute contraindication for surgery was left hepatic artery invasion, although portal vein invasion by the tumor was attempted for resection. The extent of the tumor along the bile duct was classified according to the modified Bismuth–Corlette classification and the result of this classification was as follows: four type II (25.0%), 10 type IIIa (62.5%), and two type IV (12.5%). To allow for maximum preservation of the liver function of the remnant liver after surgery, preoperative biliary drainage was performed for all patients who presented with jaundice at admission, to the remnant liver after resection. Biliary drainage was added to the contralateral hepatic lobe when cholangitis could not be controlled. After sufficient biliary decompression indicated by total bilirubin level below 3 mg/dl, surgical interventions were scheduled. Portal vein embolization (PVE) was applied for only one patient with 18.6% of the left lateral segment remaining, which was calculated by computed tomography.[24–26] Two weeks after the PVE, the volume of the left lateral segment and respectability were reevaluated again.

After evaluation and preparation for surgical resection, right trisectionectomy with caudate lobectomy was attempted. Resectability was assessed in the operative field through the detection of left hepatic artery invasion. Radical surgery was performed unless there was invasion of left hepatic artery. The bile duct was transected at the level just above the upper border of the pancreas and then the resection continued upward to the hepatic hilum. Following this, right portal vein and hepatic artery dissection was performed. In the case of tumor invading the portal vein, portal vein resection and anastomosis were conducted. The lymph nodes in the hepatoduodenal ligament and in posterior aspect of the pancreas were completely dissected. In one patient, the portal bifurcation could not be freed from the tumor mass during the dissection of the hepatoduodenal ligament, in which case the patient underwent portal vein resection and end-to-end anastomosis (Fig. 1a). To perform the caudate lobectomy, small branches of the left portal vein to the caudate lobe were ligated and divided. After mobilization of the right hemi-liver, the short hepatic veins were divided from the inferior vena cava (IVC) and ligated. The right hepatic vein was encircled extrahepatically, and then ligated by vascular endo-GIA®. Next, the

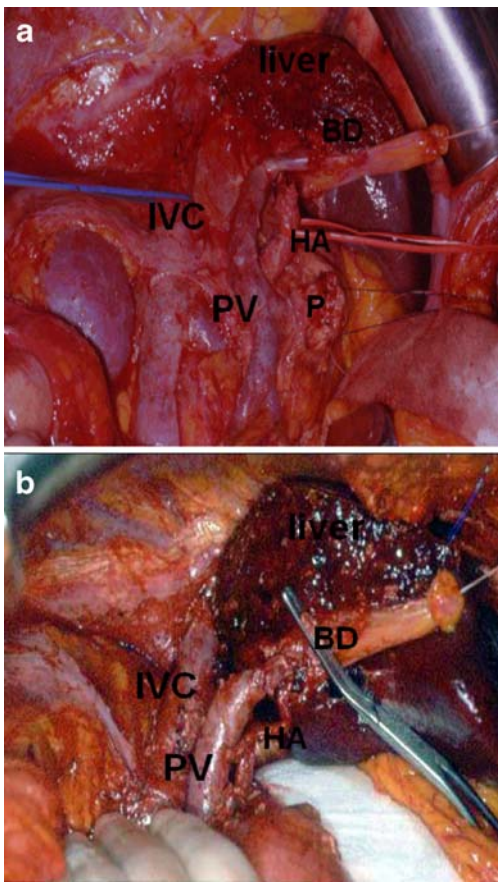

Figure 1 **a** Operative field after a hepaticopancreaticoduodenectomy for Bismuth type IIIa. (*BD* bile duct, *IVC* inferior vena cava, *HA* hepatic artery, *PV* portal vein, *P* pancreas). **b** Operative field after a right trisectionectomy with a caudate lobectomy and portal vein resection, anastomosis in Bismuth type IV. (*BD* bile duct, *IVC* inferior vena cava, *HA* hepatic artery, *PV* portal vein).

umbilical portion of the left portal vein was exposed by dissecting the serosa of the umbilical fissure. The portal branch of segment 4 was ligated and divided at its origin; a parenchymal transection was performed on the right side along the umbilical fissure. The bile duct was transected at the level of 2, 3 segmental branch bifurcation. The middle hepatic veins were ligated by vascular endo-GIA® and the left hepatic vein was preserved.

Frozen section assessment of the surgical margins of the proximal and distal bile duct was performed during surgery. Biopsy results of two patients showed distal resection margin with invasive carcinoma at the suprapancreas level, in which cases pancreatoduodenectomy was performed with liver resection (Fig. 1b). Biopsies of three of the patients were positive for carcinoma in situ at the distal resection margin. Additional pancreaticoduodenectomy was not carried out in these case. The biliary tract was reconstructed by a Roux-en-Y biliary enteric anastomosis. Postoperative complications were classified as major or minor complications according to the modification of Clavien's classification of morbidity severity.[27] All of the patients included in this study had a postoperative follow-up every month after discharge. The level of tumor markers, including CEA and CA19–9, was measured and CT of the abdomen was performed for surveillance of recurrent disease every 4 months. None of the patients was lost to follow-up during the study period. Patient survival was measured in days from hepatic resection until death and analyzed using the Kaplan–Meier method.

Results

Preoperative Treatment

Thirteen (81.3%) of 16 patients underwent biliary drainage before surgery. Endoscopic nasal biliary drainage and endoscopic retrograde biliary drainage were applied to two patients, respectively. Percutaneous transhepatic biliary drainage was applied for nine patients. Portal vein embolization (PVE) was applied to only one patient with a small volume of left lateral segment. The median liver volume of the left lateral segment was 21.9% of the total liver volume (range 18.6–26.5%).

Perioperative Findings

The median duration of the operation was 510 min and median estimated blood loss was about 800 ml. However, the median transfusion requirement was 0 unit, as only four patients received transfusion. The postoperative peak level of total bilirubin was seen on day 3 postoperation, but none of the patient's total bilirubin levels exceeded 10 mg/dl. (Fig. 2a) The prothrombin time was prolonged from the first day postoperation and reached a plateau thereafter (Fig. 2b).

Pathology

Pathologically curative resection margin was obtained in 13 patients, which accounted for 81.2% of all patients. All the patients showed a negative proximal resection margin. Two patients, who had invasive cancer present at distal resection margin at the level of suprapancreas level, underwent pancreatoduodenectomy with liver resection. However, three patients with carcinoma *in situ* at the distal margins did not undergo an additional pancreaticoduodenectomy or adjuvant therapy. Two of the three patients with carcinoma in situ (CIS) at the distal margin had local recurrence of the tumor and died within 1 year. Another patient had a rectal shelf, and palliative radiation therapy was provided. Pathology results demonstrated the infiltrative type to be most dominant. Most of the patients (81.3%) had a well-differentiated carcinoma. Most of the carcinomas invaded the liver parenchyma, and lymph node invasion was

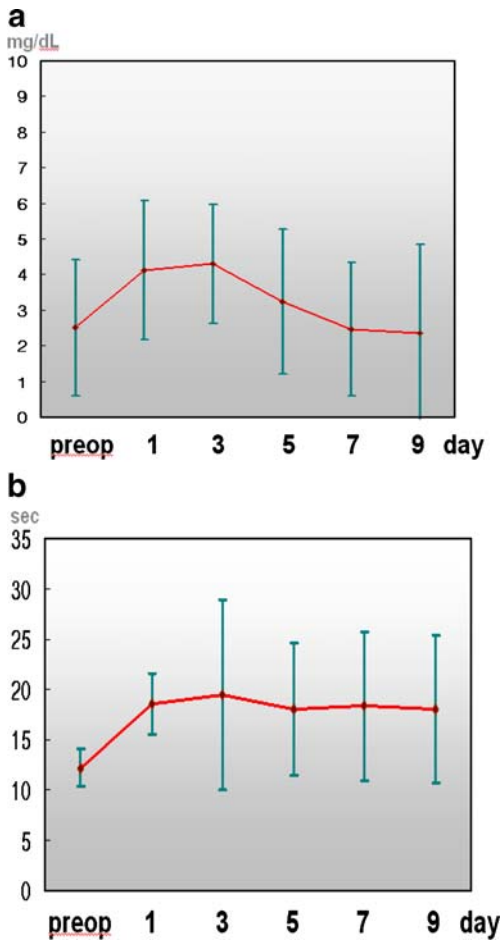

Figure 2 **a** Perioperative total bilirubin level. **b** Perioperative prothrombin time.

detected in six patients. Six patients were diagnosed as stage IIIc. Ten patients had positive perineural invasion (Table 1).

Operative Morbidity and Mortality

Twelve patients (75.0%) developed various complications, including two bile leakages and chronic liver failure in a patient who underwent hepatopancreaticoduodenectomy. All of the minor complications, including three wound infections, were treated successfully with conservative management (Table 2). However, none of the patients died of postoperative complications, so in-hospital mortality did not occur. The median postoperative hospital stay was 24 days, with its range from 13 to 52 days.

Postoperative Survival

The median follow-up period of 16 patients with hilar cholangiocarcinoma that underwent right trisectionectomy with caudate lobectomy was 36.9 months. The overall 1-, 3-, and 5-year survival rates were 94.1%, 64.2%, and 64.2%, respectively (Fig. 3).

Table 1 Pathological Findings of 16 Patients that Underwent a Right Trisectionectomy with a Caudate Lobectomy for a Hilar Cholangiocarcinoma

Pathological findings	Type	Number (*n*)
Gross findings		
	Infiltrative	12
	Protruding	4
Depth of invasion		
	Mucosa	3
	Muscle	0
	Peri-connective tissue	4
	Liver	9
Stage (AJCC 6th)		
	Ia	4
	Ib	2
	IIa	4
	IIIa	6
Cellular differentiation		
	Well	13
	Moderate	3
	Poor	0
Lymph node involvement		
	Positive	10
	Negative	6
Perineural invasion		
	Positive	6
	Negative	10
Venous invasion		
	Positive	11
	Negative	5

Table 2 Postoperative Complications

	Complication	Number (*n*)
Major		
	Bile leakage	2
	Chronic hepatic failure	1
Minor		
	Atelectasis	3
	Pleural effusion	7
	Pneumonia	1
	Abdominal fluid collection	1
	Wound infection	3
	Abundant drainage	4
	Ascites	1
	Gastroduodenostomy leakage	1
	Urinary tract infection	1
Total complication rates		12/16 (75.0%)

Discussion

A hilar cholangiocarcinoma is characterized by deep spreading of the tumor cells into the liver via the periductal lymphatic and perineural route, as well as along the bile duct wall.[28,29] Liver resection is an accepted standard treatment for hilar cholangiocarcinoma, and extended hepatic resection allows for an oncological curative resection of a hilar cholangiocarcinoma,. Many reports have proposed that an increased survival rate was obtained when resection of the hilar cholangiocarcinoma was accomplished with a negative surgical margin of the proximal bile duct.[10,14,19,30] To obtain a negative resection margin, a more extensive hepatic resection for the hilar cholangiocarcinoma is essential. In this study, right trisectionectomy with caudate lobectomy was routinely performed for the treatment of hilar cholangiocarcinoma except for bismuth type IIIb. Right trisectionectomy is suitable to gain longer resection margin of the left hepatic duct. Sakamoto et al.[31] suggested that an adequate tumor-free proximal margin of 5 mm needs to be secured in the hilar bile duct carcinoma. In this study, no patients had tumor involving the proximal resection margin. Three patients with CIS in the existing distal margin had recurrence and was not administered with adjuvant therapy; two of these patients died within 1 year after the liver resection. In these cases, we believe that there is an argument for further intervention such as adjuvant or further resection to improve patient survival. We could obtain pathologically curative resection margin in 13 patients, which accounts for 81.2% of patients.

An extended hepatectomy can cause serious complications, and liver failure is a great concern for major hepatectomy for hilar bile duct cancer.[21,32,33] Postoperative hepatic failure is derived from an insufficient functioning

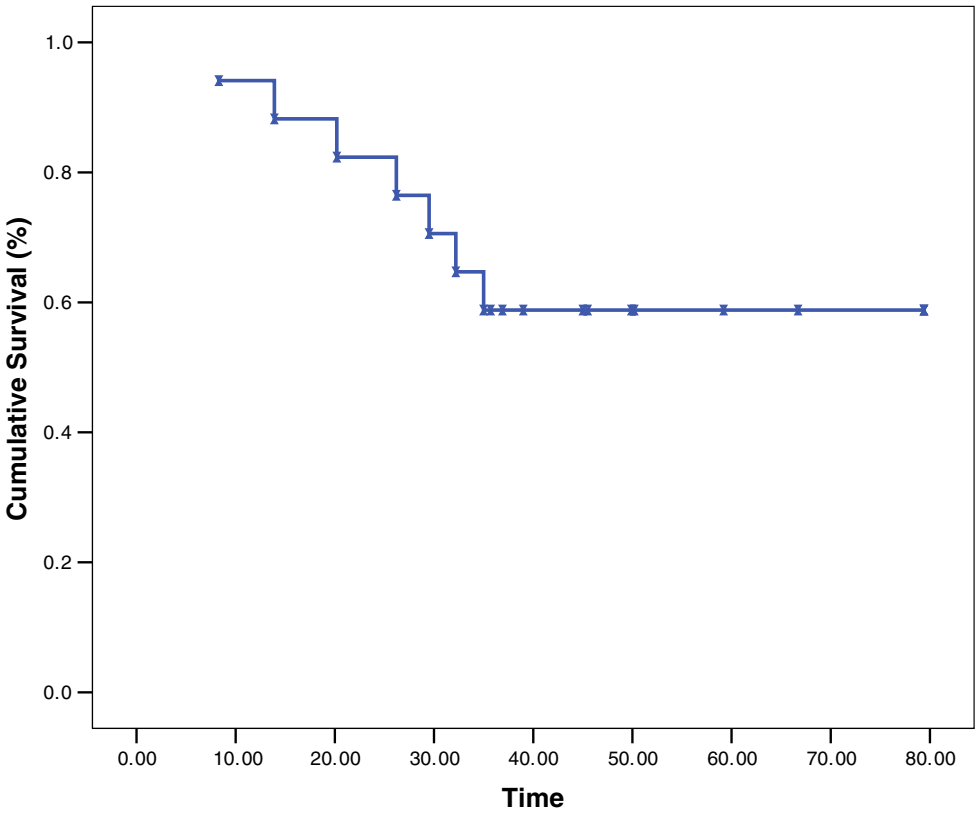

Figure 3 Overall survival of 16 patients that underwent a right trisectionectomy with a caudate lobectomy for a hilar cholangiocarcinoma.

volume of the remnant liver. Preoperative unilateral PVE of the liver can result in extended hepatic resection with increased safety.[34] Abdalla et al.[26] reported that 20% of the total liver volume appears to be the minimum safe volume that can be left after extended resection in patients with a normal underlying liver. Based on this figure, 20% of the total liver volume before surgery was considered to be an appropriate lower limit when measuring the remnant liver volume. In this study, the median remnant liver volume is 21.9% of the total volume. Chronic hepatic failure was seen in a patient who underwent hepatopancreaticoduodenectomy, in which conservative treatment was provided, and then discharged after hepatic function was recovered. Our morbidity rate was 75%, and majority of the complication was minor. No patients needed further surgical interventions. Our results do not include any operative mortality, but high rates of morbidity were evident, and this could be explained by the low threshold for remnant liver volume. PVE should be actively performed for small volume of remnant liver in future, especially for the patient who may require additional pancreaticoduodenectomy. Another obstacle for postoperative hepatic dysfunction is preoperative jaundice, which can be successfully managed with external biliary drainage of bile through intervention such as PTBD or ENBD. Trisectionectomy was performed only for patients with total bilirubin level below 3 mg/dl. Seyama et al.[35] have suggested that resectional surgery should be performed when the serum bilirubin level has decreased to 2 mg/dl.

To minimize the risk of postoperative liver failure, reduction of blood loss is an important factor.[36] Only four patients in this series had a transfusion during surgery. Two studies from Japan[18,35] emphasized that preoperative management and negative surgical margin will contribute to excellent outcome. In these series, a trisectionectomy was performed only in three patients. The overall 5-year and 3-year survival rates in these series were both 40%. The survival rate of 16 patients who underwent right trisectionectomy with caudate lobectomy in the present series was excellent. The 5-year survival rate was 64.2%. Application of a strategy similar to that of the Japanese group and carefully performed surgical procedure may be responsible for high survival rate obtained in the present series.[18,35] Since 2000, several reports have showed a 5-year survival rate for hilar cholangiocarcinoma to be 8–41%.[10–18] The best surgical outcome of an extended hepatic resection was reported by Neuhaus et al.[16] In this series, a 5-year survival rate of 72% was achieved after a right trisectionectomy with concomitant resection of the portal vein bifurcation. The investigators claimed that right trisectionectomy and combined portal vein resection represent the best way to comply with the basic rules of surgical oncology for a hilar cholangiocarcinoma. But, they did not mention combined caudate lobectomy, which is a widely accepted procedure to

increase the pathological curability for hilar cholangiocarcinoma. Also, they did not evaluate the remnant liver volume after right trisegmentectomy. We performed right trisectionectomy with caudate lobectomy for all cases, and also focused on the remnant liver volume with volumetry after extensive liver resection. Although the optimal extent of hepatic resection for a hilar cholangiocarcinoma is yet to reach consensus, this procedure may be an effective surgical procedure that can be executed with a low mortality rate and high pathological curability for hilar cholangiocarcinomas, except for Bismuth type III_B, if adequate preoperative management including preoperative biliary drainage and PVE can be applied.

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Responsiveness and Minimal Clinically Important Differences after Cholecystectomy: GIQLI Versus SF-36

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Abstract
Introduction To compare responsiveness and minimal clinically important differences (MCID) between the Gastrointestinal Quality of Life (GIQLI) and the Short Form 36 (SF-36), we prospectively analyze 159 patients undergoing cholecystectomy at two tertiary academic hospitals.
Patients and Methods All patients completed the disease-specific GIQLI and the generic SF-36 before and 3 months after surgery. Scores using these instruments were interpreted by generalized estimating equation before and after cholecystectomy. The bootstrap estimation was used to derive 95% confidence intervals for differences in the responsiveness estimates.
Results and Discussion Mean changes in all GIQLI and the SF-36 subscales were statistically significant ($p<0.05$). Comparisons of effect size (ES), standardized response means (SRM), and relative efficiency (>1) indicated that the responsiveness of the GIQLI was superior to that of the SF-36. In the equivalence test, all lower or upper confidence limits presented no equivalence (>5), indicating good MCID. The ES and SRM for emotions and physical function in the GIQLI significantly differed from those of the SF-36 ($p<0.05$).
Conclusion The data in this study indicate that clinicians and health researchers should weight disease-specific measures more heavily than generic measures when evaluating treatment outcomes.

Keywords Responsiveness · Minimal clinically important differences · GIQLI · SF-36

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Introduction

Cholecystectomy is the most common procedure for treating symptomatic cholelithiasis or cholecystitis.[1,2] The procedure may be performed via open or laparoscopic approach. This intervention has proven safe and effective for improving health-related quality of life (HRQoL).[3–5]

HRQoL is a multidimensional measure derived by subjectively and objectively assessing physical, psychological, and social attributes, as well as overall life satisfaction.[5,6] Various HRQoL instruments have been used with increasing frequency during the past decade.[6] Disease-specific measures are traditionally administered in longitudinal studies to detect progressive changes in health and quality of life after interventions and tend to focus on physical function and pain. Conversely, generic measures are designed to assess the effects of any disease or condition and are usually adopted by health service researchers to assess overall quality of life. The Medical

Outcomes Study Short Form-36 Health Survey (SF-36) is a self-administered generic HRQoL instrument commonly used to assess overall outcome.[5] The Gastrointestinal Quality of Life Index (GIQLI) measures specific and general HRQoL by including measures of overall quality of life, such as psychosocial well-being, as well as items specifically related to gastrointestinal symptoms.[5]

"Responsiveness" is the accuracy of a measure in assessing longitudinal change in health status over time.[7] A highly responsive HRQoL instrument can detect significant treatment effects in a small sample size or in a single patient. The responsiveness of HRQoL instruments have been evaluated in several studies.[8,9] The minimal clinically important difference (MCID) examines differences at the individual patient level. The MCID is a vital measure given that statistically significant group changes may not exhibit statistical significance at the individual patient level.[9]

The HRQoL is currently weighted more heavily when evaluating health status, particularly regarding medical treatments and interventions. Nevertheless, it is easy to identify the statistical significance of any such changes, but it can be harder to determine whether these changes are clinically relevant. The MCID is one of the most effective and widely used methods of HRQoL assessment and can be used to provide an indication of the minimal change that is of clinical relevance. However, it is rarely used by gastroenterologists to compare responsiveness. Additionally, responsiveness estimates derived by the SF-36 and the GIQLI before and after cholecystectomy have not been clinically compared.

In this prospective cohort study, two well-known HRQoL instruments, the SF-36 and the GIQLI, were used to compare responsiveness and MCID in cholecystectomy patients.

Patients and Methods

Patients and Data Collection

Two HRQoL instruments were used to survey all patients who underwent cholecystectomy performed by any one of three experienced surgeons (KT, HH, YH) at two tertiary academic hospitals in southern Taiwan between April and September, 2007. Twenty-two procedures performed by other low-volume surgeons were excluded from analysis. Patients with cognitive impairment (n=1), severe organ, or psychiatric diseases (n=2) were excluded. One hundred fifty-nine patients who completed preoperative and 3-month surveys after cholecystectomy were enrolled in the study. Immediately before surgery, a trained research assistant administered the SF-36 and the GIQLI in all subjects, and the same assistant used these instruments to assess HRQoL in the 3-month survey.

The study sample included 72 (45.28%) males and 87 (54.72%) females with a mean age of 56.08 years (standard deviation, 15.06 years; range, 22–86 years). Preoperatively, each patient exhibited an average of 0.56 comorbidities, and the principal comorbidities for the study population were hypertension, cardiovascular disease, chronic hepatitis, diabetes, and others, representing the relative frequency 33.7%, 22.5%, 19.1%, 12.4%, and 12.3%, respectively. The average length of stay was 5.25 days (standard deviation, 4.22 days). Patients who underwent laparoscopic cholecystectomies (n=145) and those who underwent open cholecystectomies (n=14) did not significantly differ in baseline age, gender, number of comorbidities, re-hospitalization within 30 days, SF-36 subscales, or GIQLI subscales.

Sample size analysis indicated the power of the present study between two time intervals approximated 100% across SF-36 and GIQLI subscales. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital in Taiwan.

Outcome Measures

The two HRQoL survey instruments in this study were the generic Chinese version of the SF-36 and the Chinese version of the GIQLI. The SF-36 Health Survey, a widely used measure of generic HRQoL, includes 36 items for evaluating physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Each SF-36 subscale was converted to a scale from 0 to 100; the higher the score, the better the HRQoL. A translated version of the SF-36 has been validated in Chinese populations.[10]

The GIQLI is recognized as a valid and reliable instrument for measuring HRQoL, especially in patients undergoing cholecystectomy.[11] Its 36 items include symptoms (19 items), emotions (five items), physical function (seven items), social function (four items), and the effects of medical treatment (one item). Each item is scored from 0 to 4, with a higher score indicating a better HRQoL. The total GIQLI scores range from 0 to 144. A Chinese version of the GIQLI has demonstrated validity.[11]

Statistical Analysis

The unit of analysis was the individual patient. To compare SF-36 and GIQLI subscales, raw scores were transformed and scaled from 0 to 100, with higher scores correlating with improved HRQoL.

The relationship between SF-36 and the GIQLI was first assessed by Pearson correlation preoperatively and at 3-month intervals to evaluate construct validity. Floor and

ceiling effects were estimated by proportional minimum and maximum scores for each HRQoL subscale measured preoperatively and 3 months after cholecystectomy. A floor effect occurs when a high proportion of the total respondents grade themselves at the minimum score. A ceiling effect, inversely, occurs when a high proportion of the total respondents grade themselves at the maximum score.

The generalized estimating equations (GEE) approach was employed to compare longitudinal changes in SF-36 and the GIQLI subscales before and 3 months after cholecystectomy. Each HRQoL subscale was used as a dependent variable as a function of time and covariates: age, gender, number of comorbidities, average length of stay, and laparoscopic/open surgery. Variables were entered into the GEE analysis as covariates because they were statistically significant in the univariate analysis and have proven to be consistent predictors of HRQoL in many previous studies.[12,13] Time was considered a categorical variable.

Responsiveness is the capability of an instrument to detect clinically significant differences in health outcomes important to clinicians and patients.[9] Responsiveness estimates were evaluated in terms of change ratio (CR), effect size (ES), standardized response mean (SRM), and relative efficiency (RE).[14] The CR was calculated as the mean change score divided by baseline scores. The ES was calculated by dividing mean change score by the standard deviation of baseline scores. The SRM was calculated as the mean change score divided by the standard deviation of changed scores. The responsiveness of the CR, ES, and SRM was determined using the following equations:

$$\mathrm{CR} = \frac{\text{Mean Change Score}}{\text{Mean Baseline Score}} \times 100\%$$

$$\mathrm{ES} = \frac{\text{Mean Change Score}}{\text{Standard Deviation of Baseline Scores}}$$

$$\mathrm{SRM} = \frac{\text{Mean Change Score}}{\text{Standard Deviation of Changed Scores}}$$

RE was measured as the relative efficiency of HRQoL determined by each subscale at pre- and post-operation.[15] Therefore, in this study, RE was calculated relative to total SF-36 or GIQLI scores for each HRQoL subscale using the formula $\mathrm{RE}=(t1/t2)^2$, where $t1$ is the t value of a Student paired t test for each subscale, and $t2$ is the t value of a Student paired t test for the SF-36 or the GIQLI total scores. Generally, if RE equals 1, both HRQoL subscales/instruments are equally discriminatory. If RE exceeds 1, the subscale/instrument in the numerator is more efficient in differentiating HRQoL than the subscale/instrument in the denominator and vice versa if RE is less than 1.

The MCID has been defined as the smallest difference between baseline scores and the scores at 3 months in an instrument considered worthwhile or important.[16] The MCID was estimated with a 95% confidence interval at lower and upper limits (CL, CU) by the formula $(\mathrm{CL},\mathrm{CU}) = \left[\left(\overline{d} - t_{\alpha/2}S_{\overline{d}}, \overline{d} + t_{\alpha/2}S_{\overline{d}}\right)\right]$, where $\overline{d}$ is the mean change, $t_{\alpha/2}$ is the critical t value of a Student paired t test, and $S_{\overline{d}}$ is the standard deviation of the mean change scores. A 95% confidence interval at CL and CU indicates that if a patient exhibits a change in score equal to or exceeding the critical value for MCID, the change can be considered with 95% confidence to be reliable and not due to measurement error.[17] In this study, the critical value of MCID=5 (5% or 5 points) was used as the equivalence test to detect true change due to its postoperative 3-month survey. Therefore, a change in CL or CU score of less than −5 or greater than 5 can be interpreted as a true change.

Repeated assessment of a single patient can cause complications because of highly correlated observations within the same patient. To address these issues, the bias-corrected and accelerated bootstrap method with 2,000 replications was employed to compare the responsiveness estimates of the two HRQoL instruments.[18] Differences in ES and SRM between the GIQLI and the SF-36 were estimated, and the bootstrapping method was used to obtain 95% confidence intervals for these differences. All statistical analyses were performed using Stata Statistical Package, Version 9.0 (Stata Corp, College Station, TX, USA). A p value <0.05 was considered statistically significant.

Results

The Pearson correlation coefficients between the SF-36 and the GIQLI after cholecystectomy at preoperative and 3-month surveys were evaluated (Table 1). The GIQLI subscales revealed statistically significant associations with the SF-36 subscales. The Pearson correlation coefficients exhibited statistically significant for each subscale.

Analysis of floor and ceiling effects before and after cholecystectomy indicated the GIQLI outperformed the SF-36 (less than 15% of patients with the maximum or minimum possible scores for symptoms, emotions, and physical functioning subscales; Table 2). The measures of physical and emotional roles in the SF-36 revealed major floor and ceiling effects at preoperative and 3-month surveys. Additionally, the SF-36 exhibited increasing ceiling effects in physical function, social function, and bodily pain before and after cholecystectomy. Similarly, the ceiling effects of the GIQLI subscales were high after cholecystectomy.

Longitudinal changes in all SF-36 and GIQLI subscales revealed statistically significant improvement ($p<0.05$) after adjustment for baseline age, gender, number of comorbidities, average lengths of stay, and laparoscopic/

Table 1 Pearson Correlation Coefficients between the SF-36 and the GIQLI

	SF-36								GIQLI			
	PF	RP	RE	SF	BP	VT	MH	GH	Symptoms	Emotions	Physical	Social
Before cholecystectomy												
PF	1	0.46**	0.45**	0.55**	0.35**	0.49**	0.45**	0.39**	0.56**	0.49**	0.57**	0.54**
RP		1	0.58**	0.49**	0.50**	0.42**	0.41**	0.34**	0.50**	0.45**	0.53**	0.53**
RE			1	0.54**	0.54**	0.46**	0.49**	0.37**	0.57**	0.61**	0.54**	0.60**
SF				1	0.51**	0.59**	0.55**	0.41**	0.57**	0.62**	0.68**	0.63**
BP					1	0.38**	0.38**	0.38**	0.48**	0.36**	0.49**	0.37**
VT						1	0.78**	0.49**	0.35**	0.41**	0.53**	0.41**
MH							1	0.35**	0.48**	0.65**	0.55**	0.53**
GH								1	0.36**	0.34**	0.45**	0.34**
Symptoms									1	0.72**	0.76**	0.71**
Emotions										1	0.69**	0.71**
Physical											1	0.77**
Social												1
After cholecystectomy (3 months)												
PF	1	0.41**	0.37**	0.48**	0.48**	0.41**	0.22*	0.39**	0.40**	0.43**	0.47**	0.42**
RP		1	0.78**	0.58**	0.55**	0.40**	0.37**	0.46**	0.46**	0.54**	0.65**	0.57**
RE			1	0.59**	0.56**	0.39**	0.36**	0.45**	0.46**	0.61**	0.61**	0.56**
SF				1	0.73**	0.51**	0.50**	0.45**	0.55**	0.65**	0.63**	0.64**
BP					1	0.42**	0.35**	0.40**	0.59**	0.61**	0.66**	0.60**
VT						1	0.82**	0.60**	0.51**	0.53**	0.49**	0.48**
MH							1	0.49**	0.44**	0.53**	0.38**	0.42**
GH								1	0.43**	0.56**	0.53**	0.48**
Symptoms									1	0.73**	0.68**	0.74**
Emotions										1	0.83**	0.83**
Physical											1	0.81**
Social												1

PF Physical functioning, *RP* role limitations due to physical problems, *RE* role limitations due to emotional problems, *SF* social functioning, *BP* bodily pain, *VT* vitality, *MH* mental health, *GH* general health, *Physical* physical function, *Social* social function
* $p<0.05$; ** $p<0.01$

open surgery (Fig. 1). The SF-36 and the GIQLI before and 3 months after cholecystectomy revealed improvement rates of from 6.76% to 60.83% and from 20.33% to 43.66%, respectively. Further, the GEE approach produced the highest mean scores for GIQLI symptoms 3 months after cholecystectomy. Specifically, as compared to a relatively low score of 51.26 before cholecystectomy, the mean SF-36 score for role limitations due to physical problems was 81.60 after cholecystectomy, an improvement of 59.20%. The mean SF-36 score for role limitations due to emotional problems changed from 51.90 to 83.08, indicating that the role limitations due to emotional problems was the most improved subscale, with an improvement rate of 60.83%. The least improved SF-36 subscale was general health, with an improvement rate of 6.76%.

Except for the general health subscale in the SF-36, all SF-36 and GIQLI subscales revealed considerable differences between responsiveness estimates calculated preoperatively and those calculated 3 months after cholecystectomy (Table 3). Further, equivalence test results revealed the 95% confidence interval of MCID scores (CL, CU) all exceeded 5, except for the SF-36 general health (CL=1.20). However, the estimated responsiveness and MCID in the GIQLI were generally higher than those of the SF-36 before and after cholecystectomy. Therefore, the correlation between the GIQLI and the SF-36 required use of the bootstrap method to analyze differences in responsiveness. Because the GIQLI subset symptoms cannot be compared with any SF-36 subset, we choose emotional, physical function, and social function for responsiveness differences comparison. Table 4 displayed statistical differences between the GIQLI and the SF-36 in responsiveness estimates of ES and SRM. The differences were considered statistically significant at confidence intervals other than zero. The emotional and physical function subscales statistically differed between the GIQLI and the SF-36, but the social functioning subscales did not. The GIQLI exhibited better responsiveness in the emotional and physical function subscales, whereas the SF-36 revealed better responsiveness in the social function subscale.

Table 2 Floor and Ceiling Effects before and 3 Months after Cholecystectomy

	Before cholecystectomy		After cholecystectomy (3 months)	
	Floor effect (%)	Ceiling effect (%)	Floor effect (%)	Ceiling effect (%)
SF-36				
PF	4.40	29.56	1.26	48.43
RP	21.51	44.65	16.35	67.99
RE	26.54	48.43	15.09	69.25
SF	0.63	31.45	0.63	46.54
BP	1.89	10.69	1.26	28.93
VT	0.63	1.89	0.63	2.89
MH	2.52	1.89	0.63	2.52
GH	2.52	3.77	1.26	3.14
GIQLI				
Symptoms	0.63	3.14	0.63	11.38
Emotions	0.63	5.66	0.63	12.70
Physical	0.63	1.26	0.63	4.59
Social	1.26	27.67	0.63	35.91

PF Physical functioning, *RP* role limitations due to physical problems, *RE* role limitations due to emotional problems, *SF* social functioning, *BP* bodily pain, *VT* vitality, *MH* mental health, *GH* general health, *Physical* physical function, *Social* social function

Discussion

Based on the assessments of the GIQLI and the SF-36, this comparative study yielded systematic and comprehensive data regarding responsiveness and MCID in patients undergoing cholecystectomy.

Preoperative and 3-month postoperative Pearson correlation analyses revealed significant correlation between the SF-36 and GIQLI. Thus, these two measures demonstrated construct validity, which is consistent with previous studies.[6,11]

An ideal HRQoL instrument should produce neither floor nor ceiling effects. Regarding the floor and ceiling effects of the SF-36 and the GIQLI, there seems to be room for improvement in these two measures. As Wyrich et al.[19] pointed out, 15% would be a critical value for the largest proportion of patients who should score the maximum or minimum possible scores. In this study, the GIQLI revealed no floor or ceiling effects before or after cholecystectomy, but the social functions subscale revealed a remarkable significant notable ceiling effect. Before cholecystectomy, the SF-36 exhibited a floor effect in role limitations due to physical and emotional problems and a ceiling effect in physical functioning and social functioning, as well as role limitations due to physical and emotional problems. After medical intervention and treatment management, the floor effect decreased at 3-month survey. However, as cholecystectomy is widely performed and has a high success rate, the ceiling effect is extremely problematic in postoperative outcome measurement. Therefore, discriminating between patients presenting a ceiling effect and determining the impact of underestimating its effect after cholecystectomy may be extremely difficult.

Analysis of longitudinal changes indicated the role limitations due to physical and emotional problems of the SF-36 exhibited the highest improvement rate. Before cholecystectomy, the mean scores for physical and emotional roles were relatively lower than those for other scales, probably because these roles were limited by the physical and emotional function of patients. The patients could resume their role limitations immediately after cholecystectomy. Conversely, the areas of pain relief and symptom functions revealed relatively greater improvement

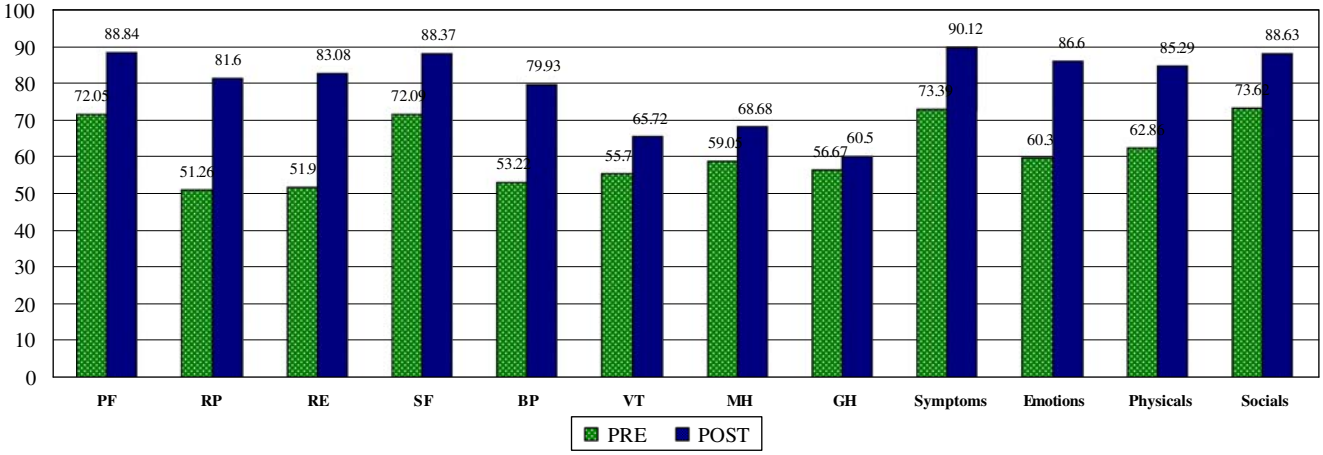

Figure 1 Longitudinal changes in each subscale of the SF-36 and the GIQLI before and 3 months after cholecystectomy. Domains: *PF* physical functioning, *RP* role limitations due to physical problems, *RE* role limitations due to emotional problems, *SF* social functioning, *BP* bodily pain, *VT* vitality, *MH* mental health, *GH* general health, *Symptoms*, *Emotions*, *Physical* function, *Social* function. All *p* values denote statistically significant differences between preoperative and 3-month postoperative baseline scores for age, gender, number of comorbidities, average lengths of stay, and laparoscopic versus open surgery.

Table 3 Estimated Responsiveness and MCID for the SF-36 and the GIQLI

	Responsiveness estimates				MCID	
	CR (%)	ES	SRM	RE	CL	CU
SF-36						
PF	23.29	0.53	0.55	0.30	12.03	21.54[a]
RP	59.20	0.64	0.61	0.37	22.59	38.10[a]
RE	60.83	0.64	0.57	0.33	22.73	39.64[a]
SF	22.58	0.63	0.64	0.41	12.33	20.22[a]
BP	50.19	1.04	0.93	0.86	22.25	31.17[a]
VT	17.99	0.52	0.53	0.28	7.11	12.93[a]
MH	16.30	0.47	0.52	0.27	6.73	12.52[a]
GH	6.76	0.17	0.23	0.05	1.20	6.46[a]
GIQLI						
Symptoms	22.79	0.86	0.87	0.76	13.75	19.70[a]
Emotions	43.66	1.12	1.10	1.20	22.59	30.05[a]
Physical	35.70	1.01	0.91	0.82	18.61	26.27[a]
Social	20.33	0.62	0.60	0.36	11.09	18.87[a]
Total scores	28.13	1.02	1.00	1.00	16.41	22.44[a]

MCID Minimal clinically important differences, *PF* physical functioning, *RP* role limitations due to physical problems, *RE* role limitations due to emotional problems, *SF* social functioning, *BP* bodily pain, *VT* vitality, *MH* mental health, *GH* general health, *Physical* physical function, *Social* social function, *CR* change ratio, *ES* effect size, *SRM* standardized response means, *RE* relative efficiency, *CL* 95% confidence interval at lower limit, *CU* 95% confidence interval at upper limit

[a] No equivalence (good responsiveness)

than other functions. Taken together, perhaps this might imply that cholecystectomy improves role limitations due to emotional or physical problems by relieving bodily pain and emotional burdens that accompany cholecystitis/symptomatic cholelithiasis. Consequently, improved role limitations, pain relief, and symptom function might improve physical, emotional, and social functions, as well as overall quality of life. However, minor improvements in physical function, vitality, and mental health were found immediately after cholecystectomy, which may explain the poorest improvement rate in the SF-36 general health subscale. This might implicate that symptomatic cholelithiasis or cholecystitis is not a severe disease to such a patient group.

This study is the first to compare the GIQLI and the SF-36 for responsiveness and MCID in cholecystectomy patients treated at two medical centers. The data derived by this study can help clinicians and health researchers decide which measure is most effective for evaluating HRQoL before and after cholecystectomy. The responsiveness estimates for the GIQLI generally exceeded 0.5, which can be interpreted as medium change.[20] The SF-36 also presented good results in all subscales except mental and general health, which revealed improvement after surgery. Additionally, ES and SRM estimates were conceptually similar, which is consistent with an earlier finding reported by Zou.[21]

Schmitt and Di Fabio[9] suggested that statistically significant group changes may not exhibit statistical significance at the individual level. Based on the patient outcomes reported in that study, MCID is an essential measure for comparing two HRQoL instruments. In a subsequent study of patients undergoing total knee replacement,[7] MCID ranged from 14.52 (stiffness) to 22.87 (pain) on the Western Ontario and McMaster Universities Osteoarthritis Index, and SF-36 ranged from 11.56 (physical functioning) to 16.86 (bodily pain). In the 6-month survey of another study of patients with obstructive sleep apnea, the SF-36 vitality scores were 20.7–24.2 points. At the 18-month survey, scores for role limitation due to physical problems, social functioning, vitality, and general health were 2.5–7.5, 5.5–6.6, 7.5–8.7, and 13.5–15.5 points, respectively.[22] A comprehensive literature review reveals no other reports of GIQLI to calculate the MCID.

The 95% confidence interval of the MCID (CL, CU) for each subscale of the GIQLI or the SF-36 in this study

Table 4 Comparative Responsiveness Estimates of Effect Size and Standardized Response Mean of the GIQLI and the SF-36

Subscale	GIQLI–SF-36 (estimate [95% CI])[a]	
	Effect size	Standardized response mean
Emotional	0.48 (0.12, 0.84)	0.53 (0.21, 0.85)
Physical function	0.48 (0.22, 0.74)	0.36 (0.13, 0.59)
Social function	−0.01 (−0.33, 0.31)	−0.04 (−0.34, 0.26)

[a] Differences are presented in effect size and standardized response mean (95% confidence interval obtained by bootstrapping).

Table 5 Comparative Effectiveness of HRQoL Instruments Reported in Previous Studies

Authors (publication date)	Country	No. of subjects	Measurement time intervals	Instrument	Findings
Shi HY et al. (present study)	Taiwan	159	Preoperative and 3-month surveys	GIQLI, SF-36	GIQLI revealed greater overall effectiveness than the SF-36 between preoperative and 3-month surveys
Drossman D et al. (2007)26	USA	402	Preoperative and 3-month surveys	IBS-QOL, SIP	IBS-QOL exhibited treatment responsiveness superior to the SIP; meaningful clinical improvement was 2.8 points for SIP and 14 for IBS-QOL
Finan KR et al. (2006)27	USA	55	Preoperative and 17.1-month surveys	GISS, SF-36	GISS was relatively more effective for GI symptoms than the SF-36
Quintana JM et al. (2005)5	Spain	650	Preoperative and 3-month surveys	GIQLI, SF-36	GIQLI was relatively more effective than the SF-36 for those who were considered appropriate candidates for cholecystectomy
Quintana JM et al. (2001)28	Spain	353	Preoperative and 3-month surveys	GIQLI, SF-36	Responsiveness of the GIQLI, as measured by mean standardized response, ranged from 0.45 to 0.82, which was superior to that of the generic questionnaire SF-36 (0.20 to 0.56)

GIQLI Gastrointestinal Quality of Life Index, *SF-36* Medical Outcomes Study Short Form-36 Health Survey, *IBS-QOL* Irritable Bowel Syndrome-Quality of Life, *SIP* Sickness Impact Profile

exceeded 5 (except SF-36 general health), indicating significantly improved health status after cholecystectomy. The MCID observed in this study was higher than that reported in previous studies of cholecystectomy patients,[7,23] which may be attributable to differing medical treatment or disease severity.

Importantly, although the improvements were in different subscales of the GIQLI and the SF-36, the estimated effectiveness of the GIQLI generally was greater than that of the SF-36. However, such effectiveness estimates in previous studies[4,5] were made using a small sample size or lacked comparative statistical data before and after interventions. Thus, the bootstrap method employed in this study generated a 95% confidence interval. Although the two measures significantly differed in responsiveness, each exhibited superior responsiveness in different subscales. The GIQLI exhibited superior responsiveness in emotional and physical function subscales, whereas the SF-36 had better responsiveness in social function. This difference may have been due to the additional SF-36 subscales for vitality, mental health, and general health, which had low responsiveness.

An acknowledged limitation of this study is the small sample size, which restricts the extent to which the findings can be generalized to larger populations. Future studies are needed to examine outcomes, patient attributes, hospital attributes, quality of care, preoperative functional status, and related factors in a larger population. Further, the patient outcome may be highly dependent on variables such as operator proficiency, advancing technology, and available facilities.[24,25] However, all procedures evaluated in this study were performed by surgeons with the most experience in cholecystectomy procedures in each of two different institutions, and the potential confounding factors in both effectiveness and MCID were controlled simultaneously. Given this design, the surgical outcomes in this study were more representative than those of a single-surgeon study.

Table 5 presents a cross-sectional comparison to confirm the data regarding the effectiveness of the GIQLI and the SF-36. Data from this and four other similar studies performed in the United States and Europe were comparatively analyzed.[5,26–28] All four studies were comparable to the current study in sample size, performance of both preoperative and postoperative surveys, and application of both disease-specific and generic HRQoL instruments. While several other studies in orthopedic surgery and medicine have used MCID to compare HRQoL instruments,[6,7] no investigators have applied MCID calculations to the GIQLI. The current finding of greater responsiveness of the disease-specific measure in comparison with the generic measure was consistent with all comparable studies examined. Specifically, the increased responsiveness of the disease-specific measure suggests that symptoms and related functions improve more rapidly and more completely than overall quality of life in patients who undergo cholecystectomy.

In conclusion, the comparative results of this prospective cohort study provide comprehensive and systematic information regarding the expected responsiveness and MCID in patients undergoing cholecystectomy. The GIQLI exhibited

responsiveness superior to that of the SF-36 between the preoperative and 3-month surveys. Therefore, clinicians and health researchers may consider weighting the disease-specific measure more heavily than the generic measure to determine treatment effectiveness. Further study may also examine the extent to which the HRQoL instrument is applicable to other forms of gastrointestinal surgery.

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Right Hemihepatectomy

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Abstract A right hemihepatectomy is frequently required for surgical removal of colorectal liver metastases. Today, this procedure can be performed quite safely provided the remaining liver is free from significant disease including steatohepatitis due to prolonged cytostatic treatment. Standard surgical techniques for liver resection are described in surgical textbooks. However, each center has developed its own modifications of important details. In this paper, we describe our technique to resect the right liver lobe using conventional surgical techniques as well as a vascular stapler and an ultrasonic dissector. This technique has proven to be quite safe, and blood loss is most often not significant despite we do not routinely apply the Pringle's manoeuvre during the division of the liver parenchyma.

Keywords Liver resection · Colorectal metastases · Hemihepatectomy

Thirty to forty years ago, a right hemihepatectomy was very infrequently performed in Europe and considered a high-risk operation. Today, it is safely performed in many centers. The very marked increase in frequency is in the Western world, to a large extent due to the fact that liver metastases from colorectal cancer can be cured by surgery alone or surgery combined with chemotherapy. Liver metastases from colorectal cancer are our dominating indication for a right hemihepatectomy. In East Asia, on the other hand, hepatocellular carcinoma secondary to hepatitis B or C dominates. However, this disease is less frequently an indication for a right hemihepatectomy, as the accompanying liver cirrhosis often precludes such an extensive procedure. Basically, the process of a right hemihepatectomy follows certain general guidelines originally outlined in the French literature.[1] Operating techniques are described in surgical textbooks (see, i.e., Blumgart et al.[2]), but there are numerous variations developed in different units. Although most surgeons do right hemihepatectomies as open procedures, it can also be performed laparoscopically.[3] To avoid excessive bleeding, the vascular supply to the liver can be dealt with in various ways including extra- or intrahepatic division of the in- and the outflow to the right liver lobe.[1,4,5] Variations due to anatomical and other circumstances depending on specific conditions in individual patients are, in addition, often necessary. There are several technical tools that can be used in this operation and which, furthermore, add to the variability. Nevertheless, it is helpful to develop a standard technique as a basis for such variations. In this paper, we report how we do a standardized right hemihepatectomy—resection of liver segments V–VIII according to Couinaud's nomenclature[6]—using some of these available tools.

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Incision and Mobilization of the Liver

We use a subcostal incision from 5 cm to the left of the midline to the lateral right side. The incision is regularly extended in the upper midline to the xiphoid process, a so-called Mercedes Benz incision. This incision has some risks, but it allows very good access. It may create weakness at the junction of the subcostal and the midline parts. This, in turn, may cause leakage of ascites in cirrhotic

patients, delayed healing, and even incisional hernias in a few percent of the patients. The first step after opening the abdomen and inspection to verify there are no contra-indications to proceed such as peritoneal carcinosis or distant extra hepatic metastases is to divide the falciform ligament down to the supra hepatic caval vein. The liver is then mobilised by dividing the adhesions dorsal to the liver and between the diaphragm and the liver—the right triangular ligament. This is done using diathermy. The initial part of the mobilization of the liver can be quite cumbersome especially in big male patients. An assistant has to apply traction of the liver to the left and/or cranially, which could be quite difficult to do effectively in the initial phase. It rapidly becomes much easier with the progress of the mobilization of the liver.

Intraoperative Ultrasound

In this phase of the operation, we proceed to the right lateral part of the caval vein. After this, we usually perform intraoperative ultrasound to verify the tumor and its location, which can be quite difficult if contrast enhancement is not used especially in small tumors with a similar echo as the liver parenchyma. It is important to localize the major hepatic venous and portal vessels. Special emphasis should be made to localize the middle hepatic vein. It could be quite useful to mark this vein on the surface of the liver with diathermy, especially if the resection can be made in such a way that this vein could be saved.

Dissection of the Hepatico-Duodenal Ligament

The next step in the procedure is to obtain inflow control of the right liver lobe by dividing the right hepatic artery, the right bile duct, and the right branch of the portal vein.[1,4] The peritoneal layer covering the right and anterior surfaces of this ligament is dissected free and cut using diathermy. The common bile duct is identified. The further dissection in the ligament is performed by means of scissors, and hemostasis is carefully achieved by use of diathermy on forceps. If both hepatic lobes are supplied by the common hepatic artery, this vessel and its main right and left branches are identified. The right hepatic artery is marked using a Vessel loop. The origin of the cystic duct is identified. The gall bladder is then mobilized starting from its fundic part using diathermia. The cystic artery is ligated and the cystic duct divided close to its origin. The remaining ductal stump is secured by a suture–ligature using a 4–0 absorbable suture. A tiny rubber band is applied around the common hepatic duct, and this structure is carefully dissected free upwards to the liver hilum. The main right and left hepatic ducts are identified, the right one divided, and the remaining part secured using suture–ligation (4–0 absorbable suture; Fig. 1). During this maneuver, the right hepatic artery is often found coming from behind (dorsal of) the common hepatic duct and running towards the right liver lobe. If this is the case, the artery is divided and ligated at this level. If the right hepatic artery originates from the superior mesenteric artery, as is the case in approximately 20% of all, this vessel is easily identified during the dissection of the common hepatic duct and divided. Using the rubber band, the common hepatic duct is then gently pulled to the left to visualize the portal vein. The portal vein is dissected free, and the right and left main branches of this vein are identified. The right main branch is divided close to the bifurcation. We usually suture the remaining stump over an angled vascular clamp (i.e., a Pilling clamp) using a vascular suture (4–0). A vascular stapler could also be used. The part close to the liver is carefully secured using a U-shaped suture–ligature (3–0, absorbable suture). A demarcation line is now most often evident on the surface of the liver. Sometimes, the bile duct and/or the portal vein might have three main branches in the liver hilum. In such cases, the branch most to the right is divided extrahepatically, whereas division of the further supply to the right liver lobe is performed while dividing the liver parenchyma.

It has been suggested that extrahepatic division of the right hepatic bile duct, artery, and portal vein is redundant, as these structures or their main branches are divided during the division of the liver parenchyma close to the hilum. In a sense, this is correct, and several centers follow these lines of thoughts.[5] We still perform the extrahepatic dissection and

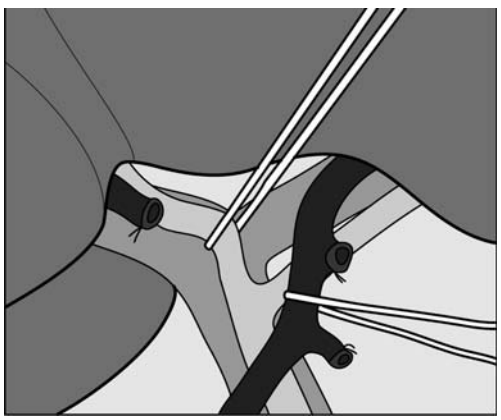

Figure 1 Schematic illustration of the dissection of the hepatico-duodenal ligament. The common hepatic duct is retracted to the left using a tiny rubber band. The cystic and the right hepatic ducts are divided and the remaining ends secured by a suture–ligature (4–0). The right hepatic artery, coming to the right in a plane dorsal to the common hepatic duct, is identified using a tiny rubber band. The portal vein is dorsal to the artery and will appear at the level of the bifurcation after dividing the right hepatic artery.

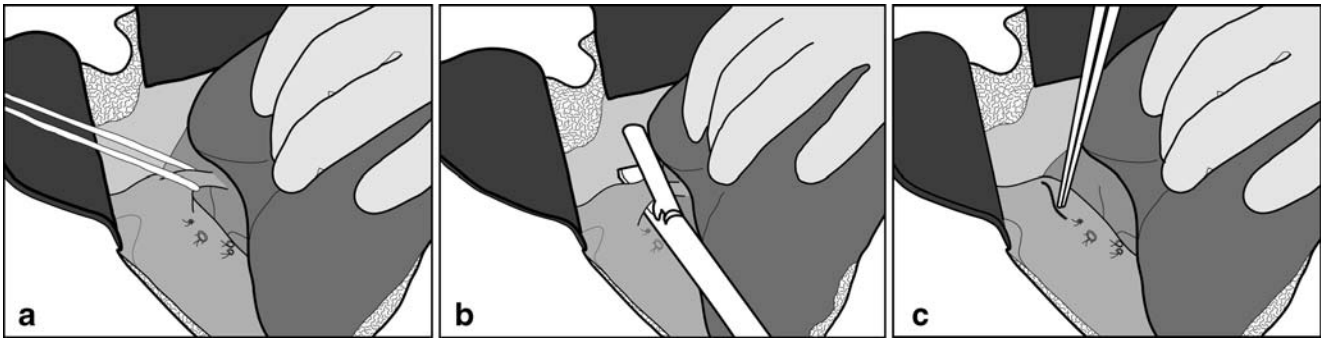

Figure 2 The dissection of the right and the anterior surfaces of the caval vein has been conducted up to the point when the right hepatic vein has been isolated and surrounded using a tiny rubber band (**a**). A vascular stapler with a 30- to 45-mm loading unit is then positioned to divide the right hepatic vein (**b**). After firing, the vascular stapler the remainder of the right hepatic vein and the staplers are demonstrated (**c**).

division, however, as we feel it adds the security of exact knowledge of the anatomy in this area.

Dissecting the Right and Anterior Surfaces of the Caval Vein

The operation then proceeds by further dissecting at the dorsal surface to the liver. The aim with this phase of the operation is to obtain outflow control or, more accurately speaking, to prevent backflow through the hepatic veins to cause bleeding during the division of the liver parenchyma.[1,4,5] Starting from the caudal end, the caval vein is dissected in such a way that the right and anterior surfaces are absolutely free. Again, part of this dissection is performed by dividing connective tissue using scissors and diathermy. Several veins, constituting direct communications between the liver and the caval vein, have to be identified and divided during this procedure. We divide these vessels between clamps and secure the caval end of the divided vessel by a suture–ligature using a vascular suture (4–0), while the hepatic end is ligated using an absorbable 3–0 suture. Clips, Harmonic scalpel® or Ligasure® could equally well be used. In some patients, one of these veins is more prominent, "the right inferior hepatic vein". This is dealt with in the same way. The right adrenal vein comes to the right of the dissection plane, and this gland is seldomly interfered with. However, the adrenal gland could be found adherent to the liver parenchyma from which it could be dissected free. An adrenal vein could drain directly into the hepatic parenchyma. If this is the case, the vein should be divided and ligated.

Above the adrenal gland, the connective tissue to the right side of the caval vein forms a ligament. Before approaching this, we make sure the division of the falciform ligament is completed and the anterior surface of the supra-hepatic caval vein is exposed. Using the cranial approach, the connected tissue located between the right and the middle/left hepatic veins is carefully dissected to create a cavity between the liver and the anterior surface of the caval vein. This is done combining sharp and blunt dissection. When we have identified the right hepatic vein in this way, as well as the caval vein above and below the right hepatic vein, the ligament like structure is divided. This is most often done between clamps, and both sides are suture-ligated using 3–0 absorbable sutures. Now, both the right and the anterior surfaces of the caval vein are completely free except for the right hepatic vein. This structure can, after the dissection described above, easily be grasped between the thumb and the first finger, and this is done well outside the liver using the created cavity. By means of an angled clamp, a tiny rubber band is placed around the right hepatic vein. This facilitates the positioning of a vascular stapler from the right side—from below.[5] This stapler is used to divide and secure the right hepatic vein (Fig. 2a–c).

Division of the Liver Parenchyma

Depending on the location of the tumor, the preferred line of dividing the liver parenchyma can be used or not. For

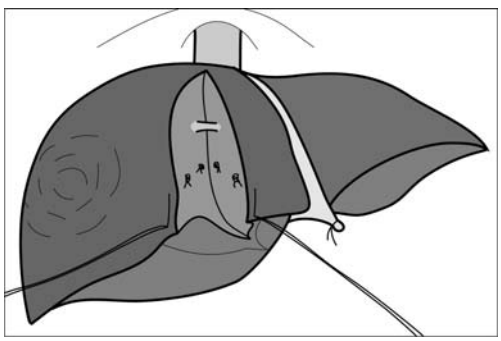

Figure 3 When dividing the liver parenchyma using an ultrasound dissector and bipolar diathermy, larger intrahepatic vessels are identified. These are dissected free using a right-angled forceps, divided between vascular clamps and secured using suture–ligature (3–0 absorbable suture) on a larger needle.

oncological reasons, the ideal anatomic line of the resection—just to the right of the demarcation line and/or the marked position of the middle hepatic vein—may not be possible to use. We start this part of the procedure by marking the planned resection line on the liver surface using diathermy. Thereafter, two absorbable sutures on large needles are placed at the anterior edge of the liver, most often at either side of the gall bladder fossa. The further division of the parenchyma is then performed using bipolar diathermy, clamp crossing, and an ultrasonic dissector.[7] Small vessels are secured using the bipolar diathermy, while larger vessels are suture-ligated using absorbable sutures (3–0; Fig. 3).

We do not routinely use Pringle's maneuver[8] during this operation except when the liver is fragile as in steatohepatitis (blue) livers in patients pretreated with heavy chemotherapeutic regimens. The dissection line in the level of the liver hilum is often a little to the right of the exact middle of the liver. If so, the right portal pedicle or its branches are divided again and secured (see above). We then frequently divide the most cranial and dorsal parts of the liver parenchyma using a vascular stapler[5] with one or two 60-mm loading units. Hemostasis is facilitated by frequent use of the argon beam coagulator. Blood loss is usually not a major problem during this procedure even if we do not use Pringle's maneuver. Frequently, the right hemihepatectomy is done without the need for blood transfusions. If there is an ongoing oozing from the surface of the parenchyma after the resection despite the use of the argon beam coagulator, we have found Tachosil® (Nycomed AB, Stockholm, Sweden) to be a useful tool.

Final Steps

After making sure we have no bile leaks and being satisfied with hemostasis, we most often place a passive drain in the cavity where the right liver lobe used to be. This routine may be questioned according to a recent study,[9] but we have until now adhered to it. If the remaining liver tilts to the right, we suture the falciform ligament using running sutures. The abdominal wall is closed by a running loop suture of the muscular layers and the fascias while the skin is stapled.

Comments

We have done more than 200 right hemihepatectomies since we have standardized our technique. We have had no mortality after a hepatectomy limited to segments V–VIII. Since we have standardized our technique for the procedure, the total hospital or 30-day mortality after liver surgery has been 4 in 465 procedures and after liver surgery for colorectal metastases 2 in 253, 0.9 and 0.8%, respectively. This is in line with what others have reported,[10] provided the remaining liver is free from functional capacity limiting disease.[11,12] The fatalities we have seen have been due to postoperative liver insufficiency—too little functioning liver left after extended resection procedures.

In uncomplicated cases (not an extended procedure, no redo procedure, and no need for bile duct reconstruction), the procedure takes about 3 h (median operating time has been 187 min for 96 consecutive uncomplicated right hemihepatectomies (interquartile range 150–210 min) during the last 5 years. Most of our patients are referrals from other hospitals in the middle part of Sweden. The total postoperative hospital stay has been 10–12 days on average. The drain is removed on the fourth to sixth postoperative day unless there is a bile leak. This is defined as >50 ml of bile or fluid with a high bilirubin concentration per 24 h in the passive drain on postoperative day 7. Bile leakage is our most frequently encountered postoperative complication seen in 9.7% of our patients undergoing uncomplicated right hemihepatectomy. It may well stop spontaneously after a few more days, but in 11 of 13 patients (85%), we have performed an endoscopic retrograde cholangiopancreatography to verify the source of the leak and provide drainage of the biliary tree by means of a naso-biliary catheter. The bile leak has then stopped within 3–5 days, which we have verified radiographically using the naso-biliary catheter before removing this and the passive drain. A papillary stent could also have been used to drain the biliary tree, but this does not provide the possibility of a radiographic control and it requires endoscopical removal. In a limited number of patients, we have seen ascites defined as fluid with low bilirubin concentration in the passive drain on the seventh day. We have then eliminated the drain while giving diuretics, and this has been uneventful.

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Modified Liver Hanging Maneuver to Facilitate Left Hepatectomy and Caudate Lobe Resection for Hilar Bile Duct Cancer

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Abstract The liver hanging maneuver (LHM) is a useful technique enabling a safe anterior approach, but it has several technical limitations for resection of the hepatic paracaval portion. We present a modified LHM that facilitates concurrent resection of the paracaval portion, a technique applicable to left liver resection for hilar bile duct (HBD) cancers. During 11 months from November 2006 to September 2007, 10 HBD cancer patients underwent left liver resection using the modified LHM. This method included initial partial transection of the caudal paracaval portion. Thus, subsequent blind tunneling over the retrohepatic inferior vena cava can become as short as 2–3 cm in length, resulting in effective prevention of short hepatic vein injury. The parenchyma transection plane was tailored to remove most of the paracaval portion. This modified LHM technique was safely and effectively applied to 10 consecutive patients, requiring a shorter time than conventional dissection method for caudate lobe dissection. No significant bleeding occurred during retrohepatic tunneling. The final parenchymal transection plane after left liver resection using modified LHM was the same as that following the conventional surgical technique for HBD cancers. In conclusion, we think that this modified LHM is an effective, technically simple procedure for resection of the left liver and caudate lobe in HBD patients.

Keywords Hilar bile duct cancer · Liver hanging maneuver · Curative resection · Segment IX · Caudate lobe

Abbreviations

HBD	hilar bile duct
IVC	inferior vena cava
LHM	liver hanging maneuver
MHV	middle hepatic vein
RHV	right hepatic vein

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Introduction

The liver hanging maneuver (LHM) is a useful technique enabling a safe anterior approach during right hepatectomy, right anterior sectionectomy, or central bisectionectomy, especially for huge hepatocellular carcinomas.[1–3] This method is also useful for concurrent resection of the left liver and caudate lobe, as in living donor hepatectomy, as the hepatic transection plane is very similar to that of conventional right hepatectomy.[2,4]

However, the usability of LHM has not been clearly demonstrated when the parenchymal transection plane is not aligned with the action plane of LHM, such as in left hepatectomy with preservation of the caudate lobe or concurrent removal of the paracaval portion.[5,6] The clinical application of LHM to conventional left hepatectomy with preservation of the caudate lobe has been described,[3,7] but there was no report of LHM for left hepatectomy with combined resection of the paracaval portion (segment IX), the surgical procedure usually required for left liver resection in patients with hilar bile duct (HBD) cancers.[8]

In this paper, we describe a modified LHM that facilitates concurrent resection of the paracaval portion, a technique applicable to left liver resection for HBD cancers.

Materials and Methods

Patient Selection

To prospectively assess the technical feasibility of LHM during left liver resection for HBD cancers, this study was planned to continue for 10 consecutive patients. As every surgeon usually uses different surgical techniques for HBD cancers, objective assessment of the technical feasibility of LHM required that all candidate patients be treated by a single surgeon (SH).

During the 11 months from November 2006 to September 2007, 28 patients with HBD cancers underwent resection of the liver and bile duct with curative intent, including 16 undergoing resection of the right liver and caudate lobe, 10 undergoing resection of the left liver and caudate lobe, 1 undergoing resection of the segments IVa (ventral portion of the segment IV) and V and the caudate lobe, and 1 undergoing isolated caudate lobe resection. Left liver resection was primarily indicated for Bismuth–Corlette type IIIB and/or left portal vein invasion or relatively small left liver volume not permitting right liver resection. Modified LHM was prospectively applied to the 10 consecutive patients undergoing left hepatectomy and caudate lobe resection.

Another 10 HBD cancer patients who had undergone resection of the left liver and caudate lobe by the same surgeon from February 2006 to October 2006 were set as the historical control group.

Modified LHM Procedure

Our usual surgical procedure for left hepatectomy and caudate lobe resection includes initial hilar dissection to assess resectability, aortocaval lymph node sampling or dissection, skeletonization of the portal vein and hepatic artery after cutting of the common bile duct, complete mobilization of the left liver including isolation of the caudate lobe through a left-side approach, hepatic parenchymal transection, right hepatic duct transection, and finally biliary reconstruction. During surgery, a sling is inserted, as for LHM, but retrohepatic tunneling was not attempted, as the caudate lobe was conventionally mobilized after extensive left-side dissection.

In the 10 study patients, just after hilar skeletonization, the intervening space between the middle hepatic vein (MHV) and right hepatic vein (RHV) trunks around the diaphragm (MHV–RHV pocket) was dissected caudally with right-angle clamps, as for conventional right lobectomy. The caudal part of the paracaval portion was mobilized from the retrohepatic inferior vena cava (IVC) after ligation of a few short hepatic veins.[9,10] This dissected part of the paracaval portion [dividing point of the segment IXR (right part of the segment IX) and IXL (left part of the segment IX)], just ventral to the right portal vein, was transected by 3 cm (Fig. 1). Detailed anatomy of the paracaval portion and caudate lobe has been described elsewhere.[5,6]

A curved (15°) vascular clamp was inserted along the imaginary line between the MHV and RHV trunks over the retrohepatic IVC (Fig. 1), which usually lacks short hepatic veins.[1,2,9–12] These sequences of initial partial transection and subsequent dissection made the longitudinal length of blind retrohepatic dissection as short as 2–3 cm, resulting in effective prevention of short hepatic vein injury. This technical point differs from the classical LHM[1] and is therefore named modified LHM.[10] The other parts of the segments I and IX were not dissected at this stage. The process of sling insertion for modified LHM was very similar to that for classical right hepatectomy (Fig. 2), but the transection plane of the segment IX portion was located more laterally than the usual plane for right hepatectomy.

Hepatic parenchymal transection was performed with a Cavitron ultrasonic aspirator and monopolar electrocautery after inflow occlusion of only the left liver. Blood flow to the right liver left intact during parenchymal transection. After passing the MHV trunk, the parenchymal transection plane was deviated toward the RHV trunk according to the direction of the dilated glissonian branches (Fig. 3a,b).

This procedure enabled us to remove all of the segment IXL parenchyma and much of the segment IXR parenchy-

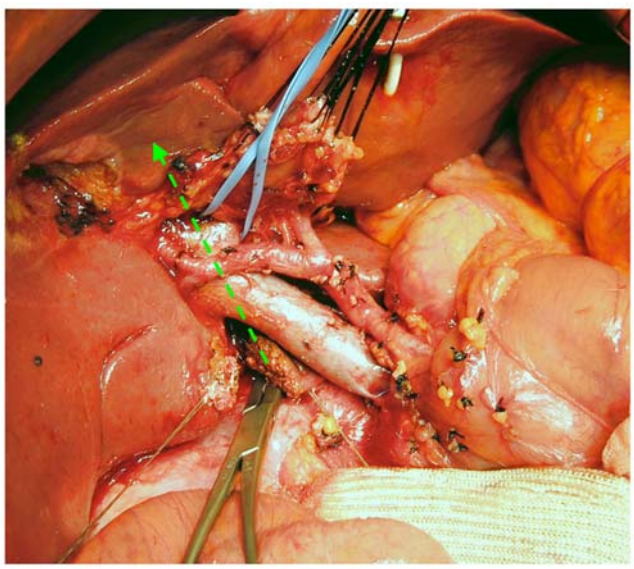

Figure 1 Prior transection of the caudal portion of the segment IXR facilitates retrohepatic dissection over the inferior vena cava (*dotted arrow*).

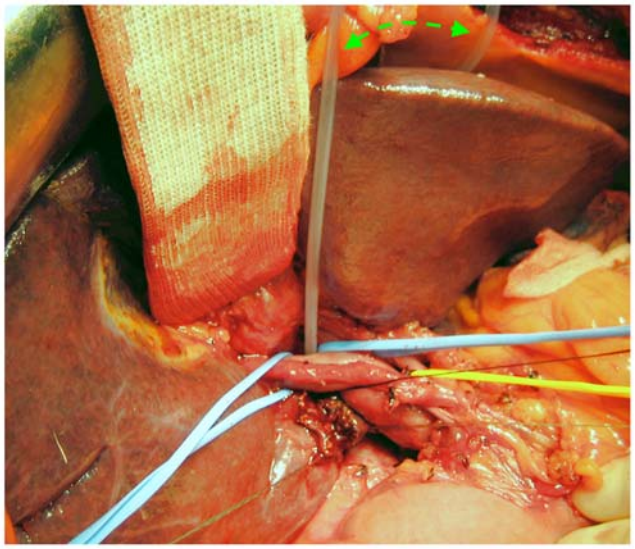

Figure 2 A silastic sling (Jackson–Pratt type drain tube, *bidirectional arrow*) was passed through the hepatic hilum and the MHV-RHV pocket.

ma, resulting in full-length exposure of the right anterolateral wall of the retrohepatic IVC. After completion of parenchymal transection, the conjoined portions of the segments I and IX were detached from the IVC after consecutive ligations of the short hepatic veins (Fig. 3c,d).

Statistics

All numeric data are reported as mean and standard deviation. Student's *t* test and two-tailed Fisher's exact test were used to compare the numeric values and incidences, respectively. A p value <0.05 was considered statistically significant.

Results

The modified LHM was applied to 10 consecutive HBD cancer patients requiring resection of the left liver and bile duct. Historical control group was allocated to another 10 consecutive patients of the same surgical conditions undergone operation just before this study. Their clinicopathologic features are summarized in Table 1.

The LHM technique was safely and effectively applied to all 10 patients. Prior transection of the caudal portion of segment IX and deep dissection of the MHV–RHV pocket made the non-dissected length for tunneling over the retrohepatic IVC only about 2–3 cm, which was meticulously penetrated with a long curved instrument (Fig. 1). No significant bleeding occurred during this retrohepatic tunneling except in one patient, in whom temporary packing was required for hemostasis.

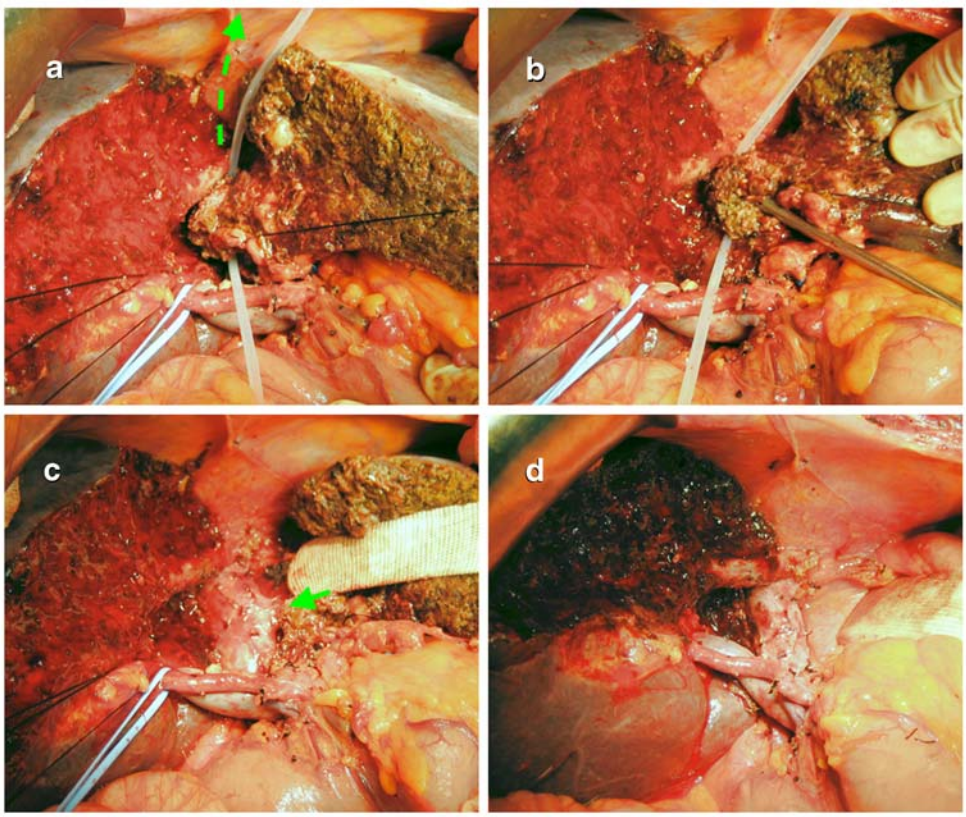

Figure 3 Parenchymal transection for left hepatectomy and concurrent removal of the segments I and IX. **a** A sling was placed in the MHV–RHV pocket until it passed the MHV trunk (*arrow*), after which it was moved between the MHV and left hepatic vein trunk. The parenchymal transection plane was deviated toward the RHV trunk to remove the dilated glissonian branches at the segment IX. **b** Forceful traction of the sling facilitated dissection of the segment IX from the right liver parenchyma. **c** No short hepatic vein was observed in the pathway of sling insertion. A 5-mm-sized draining vein from the segment I was exposed (*arrow*). **d** After removal of the conjoined portion of segments I and IX, the full length of right anterolateral wall of the retrohepatic IVC was exposed.

Table 1 Clinicopathologic Features of Patients with Hilar Bile Duct Cancers Undergoing Left Hepatectomy, Caudate Lobe Resection, and Bile Duct Resection With or Without Application of the Modified Liver Hanging Maneuver

	Modified liver hanging study group	Historical control group	*p* value
Patient no.	10	10	
Age (year, mean±SD)	59.5±6.9	56.7±7.8	0.695
Male sex (*n*, %)	9 (90%)	8 (80%)	1.000
Length of operation (h, mean±SD)	7.5±1.4	7.9±1.2	0.599
Time for caudate dissection (min, mean±SD)	30±6	50±8	0.001
Combined portal vein resection (*n*, %)	1 (10%)	2 (20%)	1.000
Curative resection (*n*, %)	9 (90%)	8 (80%)	1.000
Postoperative hospital stay (day, mean±SD)	15.2±3.3	16.4±3.9	0.611
Surgical complication (*n*, %)[a]	2 (20%)	2 (20%)	1.000

[a] All surgical complications were wound infections.

In the control group of 10 historically selected patients, the time required for caudate lobe isolation by the conventional left-side approach was close to 1 h because the surgical field for this procedure was very deep and poor. Contrarily, after using modified LHM, the procedure including retrohepatic tunneling and detachment of the segments I and IX from the IVC took only 20–30 min (p = 0.001). However, such shortening of operation time after use of modified LHM did not result in a significant shortening of the whole operation time (p = 0.599; Table 1).

After completion of parenchymal transection, we found that there was no sizable short hepatic vein at the pathway of retrohepatic tunnel on the IVC in all 10 patients (Fig. 3c).

We observed that the final parenchymal transection plane after left liver resection by using modified LHM was the same as that after use of the conventional surgical technique for HBD cancers (Fig. 3c). In the latter, the involved portion of the segment IXR was fully removed for prevention of bile leakage and for complete resection of the tumor (Fig. 4).[8] There was no patient showing major surgical complication, but 2 of 10 patients in each group suffered from wound infection (Table 1).

Discussion

LHM has become an accepted technique, as it enables an anterior approach without dissection around the retrohepatic IVC. For patients with huge hepatocellular carcinomas, LHM is preferred not only technically but also for prevention of tumor spillage.[2] The classical LHM technique, however, is not applicable to liver resection for HBD cancers because the segment IX will not be adequately removed.

For right liver resection in HBD cancer patients, complete isolation of the segments I and IX from the IVC is not difficult by using the conventional right-side approach, making retrohepatic tunneling for LHM unnecessary. For conventional left liver resection in HBD cancers, the caudate lobe should be extensively dissected before parenchymal transection. Because this procedure was often very cumbersome due to a poor and deep surgical field, we applied modified LHM to simplify the surgical procedure. This resulted in technical convenience and shortening of the time required for detachment of the segments I and IX from the retrohepatic IVC.

Our modified LHM technique has three theoretical advantages over the classical LHM. First, retrohepatic

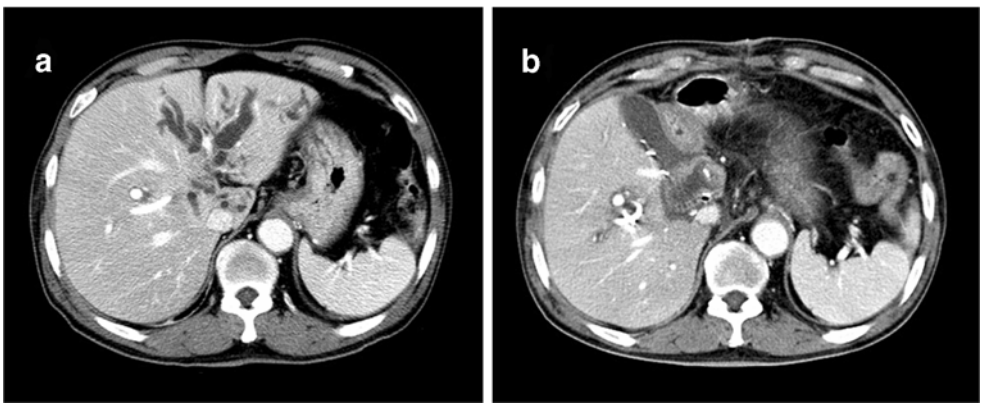

Figure 4 Computed tomography images showing the resection extent of the paracaval portion in a patient with hilar bile duct cancer requiring left liver removal. **a** Preoperative image shows the presence of dilated bile duct branches in the segment IX. **b** Postoperation 1-week image reveals that most of the paracaval portion dorsal to the RHV trunk was removed. A jejunal loop of hepaticojejunostomy was placed at the recess at the hepatic transection plane.

tunneling was simpler and safer because only about 2–3 cm would be blindly dissected after prior partial transection of the paracaval portion. Second, detachment of the segments I and IX from the IVC was simpler because it is performed in a good surgical field after parenchymal transection. Third, the hepatic parenchymal transection plane is identical to the recommended transection plane intended for concurrent excavation of the segment IX parenchyma.

During LHM, prior partial transection of the paracaval portion also appears useful for removal of huge hepatic or extrahepatic masses because it makes the retrohepatic tunneling short and safe.[13] Ultrasonographic localization of the short hepatic veins may enhance technical safety during retrohepatic tunneling,[4] but our results suggest that making the length of blind dissection as short as possible is more practical and convenient.

In conclusion, this modified LHM appears to be an effective, technically simple procedure for left hepatectomy and concurrent caudate lobe resection in HBD patients.

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Natural Orifice Translumenal Endoscopic Surgery: A Critical Review

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Abstract Natural orifice translumenal endoscopic surgery (NOTES) involves the intentional puncture of one of the viscera (e.g., stomach, rectum, vagina, urinary bladder) with an endoscope to access the abdominal cavity and perform an intraabdominal operation. Early laboratory work focused on feasibility studies, including such accomplishments as pure transgastric splenectomy and gastrojejunostomy. Contemporary laboratory work is investigating the infectious and immunologic implications of NOTES and honing the tools and techniques required for complex abdominal operations. Today NOTES has entered the clinical arena in a few cases: the first clinical series of transgastric peritoneoscopy has recently been published; multiple groups are accumulating patients in studies of NOTES cholecystectomy, either via the transgastric or transvaginal route; and a series of transgastric appendectomies has been well publicized, yet it remains unpublished. Although clinical NOTES is gaining momentum, the field should remain in check while rigorous laboratory work is performed and cogent clinical trials are undertaken. The zeal for NOTES should not take precedence over the welfare of the patient.

Keywords Endoscopic surgery · Intraabdominal · Translumenal · Peritoneoscopy · Cholecystectomy

Since Kalloo's publication of transgastic peritoneoscopy in 2004[1] the field of natural orifice translumenal endoscopic surgery (NOTES) has evolved from the ethereal to the tangible. In a brief time period, NOTES has been shown to be feasible in numerous laboratory animal studies and NOTES-specific instrumentation has entered the research and development stages (Fig. 1). Furthermore, rigorous laboratory research into the infectious and immunologic impact of NOTES has, in many cases, shown the equivalence of NOTES to laparoscopy and conventional abdominal surgery. Today careful clinical trials of NOTES peritoneoscopy and cholecystectomy are being conducted. As the data accumulate and instrumentation improves, NOTES may play a role in the future of abdominal surgery.

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The Fundamentals

The central tenets of NOTES consist of passage of a flexible endoscope through one of the body's natural orifices, perforation of a viscus, and performance of abdominal surgery using endoscopic visualization. The endoscope may be inserted through the mouth, anus, urethra, or vagina with puncture of the stomach (the esophagus for mediastinal exploration), rectum, urinary bladder, or vagina, respectively.

Although precise details of NOTES procedures vary between centers, most groups adhere to the same general principles. For transgastric surgery, a standard gastroscope is passed through the mouth into the stomach. A small anterior gastrotomy is made, typically with an endoscopic needleknife. A wire is passed through the site into the abdominal cavity, and then the tract is enlarged with an endoscopic dilating balloon to accommodate the endo-

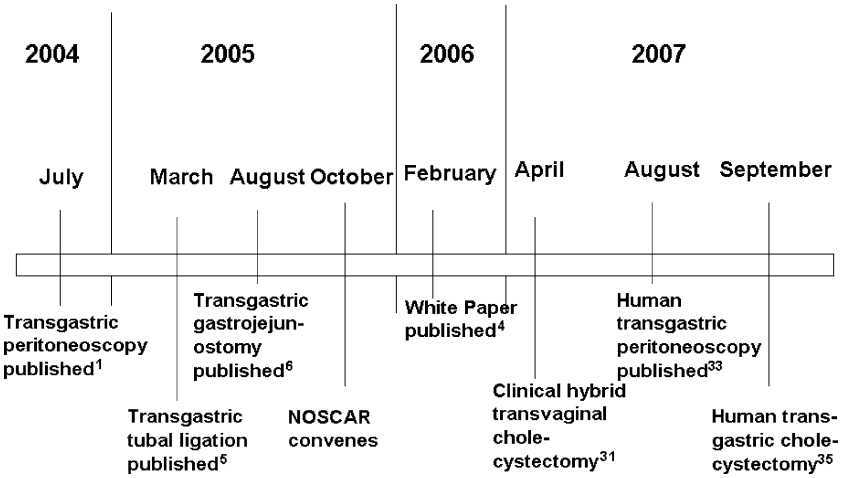

Figure 1 Timeline of significant achievements in the field of NOTES. In a compressed time period NOTES has progressed from laboratory work to meaningful clinical studies.

scope. Transcolonic and transvesical operations use similar methods for entering the peritoneal cavity.

Once the endoscope in advanced into the abdominal cavity, a pneumoperitoneum is generated using endoscopic insufflation. The scope is maneuvered to view the organ of interest. Standard endoscopic instruments, such as biopsy forceps and polypectomy snares, are then passed through the working channels and used for tissue manipulation. When the operation is completed, the endoscope is returned to the lumen of this viscus and the viscerotomy is closed.

Shortcomings of Contemporary Techniques

From the description above, many limitations of current NOTES techniques are evident. Foremost is the fact that a hole is intentionally made in one of the viscera, which repudiates decades of surgical dogma. The patient might be susceptible to infectious and immunologic consequences that are not present in laparoscopy and conventional surgery.

The inherent flexibility of the endoscope impedes achieving a stable operating field. During transgastric surgery, a deep loop into the pelvis might be required to view the right upper quadrant, for example, and the endoscope might resist this positioning. Because of retroflexion, the endoscopic image might be inverted or reversed, further complicating the operation.

The current unavailability of adequate instrumentation restricts the ability to perform meticulous dissection in NOTES. In-line endoscopic tools have a restricted range of motion and limited degrees of freedom. There is not widespread availability of endoscopic scissors and graspers, which would be critical for retraction and dissection. In addition, in-line instrumentation and optics do not allow triangulation of the visual field and instruments, a concept found to be critical in laparoscopy.

As a purposeful viscerotomy is made in NOTES, its secure closure is imperative to ensure the safety of the operation. Initial laboratory work managed the viscerotomy without closure or by occlusion using a percutaneous endoscopic gastrostomy (PEG)-type gastrostomy tube.[2] Both methods were fraught with high rates of intra-abdominal contamination in the porcine model. Thus, more reliable methods that achieve full-thickness closure of the viscerotomy are currently being investigated.

Advantages of NOTES

Some critics are disenchanted with NOTES, given its dissonance with conventional surgical teaching. However, advances are being made in mitigating some of the current shortcomings of NOTES. To that end, there may be some benefits of natural orifice surgery that make its pursuit rewarding.

The immunologic impact of NOTES may be favorable for the patient. A recent laboratory study from Case Western Reserve University showed lower levels of tumor necrosis factor-α (TNF-α) after NOTES peritoneoscopy compared to laparoscopic abdominal exploration and laparotomy.[3] NOTES may lead to less impairment of the peritoneal immune system and possibly even improved oncologic and infectious outcomes.

Natural orifice surgery may decrease the degree of abdominal adhesion formation. Much like laparoscopy, the minimal access nature of NOTES might diminish the stimuli for adhesions and, subsequently, reduce the incidence of postoperative bowel obstruction or simplify future abdominal operations.

NOTES can likely be performed without the need for general anesthesia. As no skin incision is made, the requirement for analgesia might be satisfied with conscious sedation. Therefore, NOTES could be performed in the

intensive care unit or endoscopy suite, rather than a standard operating room.

The NOTES team and its equipment are portable. A single endoscopy tower houses all of the necessary equipment. Furthermore, most NOTES procedures are performed without sterile instruments, but with scopes subjected to high-level disinfection. This makes NOTES amenable to austere environments, such as battlefields and developing countries, where sterilization equipment is not available.

Finally, the esthetic benefits of NOTES. The public at large has become captivated with the concept of "no-scar" abdominal operations. This is feasible with pure NOTES cases, although esthetics should not be the driving force behind NOTES.

NOSCAR: An Influential Organization

The initial enthusiasm for "no-scar" abdominal surgery, coupled with the limitations of NOTES techniques, could have resulted in premature clinical applications of natural orifice surgery. So that the field of NOTES did not proceed unfettered, a new organization was formed: Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR). In a collaborative effort, members of the American Society for Gastrointestinal Endoscopy and the Society of American Gastrointestinal Endoscopic Surgeons joined to form NOSCAR. The purpose of this organization is to regulate the progress of NOTES and ensure the safety of clinical applications.

An influential treatise from NOSCAR has been deemed the "White Paper,"[4] which delineates the guidelines for laboratory and clinical natural orifice surgery. In the White Paper, the authors outlined the current shortcomings of NOTES techniques and some of the potential solutions. A call for rigorous scientific research was sounded before clinical employment of NOTES. Finally, and perhaps most importantly, cooperation between the fields of gastroenterology and surgery was mandated, ensuring the liberal communication of research findings and the multidisciplinary makeup of NOTES teams.

Recently, NOSCAR launched a comprehensive NOTES database. All patients throughout the world who are enrolled in NOTES trials will be entered into the database. This fosters sharing of information and engenders a sense of full disclosure.

Laboratory Achievements to Date

The seminal publication by Kalloo and colleagues led to the organization of the Apollo group. Shortly after the publication of transgastric peritoneoscopy, the Apollo group published reports on transgastric tubal ligation,[5] gastrojejunostomy,[6] and splenectomy[7] in a porcine model. Recently, members of the Apollo Group collaborated in the performance of peroral transgastric ventral hernia repairs in a porcine model. These publications were significant in that complex operations were shown to be feasible using NOTES techniques and the animals survived without undue complications.

Many teams followed the Apollo Group's lead and performed animal feasibility studies. Transgastric appendectomy,[8] cholecystectomy,[9] and oopherectomy[10] were performed. The transcolonic[9] approach has been used to perform cholecystectomy, and the transvaginal approach has been used in laboratory animals to perform nephrectomy.[11] Combined transrectal and transgastric approaches allow performance of complex small bowel resections with intracorporeal formation of anastomoses.[12]

Much of the initial laboratory research focused on the feasibility of NOTES. Although plagued with restrictions, practically any abdominal operation could be performed using the available natural orifice techniques. As outlined in the White Paper, the more poignant questions concerned the infectious and immunologic implications of natural orifice surgery.

Reliable closure of the viscerotomy is the critical step in avoiding intraabdominal infection. As mentioned above, leaving the viscerotomy open and PEG tube occlusion of the gastrotomy were shown to be inadequate in the porcine model. Endoscopic clips, as might be used in a bleeding vessel, have also been used with some success.[13] However, clips only provide mucosal approximation, and a full-thickness closure comports with proven surgical principles.

Numerous devices have been used to attempt full-thickness closure. One such instrument is the NDO Plicator. This device was initially developed for the endoscopic management of gastroesophageal reflux disease. It is a 15-mm instrument whose jaws place a full-thickness permanent suture with polytetrafluoroethylene bolsters. A 6-mm endoscope is advanced through the working channel of the scope to provide visualization. In addition, a patented retracting device permits grasping of tissue and more accurate placement of sutures.

Closure of full-thickness gastrotomies has been shown to be reliable with the NDO Plicator.[14,15] Bursting pressures of the porcine stomach after closure exceed 90 mmHg and a water-tight closure is achieved, as evidenced by fluoroscopic contrast studies. Survival studies in laboratory animals have shown minimal rates of intraabdominal infections after transgastric peritoneoscopy and closure with the NDO Plicator.

Another group has developed a method of gastrotomy closure using a commercially available overtube and

suturing device.[16] The overtube is steerable, torque-stable, fixable, and accommodates a slim endoscope and a suturing device. The suturing device consists of a grasper that locks at 45 degrees relative to the instrument shaft. A needle and suture passes through the device and can be bolstered with polyester tissue anchors. In the porcine stomach, robust, full-thickness sutures and fine tissue manipulation was achievable using this platform.

A method of translumenal access has been developed by the Penn State group that might obviate the need for full-thickness closure, deemed the self-approximating translumenal access technique (STAT).[17,18] An incision is first made in the gastric mucosa. The submucosal space is developed and a tunnel of at least 5 cm length is created using a dissecting balloon. After tunneling away from the mucosal defect, the muscularis and serosa are punctured, and the abdomen is entered. After the abdominal portion of the operation, the scope is withdrawn and only the mucosa is closed. In a porcine model, this technique has yielded favorable results.

Sumiyama and colleagues have performed transgastric cholecystectomies in laboratory animals using an offset gastrostomy, similar to STAT, to access the abdominal cavity. A submucosal tunnel was created using high-pressure carbon dioxide followed by a myotomy to puncture the remaining gastric wall. The endoscope was advanced through the tunnel into the peritoneal cavity and a cholecystectomy was performed. The submucosal plane was angled cephalad to position the endoscope for operating in the right upper quadrant. At the conclusion of the operation, the mucosal entry point was closed with endoscopic clips or tissue anchors. The animals that survived the operation were followed for 1 week and then sacrificed.

In animal studies, the Ohio State group has closed gastrotomies with a bioabsorbable plug, such as might be employed in inguinal hernia repair.[19,20] This eliminated the need for complex tissue manipulation and provided water-tight closure with minimal infectious complications. This technique might simplify the process of viscerotomy closure, provided that it is as reliable as a full-thickness tissue approximation.

The pneumoperitoneum from NOTES is commonly created using endoscopic insufflation. As in laparoscopy, the intraabdominal pressure requires continuous monitoring during NOTES. Unchecked insufflation might lead to abdominal compartment syndrome. A recent study has shown that pressure transducers fitted to the end of a gastroscope or passed through a working channel detect intraabdominal pressure with a high degree of correlation with actual intraabdominal pressure.[21] Such devices could be easily incorporated into NOTES operating endoscopes. Alternative means to monitor intraabdominal pressure include passage of a transabdominal Verees needle or other similar transabdominal catheter.

Adequate retraction is imperative to safely perform complex abdominal operations, such as cholecystectomy. Given the nature of endoscopic instruments, appropriate retraction has been difficult to achieve. The group from the University of Texas-Southwestern has developed a clever method using intraabdominal magnets to provide retraction during NOTES procedures.[22,23] In their technique, an extraabdominal magnet is paired to its intraabdominal counterpart. The organ of interest is affixed with a metal device, such as a clip, and coupled to the magnet. Tissue manipulation is performed by moving the external component of the magnet to achieve the desired retraction.

To provide a stable operating platform for natural orifice surgery, new endoscopes are under development. Swanstrom[24] and others[16] are using endoscopes that allow the surgeon to operate with both hands, rather than using one hand to stabilize the endoscope. Others[25] are using commercially made multibending endoscopes with dual instrument channels to provide better maneuverability and stability. The NOTES endoscope of the future might have the ability to maintain a fixed position and its multiple working channels could be offset from the optics so as to provide for triangulation.

Some groups have overcome the obstacles of triangulation and retraction by inserting multiple endoscopes into the abdomen. The group from the University of California-San Diego has performed complex small bowel resections by inserting endoscopes and staplers through both the stomach and rectum.[12,26] While these procedures were done under laparoscopic supervision, the lessons learned from the dual-scope technique might be applied to pure NOTES cases.

Recently, laboratory NOTES sigmoid colectomy has been performed without a flexible endoscope. Swanstrom and colleagues used transanal endoscopic microsurgery techniques to perform a radical sigmoid colectomy.[27] Human cadavers were used in performing the sigmoid resection with high ligation of the vessels and generous lymphadenectomy.

Clinical NOTES

Some might suggest that natural orifice surgery has been practiced for years. Translumenal drainage of pancreatic pseudocysts[28] and transgastric pancreatic debridement[29] are considered standard procedures for many advanced endoscopists. Culdoscopy, in which a laparoscope is inserted into the abdomen through the vagina, is commonly used in the management of infertility and sometimes employed for tubal ligation. Some might even note that percutaneous endoscopic gastrostomy, first described in 1979,[30] was the

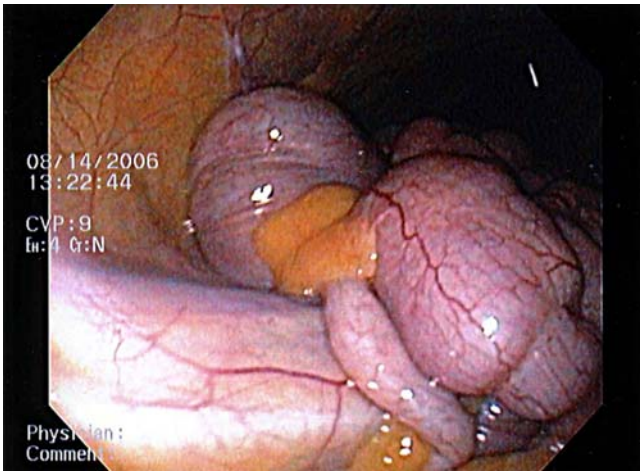

Figure 2 View of the appendix from a transgastric endoscopic approach.

first endoscopic procedure that purposely breached the gastric lumen and supplanted a standard operation, thus qualifying as NOTES.

The first case of contemporary natural orifice surgery was performed nearly a decade ago by a surgeon practicing in the United States. A hybrid laparoscopic/endoscopic cholecystectomy was undertaken. Needlescopic instruments were used to perform a laparoscopic cholecystectomy using standard techniques. An anterior gastrotomy was made and the specimen was placed into the stomach and removed by mouth with the endoscope. The gastrotomy was then closed using intracorporeal suturing techniques.

After the first unpublished hybrid case, natural orifice techniques went largely ignored until Kalloo's 2004 publication. After the successes of the Apollo group with laboratory natural orifice surgery, a group in India performed a series of transgastric appendectomies and transgastric tubal ligations (Fig. 2). Although unpublished, the videos have been widely disseminated at meetings across the world. The series has accumulated at least 12 patients, reportedly with salutary results.

A recent hybrid procedure generated a great deal of publicity in the lay press and at surgical meetings. The Columbia group in New York City performed a hybrid cholecystectomy with extraction of the specimen through the vagina.[31,32] Dissection and retraction were performed with both the laparoscopic and endoscopic instruments. The patient, a middle-aged woman, reportedly recovered well after this procedure without complications.

Additional cases of hybrid cholecystectomy have circulated across the world (Fig. 3). From France to Brazil to Peru, anecdotal case series of hybrid cholecystectomy, using a variety of techniques, have been publicized at international surgery and gastroenterology meetings.

The Ohio State group has performed the first institutional review board-approved series of hybrid transgastric peritoneoscopy.[33] NOTES peritoneoscopy was performed in all patients with suspected adenocarcinoma in the head of the pancreas. An initial diagnostic laparoscopy was performed followed by the creation of an anterior gastrotomy and transgastric peritoneoscopy under laparoscopic supervision. In most cases, NOTES abdominal exploration was found to be equivalent to laparoscopy in detecting peritoneal metastases or other unresectable disease. There were no complications directly related to the transgastric procedure. The authors concluded that transgastric peritoneoscopy in humans is feasible and safe.

Perhaps the first case of pure NOTES published from the United States was completed at Case Western Reserve University in Cleveland.[34] A PEG tube placed for nutritional support was dislodged 3 days after its initial placement. The stomach had not yet adhered to the anterior gastric wall, therefore there was a free communication between the gastric lumen and the abdomen. The abdomen was explored and irrigated, and the gastrostomy tube was restored using pure NOTES techniques.

To rescue the PEG without laparotomy or laparoscopy, a gastroscope was advanced into the stomach with identification of the prior gastrotomy site. The aperture was dilated with a balloon and the endoscope advanced into the abdominal cavity. Some soilage was identified, which was cleansed using the endoscopic irrigation channel. The prior abdominal incision was used to pass a wire into the peritoneal cavity, and the PEG was restored using the pull technique. After the "PEG Rescue" the patient recovered well, without evidence of intraabdominal infection.

The first purely translumenal cholecystectomy was reported by Marescaux and colleagues from Strasbourg, France.[35] The transvaginal route was used to access the abdomen in a 30-year-old woman with symptomatic cholelithiasis. A 2-mm needleport was used for insufflation

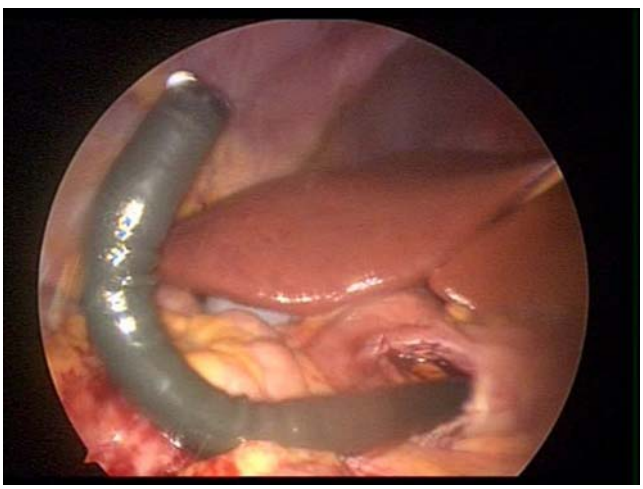

Figure 3 Laparoscopic view of the transgastric approach to the right upper quadrant. To visualize the gallbladder, the endoscope typically requires a deep loop into the peritoneum.

and monitoring of intraabdominal pressure. The cholecystectomy was performed without the aid of a laparoscope using only NOTES techniques. The patient's recovery was uneventful.

NOTES: The Domain of Surgeons or Gastroenterologists?

The question arises as to whether surgeons or gastroenterologists will be the primary practitioners of NOTES.[36,37] After all, abdominal operations are typically under the purview of the general surgeon, but gastroenterologists are usually expert in flexible endoscopy. In all likelihood, a small subset of endoscopic surgeons and advanced gastrointestinal endoscopists will be the NOTES surgeons of the future.

The NOTES surgeon should be expert in flexible endoscopy, abdominal anatomy, and surgical technique. He or she should be facile in managing the pre- and postoperative care of the patients and, in particular, should be capable of handling complications from the procedure. Many would argue that NOTES surgeons should be able to perform an operation laparoscopically and conventionally, as conversion to one of these modalities is a possibility in any NOTES procedure.

Those qualifications transcend the boundaries of most general surgery and gastrointestinal endoscopy teaching programs; hence, a new training model will likely be adopted. A gastrointestinal surgeon wishing to practice NOTES will likely pursue fellowship training in advanced endoscopy. A gastroenterologist might complete a year of advanced interventional endoscopy and possibly an additional year dedicated to NOTES. Trainees from both the fields of surgery and gastroenterology should dedicate a substantial amount of time to laboratory endeavors, as this is where skills can be safely honed before clinical application.

By necessity, training for a future in NOTES surgery will be different for surgeons and gastroenterologists. A gastrointestinal surgeon will likely focus on the technical aspects of flexible endoscopy, and a gastroenterologist might need familiarization with gross abdominal anatomy and laparoscopy.

Neither surgeons nor gastroenterologists should consider NOTES an infringement on their territory or the demise of traditional surgery or endoscopy. In the near term, NOTES will be practiced by only a small proportion of surgeons and gastroenterologists with a limited number of indications. Most cases will likely be performed at specialized tertiary centers with expertise in the field, and gastrointestinal surgery and endoscopy will remain largely unchanged by NOTES.

The Future of NOTES

While it is improbable that we are on the brink of widespread pure clinical NOTES, there are many potential applications of NOTES that will likely manifest. Given the portability of NOTES equipment and the requirement for only conscious sedation, natural orifice surgery is ideally suited for the intensive care unit. There are two potential scenarios that have been described that are amenable to ICU NOTES: diaphragm pacing and peritoneoscopic examination for ischemic bowel.

Diaphragm pacing has been shown to be effective in promoting ventilator weaning in a wide variety of clinical situations.[38] The procedure is commonly performed laparoscopically in the operating room with insertion of pacing wires into both hemidiaphragms and externalization of the wires. The procedure of insertion could be performed through a gastrotomy. Performing a NOTES placement of diaphragm pacing wires in the ICU might obviate the need to transport a critically ill patient to the operating room.

Another ICU scenario amenable to NOTES is the question of necrotic small bowel in cases of potential mesenteric ischemia.[39] These types of patients are usually critically ill and cannot tolerate a trip to the comuted tomography (CT) scanner. The presence of ischemic small bowel might be confirmed with transgastric peritoneoscopy. Should a short segment of ischemic small bowel be visualized, the patient could be triaged to the operating room. Extensive small bowel necrosis might not be suitable for an operation, and the costs associated with a nontherapeutic laparotomy would be spared.

The minimal equipment requirements and the need for high-level disinfection, rather than sterilization, make NOTES appropriate for developing regions of the world. NOTES could be performed without the infrastructure requirements of an operating room and sterilization equipment. The light source, video processor, and monitor could be easily transported from region to region to best serve populations in need. NOTES might be the means to bring surgical care to underserved peoples.

The transportable nature of NOTES might be applicable for battlefield abdominal exploration. A far-forward facility could be arranged to explore the abdomen after serious blunt trauma. Hemostasis might be achieved with topical hemostatics or endoscopically placed packing. Once stabilized, the patient could then be transported to a higher echelon of care for definitive management.

Even if pure NOTES does not reach clinical fruition, there are many offshoots from NOTES technology that will likely be applicable to gastrointestinal surgery and endoscopy. The need for improved endoscopic instrumentation has been identified through NOTES research. Endoscopic scissors, graspers, and sewing devices developed for

NOTES might be useful in performing endoscopic mucosal resections or even full-thickness resections and closure of inadvertent perforations.

Another possible derivative of NOTES is single port laparoscopy. As an example, a cholecystectomy might be performed through a single 10-mm umbilical port. A flexible laparoscope could be maneuvered into position and locked into place. Novel triangulating instruments with multiple degrees of freedom could then be used for the dissection. Specimen removal would then occur through the single umbilical port.

Critiques

It is tempting to be swept up in the enthusiasm for NOTES, but hard data supporting the clinical applications of NOTES need to be accumulated before widespread enactment. NOSCAR posed the germane questions regarding the safety and utility of NOTES in the White Paper, and some of the answers are manifesting.

The infectious implications of transvisceral surgery may not be as detrimental as originally presumed. Certainly, bacteria will gain access to the abdominal cavity, but the peritoneum may be efficient at clearing the microbes. After all, the bariatric surgeon is not overly concerned about the gastrotomy contaminating the peritoneal cavity during construction of the proximal anastomosis. Whereas a temporary open gastrotomy is likely not harmful, peritoneal soilage from a leaking closure may be devastating. Therefore, a substantial amount of effort should be devoted to assuring a reliable method of viscerotomy closure.

Other laboratory work substantiates optimism regarding NOTES. Evidence is accumulating that the immune impact of NOTES is equivalent to laparoscopy. Some groups are developing ingenious methods of intraabdominal retraction and dissection. Novel methods of transgastric access might simplify the issue of reliable closure. In aggregrate, these data might be a further evidence that there is a role for NOTES in gastrointestinal surgery.

However, an overly sanguine view of NOTES is unrealistic. Besides the prototypes used in the laboratory, most currently available equipment is inadequate for performing retraction, meticulous dissection, and bimanual manipulations. Importantly, there is no reliable, simple, and safe method for achieving full-thickness, water-tight closure of the viscerotomy. NOTES will remain constrained until better instruments are developed.

Many consider NOTES a technology without an application. At present, this is generally true. Routine NOTES cholecystectomies or appendectomies (i.e., those not under the aegis of an approved clinical trial) should probably not be performed until laboratory and technical advances materialize. Contrarily, there are likely a limited number of applications that are well-suited to the current iteration of NOTES. PEG rescue is a simple procedure that relies on available equipment and could have a role in patients with early dislodgement of a PEG tube.

NOTES does not signal the demise of traditional gastrointestinal surgery or laparoscopy. It is plainly evident that extraordinary advances are required before NOTES can be considered for widespread application. Rather than succumbing to the fervor for NOTES, we must take a circumspect view of NOTES. Diligent laboratory research is imperative, followed by cogent clinical trials.

Above all, regard for patient safety must prevail. Only those with vast laboratory experience with NOTES should contemplate clinical NOTES procedures. Initially, only patients enrolled in clinical trials should undergo NOTES. Finally, the burden is on NOTES investigators to perform due diligence on this nascent field and ensure that we are doing the right thing for our patients.

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Synchronous Adenocarcinoma of the Major and Minor Duodenal Papilla

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Abstract A 50-year-old woman presented with pancreatitis, fluctuant jaundice, weight loss, and abdominal pain. Contrast-enhanced computed tomography and abdominal ultrasound showed slight dilatation of the biliary tree and gallbladder without calculi. Endoscopy demonstrated a tumor protruding from the papilla of Vater. First endoscopically biopsy diagnosed no tumor, and a second biopsy diagnosed as papillary adenocarcinoma. The patient underwent duodenopancreatectomy. The specimen was fixed in formalin (10%). The tissue was processed routinely, and paraffin sections were stained with hematoxylin–eosin and periodic acid Schiff. Gross examination showed two tumors seen as prolapsed nodules growing isolated from the minor and major duodenal papillae measuring 1.5 and 1.0 cm, respectively, both covered by duodenal mucosa and the histologic study of both lesions demonstrated a moderately differentiated tubular adenocarcinoma, which invaded duodenal wall. After surgery, she is alive 24 months without evidence of recurrence.

Keywords Adenocarcinoma · Duodenal papilla · Synchronous tumor · Pancreaticoduodenectomy

Periampullary cancers can be broadly considered as those tumors arising out of or within 1 cm of the ampulla of Vater and include ampullary, pancreatic, bile duct, and duodenal cancer.[1,2]

Adenocarcinoma of the duodenal papilla is a relatively uncommon tumor, as it accounts for less than 1% of all gastrointestinal malignancies. However, it remains the second most common periampullary malignancy and has the best prognosis with a high resectability rate, with 5-year survival rates after resection between 30 and 60%.[3–5]

The duodenal major papilla is the joint opening of the common bile duct and main pancreatic duct into the duodenum and is composed of the bile duct, main pancreatic duct, pancreatic tissue of the ventral pancreas, and surrounding fibrous connective tissue, and the duodenal minor papilla is the opening of the accessory pancreatic duct into the duodenum and is composed of the accessory pancreatic duct, pancreatic tissue of the dorsal pancreas, and surrounding fibrous connective tissue.[6]

Synchronous carcinoids of the major and minor duodenal papilla have been rarely described.[7] Primary adenocarcinoma of the duodenal minor papilla has also been reported once.[8] Synchronous adenocarcinoma of the major and minor duodenal papilla has never been previously reported.

We describe herein a case of synchronous adenocarcinoma of the major and minor duodenal papilla. A 50-year-old woman presented with a past history of pancreatitis, episode fluctuating jaundice, and abdominal pain. Contrast-enhanced computed tomography and abdominal ultrasound showed slight dilatation of the biliary tree and gallbladder without biliary stones. Upper gastrointestinal endoscopy showed a tumor protruding from the major papilla. The initial endoscopic biopsy was negative for adenocarcinoma

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and showed only an inflammatory process. A second biopsy revealed a moderately differentiated duodenal papilla adenocarcinoma. At this time, there was no description of minor papilla by the endoscopist.

The patient underwent a pylorus-preserving pancreaticoduodenectomy. The macroscopic examination of the surgical specimen revealed a 1.5-cm tumor at the major papillary region and another tumor, with 1.0 cm, at the minor papillary region. The specimen was fixed in 10% formalin. The tissue was processed routinely, and paraffin sections were stained with hematoxylin–eosin and periodic acid Schiff.

Gross pathology examination showed two completely separated tumors seen as prolapsed nodules growing from the minor and major duodenal papilla measuring 1.5 and 1.0 cm, respectively (Fig. 1).

The histologic study of both lesions demonstrated a moderately differentiated tubular adenocarcinoma that invaded duodenal wall. Both tumors consisted of simple or branching glands and papillary formations surrounded by a desmoplastic stroma. The cuboidal to columnar cells of the pancreatobiliary type were generally arranged in a single layer and showed moderated pleomorphism (Fig. 2). Focal intestinal-type cells were present. Perineural invasion was extensively present, but vascular or lymphatic invasion was not detected. Necrosis was not present. There were no lymph node metastases. The final pathological tumor stage was pT2 pN0 pMx.

After an uneventful postoperative recovery, the patient was discharged on postoperative day 9. She did not receive postoperative chemotherapy and is alive after 24 months of follow-up without evidence of recurrence. A colonoscopy performed in the postoperative period did not show poliposis.

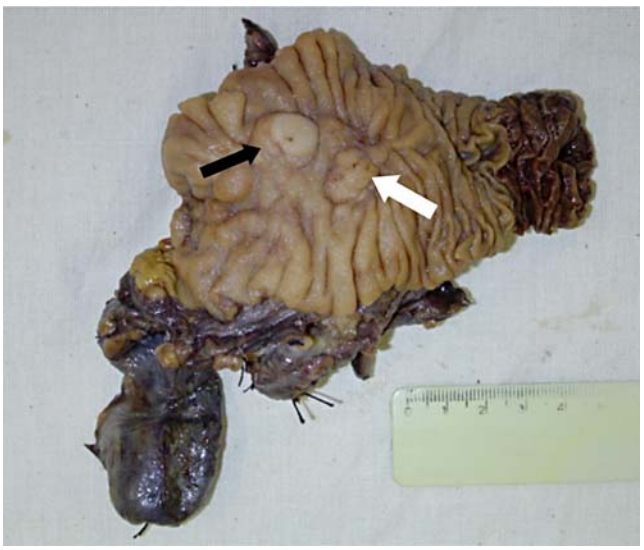

Figure 1 Prolapsed nodules growing isolated from the major (*black arrow*) and minor (*white arrow*) duodenal papilla measuring 1.5 and 1.0 cm, respectively, both covered by duodenal mucosa.

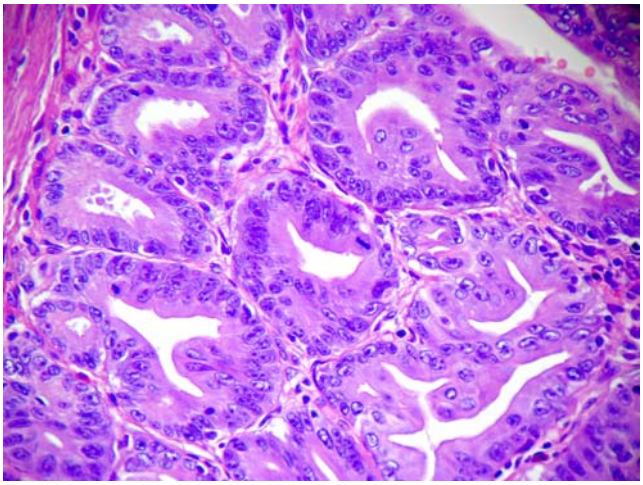

Figure 2 Microscopically both tumors consisted of simple or branching glands and papillary formations surrounded by a desmoplastic stroma.

Discussion

Besides previous descriptions of synchronous carcinoids of the major and minor duodenal papilla and a previous description of primary adenocarcinoma of the duodenal minor papilla, this report is the first of concomitant adenocarcinoma of the major and minor papilla.[7,8]

This patient presented with a chief complaint of epigastric pain with a high amylase level. The histologic diagnosis of tumors originating at the duodenal papilla can be difficult because of a low positive finding in papilla biopsies, resulting in misdiagnosis. In this case, the biopsy was negative in the first endoscopy, and the patient was refereed as pancreas divisum associated with abdominal pain.[2,9]

Preoperative diagnosis of carcinoma of the duodenal papilla is useful for taking therapeutic decisions, although the positive rate of endoscopic biopsy is low, and the diagnostic value of the endoscopic appearance seems to be superior to endoscopic biopsy.[2,3,10] The first examination of the second portion of the duodenum described a tumor protruding from the major papilla, and the biopsy was negative for adenocarcinoma, showing the importance of endoscopic description of papilla lesions. Although endoscopic resections of mucosal and submucosal lesions of the major and minor papillae have been reported,[11,12] the histologic diagnosis of an adenocarcinoma is indicative for a pancreaticoduodenectomy, which is the curative treatment with best results, low incidence of recurrence, and high survive rate; surgery should be avoided based only in the patient's clinical conditions.[12,13] The patient underwent R0 pylorus-preserving pancreaticoduodenectomy with an uneventful recovery, did not receive adjuvant chemotherapy, and is alive at present, 24 months after the treatment.

The occurrence of primary adenocarcinoma of the duodenal minor papilla is extremely rare; Yamao et al., who first described primary adenocarcinoma of the duodenal minor papilla, believed that one of the reason for tumors of the minor papilla to be rarely seen is because of poor clinical symptoms; they are detected only in advanced stages, when it is not possible to determinate the origin of the tumor.[8] This hypothesis can be used also to justify the absence of a previous description of synchronized adenocarcinoma of the major and minor papillae, probably the tumor of the minor papillae was an incidental finding and the symptoms are related only to the tumor of major papillae. Other important aspect is the time of the diagnosis; tumors in the advanced stage make the origin identification very difficult.[14,15]

In this case, the tumor was moderately differentiated tubular adenocarcinoma. Cancerous cells continuous from the main tumor replaced the pancreatic duct and accessory pancreatic duct epithelium; microscopic findings showed no invasion of the surface epithelium and no invasion of the lamina propria between both papillas, and these findings assured the synchronicity of both tumors.

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Ciliated Hepatic Foregut Cyst: A Rare Cystic Liver Lesion

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Abstract Ciliated hepatic foregut cysts are an unusual congenital cause of cystic liver lesions. Although most are benign, 4.4% of reported cases have been shown to harbor squamous cell carcinoma. Diagnostic uncertainty or misdiagnosis frequently results in surgical exploration. We present a case of a ciliated hepatic foregut cyst and review this uncommon condition.

Keywords Ciliated hepatic foregut cyst · Cystic · Liver

Introduction

Ciliated hepatic foregut cysts (CHFC) are rare congenital cystic lesions of the liver, which are usually asymptomatic but may present with vague abdominal symptoms. CHFCs are clinically important because of the possibility of malignant transformation[1] and the diagnostic difficulties they pose. We report the details of a patient with a large, symptomatic CHFC.

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Case Report

A 50-year-old woman presented with a 4-month history of right-upper-quadrant pain. The pain fluctuated in severity and was controlled with oral analgesia. There was no associated jaundice, rigors, or weight loss. Apart from minimal right-upper-quadrant tenderness, physical examination was unremarkable. Full blood count, liver, and renal function tests and clotting profile were normal. The CA 19-9 serum level was 27 IU/l (normal 0–37 IU/l). An abdominal ultrasound scan reported a 50-mm-diameter proximal common bile duct with no intrahepatic biliary dilatation or gallstones, suggesting a type-I choledochal cyst. Computed tomography (CT) and magnetic resonance imaging (MRI) confirmed a cystic mass in the porta hepatis (Fig. 1). Included in the differential diagnosis was a type I choledochal cyst, a phrygian cap of the gall bladder, biliary cystadenoma, duplicated gallbladder, or a hydatid cyst.

At laparotomy, an 8-cm isolated cyst was found in segment 5 of the liver overlying the common bile duct and displacing the normal gallbladder from its bed. The common bile duct was macroscopically normal, and intraoperative cholangiography demonstrated a normal intra- and extrahepatic biliary system. The cyst had no communication with the biliary system. A retrograde cholecystectomy was performed and the cyst was excised after aspirating its contents. The cyst contained viscid green fluid yielding histiocytes on cytology and the following chemistry: bilirubin 22 μmol/l (normal 5–19), cholesterol 2.4 mmol/l, and amylase 422 IU/l. The patient made an uneventful postoperative recovery and was discharged on day 4.

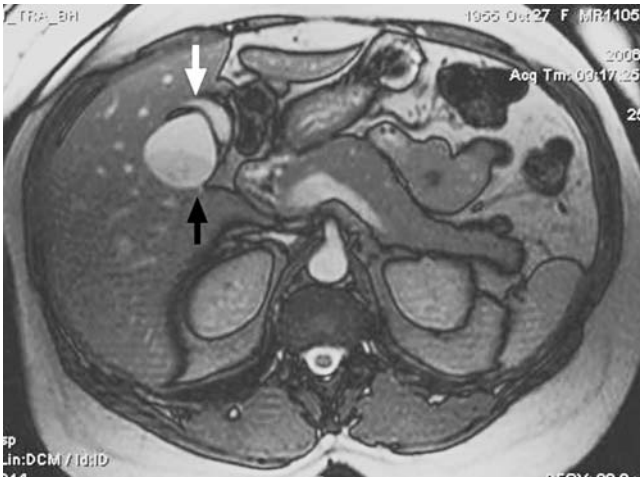

Figure 1 Axial MRI showing CHFC (*black arrow*) containing low-intensity sediment. Note gallbladder anteriorly (*white arrow*).

Histopathologic examination of the surgical specimen confirmed a CHFC with a fibrous cyst wall containing scattered bundles of smooth muscle and lined by pseudostratified ciliated columnar epithelium, reminiscent of bronchial mucosa (Fig. 2). There was no evidence of malignancy.

Discussion

Intrahepatic ciliated foregut cysts are rare, with only 67 cases reported since the first description as a congenital malformation by Friederich in 1857.[2] Most (55) of the cases have been reported in the last 25 years with improvements in imaging techniques. CHFCs are thought to arise from the embryologic foregut, as do bronchial and esophageal cysts but do not contain cartilage.[3] Most cases have been reported in adults and seldom exceed 4 cm in diameter. The average age of presentation is 52 years but ranges from neonates to the ninth decade. Forty percent of the reported cases have been found incidentally on imaging studies, 26% incidentally at autopsy, and 6% incidentally at surgery and 22% presented with abdominal symptoms. CHFCs are most frequently located superficially in the median segments of the liver (segments 4, 5, and 8), are rarely multiloculated or septated, and are mostly asymptomatic.[4] Although, as in our patient, sludge-like bile and viscid mucoid content[5] of the cyst have been described, no communication with the biliary tree has been demonstrated in any reported cases.

The appearances on imaging of CHFCs are variable and may appear as anechoic or hypoechoic liver cysts on ultrasound. The CT findings are of a nonenhancing, rounded liver lesion of varying density depending on the contents of the cyst, which can include calcium crystals and cholesterol.[6] Typical MRI features are a hyperintense cyst on T2-weighted images and a variable appearance on T1-weighted images.[7]

Pathologically, the cysts are typically single and unilocular and have four layers: an outer fibrous rim; a layer of smooth muscle (often incomplete); subepithelial connective tissue; and a lining of ciliated, pseudostratified, mucin-secreting columnar epithelium.[8] The differential diagnosis includes any cystic lesion of the liver but also noncystic lesions if the cysts contain dense fluid or contain malignant change.

The management of CHFC is not well established due to the rarity of the condition. Diagnostic uncertainty or misdiagnosis frequently results in surgical exploration. Of concern are reports of CHFC harboring squamous cell carcinoma (4.4% in reported cases),[1,9,10] as CHFC was previously thought to be a benign condition. This fact may mandate exploration of CHFCs diagnosed preoperatively. There is also a report of portal vein compression secondary to the mass effect of a CHFC.[11]

In conclusion, we report a rare case of a large, 8-cm CHFC. The location in segment 5 of the liver and the absence of biliary communication are features consistent with other case reports. Due to the risk of malignant transformation and

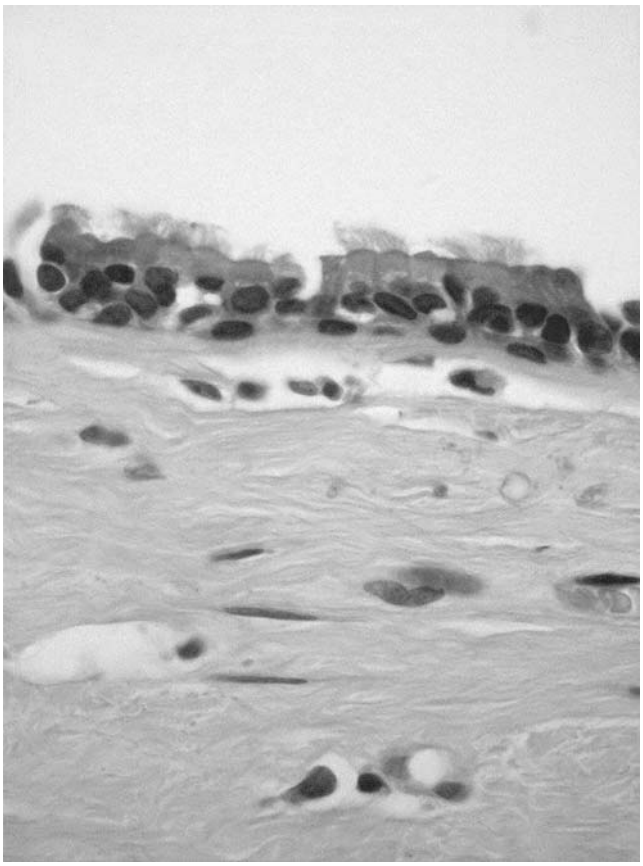

Figure 2 High-power photomicrograph showing ciliated columnar epithelium lining the cyst.

potential confusion with other benign and nonbenign conditions, surgical resection is warranted.

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ERRATUM

Does a 48-Hour Rule Predict Outcomes in Patients with Acute Sigmoid Diverticulitis?

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In the above-mentioned article, published in *Journal of Gastrointestinal Surgery* online via SpringerLink on January 3, 2008 and appearing in Volume 12, Number 3, pages 577–582, six of the seven authors names were inadvertently omitted. The correct list of authors and their affiliations is shown above.

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