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ORIGINAL ARTICLE

Management of Leaks After Laparoscopic Sleeve Gastrectomy in Patients with Obesity

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Abstract
Introduction Laparoscopic sleeve gastrectomy (LSG) is a surgical procedure that is being increasingly performed on obese patients. The most frequent postoperative complication is the appearance of a gastric leak.
Purpose To determine the main clinical features of a group of patients who developed a gastric leak after LSG.
Material A total of 343 obese patients were submitted to LSG, two hundred and sixty-two women and 81 men with a mean age of 37.3 years and a BMI of 37.5 kg/m^2. Radiological evaluations were performed on all patients on the third day after surgery using liquid sulfate barium, as well as a close clinical control evaluation to monitor the appearance of epigastric pain, fever, tachycardia, C-reactive protein, and leukocytosis. Medical or surgical management of the leak were employed.
Results Fever was the earliest and most frequent symptom, followed by epigastric pain and tachycardia. Leaks were classified based on three parameters: severity or magnitude, location, and time of appearance after surgery. Leaks were classified as early if they appeared 1 to 4 days after surgery, intermediate if they appeared 5 to 9 days after surgery, and late 10 days after surgery. The diagnosis of a leak was confirmed with a barium liquid taken orally by six patients and with an abdominal CAT scan in ten. Surgical management was performed in eight patients, usually in those with early leaks (six patients). Early re-suturing in three patients was successful; however, re-suturing leaks after the third day resulted in failure. Medical management was performed mainly in patients with intermediate and late leaks, mainly through enteral nutrition and percutaneous drainage of the intra-abdominal fluid collection. There was no mortality. The mean healing days of these leaks was 45 days after surgery.
Conclusion Close clinical observation detects gastric leaks early on inpatients who underwent LSG. We suggest evaluating these leaks based on three parameters: time of appearance, the location, and its severity, in order to propose the best medical or surgical treatment in these patients.

Keywords Laparoscopic sleeve gastrectomy · Leak

Introduction

Laparoscopic sleeve gastrectomy (LSG) has become a standard and single bariatric procedure for the surgical treatment of patients with different degrees of obesity.[1–8] This procedure may cause three important adverse effects: staple-line bleeding, stricture (usually located at the middle or distal portion of the residual stomach), and stapler line leaks, which cause the greatest morbidity.

The purpose of this prospective study was to determine the main clinical features of patients who presented a gastric leak after a sleeve gastrectomy. The study was carried out on a group of 343 consecutive patients.

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Material and Methods

1. Patients studied: This prospective surgical protocol started on October 2005 when the first LSG was performed. Since that time and up to August 2009, a

total of 343 consecutive obese patients were included in this protocol: 262 women (76.6%) and 81 men (23.4%) with a mean age of 37.3 years (range 14 to 68). The mean body mass index (BMI) was 37.5±4.4 kg/m^2. Exclusion criteria were the presence of severe esophagitis, Barrett's esophagus, or a hiatal hernia over 5 cm in length, as well as the presence of a gastric or duodenal ulcer.

2. Surgical procedure: The details of the surgical technique have been extensively reported in previous publications.[9–11] We start 2–3 cm from the pylorus up to 1 cm from the His' angle using two 4.8-mm green staples and four to five 3.5 mm blue staples, placing a 38-F bougie inside the gastric lumen up the second portion of the duodenum. Reinforcement of the stapler line with Maxon 3-0 or 2-0 was performed in 85% of the patients. In all patients, a methylene blue test was performed to prove the impermeability of the stapler line. A silastic drain was placed on the left side of the gastric suture line in 98% of the patients.
3. Clinical evaluation: In all patients, a careful observation of normal or pathological symptoms and signs was performed during the hospital stay and during the posterior clinical controls. The presence of fever (over 37.5°C), tachycardia (over 100 beats/min), tachypnea (over 20 breathing/min), abdominal pain, distension, vomiting, etc., were carefully recorded. Consecutive laboratory examinations were also performed.
4. Radiological evaluation: In all 343 patients, an upper gastrointestinal radiologic procedure was performed on the third postoperative day (POD), using liquid sulfate barium, not Gastrographin or Hypaque. The anatomical characteristics of the tubular stomach, the mean gastric capacity, the rate of emptying, the presence of strictures, and mainly the presence or absence of leaks were carefully evaluated by the staff members of the Radiology Department.
5. Classification of leaks: We have proposed a classification of the leaks based on three parameters: time of appearance after surgery, magnitude or clinical severity, and location of the leaks.[12–14] Thus, early leaks were classified as those that appeared 1 to 4 days after surgery; intermediate leaks those that appeared 5 to 9 days after surgery, and late leaks those that appeared 10 or more days after surgery. Furthermore, type I or subclinical are those that appear as a localized leak, without spillage or dissemination, with few clinical manifestations and easy to treat medically. Type II leaks are those with dissemination or diffusion into the abdominal or pleural cavity, by way of an irregular pathway, with the appearance of contrast medium (methylene blue, radiological contrast) or food through any of the abdominal drain, with severe clinical consequences. In this study, the exact day of the appearance of symptoms, the diagnosis of the presence of a leak, the medical or surgical treatment, the evolution, and the day of closure were carefully recorded.
6. Statistical analysis: The data reported here are expressed as mean±SD. For statistical evaluation, the Chi-square test was employed, taking a $p < 0.05$ as significant.

Results

Out of 343 patients, three patients (0.9%) had a stricture which required endoscopic dilatation, eight patients (2.3%) developed postoperative bleeding that required reoperation in two of them, and 16 patients (4.66%) developed a gastric leak: They were nine women and seven men, with a mean age of 40±14 years (range 17 to 64). The mean BMI was 35.9±9.7 kg/m^2 (range 32 to 42). Table 1 shows the symptoms, signs, and laboratory examinations which suggest the presence of a gastric leak. Fever was the most frequent clinical finding, followed by abdominal pain (epigastric or left flank) and tachycardia. C-reactive protein was significantly increased in all, as well as leukocytosis. The types of leaks based on the time of appearance after surgery and the exact time when abnormal symptoms or signs appeared are shown in Table 2. Early leaks corresponded to 44% of the patients, with the presence of abdominal pain in the upper portion being the initial symptom, followed by the presence of fever. Patients with intermediate leaks corresponded to 25% of the entire group.

Table 1 Symptoms, Signs, and Laboratory Parameters in Patients with Leaks After Sleeve Gastrectomy

Parameter	Mean±SD	No. of patients with (+) findings
Epigastric pain		11 (68.7%)
Fever> 37.5°	38.08±0.7 (37.6–40.0)	13 (81.2%)
Tachycardia>100–150/min	115±9.6 (100–129)	7 (43.7%)
Leukocytosis>10,000/mm^3	15,775±3,148 (10,600–22,300)	12 (75%)
Left deviation>4%	10.4±5.5 (7–29)	5 (31.2%)
CRP mg/lt>11	268±107 (69–547)	16 (100%)

N=16

CRP C-reactive protein

Table 2 Classification of Leaks Based on the Time of Appearance of the Clinical Findings After the Sleeve Gastrectomy

Type of leaks	Day of diagnosis of leak after surgery	Day of appearance of clinical findings[a]			
		No. of patients	Epigastric pain	Fever	Tachycardia
Early (1–4 days), *N*=7 (43.7%)	2	2	2	0	0
	3	4	1/0/0	2/2/1/3	1/2/1/0
	4	1	4	0	0
Intermediate (5–9 days), *N*=4 (25%)	5	1	4	4	4
	6	2	0/6	5/1	7/0
	7	1	0	7	0
Late (≥10 days), *N*=5 (31.2%)	10	2	6/10	10/8	12/0
	18	1	0	18	0
	20	2	22/23	20/20	0/21

N=16

[a] Each number represents the precise day of appearance of any of the clinical findings in each patient

0 means absence of symptoms or sign

Among them, fever was the most important sign. Late leaks, which appeared between 10 and 20 days after surgery, corresponded to 31% of the cases, with the presence of fever being the most constant clinical finding. When analyzing the entire group, it can be seen that fever was the most frequent early clinical abnormal finding (present in seven patients from the first to the fifth postoperative day) even before the confirmation of the presence of a leak through radiological techniques.

Table 3 shows the method of diagnosis of the presence of a leak. Since our routine protocol is to perform a contrast study on the third postoperative day, this examination was diagnostic in all six patients in whom early leaks developed. We had no special difficulty with spilled intra-abdominal Barium. However, in the other ten patients, the study was normal because the leaks developed later on. However, it is an excellent document showing that on the third POD, anatomy of the tubular stomach was normal. Therefore, the diagnosis was confirmed in all ten patients using a computed axial tomography that indicated the presence of extravasation of the swallowed liquid contrast, air bubbles around the sutures, and different volumes of liquid collections.

The precise location of the leak at the stapler line corresponded in 14 patients (87.5%) to the upper portion of the gastric resection, near the His' angle, and in two patients (12.5%) to the lower portion of the remnant gastric tube. In five patients, the leak corresponded to type I or subclinical (31.2%) and in 11 patients (68.8%) to type II or clinical. The five type I leaks corresponded to patients with late leaks, in whom radiological examination showed the presence of a localized minimal leak which was medically managed either by enteral or parenteral nutrition or with the re-installation of a drainage tube. These patients demon-

Table 3 Method of Diagnosis of Leak Presence After a Sleeve Gastrectomy

Type of leak	Time of diagnosis POD	No. of patients	Radiological method
Early (1–4 days), *N* = 7	2	2	Barium swallow (+) in all
	3	4	Barium swallow (+) in all
	4	1	Barium swallow normal
			Abdominal scanner (+)
Intermediate (5–9 days), *N*= 4	5	1	Barium swallow normal in all at third day after surgery
	6	2	
	7	1	Abdominal scanner (+) in all
Late (≥10 days), *N*=5	10	2	Barium swallow normal in all at third day after surgery
	18	1	
	20	2	Abdominal scanner (+) in all

POD=postoperative day

Table 4 Surgical Management of Patients with Post Sleeve Gastrectomy Leaks

Day of diagnosis leak (POD)	Days of reoperation after surgery	Type of surgical method	Results
3-6-10	3-8-12	Exploration Cleaning Drains	Satisfactory
2-2-3	2-2-3	Exploration Cleaning Re-suture Drains	Satisfactory
3-4	3-4	Exploration Cleaning Re-suture Drain	Failure of re-suture, prosthesis in 1 case

N=8, mean 4.6, mortality 0

POD postoperative day

strated complete healing of the leak at a mean of 38.4± 23 days after surgery. The patients with type II leaks corresponded to patients with early or intermediate leaks, in whom important clinical findings were present, requiring aggressive medical or surgical treatment. These patients showed complete healing of the leak at a mean of 50.1± 25 days after surgery, which was significantly longer than type I patients ($p<0.01$). The surgical management of patients was performed in eight patients (Table. 4). They corresponded to six patients with early leaks, one patient with an intermediate leak, and one patient with a late leak. In three of the patients with the earliest diagnosis of a leak (2 to 3 days after surgery), re-suturing and drainage resulted in a satisfactory postoperative course. However, the same procedure in two other patients resulted in a reopening of the leak that was managed with drains in addition to enteral nutrition. In three other patients, only abdominal lavage and placement of drains were performed resulting in a satisfactory clinical course. Eight patients were medically managed; three of them had intermediate leaks, one an early leak, and four patients late leaks. Medical treatment consisted of enteral nutrition using a nasojejunal tube placed endoscopically, antibiotics, and drains placed percutaneously with the help of a CAT scan. There was no mortality in the entire group of patients (Table 5). Endoscopic placement of prosthesis was performed in one patient with no significant improvement. The mean healing time or definitive closure of the leak occurred 43.6±23 days after medical treatment and at 48.0±25 days ($p>0.3$) after surgical treatment.

Discussion

The results of the present study suggest that gastric staple-line leaks are the most frequent adverse effect seen after a laparoscopic sleeve gastrectomy. This bariatric procedure has been increasingly employed among surgeons dedicated to obesity. It has some advantages over a laparoscopic gastric bypass such as maintenance of gastrointestinal tract continuity and less adverse metabolic effects, and it is easier to perform using a laparoscopic approach. The three most important complications are bleeding of the staple-line in nearly 2%, stricture of the mid portion of the tubular stomach (1%), and gastric leaks in a proportion reported by different authors that varies from 0.7% to 5%.[3–8,11,15,16] We have previously reported an incidence of 3.3% in 214 patients.[11] In the present study, we have already operated on 343 patients with leaks appearing in 4.7% of them. The appearance of a leak represents a serious alteration of the normal healing process. These leaks may occur as a staple-line dehiscence or when there is the presence of local ischemia near the stapler line due to the use of electrocautery or other coagulating devices. In our vast experience in upper gastrointestinal surgery, we have rarely seen a dehiscence of the stapler line, especially after using

Table 5 Medical Management of Leaks after Sleeve Gastrectomy

Day of leak diagnosis after surgery	No. of patients	Management
3-10	2	Total parenteral nutrition plus antibiotics
20	1	Parenteral and enteral nutrition
5-6-7-18-21	5	Enteral nutrition plus percutaneous drainage

N=8

EndoGIA, which has three lines of staplers. We believe that local ischemia due to heat is the major cause of this complication. Besides, simultaneous higher intraluminal pressure during the early postoperative period[17] contributes to the occurrence of a leak.

Our leak incidence may be considered high when compared to other reports of 0.7%, 0.8%, 1.5%[3,4,15] occurring either 118 in 148 patients. We believe that there are several reasons to explain our leak rate. We are a postgraduate teaching center, where the majority of the operations are performed by residents who are always assisted by staff surgeons. We routinely perform radiological contrast studies in every patient on the third day after surgery with Barium sulfate that has a much greater possibility of detecting small leaks which are not seen using a liquid contrast. In fact, 31% of our leaks corresponded to type I, which have not been mentioned by other authors. Furthermore, we perform a thorough follow-up of each patient using clinical and laboratory parameters, and our patients remain hospitalized for at least 4 days after surgery. It is a common practice among North American surgeons to discharge patients on the first or second day after surgery, after having performed a radiological study with liquid contrast (Gastrographin). This study is usually carried out on the first postoperative day, a time when no leaks are seen. Therefore, this routine examination is absolutely misleading, giving a false impression that the surgical procedure was performed correctly. On the second day after surgery, only two patients (12.5%) out of the group of 16 who developed a gastric leak manifested this complication, as can be seen in Table 3. In the six patients presenting a leak 2 or 3 days after surgery, barium contrast studies confirmed the presence of a leak in 100%, as can be seen, according to our results, a contrast study performed in the first or second days after surgery, would detect a leak only in a very small proportion of patients.

In the other ten patients, this study was normal because the leaks occurred later on. We routinely perform laboratory examinations on the first, third, and fifth day after surgery, evaluating the white cell count and C-reactive protein, as described for patients submitted to gastric bypass.[18]

The crucial aspects of a gastric leak are its early diagnosis and prompt treatment. We have learned that close clinical observation of a patient several times a day may help to detect an early complication, before systemic repercussion and the appearance of organ failure, resulting in death. Tables 2 and 3 show that the presence of unexplained fever on the second postoperative day in addition to tachycardia over 100 beats/mm is an alert of possible complications, and the surgeon should proceed to perform radiological studies to confirm or to discard the presence of a leak. We have also observed that the clinical findings of tachycardia over 120 beats/min and respiratory distress proposed by Hamilton et al.[19] represent severe systemic compromise. We believe that the leak classification proposed by us is useful for clinical management because it combines three important aspects: the day of leak appearance, its location and its severity. The careful evaluation of these three parameters could allow taking correct surgical decisions. It is not the same to detect a small localized type I leak than a diffuse, severe type II. The majority of authors usually are confined to the analysis of type II leaks because type I is difficult to diagnose using a liquid contrast medium such as gastrographin. The question whether we would apply selectively postoperative constant studies given our increasing experience is difficult to answer. For decades, it has been our policy to perform these studies in every patient submitted to esophageal or gastric surgery. Up to know, our results have been management with our policy. In the special case of patients with a sleeve gastrectomy, most patients with a postoperative leak (nearly 90%) present this complication located in the proximal upper third of the tubular stomach, near the His' angle, in contrast to patients with a gastric bypass, in whom there are five different potential locations of a leak.[13,14] Finally, the time of appearance and diagnosis of a leak is crucial for medical or surgical management. We strongly believe that it is very important to state clearly in each report if the leak is early, intermediate, or late, in order to define it and to compare the results of medical or surgical management. It is not correct to mix all leaks in one group and postulate a unique approach. As can be seen in Table 4, patients who present early leaks need a prompt surgical approach, as occurred in six out of seven patients. On the contrary, patients with intermediate leaks are managed in the majority of cases through medical treatment (three out of four), as well as patients with late leaks (four out of five). Medical treatment implies adequate nutrition, preferably using an enteral route with a nasojejunal tube, the administration of antibiotics, and the adequate and complete drainage of the fluid or infected collection surrounding the leak through percutaneous drainage guided by CAT scan. On the contrary, optimal surgical treatment is difficult to propose, because local and systemic conditions in each patient differ. Based on our modest experience, we have seen that re-suturing the orifice of the gastric leak, early after surgery and before the third POD, may result in prompt healing and recovery. After the third POD, tissues are severely inflamed and infected, and re-suturing results in complete failure. In these cases, complete and intense abdominal lavage with saline, the correct placement of drains, and the intraoperative placement of a nasojejunal feeding tube result in a favorable clinical evolution.

We have never performed a jejunostomy in order to avoid an extra intra-abdominal suture in these patients,

avoiding the eventual occurrence of a leak at the location of the jejunostomy. In our experience, in a great number of patients, the use of a nasojejunal tube has been very useful. The healing time of a gastric leak after a sleeve gastrectomy is significantly longer than the healing time of a leak after a gastric bypass (45 vs. 30 days, respectively). We have no clear explanation for this peculiar finding. However, we could postulate two probable factors, among several reasons: The first is that after a gastric bypass, the only fluid that is collected through the drain is saliva, because gastric juice is nil in the gastric pouch and no reflux of intestinal content is present due to a long Roux-en-Y limb. On the contrary, in patients with a sleeve gastrectomy, in addition to the presence of saliva, there is residual gastric acid secretion and eventual reflux of duodenal content through an open pylorus. Secondly, an increased intraluminal pressure has been described after SG[17] that could contribute to the development of a leak, which is not present in gastric bypass.

How can a leak be prevented? It is obvious that general surgical principles such as the careful selection of patients, the experience of the surgeon, gentle handling of tissues, adequate selection of surgical techniques, and avoidance of stricture at the mid or distal portion of the tubular stomach are very important details. We are convinced also that careful management of electrocautery and vessel sealing systems is essential, because we strongly believe that thermal damage is one of the most important pathogenetic factors. We routinely perform the methylene blue test at the end of surgery with negative results in all cases. However, this maneuver only demonstrates that the surgical technique was adequate at that time, but it does not prevent the appearance of a leak. Suture and reinforcement of staple line has been advocated, but in the majority of our patients, this surgical step was performed, and in spite of it, leaks developed after surgery. Therefore, we insist in close clinical observations and the early detection of a leak for its proper management.

In conclusion, we propose to define precisely three main characteristics of a leak, in order to proceed to a correct medical or surgical management: time of appearance of a leak after surgery, its location, and its severity or magnitude. It is ethically impossible to perform randomized studies in these patients. Therefore, the description of broader experiences concerning its management may help other surgical groups to choose the proper management in each individual patient with a gastric leak.

References

1. Baltasar A, Serra C, Perez N, et al. Laparoscopic sleeve gastrectomy; a multi-purpose bariatric operation. Obes Surg. 2005;15:1124–8.
2. Baltasar A, Bou R, Bengochea M, et al. Mil operaciones bariátricas. Cir Esp. 2006;79:349–55.
3. Han SM, Kim WW, Oh J. Results of laparoscopic sleeve gastrectomy at 1 year in morbidly obese Korean patients. Obes Surg. 2005;15:1469–75.
4. Hamoui N, Anthone GJ, Kaufman HS, et al. Sleeve gastrectomy in the high-risk patient. Obes Surg. 2006;16:1445–9.
5. Roa PE, Kaidar-Person O, Pinto D, et al. Laparoscopic sleeve gastrectomy as treatment for morbid obesity: technique and short-term outcome. Obes Surg. 2006;16:1323–6
6. Melissas J, Koukouraki S, Askoxylakis J, et al. Sleeve gastrectomy—a restrictive procedure? Obes Surg. 2007;17:57–62.
7. Felberbauer FX, Langer F, Shakeri-Manesch S, et al. Laparoscopic sleeve gastrectomy as an isolated bariatric procedure: intermediate-term results from a large series in three Austrian centers. Obes Surg. 2008;18:814–8.
8. Tucker ON, Szomstein S, Rosenthal RJ. Indications for sleeve gastrectomy as a primary procedure for weight loss in the morbidly obese. J Gastrointest Surg. 2008;12:662–7.
9. Braghetto I, Korn O, Valladares H, et al. Laparoscopic sleeve gastrectomy: surgical technique, indications and clinical results. Obes Surg. 2007;17:1442–50.
10. Csendes A., Braghetto I. Sleeve gastrectomy. Surg. Today 2008;38:479.
11. Burgos AM., Braghetto I., Csendes A., Maluenda F., Korn O., Yarmuch J., Gutierrez L. Gastric leak after laparoscopic sleeve gastrectomy for obesity. Obes. Surg. 2009;19:1672-1677.
12. Csendes A, Diaz JC, Burdiles P, et al. Classification and treatment of anastomotic leakage after extended total gastrectomy in gastric carcinoma. Hepatogastroenterology. 1990;37:174–7.
13. Csendes A, Burdiles P, Burgos AM, et al. Conservative management of anastomotic leaks after 557 open gastric bypasses. Obes Surg. 2005;15:1252–6.
14. Csendes A. Conservative management of anastomotic leaks. Obes. Surg. 2006;16:375-6.
15. Cottam D., Qureshi Fg., Mattar SG., et al. Laparoscopic sleeve gastrectomy as an initial weight loss procedure for high risk patients with morbid obesity. Surg. Endosc. 2006;20:859-63.
16. Weiner RA, Weiner S, Pomhoff I, et al. Laparoscoic sleeve gastrectomy—influence of sleeve size and resected gastric volume. Obes Surg. 2007;17:1297–305.
17. Yehoshua RT, Eidelman LA, Stein M, et al. Laparoscopic sleeve gastrectomy—Volume and pressure assessment. Obes Surg. 2008;18:1083–8.
18. Csendes A., Burgos AM., Roizblatt D., Garay C., Bezama P. Inflammatory response measured by body temperature, C-reactive protein and white blood cell count 1,3 and 5 days after laparotómica or laparoscopic gastric bypass surgery. Obes. Surg. 2009;19:890-893.
19. Hamilton EC, Sims TL, Hamilton TT, et al. Clinical predictors of leak after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Surg Endosc. 2003;17:679–84

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ORIGINAL ARTICLE

Quo Vadis STARR? A Prospective Long-Term Follow-Up of Stapled Transanal Rectal Resection for Obstructed Defecation Syndrome

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Abstract
Introduction Functional and clinical long-term outcome after stapled transanal rectal resection (STARR) in patients with an isolated symptomatic rectocele are investigated. Short-term results after 1 year are comparable with the functional outcome even after 5 years. Eighty per cent of the patients were still satisfied. STARR is an alternative procedure to the conventional surgical approaches for patients with an obstructed defecation syndrome and rectocele. Several studies have reported short-term outcome after STARR, but long-term results are still missing. The objective of this study was to evaluate long-term clinical outcome after STARR with a follow-up of 5 years.
Materials and Methods Twenty patients with only an isolated symptomatic rectocele due to obstructed defecation syndrome were subjected to STARR. Functional and clinical outcome was assessed by Outlet Obstruction Syndrome score (OOS score), Wexner score (WS), and Symptome Severity score (SSS score). Data were prospectively collected over 7 years.
Results The perioperative morbidity after STARR accounted for 20% (n = 4). One patient was subjected to reoperation due to perforation, two postoperative bleedings occurred, and one patient developed an increasing local granulomatous reaction at the stapler line. The median follow-up accounted for 66 months (range 60–84). Sixteen patients (80%) were satisfied with the functional outcome. The median OOS, SSS and WS score improved significantly already after 1 year in these patients and remained stable at 5-year follow-up. In contrast, four patients were classified as treatment failures since the OOS score and the SSS score showed no improvement. At 5-year follow-up, these patients remained symptomatic without improvement in OOS and SSS scores.
Conclusions The STARR procedure is an effective operation in isolated symptomatic rectoceles with regard to relief of the obstructed defecation syndrome. The short-term improvement after STARR predicts long-term outcome in obstructed defecation syndrome caused by a rectocele.

Keywords STARR · Long-term results · Rectocele · Obstructed defecation syndrome

Oliver Zehler and Yogesh K. Vashist contributed equally to this work.

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Introduction

Obstructed defecation syndrome (ODS) is common in women suffering from a prolonged and/or incomplete and/or painful evacuation. Quality of life in these patients is severely impaired since they are dependent upon chronic use of enemas and finger insertion into the vagina or anal canal to release evacuation. The symptoms can be caused either by functional or anatomical alterations. Rectocele, intussusception and rectal prolapse are the dominating

anatomic findings. In addition, an association or coincidence with the anterior compartment, enterocele or sigmoidocele is possible. Especially in case of uncoordinated inhibitory muscular pattern as the cause of ODS, surgery is considered unnecessary or even harmful.[1–4] Rectoceles are seen in a high number of asymptomatic patients,[5] hence, only symptomatic rectoceles even combined with intussusception represent true indication for surgery.[6,7]

Patient selection and exhaustion of conservative treatment options are the utmost predictor of operative treatment success in ODS. Surgical approaches for rectocele encompass a vaginal[8,9] or perineal approach[10] to restore the normal anatomy. These procedures are often time-consuming,[11] technically demanding[12,13] and associated with high morbidity and may even worsen the symptoms.[14–16]

Stapled transanal rectal resection (STARR) has been proven as a time-saving and a relatively easy to perform procedure with satisfactory short-term outcome.[17–25] However, STARR can also cause serious perioperative and long-term complications.[26–29]

The aim of this prospective study was to evaluate the long-term clinical outcome after STARR as a treatment option for ODS caused by an isolated and symptomatic rectocele.

Material and Methods

Between 2001 and 2004, 68 patients with symptoms of obstructed defecation were seen. Out of these, 20 patients with an isolated and symptomatic rectocele referred to the Department of General, Visceral and Thoracic Surgery of the University Hospital of Hamburg Eppendorf were considered for the study and entered in a computerized prospective database. Preoperatively, all patients underwent clinical examination, proctoscopy and rectoscopy, dynamic defecography, anorectal manometry and transanal ultrasound. In all women, a gynaecological evaluation was also performed. Patients with large intussusception, rectal prolapse, enterocele, intestinal inertia or more advanced pelvic floor disease due to genital prolapse or cystocele in combination with the diagnosed rectocele were excluded. Other exclusion criteria for this study were a prolonged colon transit time, previous operation at the rectum, severe incontinence or chronic inflammatory bowel disease and intussusception alongside with the existence of a rectocele.

The grade of ODS was assessed using the Outlet Obstruction Syndrome (OOS) score,[30] Symptome Severity score (SSS score)[31,32] and Wexner score (WS).[33]

Selection criteria for surgical treatment were as follows: typical symptoms of ODS with at least OOS score ≥6, e.g. need for digital assistance for defecation, sense of incomplete evacuation, use of enema more than once a week, laxative use and failure of the conservative treatment with biofeedback and dietary modifications over a period of 6 months.

Surgical Procedure

After bowel cleansing and single-shot antibiotic prophylaxis, the operation was performed in general or spinal anaesthesia with the patient in lithothomy position.

Two PPH01 circular staplers were used (Ethicon Endo-Surgery, Norderstedt, Germany). A circular anal dilatator (CAD 33) was gently introduced into the anus. The anoscope (PSA 33) was introduced into the CAD 33, and three half (180°) anterior purse strings with Prolene 2–0 (Ethicon), including prolapsed rectal wall with mucosa, submucosa and rectal muscle wall, were placed at least 5 cm above the dentate line. A thin malleable spatula was inserted through a hole of the CAD 33 to protect the posterior rectal wall during firing.

The opened circular stapler was introduced, and the anvil was placed above the anterior half purse strings whilst keeping the sutures under tension, the stapler device was then closed, fired and gently withdrawn. The posterior circumferential stapled line (so-called bridge) was transected and the mucosal endings were sutured with 3–0 Vicryl (Ethicon). The stapled line was inspected for bleeding and haemostatic stitches were placed, if necessary. Posteriorly, the procedure was performed 3 cm cranial to the anterior stapler line in the same technique with anteriorly placed spatula to avoid circumferential stapling of the wall. Finally, the CAD was removed and a self-releasing haemostatic gauze was placed in the rectum.

The removed rectal wall was sent for routine histopathological examination.

Postoperative Follow-up

The patients were dismissed if there were no signs of local complication and after the first evacuation (median hospital stay 8 days, range 3–22). In the first month after the primary surgery and discharge from the hospital, the patients were routinely physically examined and received a proctoscopy in the outpatient clinic. Follow-up time points were scheduled at 1 and 5 years after the operation. Postoperatively, the clinical results were compared with the symptoms resolution rate according to the OOS score, SSS score and Wexner score used, respectively.

At 1 and 5 years after the STARR procedure, the patients completed the same questionnaire used preoperatively to evaluate changes in evacuation and symptoms. For all patients, the OOS score, SSS score and Wexner score were determined.

The patients' contentment with the STARR procedure was verified using a scale from 1 (totally unsatisfied) to 10 (totally satisfied).

Table 1 Patients who Matched the Selection Criteria and with an Isolated and Symptomatic Rectocele and underwent STARR Operation

Patient characteristics		
Patients	19 female	1 male
Mean age (years)	60.5 (range 45.3–78.6)	
Mean hospital stay (days)	8 (range 3–22)	
Mean duration of ODS preoperatively (years)	9.5±6.5	
Follow up (months)	66±4	
Complications	Rectal perforation	1
	Allergic reaction	1
	Postoperative bleeding	2

Statistical Analysis

The outcome of the patients with ODS was compared using three different scores (OOS, SSS and WS score) preoperatively and after 1 and 5 years with the Wilcoxon signed ranks test (SPSS 13.0). Differences were considered significant at $p<0.05$.

Results

Between January 2001 and March 2004, a total of 68 patients with ODS were treated at the University Medical Centre Hamburg-Eppendorf. Out of these, 20 patients (29.4%) [19 women (95%) and one man (5%)] with a median age of 60.5 years (range 45.5–75.3) matched the selection criteria of an isolated and symptomatic rectocele and underwent STARR operation (Table 1). Among female patients, nine (47%) were multiparous, with a median of two (range 1–3) vaginal deliveries.

All patients underwent preoperative defecography with vaginal contrast in the lateral projection at rest, during and after straining until evacuation of the contrast, except the remaining contrast in the rectocele. The size and shape of the rectocele was classified using the Marti graduation: type 1: digit form rectocele was found in 13 patients (65%); type 2: big sacculation with anterior rectal mucosal prolapse was found in 7 patients (35%); type 3: rectocele associated with an intussusception and/or prolapse of the rectum was considered as an exclusion criterion in this study to generate a homogeneous study population.

All patients had a descent perineum. The descent of anorectal junction was evaluated by the posterior rectal inclination, defined as the angle between the horizontal line passing through the apex of coccyx and the line of the apex of coccyx to the anal junction.

Patients were followed postoperatively for a median of 66.6±4.2 months (range 60–76 months).

Spinal anaesthesia was used in seven and general anaesthesia in 13 patients. Median operating time was 53.5 min (range 45–65), with a median in hospital stay of 8 days (range 3–22).

In two patients, bleeding occurred postoperatively within 48 h and required immediate reoperation. One major complication occurred with a perforation of the anterior rectal wall caused by the inserted spatula, which resulted in a laparotomy with suturing the perforation in the proximal rectum and a derivative ileostomy. After 8 weeks, stoma closure was performed, and the patient had an uneventful course. One patient developed an increasing local granulomatous reaction at the stapler line with prolonged bleeding and was successfully reoperated 4 weeks after the primary surgery by removal the stapler line.

Sixteen patients were totally satisfied with the functional result of the operation and would consent to the STARR procedure if symptoms were the same.

OOS Score

In the present series, a significant improvement ($p<0.001$) of the OOS score decreasing from 8±2.3 to 3±2.7 was seen in the first year. The median improvement of the OOS score remained stable for the next 4 years, reaching 3±2.2 in the fifth year (Table 2).

Four patients (two psychiatric disorder patients; the patient with the rectal wall perforation and one other) have shown no improvement after 5 years, respectively, whereas one of the psychiatric patients has shown a decreasing score rate from 12 to 9 in the first year, but an increasing rate up to 12 again after 5 years. Slightly increasing OOS score rates between year 1 and 5 after the operation was seen in two patients, but the median score rate of all patients was still significant to the preoperative data. One patient did not improve over the whole study period (Fig. 1).

Table 2 Median improvement of OOS, SSS and WS

	Preoperative	After 1 year	After 5 years	Follow-up interval 0–1 year	Follow-up interval 1–5 years
Median OOS	8	3	3	$p<0.001$	$p<0.285$
Median SSS	5	3	3	$p<0.0001$	$p<0.705$
Median WS	4	2	2	$p<0.0001$	$p<0.25$

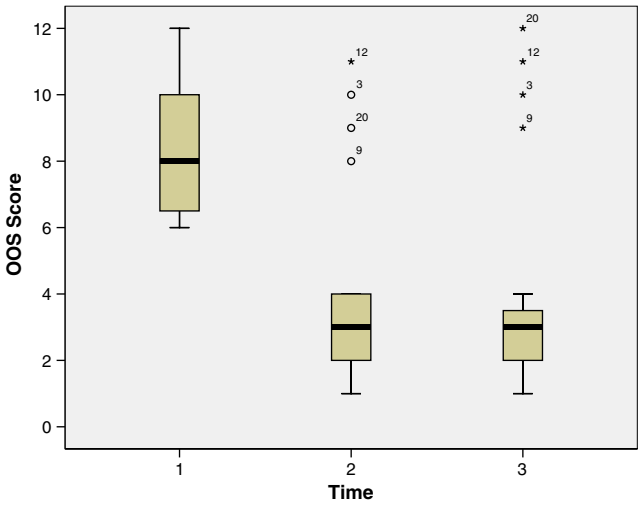

Fig. 1 Box plot showing preoperative and postoperative outlet obstructive syndrome score in all included 20 patients. *Horizontal lines within boxes*, *boxes* and *error bars* represent median, interquartile range (*IQR*) and range respectively, excluding outliers (*asterisk, circle*). Two patients[3,12] have shown no improvement or an increasing rate[9,20] at time points 2 and 3 and were not in the IQR. Time point 1 = (preoperative); Time point 2 = (1 year after STARR procedure); Time point 3 = (5 years after STARR procedure).

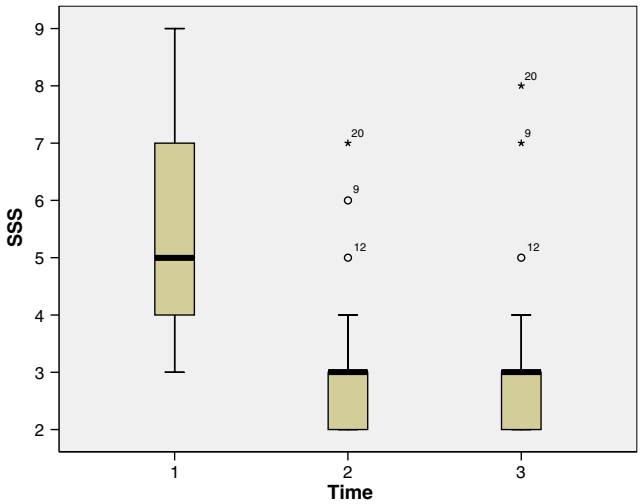

Fig. 2 Box plot showing preoperative and postoperative symptom severity score in all included 20 patients. *Horizontal lines within boxes*, *boxes* and *error bars* represent median, interquartile range (*IQR*) and range, respectively, excluding outliers (*asterisk, circle*). Four patients have shown no improvement at time points 2 and 3. Three of them (*asterisk, circle*) were not in the IQR. Time point 1 = (preoperative); Time point 2 = (1 year after STARR procedure); Time point 3 = (5 years after STARR procedure).

SSS Score

The mean SSS score also improved significantly ($p<0.001$) from 5±2.2 preoperatively to 3±1.4 in the first year and remained stable for the next 4 years at 3±1.2 (Table 2).

Sixteen patients had an improvement after 5 years. Two psychiatric patients were still using enemas and considered themselves still constipated. One woman with the highest SSS score could reduce the use of enema after 1 year, but had a slight worsening of her symptoms after 5 years. One patient with the lowest rate preoperatively had no change of bowel frequency rate after 1 and 5 years (Fig. 2).

Wexner Score

Signs of incontinence for solid bowels, loose bowels or flatus, use of sanitary napkin and reduction for social life according to the Wexner score improved also. The STARR procedure reduced the WS from 4±1.2 preoperatively to 2±0.9 in the first year and to 2±1 within 5 years ($p<0.001$; Table 2). Preoperative incontinence problems for loose bowels occurred once a month or even weekly and were decreased by STARR procedure. Nineteen patients had an improvement of their incontinence after the operation. One patient with incontinence for flatus had no alteration of the incontinence symptoms (Fig. 3).

Discussion

The first reports on STARR for the cure of ODS raised not only great interest, and was therefore enthusiastically adopted, but also caused a still ongoing debate about indications and benefit.[6] Different investigators have out-

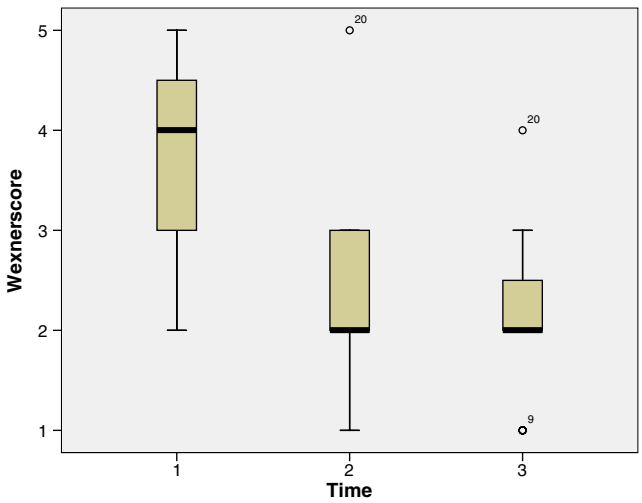

Fig. 3 Box plot showing preoperative and postoperative Wexner score in all included 20 patients. *Horizontal lines within boxes*, *boxes* and *error bars* represent median, interquartile range (*IQR*) and range, respectively, excluding outliers (*circle*). Two patients (*circle*) have shown an improvement at time point 3, but both were not in the IQR. Time point 1 = (preoperative); Time point 2 = (1 year after STARR procedure); Time point 3 = (5 years after STARR procedure).

lined the safe and efficient results of the STARR procedure if the patients with obstructed defecation syndrome are carefully selected. However, follow-up in these studies has been very short so far.[18–20,24,25] As to our knowledge, this is the first prospective study which shows long-term outcome of 5 years after STARR operation with regard to clinical findings.

The first international published results of the STARR procedure originated from the Italian multicenter study have shown impressively that the functional and surgical results in both rectocele and intussusception are excellent within and after 12 months.[18] Equivalent positive results were achieved from other centres.[19–25] In addition, we focused on symptomatic patients which had at least only a rectocele with an OOS score of 6 without a coexisting intussusception. Severe constipated patients or patients with a multifactorial determined obstructed defecation were not enrolled into this study. This may bias and influence the results of this study with its high satisfaction of 80%, but underlines the basic necessity of a careful selection of patients.

The reports about minor and major surgical complications (bleeding, retroperitoneal hematoma, pelvic sepsis, necrotizing pelvis fasciitis, rectovaginal fistulas), unsatisfied functional results (persistence of the obstruction symptoms) or as here described rectal perforation after STARR procedure[26–30] strengthened the still sceptical opinion of colorectal surgeons. Our morbidity rate of 20% is comparable to other studies with up to 40%.[18,34] Postoperative bleeding can be avoided if the stapled line receives haemostatic stitches.[35] Since we implemented these prophylactic stitches at the stapler line, no further postoperative bleeding occurred. The rectal perforation caused by the insertion of the spatula is an avoidable self-critical technical, surgical error, whereas the allergenic, granulamatous reaction at the stapled line remains, even after many clarifying investigations, still uncertain and has not been described before. Other major complications like urge incontinence, pain persistence or urine retention were not seen in our study population.

Boccasanta et al.[18] identified a transient incidence of incontinence for flatus and urge to defecate which disappeared 6 months after the operation. A possible explanation was that the inserted anal dilatator might cause a transient dysfunction of the anal sphincter without irreversible damage. This negative effect on the anal sphincter was not seen in our patients. In contrast, our slightly incontinent patients due to rectocele improved after restoring the anatomy of the rectum.

Therefore, some series had been designed to identify preoperative factors and to create selection criteria for predicting the outcome in this challenging field.[7]

Improvement of symptoms related to the correction of the rectocele was very satisfactory. A way of interpretation that 16 out of 20 patients were satisfied after STARR is that none of these patients suffered from puborectal dyssynergia, lower bowel frequency, rectal inertia, presence of an enterocele, intussusception or rectal prolapse, which is more likely defined as a subset of patients with a more advanced pelvic floor disease. In our study population, the incontinence for loose bowel and flatus, use of sanitary napkins and a reduction of social life could be reduced from weekly to monthly occurrences.

Conclusion

In conclusion, our results demonstrate that STARR is a safe and effective procedure in the surgical treatment of ODS caused by an isolated and symptomatic rectocele and that even after a 5-year follow-up, the results are still promising. Patients with a complete unsuccessful conservative treatment course are possible candidates for an operative treatment.

References

1. Fucini C. Ronchi O, Elbetti C (2001) Electromyography of the pelvic floor musculature in the assessment of obstructed defecation symptoms. Dis Colon Rectum 44: 1168–1175
2. Mellgren A. Bremmer S, Johannson C et al. (1994) Defecography, results of investigation in 2816 patients. Dis Colon Recum 37: 1133–1141
3. Choi JS, Hwang YH, Salum MR et al. (2001) Outcome and management of patients with large recto-anal intussusception. Am J Gastroenterology 96: 740–744
4. Lehur PA, Stuto A, Fantoli M et al. (2008) ODS II Study Group. Outcomes of stapled transanal rectal resection vs. biofeedback for the treatment of outlet obstruction associated with rectal intussusception and rectocele: a multicenter, randomized, controlled trial. Dis Colon Rectum. 51(11):1611–8
5. Shorvon PJ, McHugh S, Diament NE et al. (1989) Defecography in normal volunteers: results and implications. Gut 30(12): 1737–49
6. Schwandner O, Fürst A (2008) Actual Role of Stapled Transanal Rectal Resection (STARR) for obstructed defecation syndrome. Zentralbl Chir. 133(2):116–22. Review. German
7. Jayne DG, Schwandner O, Stuto A (2009) Stapled transanal rectal resection for obstructed defecation syndrome: one-year results of the European STARR Registry. Dis Colon Rectum. 52(7):1205–12; discussion 1212–4.
8. Oliveira J, Pfeifer J, Wexner SD (1996) Physiological and clinical outcome of anterior sphincteroplasty. Br J Surg 83: 502–505
9. Singk H., Cortes E, Reid WM (2003) Evaluation of the fascial technique for surgical repair of isolated posterior vaginal wall prolaps, Obstet Gynecol; 101: 320–324
10. Watson SJ, Loder PB, Halligan S et al. (1996) Transperineal repair of symptomatic rectocele with marlex mesh: a clinical, physiological and radiological assessment of treatment. J Am Coll Surg 183: 257–261
11. Boccasanta P, Rosati R, Venturi M et al (1999) Surgical treatment of complete rectal prolapse: results of abdominal and perineal procedures. J Laparoendosc Adv Surg Tech 9: 235–238

12. Liebermann H, Hughes C, Dippolito A (2000) Evaluation and outcome of the Delorme procedure in the treatment of rectal outlet obstruction. Dis Colon Rectum 43: 188–92
13. Zacharin FR, Hamilton NT (1980) Pulsion Enterocele: long term results of abdominoperineal technique. Obstet Gynecol 2: 141–148
14. Holmstrom B, Broden G, Dolk A (1986) Results of the Ripstein operation in the treatment of rectal prolapse and internal rectal procidentia. Dis Colon Rectum 29: 845–848
15. Bruch HP, Herold A, Schiedeck T et al. (1999) Laparoscopic surgery for rectal prolapse and outlet obstruction. Dis Colon Rectum 42: 34; 1189–1195
16. Orrom WJ, Bartolo DC, Miller R et al. (1991) Rectopexy is ineffective treatment of obstructed defecation. Dis Colon Rectum 34; 41–46
17. Longo A (2003) Obstructed defecation because of rectal pathologies. Novel surgical treatment: stapled transanal rectal resection (STARR). In Acts of the 14th International Colorectal Disease Symposium. Fort Lauderdale, FL.
18. Boccasanta P, Venturi M, Stuto A, et al. (2004) Stapled transanal rectal resection for outlet obstruction. Prospective, multicenter trial. Dis Colon Rectum; 47: 1285–1297
19. Schwandner O, Farke S, Bruch HP (2005) Transanale Stapler Resection des distalen Rectums (STARR) bei Defäkationsobstruktion infolge ventraler Rektocele und rectoanaler Intussuszeption. Viszeralchirurgie, 40; 331–341
20. Ommer A, Albrecht K, Wenger F(2006) Stapled transanal rectal resection (STARR) A new option in the treatment of obstructed defecation syndrome. Langenbeck's Arch Surg; 391: 32–37
21. Petersen S, Hellmich G, Schuster A et al. (2006) Stapled transanal resection under laparoscopic surveillance for rectocele and concomitant enterocele. Dis Colon Rectum, 49, 685–689
22. Jane DG, Finan PJ (2005) Stapled transanal resection for obstructed defaecation and evidence-based practice. Br J Surg; 92: 793–94
23. National Institute for Health and Clinical Excellence: interventional procedure guidance: 169 stapled transanal rectal resection for obstructed defaecation. London: National Institute for Health and Clinical Excellence, 2006. Available at: http://www.nice.org.uk.
24. Sielaff M, Scherer R, Gögler et al. (2006) Die STARR operation. Erfahrungen bei 60 Patienten. Coloproctology 28:217–223
25. Ellis CN (2007) Stapled rectal resection (STARR) for rectocele. J Gastrointest Surg 11:153–154
26. Binda GA, Pescatori M, Romano G (2005) The dark side of double stapled transanal resection. Dis Colon Rectum 47: 1285–1296
27. Dodi G, Pietroletti R, Milito G et al (2003) Bleeding, incontinence, pain constipation after STARR transanal double stapling rectotomy for obstructed defecation. Tech Coloproctol 7; 148–153
28. Pescatori M, Dodi G, Salafia C et al. (2003) Recto-vaginal fistulae after STARR procedure. Int J Colorectal Dis 20:83–85
29. Bassi R, Rademacher J, Savoia A. (2006) Rectovaginal fistula after STARR procedure complicted by haematoma of the posterior vaginal wall : report of a case. Tech Coloproctol; 10: 361–363
30. Agachan F, Chen T, Pfeifer J et al (1996) A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum, 39, 681–685
31. Thompson WG, Irvine EJ, Pare P et al (2002) Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. Dig Dis Sci. 47(1):225–35.
32. Osterberg A, Graf W, Karlbom U et al. (1996). Evaluation of a questionnaire in the assessment of patients with faecal incontinence and constipation,Scand J Gastroenterol. 31(6):575–80.
33. Jorge JM, Wexner SD. (1993) Etiology and management of fecal incontinence. Dis Colon Rectum 36; 77–9
34. Schwandner O, Stuto A, Jayne D et al. (2008) Decision-making algorithm for the STARR procedure in obstructed defecation syndrome: position statement of the group of STARR Pioneers. Surg Innov. 15(2):105–9. Epub 2008 Apr 9.
35. Frascio M, Stabilini C, Ricci B et al. (2008) Stapled transanal rectal resection for outlet obstruction syndrome: results and follow-up. 32(6):1110–5

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ORIGINAL ARTICLE

Node Yield and Node Involvement in Young Colon Cancer Patients: Is There a Difference in Cancer Survival Based on Age?

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Abstract
Background The effect on cancer-specific survival (CSS) from the number of resected nodes (node yield) and the number of nodes involved with colon cancer has not been studied with respect to age.
Patient and Methods Data from 1992 to 2006 from the Surveillance, Epidemiology and End Results (SEER) registry were analyzed for colon cancer patients undergoing curative resection, comparing younger (<40; n=2,642) and older (≥40; n=138,769) patients.
Results The mean number of positive nodes and mean node yield was higher for the younger group. Younger patients were more likely to have metastatic disease and to have a nodal yield of ≥12 nodes, and were less likely to have node-negative colon cancers (all $p<0.0001$). Younger age was associated with a lower risk of death from colon cancer (HR=0.65; $p<0.0001$). No CSS effect was noted with the interaction of age with either node yield or node involvement. Node yield <12 created a higher risk of cancer-specific death (HR=1.22; $p<0.0001$) regardless of stage. KM plots by stage demonstrated a CSS advantage ($p<0.0001$) for younger patients.
Conclusions Younger patients with colon cancers do not have a worse CSS simply because of their young age, so long as proper oncologic surgical principles are adhered to.

Keywords Colon cancer · Age · Young · Survival · Node yield

Introduction

Colorectal cancer is the third leading cancer diagnosis in the USA, with approximately 150,000 cases diagnosed per year in the USA.[1] In its sporadic form, this disease usually occurs in patients older than 50 years of age, which is the age that screening begins for patients considered to be at average risk for developing colorectal cancer. Though colon cancer often occurs in younger patients who have inheritable genetic syndromes that predispose to the early onset of disease, several hospital and population-based studies[2–4] have demonstrated a rising incidence of sporadic colon cancer in younger age groups. It has been observed by some,[5,6] though not all, studies of younger colon cancer patients that this younger group of patients often presents for treatment at later stages of disease. There are several factors that contribute to this trend. In part, the slower presentation of the younger colon cancer patient is due to this population not meeting the standard criteria for screening. Adding to their delay in diagnosis is the common practice of attributing symptoms of colon cancer in young patients as being secondary to a benign process, with the treating physician having a lower suspicion for the diagnosis of colon cancer due to the patient's young age. Since most young colon cancer patients do not present for medical evaluation until the onset of symptoms, they have a

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higher likelihood of being diagnosed at a more advanced stage. Though there is some evidence that younger colon cancer patients have more aggressive cancers[7,8] and a resultant lower survival,[9,10] there is a recognized discrepancy in the literature[11,12] as to whether younger patients with colon cancers have a significant difference in survival when compared with patients of a more traditional age, in spite of the recognized differences between these age groups regarding their stage of disease at the time of their diagnosis.

In addition to the patient's age at diagnosis, the number of lymph nodes retrieved in colon cancer resection specimens has emerged as an important issue, serving as a marker for an adequate oncologic resection,[13] ensuring accurate stage discrimination between node-positive and node-negative cancers,[14,15] and serving as a possible prognostic factor.[16,17] To date, no study has investigated whether the total number of lymph nodes in a colon cancer resection specimen (designated in this paper as node yield) or the number of positive nodes in the resection specimen has a different prognostic significance with respect to cancer-specific survival in younger age groups when compared with the more typical colon cancer patient of an older age.

This study provides a review of a population-based cancer registry in the USA comparing the survival from colon cancer in younger and older age groups, and specifically focuses on the significance of node yield and the number of positive nodes in cancer-specific survival from colon cancer.

Methods

A review of the Surveillance, Epidemiology and End Results (SEER) cancer registry was performed, analyzing data from 1992 to 2006 on all patients with colon cancer. Only patients with a documented age, who underwent a surgical resection for a primary colon adenocarcinoma, who had mesenteric lymph nodes both quantified and examined, and where the reporting source of the data was the hospital where surgery was performed were included in the analysis. Rectal cancer patients were excluded from the analysis, as were patients who received external beam radiation and patients where the exact number of mesenteric nodes examined was unknown. Colon cancer patients were divided into two groups based upon their age at the time of their diagnosis, with one group younger than 40 years of age (n=2,642) and the other group with patients 40 years of age or older (n=138,769). As expected, the two groups had significantly different sizes given the relative rarity of patients developing colon cancer in younger age. Though the younger and older age cohorts were unbalanced in size, the original sample, based on the above-mentioned inclusion and exclusion criteria, was used in the analysis rather than implementing techniques such as propensity score matching as the large sample sizes of both groups provided statistical power, with study results that were strongly statistically significant rather than marginally significant. This allowed the avoidance of sub-setting the study population, which would introduce bias and information loss.

Chi-square tests were conducted to compare differences between the two age groups. Given the skewed distribution of the number of positive nodes, this variable was organized into N_0 (node negative), N_1 (one to three positive nodes), and N_2 (four or more positive nodes) designations corresponding to the AJCC nodal staging system,[18] rather than counting the number of positive nodes individually as a continuous variable. Cox proportional hazards (PH) models for the outcome of cancer-specific death, as defined in this study as death from colon cancer, were estimated using race, gender, cancer stage, age group (<40 or ≥40 years), and the number of lymph nodes involved with cancer as covariates. Additionally, an interaction term between age group and the number of nodes involved with cancer was introduced in the model to assess whether there was a differential effect of lymph node involvement on cancer-specific survival between the two age groups. The historic SEER cancer stage was used, which was chosen as it was consistently defined by the SEER program over the time period studied. This system defines localized disease as being completely confined to the colon, while regional disease includes cancer that has extended into surrounding organs/tissues, lymph nodes, or both. Distant disease represents cancer that involves regions which are remote to the site of origin of the cancer. Patients who did not die, who died of unknown causes, or who died from known causes other than colon cancer were considered censored for survival analysis as they did not experience the outcome of interest, death from colon cancer. This process of censoring has been accounted for in all commonly used statistical methods in survival analysis.

A similar analysis using Cox PH was performed with node yield, defined in this study as the number of mesenteric nodes in the resection specimen regardless of their involvement with cancer. Due to its highly skewed distribution, node yield was analyzed to assess whether having 12 or more nodes examined had an effect on cancer-specific survival, and if so, whether the effect was different between younger and older age groups. Cox PH models were fit with race, gender, cancer stage, age group, and an indicator of less than 12 versus 12 or more mesenteric nodes in the resection specimen as the covariates. An interaction term between age group and the indicator of node yield was introduced to assess whether there was a differential survival effect from node yield between the two age groups.

Cancer stage was highly correlated with nodal staging, and this created a potential problem of collinearity. To account for this, subgroup analyses stratified by cancer stage was also performed. With the exception of excluding cancer stage as a variable, the same covariates were used in

Table 1 Demographic and Oncologic Information for Younger (<40 years) and Older (≥40 years) Colon Cancer Patients

	<40 (n=2,642)	≥40 (n=138,769)
Sex (p<0.0001)		
Male	1,360 (51.4%)	65,785 (47.4%`)
Female	1,282 (48.5%)	72,984 (52.5%)
Race (p<0.0001)		
White	1,880 (71.1%)	113,223 (81.5%)
Black	370 (14.0%)	13,525 (9.7%)
Other	392 (14.8%)	12,021 (8.6%)
SEER historic stage (p<0.0001)		
Localized	740 (28.0%)	53,748 (38.7%)
Regional	1,255 (47.5%)	63,829 (46.0%)
Distant	647 (24.4%)	21,192 (15.2%)
Nodes examined (p<0.0001)		
1–5	267 (10.1%)	27,637(19.9%)
6–11	589 (22.2%)	47,635 (34.3%)
≥12	1,786 (67.6%)	63,497 (45.7%)
Positive node (p<0.0001)		
0	1,207 (45.6%)	83,820 (60.4%)
1–3	741 (28.0%)	33,830 (24.3%)
≥4	694 (26.2%)	21,119 (15.2%)
Cause of death (p<0.0001)		
Alive at last follow-up	1,822 (68.9%)	69,097 (49.7%)
Cancer-specific death	699 (26.4%)	35,314 (25.4%)
Other cause of death	121 (4.5%)	34,358 (24.7%)

Cox PH models for the subgroup analysis as were used for the overall analysis.

Five-year survival rates were estimated by the Kaplan–Meier method and survival by stage was illustrated using Kaplan–Meier plots for both age groups to describe the effect of age on cancer-specific survival by SEER stage.

Results

Demographic Information

Table 1 provides general demographic and oncologic information for both younger and older cancer groups; all differences between the two groups were of statistical significance (p<0.0001). The younger age group had a higher percentage of males and non-white ethnic groups. Younger patients were more likely to be diagnosed with distant metastatic disease (younger, 24.4%; older, 15.2%) and were less likely to be diagnosed with localized disease (younger, 28.0%; older, 38.7%). Additionally, younger patients were more likely to have a node yield of 12 or more nodes (younger, 67.6%; older, 45.7%), were less likely to have node-negative colon cancers (younger, 45.6%; older, 60.4%), and more likely to have N_1 (younger, 28.0%; older, 24.3%) and N_2 disease (younger, 26.2%; older, 15.2%). Younger patients had a higher percentage of overall survival (younger, 68.9%; older, 49.7%), and despite the higher percentage of advanced disease in this group, younger patients had only a slightly higher percentage of death from colon cancer within the younger age group when compared with the proportion of deaths in the older cohort (younger, 26.4%; older, 25.4%).

Effect of Node Involvement on Cancer-Specific Survival Between Age Groups

Table 2 provides a comparison of the number of positive nodes between both age groups. The mean number of positive nodes was 2.6±4.4 for patients <40 years and was 1.6±3.2 for patients ≥40 years (p<0.0001). The distribution of the number of positive lymph nodes in the study population was highly skewed, with the majority of the patients having less than three positive nodes. For those patients with a node yield of <12 nodes, both age groups had a similar number of mean positive nodes (younger, 1.8±2.4; older, 1.06±1.9), a finding which was also observed for those patients with a node yield greater than 12 nodes (younger, 3.0±5; older, 2.2±4.2).

Table 3 provides results for a Cox PH model related to the risk of colon cancer-specific death. Age less than 40 years was associated with a lower risk of death from colon cancer (HR=0.65; CI, 0.61–0.70; p<0.0001) compared with the older age group. A higher risk of cancer-specific death was noted in regional (HR=2.17; CI, 2.09–2.26; p<0.0001) and distant disease (HR=10.38; CI, 9.97–10.81; p<0.0001) compared with SEER localized disease as would be

Table 2 Comparison of Number of Positive Nodes Between Younger and Older Age Groups

No. nodes examined	Age	Samples	Mean	Median	SD	Min	Max
Any number examined	<40	2,642	2.62	1	4.37	0	55
	≥40	138,769	1.56	0	3.22	0	80
<12 examined	<40	856	1.82	1	2.36	0	11
	≥40	75,275	1.06	0	1.91	0	11
≥12 examined	<40	1,786	3.00	1	5.02	0	55
	≥40	63,497	2.16	0	4.21	0	80

Table 3 Cox Proportional Hazard Model for the Effect of Positive Nodes on Cancer-Specific Survival

Variable	Reference group	Hazard ratio	95% CI	*p* value
Age <40	≥40	0.65	0.61, 0.70	<0.0001
Female	Male	1.03	1.01, 1.06	0.0017
Black race	White	1.12	1.08, 1.16	<0.0001
Other race	White	0.83	0.80, 0.86	<0.0001
Regional stage	Localized	2.17	2.09, 2.26	<0.0001
Distant stage	Localized	10.38	9.97, 10.81	<0.0001
1–3 positive nodes	No positive nodes	1.68	1.63, 1.73	<0.0001
≥4 positive nodes	No positive nodes	2.83	2.74, 2.91	<0.0001

expected. When the interaction between age group and node stage was introduced as a covariate in the PH model, the interaction effect was not statistically significant (p=0.20), whereas the previously included covariates in Table 3 continued to be statistically significant to the same degree and with the same direction of effect. The lack of statistical significance of the node stage-age interaction term indicated that there was no difference in how nodal involvement affected younger versus older age groups with respect to cancer-specific survival.

Subgroup analysis stratified by cancer stage was performed to control for the correlation between cancer stage and nodal staging. Since SEER localized disease designates a stage of disease where there is no nodal involvement, subgroup analysis was performed with SEER regional and distant stage with respect to node stage. The interaction term between age group and nodal involvement was not significant (regional stage: p=0.59; distant stage: p=0.97), further substantiating the finding that there was no difference in survival effect from nodal involvement between age groups stratified by SEER stage of disease. Patients younger than 40 years of age had a statistically significant lower risk of death from cancer compared with older patients with both regional disease (HR=1.59; CI, 1.41–1.80; p<0.0001) and distant disease (HR=1.43; CI, 1.30–1.58; p<0.0001).

With regard to race, blacks were noted to have higher risk of death from colon cancer than other races (HR=1.12; CI, 1.08–1.16; p<0.001). Conversely, non-black, non-white races had a lower risk of death compared with white patients (HR=0.83; CI, 0.80–0.86; p<0.001). These trends remained consistent across age groups.

Effect of Node Yield on Oncologic Outcome Between Age Groups

Table 4 provides information on node yield between the age groups. The younger age group had a higher mean node yield (younger, 19.2±14.1; older, 12.7±9.1; p<0.001). Table 5 provides the results of a Cox PH model for the effect of node yield on the risk of death from colon cancer. An analysis of all patients with all stages of disease demonstrated that a node yield of less than 12 nodes was associated with a higher rate of death from colon cancer (HR=1.22; CI, 1.20–1.25; p<0.0001). Factors that also affected cancer-specific survival included age, race, gender, and cancer stage, all of which were statistically significant (see Table 5). When the interaction term for age and node yield was introduced in the Cox PH model which included all patients, it was not statistically significant (p=0.50) with no resultant change to the level of significance of any of the covariates in Table 5.

Patients with a node yield less than 12 were found to have a higher risk of cancer-specific death in subgroup analysis (localized disease: HR=2.65; CI, 1.83–3.86; p<0.0001; regional disease: HR=1.30; CI, 1.15–1.47; p<0.0001; distant disease: HR=1.31; CI, 1.18–1.44; p<0.0001). When the interaction term between age group and node yield was introduced in subgroup analysis, it was not significant for localized (p=0.39), regional (p=0.99), or distant (p=0.26) stage disease, indicating that the effect of node yield did not have a variable survival effect based on the age of the patient stratified by SEER stage of disease.

Kaplan–Meier Estimates by Age

Figures 1, 2, and 3 show the Kaplan–Meier survival plots for patients <40 years of age compared with patients ≥40 years old, stratified for SEER local, regional, and distant stages of disease. Log-rank tests indicated a significant difference in cancer-specific survival curves by age (p<0.0001). The 5-year survival for the younger age group was 97%, 77%, and 22%, for local, regional, and distant disease, respectively, while the older group had corresponding 5-year survival rates of 91%, 70%, and 15%.

Table 4 Comparison of Node Yield Between Younger and Older Age Groups

Age	Samples	Mean	Median	SD	Min	Max
<40	2,642	19.22	16	14.16	1	89
≥40	138,769	12.66	11	9.11	1	89

Table 5 Cox Proportional Hazard Model for the Effect of Node Yield on Cancer-Specific Survival

Variable	Reference group	Hazard ratio	95% CI	*p* value
Age <40	≥40	0.74	0.69, 0.80	<0.0001
Female	Male	1.03	1.01, 1.05	0.0027
Black race	White	1.13	1.09, 1.16	<0.0001
Other race	White	0.86	0.82, 0.89	<0.0001
Regional stage	Localized	3.47	3.36, 3.59	<0.0001
Distant stage	Localized	18.79	18.16, 19.44	<0.0001
<12 nodes examined	≥12 nodes	1.22	1.20, 1.25	<0.0001

Discussion

There is evidence from population-based studies that the incidence of colon cancer in patients 20–40 years of age is increasing.[3] In spite of a general consensus that younger patients tend to present with cancers of a more advanced stage and with more aggressive histological features,[19] the outcome of young colon cancer patients is debated due to contradicting results of equivalent,[20] worse,[3] or even improved[2] survival compared with older patients. Though patient and physician perception may be that younger colon cancer patients have a worse outcome, a comparatively decreased survival even in the setting of advanced disease should not be a foregone conclusion, especially with the general improvement in disease-free and cancer-specific survival seen with metastatic colorectal cancer treated with newer regimens of adjuvant chemotherapy.[21,22] Much of the colon cancer survival data, therefore, requires updating given the development of more effective adjuvant therapy. Conventional opinion that younger patients fare worse than older colon cancer patients has less substantial, empirical support than it does a psychological component in response to the unfortunate situation of a younger person contracting a potentially deadly disease.

To the authors' knowledge, the present study is the first to use a population-based database to specifically investigate whether there is a difference in survival effected by node involvement and node yield between younger and older age groups with colon cancer, though it is not the first study to describe the relationship between node yield and survival in colon cancer in general. An important secondary analysis of the Intergroup Trial INT-0089 data was undertaken by Le Voyer et al.[23] The authors performed a multivariate analysis for both node-positive and node-negative colon cancer patients. For node-positive patients, predictors of overall, disease-free and cause-specific survival included age, T stage, tumor grade and differentiation, the number of positive nodes, and the total number of nodes recovered. When the same covariates were analyzed with respect to node-negative patients, only age and the number

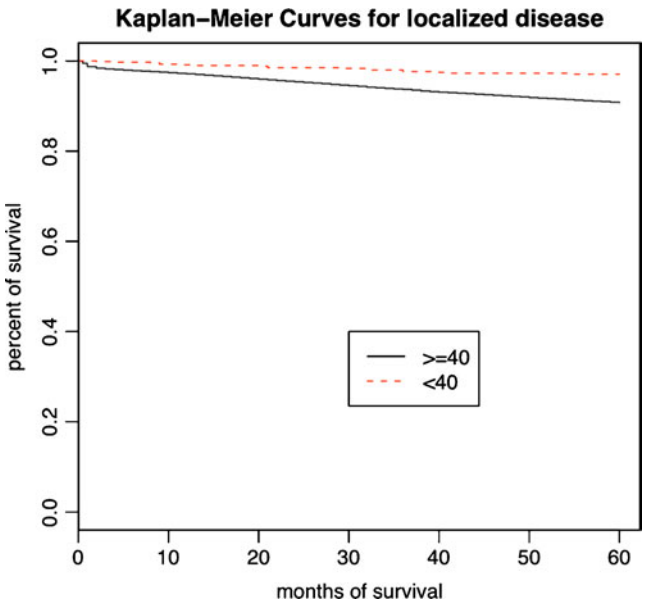

Fig. 1 Kaplan–Meier for SEER localized stage colon cancer-specific survival for younger versus older patients (log rank, $p<0.0001$).

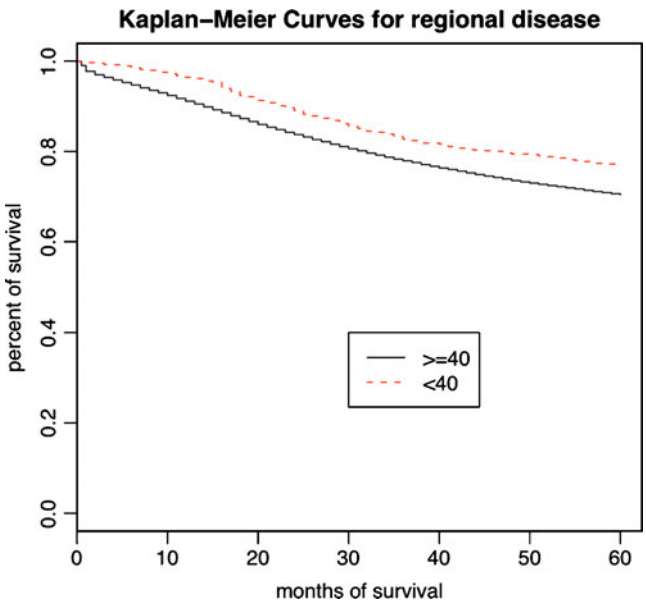

Fig. 2 Kaplan–Meier for SEER regional stage colon cancer-specific survival for younger versus older patients (log rank, $p<0.0001$).

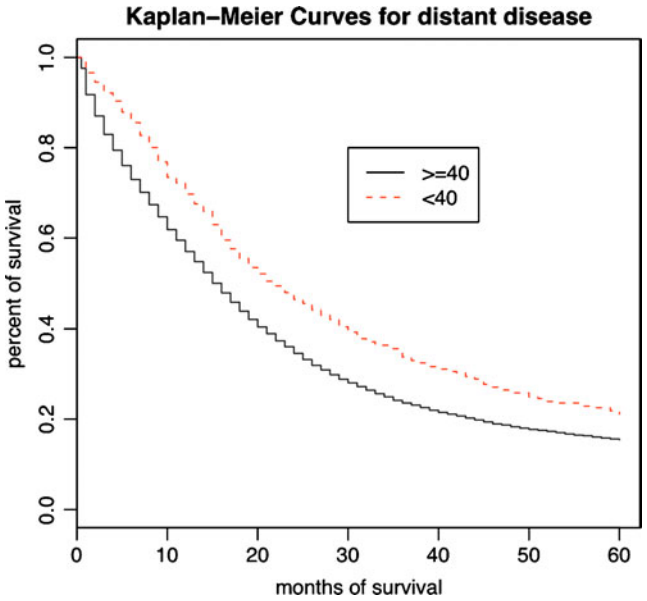

Fig. 3 Kaplan–Meier for SEER regional stage colon cancer-specific survival for younger versus older patients (log rank, $p<0.0001$).

of nodes recovered affected survival. For both node-positive and node-negative patients, the improvement in survival behaved as a continuum depending on the number of nodes removed in the cancer resection specimen, with survival increasing in node-negative patients with the greater number of nodes removed. This study demonstrated that the number of nodes removed and analyzed is a significant variable that affects survival regardless of nodal involvement, and based on this finding, the authors correctly emphasized the importance of the surgeon's experience and training as well as hospital volume in improving oncologic outcomes. As pointed out by the authors, all of the patients in the INT-0089 received chemotherapy, which removes the bias otherwise introduced by a falsely node-negative patient who did not receive the benefit of adjuvant chemotherapy, and thus, the results of this study point to a survival benefit with a complete excision which cannot be dismissed as being due to stage migration alone.

In the present study, there was a statistically significant decrease in the odds of death from colon cancer in younger patients overall and by stage of disease. Death from colon cancer was chosen as a more accurate assessment of oncologic outcome, as opposed to overall survival which younger patients would obviously have an advantage toward. It should be noted that though the proportion of younger patients with more advanced stage disease at diagnosis was greater when compared with the older group, there was only a minimal difference in the mean number of positive nodes between the younger (2.6) and older cohorts (1.6). While this may indicate a similarity in stage distribution between the two age groups, it would also lend to the conclusion that when adjusted for stage, younger patients do not have a worse outcome despite their age at presentation. A greater discrepancy in mean node yield was observed in our data (younger, 19.2; older, 12.7). Though information on fat-clearance techniques were not available in the SEER data, the dissimilarity in node yield would suggest that younger patients undergo more extensive resections on average when compared with older patients. This may be due to the better health of younger patients, who can more readily tolerate larger surgeries, and may also be related to the physician's response to the perceived greater loss of potential years of life with a colon cancer in a younger patient. With a smaller difference in the number of positive nodes, and with a wider divergence between node yields between the age groups, it is possible that younger patients with a more advanced stage of disease can have their higher stage disease compensated for, to some degree, with aggressive surgical resection. Good oncologic surgical technique is associated with other practices that would, in turn, favorably impact on survival, such as the proper selection of patients to undergo surgery, proper selection of patients for genetic testing for inheritable cancer syndromes, the appropriate handling of extended resections with curative intent to leave no visible disease behind, and the proper selection of patients for adjuvant chemotherapy, especially those patients who are node negative but are at a higher risk for recurrence.

The minimum requirement of 12 lymph nodes[24] for an adequate colon cancer surgery has been previously discussed in terms of accurate stage differentiation, ensuring that patients are not undertreated by being misdiagnosed as node-negative patients. This benchmark, as a reflection of the adequacy of surgical resection, is complicated to broadly assess since the node yield of patients can vary with such factors as age, obesity, neoadjuvant chemotherapy or radiation, and the technique of the pathologist,[25–27] all of which are beyond the surgeon's direct control. Node yield is being discussed as a marker for quality with respect to physician reimbursement as well, though interestingly there is still no national standard approach among pathologists for assessing node yield or in deciding when to perform various fat-clearance techniques, which makes comparisons among institutions more difficult and can give the appearance of poor surgical technique. Whether a minimum of 12 nodes is an adequate benchmark of oncologic adequacy is still debated by surgeons and pathologists, though its use as a quality measure will likely continue for the foreseeable future as issues related to quality and cost retain their central positions in discussions of health care. Since node yield may be a prognostic factor even for node-negative patients, the handling of surgical specimens by the pathologist has implications in predicting outcome following curative resection that reaches beyond the number of involved nodes.

Conclusion

The effect of node involvement on colon cancer-specific survival is not significantly affected by the age of the patient undergoing surgery, and the benefit of an adequate oncologic resection as reflected by a minimum of 12 mesenteric lymph nodes is comparable between younger and older patients. Younger patients generally have a greater overall survival, in part reflecting their better health status. In this study, younger colon cancer patients had a higher proportion of colon cancer deaths as a group, though the absolute difference between younger and older age groups was miniscule. In spite of a higher percentage of patients presenting with node-positive and distant metastatic disease, younger colon cancer patients had a statistically significant greater cancer-specific survival than older patients, though the absolute difference was small. Younger patients who develop colon cancers do not have a worse cancer survival simply because of their young age, so long as proper oncologic surgical principles are adhered to.

References

1. American Cancer Society. Cancer facts and figures 2004. http://www.cancer.org/downloads/STT/CAFF_finalPWSecured.pdf. Accessed March 10, 2010.
2. Mitry E, Benhamiche AM, Jouve JL, Clinard F, Finn-Faivre C, Faivre J. Colorectal adenocarcinoma in patients under 45 years of age: comparison with older patients in a well-defined French population. Dis Colon Rectum 2001;44:380–387.
3. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Rates of colon and rectal cancers are increasing in young adults. Am Surg 2003;69:866–872.
4. Heys SD, O'Hanrahan TJ, Brittenden J, Eremin O. Colorectal cancer in young patients: a review of the literature. Eur J Surg Oncol 1994;20:225–231.
5. Minardi AJ, Jr., Sittig KM, Zibari GB, McDonald JC. Colorectal cancer in the young patient. Am Surg 1998;64:849–853.
6. Lee PY, Fletcher WS, Sullivan ES, Vetto JT. Colorectal cancer in young patients: characteristics and outcome. Am Surg 1994;60:607–612.
7. Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg 2003;90:205–214.
8. Chiang JM, Chen MC, Changchien CR, Chen JS, Tang R, Wang JY, Yeh CY, Fan CW, Tsai WS. Favorable influence of age on tumor characteristics of sporadic colorectal adenocarcinoma: patients 30 years of age or younger may be a distinct patient group. Dis Colon Rectum 2003;46:904–910.
9. Smith C, Butler JA. Colorectal cancer in patients younger than 40 years of age. Dis Colon Rectum 1989;32:843–846.
10. Cusack JC, Giacco GG, Cleary K, Davidson BS, Izzo F, Skibber J, Yen J, Curley SA. Survival factors in 186 patients younger than 40 years old with colorectal adenocarcinoma. J Am Coll Surg 1996;183:105–112.
11. Ohman U. Colorectal carcinoma in patients less than 40 years of age. Dis Colon Rectum 1982;25:209–214.
12. Beckman EN, Gathright JB, Ray JE. A potentially brighter prognosis for colon carcinoma in the third and fourth decades. Cancer 1984;54:1478–1481.
13. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, Miedema B, Ota D, Sargent D. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583–596.
14. Sobin LH, Greene FL. TNM classification: clarification of number of regional lymph nodes for pNo. Cancer 2001;92:452.
15. Wong JH, Severino R, Honnebier MB, Tom P, Namiki TS. Number of nodes examined and staging accuracy in colorectal carcinoma. J Clin Oncol 1999;17:2896–2900.
16. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10:65–71.
17. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433–441.
18. Greene H, Page DL, Flemin ID. AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer; 2002.
19. Parramore JB, Wei JP, Yeh KA. Colorectal cancer in patients under forty: presentation and outcome. Am Surg 1998;64:563–567.
20. Quah HM, Joseph R, Schrag D, Shia J, Guillem JG, Paty PB, Temple LK, Wong WD, Weiser MR. Young age influences treatment but not outcome of colon cancer. Ann Surg Oncol 2007;14:2759–2765.
21. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–237.
22. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342.
23. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912–2919.
24. Fielding LP, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, Hermanek P, Jass JR, Newland RC. Clinicopathological staging for colorectal cancer: an International Documentation System (IDS) and an International Comprehensive Anatomical Terminology (ICAT). J Gastroenterol Hepatol 1991;6:325–344.
25. Dworak O. Number and size of lymph nodes and node metastases in rectal carcinomas. Surg Endosc 1989;3:96–99.
26. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005;97:219–225.
27. Gorog D, Nagy P, Peter A, Perner F. Influence of obesity on lymph node recovery from rectal resection specimens. Pathol Oncol Res 2003;9:180–183.

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ORIGINAL ARTICLE

Living Donor and Deceased Donor Liver Transplantation for Autoimmune and Cholestatic Liver Diseases—An Analysis of the UNOS Database

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Abstract
Introduction Autoimmune hepatitis and cholestatic liver diseases have more favorable outcomes after liver transplantation as compared to viral hepatitis and alcoholic liver diseases. However, there are only few reports comparing outcomes of both living donor liver transplants (LDLT) and deceased donor liver transplants (DDLT) for these conditions.
Aim We aim to study the survival outcomes of patients undergoing LT for autoimmune and cholestatic diseases and to identify possible risk factors influencing survival. Survival outcomes for LDLT vs. DDLT are also to be compared for these diseases.
Patients and Methods A retrospective analysis of the UNOS database for patients transplanted between February 2002 until October 2006 for AIH, PSC, and PBC was performed. Survival outcomes for LDLT and DDLT patients were analyzed and factors influencing survival were identified.
Results Among all recipients the estimated patient survival at 1, 3, and 5 years for LDLT was 95.5%, 93.6%,and 92.5% and for DDLT was 90.9%, 86.5%, and 84.9%, respectively (p=0.002). The estimated graft survival at 1, 3, and 5 years for LDLT was 87.9%, 85.4%, and 84.3% and for DDLT 85.9%, 80.3%, and 78.6%, respectively (p=0.123). On multivariate proportional hazard regression analysis after adjusting for age and MELD score, the effect of donor type was not found to be significant.
Conclusion The overall survival outcomes of LDLT were similar to DDLT in our patients with autoimmune and cholestatic liver diseases. It appears from our study that after adjusting for age and MELD score donor type does not significantly affect the outcome.

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Randeep Kashyap participated in research design, writing of the paper, and data analysis. Saman Safadjou participated in research design and data analysis. Rui Chen, Rajeev Sharma, and Vrishali Patil participated in data analysis. Parvez Mantry, Manoj Maloo, Gopal Ramaraju and Benedict Maliakkal participated in research design. Charlotte Ryan participated in the writing of the paper. Carlos Marroquin and Christopher Barry participated in the performance of the research. Mark Orloff participated in research design, writing of the paper, and performance of the research.

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Keywords Liver transplantation · Autoimmune diseases · Survival outcomes

Introduction

Autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC) all progress to end-stage liver disease and share some common etiopathogenesis and natural history. Autoimmune and cholestatic liver diseases have more favorable outcomes after liver transplantation (LT) as compared to hepatitis and alcoholic liver diseases.[1] Based on data reported to the Organ Procurement Transplant Network (OPTN)/UNOS liver transplant registry between 1988 and 2004 on adult transplants, the 5-year graft survival for autoimmune-related diseases, PBC (77.3%), PSC (73.3%), and AIH (74.2%) yielded higher rates than those for hepatitis B (71.5%) and hepatitis C (63.2%).[2] Recently, several retrospective reviews on LT for AIH and other cholestatic liver diseases have emerged from various transplant programs.[3–21] There are no comparisons of the long-term outcome of patients undergoing LT for each of these autoimmune diseases, and no comparative data for living donor liver transplants (LDLT) vs. deceased donor liver transplants (DDLT) for these conditions.

Aim

We aim to study the survival outcomes of patients undergoing LT for autoimmune and cholestatic diseases and to identify possible risk factors influencing survival. Survival outcomes for LDLT vs. DDLT are also to be compared for these diseases.

Patients and Methods

Demographic data of donors and recipients, as well as follow-up transplant data, were obtained from the OPTN/UNOS database, Standard Transplant and Analysis Research file (STAR file). We excluded all patients transplanted before February 2002, multiorgan transplants, non-heart beating donors, donor age <18 years, and those with unknown diagnosis and diagnosis other than autoimmune, PBC, and those lost to follow-up.

For the purpose of the study, we included a total of 2,595 adult patients transplanted for AIH, PSC, and PBC after February 2002 based on lab MELD at time of transplant. Three hundred twenty-one received live donor grafts 37 (11.5%) of which were for AIH, 99(30.8%) for PBC, and 185 (57.6%) for PSC. Two thousand two hundred seventy-four received deceased donor grafts, 545 (24%) for AIH, 757 (33.3%) for PBC, and 972 (42.7%) for PSC. For patients identified with AIH, PSC, and PBC, we obtained information on donor and recipient characteristics form the database. In addition the covariates that were considered for univariate analysis included: recipient age, donor age, lab MELD, donor gender, recipient gender, total bilirubin and creatinine at time of transplant, donor type, and BMI. For multivariate risk factor analysis, we included all the above covariates except for total bilirubin and creatinine at the time of transplant since both variables were already factored in MELD score.

Statistical Analysis

Demographic and clinical characteristics were summarized as means (for continuous variables) or proportions (for categorical variables) and compared using t tests or χ^2 tests, respectively. Survival times were calculated from the date of liver transplant. Death was considered as an event, whereas re-transplant or lost to follow-up was considered as censored observation. The survival rates were estimated using the Kaplan–Meier method. Log-rank tests were used to assess the differences in survival times across groups. Multivariate Cox proportional regression analyses were conducted to investigate the effect of independent risk factors on the survival times. All statistical tests are two-sided with significant level of p values smaller than 0.05. All statistical analyses were done using Statistical Package for Social Sciences (SPSS) software version 17.03 (SPSS Inc., Chicago, IL, USA).

Results

The demographics of donors and recipients as well as their clinical characteristics were reported between LDLT and DDLT for AIH, PBC, and PSC patients, respectively, in Table 1. MELD scores, total bilirubin and creatinine at the time of transplant were significantly lower for LDLT comparing to DDLT for all three disease groups. BMIs are lower for LDLT in both AIH and PSC groups. There were no differences in donor's age between LDLT and DDLT in all three groups, and recipients were younger (p=0.003) for LDLT in PSC. There were more male recipients (p=0.033)

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Table 1 Demographics and Comparison of Donor and Recipient Factors

		Autoimmune			PBC			PSC		
		DDLT	LDLT	*p* value	DDLT	LDLT	*p* value	DDLT	LDLT	*p* value
Recipient Age		47±14	45±14	0.39	55±9	53±8	0.102	47±13	44±13	0.003
Donor Age		38±18	37±10	0.7	41±18	37±10	0.012	39±18	39±10	0.619
Recipient Gender (M/F, %)		26.4/73.6	10.8/89.2	0.033	14.5/85.5	13.1/86.9	0.87	71.3/28.7	63.8/36.2	0.44
Donor Gender (M/F, %)		54.1/45.9	54.1/45.9	1.0	49/51	45.5/54.5	0.52	59.2/40.8	51.4/48.6	0.51
Recipient Race	White	65	67.6	0.006	80.8	81.8	0.001	80.2	83.2	0.001
	AA	15.4	2.7		5	2		13.8	3.8	
	Hispanic	15.2	16.2		10.8	5.1		3.7	4.9	
	Asian	2.4	2.7		1.5	0		1.6	0	
	Others	2	10.8		1.8	11.1		0.6	8.1	
Donor Race	White	71.9	81.1	0.64	70	87.9	0.002	75.1	91.4	0.001
	AA	11.4	2.7		12.5	2		14	4.9	
	Hispanic	13.6	13.5		13.9	9.1		8.7	2.7	
	Asian	2.4	2.7		2.6	0		1.1	0	
	Others	0.7	0		0.9	1		1	1.1	
MELD Score		22±10	15±6	0.001	21±9	14±5	0.001	20±8	13±5	0.001
BMI		28±6	26±5	0.008	26±5	26±5	0.83	25±4	24±4	0.039
Total Bilirubin (At Time of Txp)		10±13	4±6	0.004	10±11	5±5	0.001	10±10	5±8	0.001
Creatinine (At Time of Txp)		1.3±1.06	0.9±0.42	0.008	1.2±1.0	0.88±0.32	0.001	1.1±1.04	0.86±0.26	0.001

with DDLT in AIH. The overall median follow-up for all patients was 24 months.

Overall Survival

Among all recipients the estimated patient survival at 1, 3, and 5 years for LDLT was 95.5%, 93.6%, and 92.5% and for DDLT was 90.9%, 86.5%, and 84.9%, respectively (p=0.002; Fig. 1). The estimated graft survival at 1, 3, and 5 years for LDLT was 87.9%, 85.4%, and 84.3% and for DDLT was 85.9%, 80.3%, and 78.6%, respectively (p=0.123; Fig. 1).

Survival for AIH

The 1-, 3-, and 5-year patient survival among LD/DD for AIH was 94.3%, 94.3%, and 94.3%/89.1%, 84.1%, and 80.4%, respectively (Fig. 2). The 1-, 3-, and 5-year graft survival among LD/DD for AIH was 89%, 89% and 84%/84.9%, 78.2%, and 74.5%, respectively (Fig. 2). The results from univariate and multivariate Cox regression overall survival are shown in Tables 2 and 3, respectively. It is indicated in the univariate analysis that recipients of older age, higher MELD score, and higher creatinine at the time of transplant were significantly associated with higher mortality in the AIH population. Multivariate analysis identified two risk factors; recipient's age and MELD score at the time of transplant, for AIH patient's survival. More specifically, every unit increase in recipient's age was associated with an increase of 3% of hazard in mortality (p=0.001) and MELD score (p=0.02) were associated with higher mortality. The risk for AIH patients with MELD score between 15 and 25 was more than two times higher for those with MELD values lower then 15 (HR=2.26; p=0.02) and almost three times higher for those with MELD score greater than 25 (HR=2.85; p=0.0007). The effect of donor type among AIH patients was not found to be significant after adjusting for all the other covariates (p=0.35).

Survival for PBC

The 1-, 3-, and 5-year patient survival among LD/DD for PBC was 92.8%, 90.1% and 86.4%/89.6%, and 87% and 85.1%, respectively (Fig. 3). The 1-, 3-, and 5-year graft survival among LD/DD for PBC was 85.6%, 80.9% and 77.4%/85.2%, 82.5%, and 80.7%, respectively (Fig. 3). For PBC patients, multivariate analysis suggested that recipient age and MELD score effected survival similar to AIH patients (Tables 4 and 5).

Survival for PSC

The 1-, 3-, and 5-year patient survival among LD/DD for PSC was 97.2%, 95.4% and 95.4%/93%, and 87.5% and

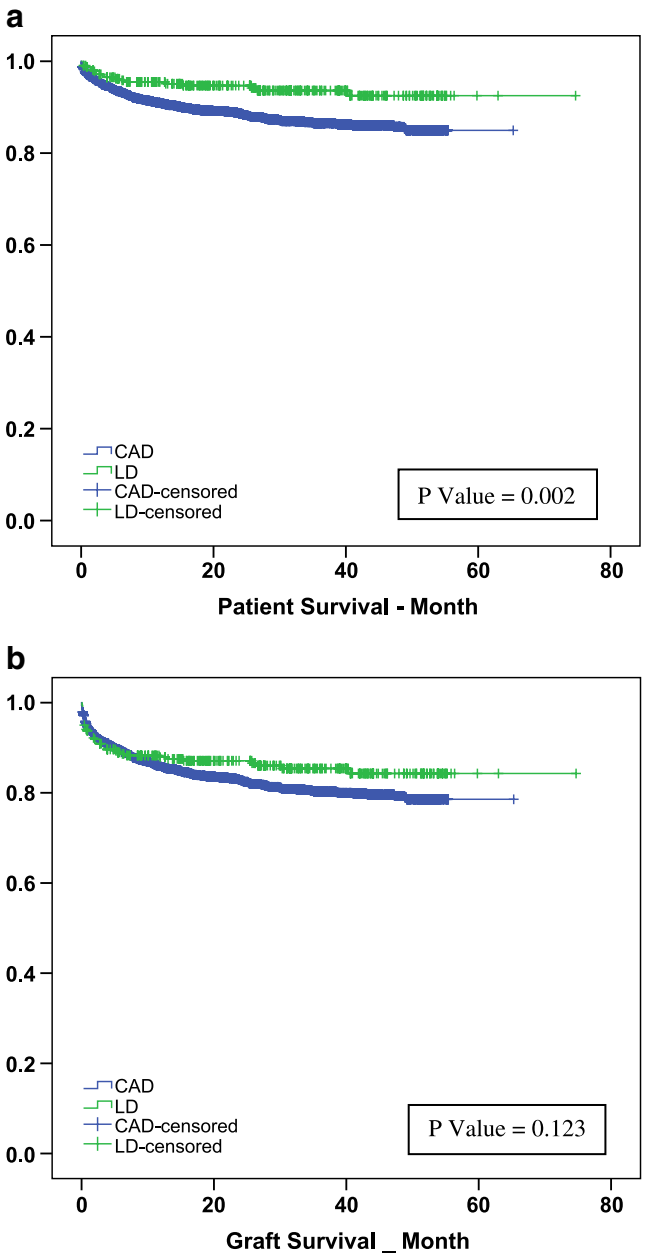

Fig. 1 **a** Patient survival outcomes all patients (living/deceased donor). **b** Graft survival outcomes all patients (living/deceased donor).

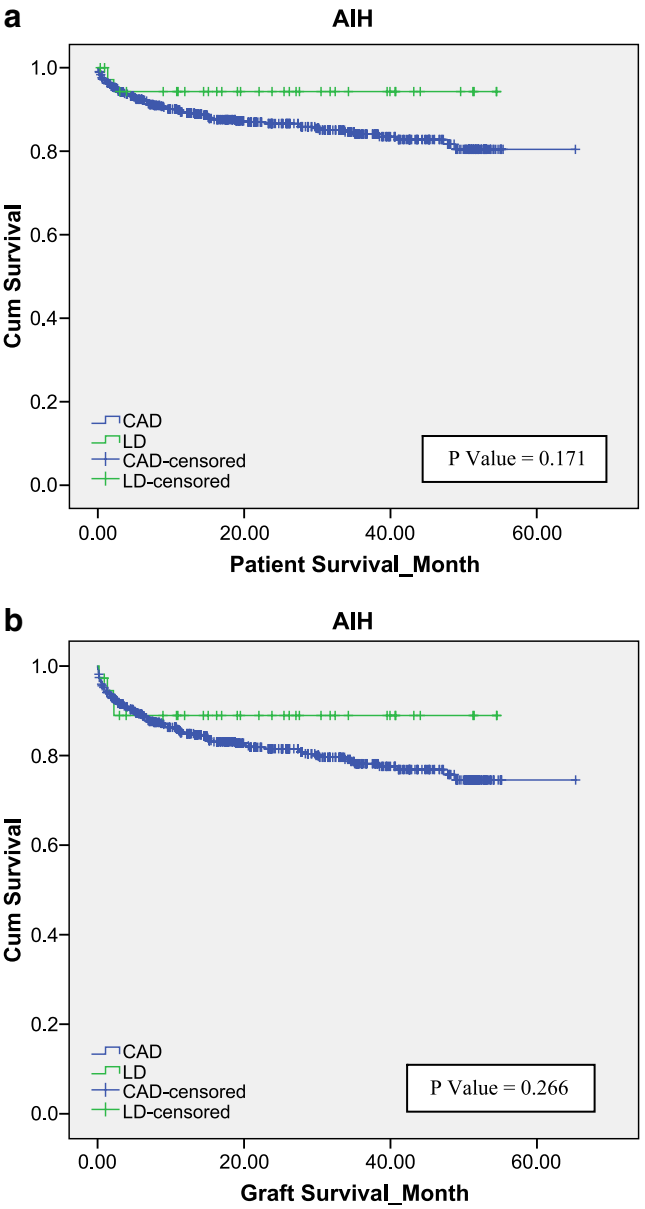

Fig. 2 **a** Patient survival outcomes in AIH: living/deceased donor. **b** Graft survival outcomes in AIH: living/deceased donor.

87.5%, respectively (Fig. 4). The 1-, 3-, and 5-year graft survival among LD/DD for PSC was 89.6%, 87.1% and 87.1%/87%, and 79.7% and 79.2%, respectively (Fig. 4). For PSC patients, multivariate analysis (Tables 6 and 7) suggested that female recipients were associated with 17% (p=0.028) increase of hazard in mortality comparing to their male counterpart. The risk for patients with LDLT was 60% lower comparing to those with DDLT (p=0.023). The effect of MELD score was no longer significant.

Re-transplant

The total number of retransplants among living donors were 25 (7.8%) vs. 127 (5.6%) in deceased donor transplants. Among the living donors, the rate of re-transplant for AIH, PBC, and PSC was 2 (5.4%), 8 (8.1%), and 15 (8.1%), respectively. Among the deceased donor rate of re-transplant for AIH, PBC, and PSC was 27 (5%), 32 (4.2%), and 68 (7%), respectively. Among living donors 24 patients required re-transplant within 1 year, 17 (68%) of

Table 2 Univariate Cox Regression Analysis for AIH (n=582)

		Autoimmune			
		Hazard Ratio	95.0% CI for Risk Ratio		p value
			Lower	Upper	
Age (Recipient)		1.028	1.01	1.04	0.02
Age (Donor)		1.001	0.98	1.01	0.9
MELD	<15				0.02
	15–25	2.26	1.09	4.66	0.02
	>25	2.7	1.31	5.89	0.008
Gender (Recipient)	M F	1.06	0.63	1.77	0.81
Gender (Donor)	M F	0.96	0.61	1.51	0.87
Total Bilirubin (At Txp)		1.00	0.99	1.02	0.47
Creatinine (At Txp)		1.29	1.12	1.5	0.002
Donor Type	DDLT LDLT	0.38	0.09	1.58	0.18
BMI		1.01	0.97	1.05	0.47

these patients underwent re-transplant within 1 month, and only one (4%) patient required re-transplant after 1 year. Among deceased donors 108 patients required re-transplant within 1 year, 57 (44.9%) of these patients underwent re-transplant within 1 month and 19 (15%) patients required re-transplant after 1 year.

Table 3 Multivariate Cox Regression Analysis for AIH (n=582)

		Autoimmune			
		Hazard Ratio	95.0% CI for Risk Ratio		p value
			Lower	Upper	
Age (Recipient)		1.03	1.01	1.04	0.001
Age (Donor)		0.99	0.98	1.01	0.88
MELD	<15				0.02
	15–25	2.26	1.09	4.68	0.02
	>25	2.85	1.33	6.10	0.007
Gender (Recipient)	M F	1.11	0.66	1.87	0.67
Gender (Donor)	M F	0.97	0.61	1.55	0.92
Donor Type	DDLT LDLT	0.51	0.12	2.12	0.35
BMI		1.00	0.96	1.04	0.86

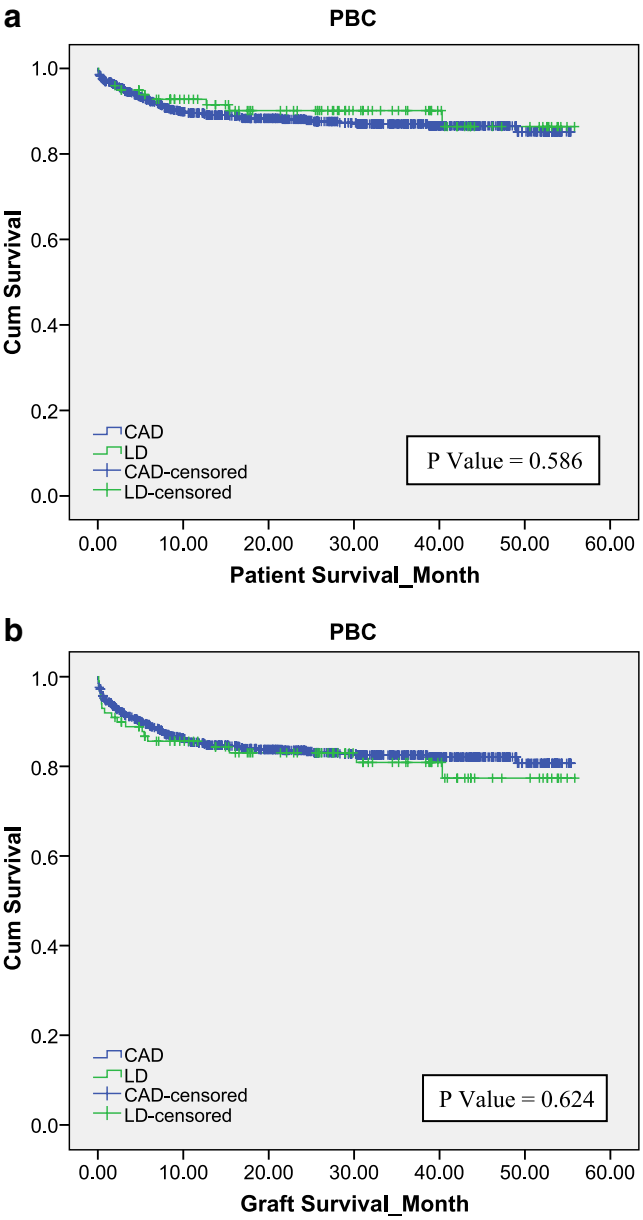

Fig. 3 **a** Patient survival outcomes in PBC: living/deceased donor. **b** Graft survival outcomes in PBC: living/deceased donor.

Discussion

The results of LDLT were similar to DDLT in terms of overall outcomes in our patients with autoimmune and cholestatic liver diseases and there were no difference in survival among these three diseases. It appears from our study that donor type does not significantly affect the outcome after adjusting for age and MELD score among these patients. The difference in survival arises from differences in clinical characteristics at the time of transplantation. In our univariate analysis for all AIH patients, recipient age, serum creatinine at the time of transplant, and MELD score were significant risk factors

Table 4 Univariate Cox Regression Analysis for PBC (n=856)

		PBC			
		Hazard Ratio	95.0% CI for Risk Ratio		p value
			Lower	Upper	
Age (Recipient)		1.037	1.013	1.062	0.002
Age (Donor)		1.010	0.999	1.021	0.078
Gender (Recipient)	M F	0.905	0.505	1.624	0.738
Gender (Donor)	M F	0.908	0.609	1.353	0.636
MELD	<15				0.197
	15–25	1.250	0.736	2.124	0.409
	>25	1.676	0.939	2.989	0.080
Total Bilirubin (At Txp)		1.009	0.990	1.029	0.354
Creatinine (At Txp)		1.237	1.061	1.442	0.007
Donor Type	DDLT LDLT	0.834	0.433	1.604	0.586
BMI		1.028	0.992	1.065	0.126

influencing the mortality. Only recipient age and MELD score were identified as significant factors affecting mortality in patients transplanted for AIH in the multivariate analysis. Several retrospective reviews on LT for AIH have emerged from various transplant programs.[3–7,9–11,22,24–27] Patients transplanted for AIH have been reported to have 80–92% 5-year survival with a graft survival rate of 74–76%.[1,3,4,7,23] However, the 10-year patient survival rate reported by Gonzalez-Koch and Vogel et al. is approximately 75% and the recurrence rate is as high as 42%[5,6] *for AIH*.

Futagawa et al. reported a better 5-year graft survival for adult patients with autoimmune-related diseases[1] than for hepatitis B (71.5%) and C (63.2%).[1,2] Data from the European Liver Transplant Registry also showed comparable results for PBC, with 1-, 5-, and 10-year survival rates noted as 83%, 72%, and 62%, respectively, when compared with those grafted for virus related cirrhosis.[17] In our study there was no difference in survival among patients with AIH, PBC, or PSC. However, it appears that for AIH patients multivariate analysis identified recipient age and MELD score at time

Table 5 Multivariate Cox Regression Analysis for PBC (n=856)

		PBC			
		Hazard Ratio	95.0% CI for Risk Ratio		p value
			Lower	Upper	
Age (Recipient)		1.045	1.018	1.071	0.001
Age (Donor)		1.009	0.998	1.021	0.114
Gender (Recipient)	M F	0.799	0.441	1.449	0.460
Gender (Donor)	M F	1.057	0.696	1.605	0.793
MELD	<15				0.092
	15–25	1.410	0.811	2.451	0.223
	>25	1.989	1.066	3.712	0.031
Donor Type	DDLT LDLT	1.237	0.614	2.495	0.552
BMI		1.027	0.991	1.064	0.145

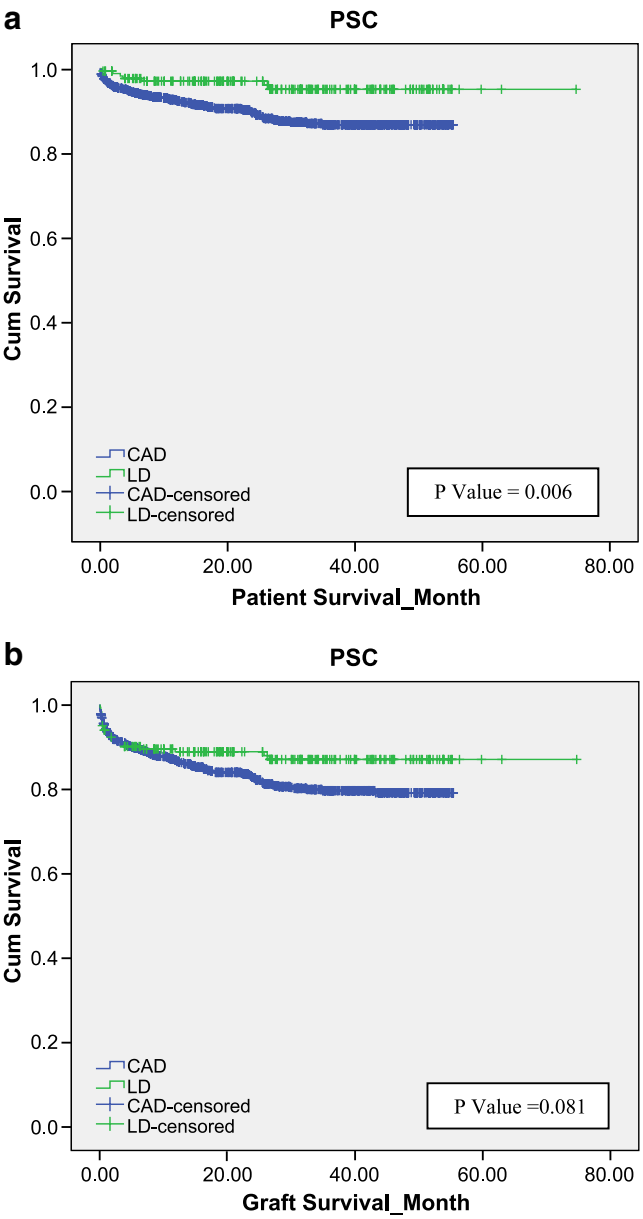

Fig. 4 **a** Patient survival outcomes in PSC: living/deceased donor. **b** Graft survival outcomes in PSC: living/deceased donor.

Table 6 Univariate Cox Regression Analysis for PSC (n=1,157)

		PSC			
		Hazard Ratio	95.0% CI for Risk Ratio		p value
			Lower	Upper	
Age (Recipient)		1.027	1.010	1.043	0.001
Age (Donor)		0.999	0.988	1.011	0.901
Gender (Recipient)	M F	1.608	1.003	2.577	0.049
Gender (Donor)	M F	0.921	0.623	1.362	0.681
MELD	<15				0.011
	15–25	0.894	0.566	1.413	0.631
	>25	1.830	1.096	3.056	0.021
Total Bilirubin (At Txp)		1.019	1.002	1.036	0.03
Creatinine (At Txp)		1.223	1.070	1.398	0.003
Donor Type	DDLT LDLT	0.355	0.165	0.765	0.008
BMI		1.000	0.956	1.046	0.99

of transplant affecting survival. The effect of donor type among AIH and PBC patients was not found to be significant after adjusting for other risk factors. Among PSC patients the risk for patients with LDLT was 60% lower compared to those with DDLT. Five-year survival of AIH patients was lower compared to PBC and PSC. Every unit increase in recipient age was associated with an increase of 3% hazard in mortality and three times higher for those with MELD score greater than 25. Recent study by Schramm et al. concluded that age significantly affects patient survival after liver transplantation for AIH.[28]

Garcia et al.,[8] in a retrospective study of 301 PBC recipients, analyzed donor and operative factors affecting recipient outcome. They found that factors leading to decreased total patient survival were recipient old age (p= 0.002) and low recipient albumin (p=0.01). Cold ischemic time of 18 h also adversely impacted patient survival (p= 0.025). Obesity in donors (BMI>30) decreased survival by 50% in 5 years.

In our study, compared to DDLT better survival results in AIH with LDLT could be explained due to the fact that these patients are transplanted earlier while patients who underwent DDLT were older and tend to have renal impairment at the time of transplantation, thus resulting in a more negative impact on the survival with DDLT. Among PSC patients, donor type was found to be significant. This study confirms the findings of our previous study that superior graft quality as well as the favorable elective timing of LDLT conferred better patient and graft survival.[29] Also from this study, it appears that there has been an overall improvement in the 5-year survival for autoimmune and cholestatic diseases; however, it would be interesting to see the long-term outcome of these patients.

Table 7 Multivariate Cox Regression Analysis for PSC (n=1,157)

		PSC			
		Hazard Ratio	95.0% CI for Risk Ratio		p value
			Lower	Upper	
Age (Recipient)		1.026	1.010	1.043	0.002
Age (Donor)		0.997	0.985	1.008	0.568
Gender (Recipient)	M F	1.739	1.063	2.844	0.028
Gender (Donor)	M F	0.776	0.515	1.168	0.224
MELD	<15				0.036
	15–25	0.738	0.462	1.179	0.204
	>25	1.396	0.819	2.380	0.220
Donor Type	DDLT LDLT	0.400	0.181	0.883	0.023
BMI		0.988	0.943	1.035	0.615

Conflicts of Interest None

Support Self

References

1. Futagawa Y, Terasaki PI. An analysis of the OPTN/UNOS Liver Transplant Registry. Clin Transpl. (2004); 18:315
2. Futagawa Y, Terasaki PI, Waki K, Cai J, Gjertson DW. No improvement in long-term liver transplant graft survival in the last decade: an analysis of the UNOS data. Am J Transplant. 2006; 6(6): 1398
3. Molmenti EP, Netto GJ, Murray NG, et al. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. Liver Transpl 2002; 8 (6): 519.
4. Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006; 354 (1): 54.
5. Gonzalez-Koch A, Czaja AJ, Carpenter HA, et al. Recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver Transpl 2001; 7 (4): 302.
6. Vogel A, Heinrich E, Bahr MJ, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant 2004; 18 (1): 62.
7. Mottershead M, Neuberger J. Transplantation in autoimmune liver diseases. World J Gastroenterol 2008; 14 (21): 3388.
8. Garcia CE, Garcia RF, Gunson B, et al. Analysis of marginal donor parameters in liver transplantation for primary biliary cirrhosis. Exp Clin Transplant 2004; 2 (1): 183.

9. Schreuder TC, Hubscher SG, Neuberger J. Autoimmune liver diseases and recurrence after orthotopic liver transplantation: what have we learned so far? Transpl Int 2009; 22 (2): 144.
10. Ayata G, Gordon FD, Lewis WD, et al. Liver transplantation for autoimmune hepatitis: a long-term pathologic study. Hepatology 2000; 32 (2): 185.
11. Duclos-Vallee JC, Sebagh M, Rifai K, et al. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. Gut 2003; 52 (6): 893.
12. Brandsaeter B, Schrumpf E, Bentdal O, et al. Recurrent primary sclerosing cholangitis after liver transplantation: a magnetic resonance cholangiography study with analyses of predictive factors. Liver Transpl 2005; 11 (11): 1361.
13. Charatcharoenwitthaya P, Pimentel S, Talwalkar JA, et al. Long-term survival and impact of ursodeoxycholic acid treatment for recurrent primary biliary cirrhosis after liver transplantation. Liver Transpl 2007; 13 (9): 1236.
14. Jacob DA, Neumann UP, Bahra M, et al. Long-term follow-up after recurrence of primary biliary cirrhosis after liver transplantation in 100 patients. Clin Transplant 2006; 20 (2): 211.
15. Khettry U, Keaveny A, Goldar-Najafi A, et al. Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. Hum Pathol 2003; 34 (11): 1127.
16. Kugelmas M, Spiegelman P, Osgood MJ, et al. Different immunosuppressive regimens and recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl 2003; 9 (7): 727.
17. Vera A, Moledina S, Gunson B, et al. Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. Lancet 2002; 360 (9349): 1943.
18. Maheshwari A, Yoo HY, Thuluvath PJ. Long-term outcome of liver transplantation in patients with PSC: a comparative analysis with PBC. Am J Gastroenterol 2004; 99 (3): 538.
19. Rowe IA, Webb K, Gunson BK, Mehta N, Haque S, Neuberger J. The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. Transpl Int 2008; 21 (5): 459.
20. Tamura S, Sugawara Y, Kaneko J, et al. Recurrence of cholestatic liver disease after living donor liver transplantation. World J Gastroenterol 2008; 14 (33): 5105.
21. Tanaka K, Ogura Y, Kiuchi T, Inomata Y, Uemoto S, Furukawa H. Living donor liver transplantation: Eastern experiences. HPB (Oxford) 2004; 6 (2): 88.
22. Prados E, Cuervas-Mons V, de la Mata M, et al. Outcome of autoimmune hepatitis after liver transplantation. Transplantation 1998; 66 (12): 1645.
23. Waki K. UNOS Liver Registry: ten year survivals. Clin Transpl (2006) 1: 29
24. Neuberger J. Liver Transplantation for Cholestatic Liver Disease. Curr Treat Options Gastroenterol 2003; 6 (2): 113.
25. Mackie J, Groves K, Hoyle A, et al. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. Liver Transpl 2001; 7 (5): 418.
26. Guy JE, Qian P, Lowell JA, Peters MG. Recurrent primary biliary cirrhosis: peritransplant factors and ursodeoxycholic acid treatment post-liver transplant. Liver Transpl 2005; 11 (10): 1252.
27. Balan V, Abu-Elmagd K, Demetris AJ. Autoimmune liver diseases. Recurrence after liver transplantation. Surg Clin North Am 1999; 79 (1): 147.
28. Schramm C, Bubenheim M, Adam R et al. Primary liver transplantation for Autoimmune Hepatitis; A comparative analysis of European liver transplant registry. Liver Transpl 2010; 16(4): 461.
29. Kashyap R, Mantry P, Sharma R, et al. Comparative analysis of outcomes in living and deceased donor liver transplants for Primary Sclerosing Cholangitis. J Gastrointest Surg (2009) 13:1480.

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ORIGINAL ARTICLE

Clinicopathological Determinants of Survival After Hepatic Resection of Hepatocellular Carcinoma in 97 Patients—Experience From an Australian Hepatobiliary Unit

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Abstract
Background Identification of clinicopathological determinants that predict for risk of recurrence and overall survival after undergoing potentially curative hepatic resection for hepatocellular carcinoma is a strategy towards personalizing therapy to improve outcome. Through evaluation of a center's experience with treatment of a disease, determinants unique to the treated patient cohort may be identified.
Methods Ninety-seven patients with hepatocellular carcinoma underwent liver resection. Clinical, treatment, and histopathological variables were collected and evaluated using univariate and multivariate analyses with disease-free survival (DFS) and overall survival (OS) as the endpoints.
Results The median follow-up period of 19 (range, 1 to 188) months from the time of hepatic resection. The median DFS and OS after resection of HCC were 17 and 41 months, respectively. Five-year overall survival rate was 45%. Eight independent factors associated with disease-free and overall survival were identified through a multivariate analysis. Three factors: Child–Pugh score (DFS $p=0.045$, OS $p=0.001$), histopathological grade (DFS $p<0.001$, OS $p<0.001$), and histological diagnosis of cirrhosis (DFS $p<0.001$, OS $p<0.001$) predicted for both disease-free and overall survival.
Conclusion Integrating the knowledge of identified prognostic factors into clinical decision making may provide a clinicopathological signature that could identify patients at greatest risk of treatment failure such that novel interventions may be applied to improve the survival outcome.

Keywords Hepatocellular carcinoma · Hepatectomy · Prognostic factors · Survival analysis · Clinicopathological factors · Biomarkers

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy with an annual incidence of 626,000 in 2002.[1] Although this disease is endemic in sub-Saharan African and Southeast Asian populations, recent epidemiological data has demonstrated an increased incidence in developed countries worldwide, including Australia.[2–4] Without early and aggressive treatment, HCC is invariably fatal and patients managed with best supportive care have a median survival <1 year.[5] The only curative treatment options are surgical resection and liver transplantation. For both treatment modalities, judicious patient selection is essential and 5-year survival rates from high-volume institutions vary between 30% and 70%.[6–9] Unfortunately, the role of liver transplantation in the context of treatment for HCC is limited by the scarcity of donors which

has led to excessive waiting lists and a dropout rate of up to 30%.[5] Surgical resection, therefore, remains the mainstay of treatment. Given the need to optimize treatment outcome and improve survival, several adjuvant therapies to prevent recurrence following resection have been evaluated including chemoebolization/lipiodolization,[10,11] internal radiation,[12,13] chemotherapy,[14,15] retinoid therapy,[16] and adoptive immunotherapy.[17] Unfortunately, there is insufficient data to recommend the routine use of any adjuvant therapy. Therefore, an optimal management strategy for patients with resectable HCC remains to be defined.

`Prognostication of clinicopathological factors in patients who undergo resection for HCC allows identification of patients who are most likely to benefit from this procedure and thereby facilitate the patient selection process and tailoring of adjuvant therapies to optimize overall outcomes. Several series have identified independent predictors for survival although there is significantly less data for disease-free survival.[7,8,18–22] The majority of these studies originate from specialized Asian or Western institutions where the disease and treatment profile is unique to own center. The current study evaluates the prognostic value of clinicopathogic variables for disease-free survival and overall survival following hepatic resection of HCC at a high volume hepatobiliary tertiary referral center in Australia. The aim is to identify prognostic factors unique to this patient cohort and thereby facilitate the patient selection process.

Patients and Methods

Patient Selection

Prospectively collected data of 97 patients with hepatocellular carcinoma underwent hepatic resection (resection or resection combined with ablation) by the Hepatobiliary Service of the University of New South Wales, Department of Surgery, St George Hospital over an 18-year period between April 1991 and August 2009. All patients had histologically confirmed hepatocellular carcinoma and were treated with a curative intent. Patients were evaluated with a baseline medical history, clinical examination, serum laboratory tests including alpha fetoprotein, computed tomography (CT) scan (triple phase and/or lipiodol scan), hepatobiliary ultrasound, chest radiography and with or without magnetic resonance imaging.

Patients who had ablation without resection, underwent open and close procedures without hepatic resection of the tumor, were excluded from the study.

Preoperative Work-up

Preoperative diagnosis of HCC was based on typical imaging findings (such as early arterial enhancement with early portal-venous washout) on CT or magnetic resonance imaging and/or serum alpha-fetoprotein (AFP) level higher than 400 ng/ml. Percutaneous needle biopsy was not performed routinely in patients with resectable tumors to avoid needle-tract seeding of tumor cells. The criteria determining tumor resectability were: absence of major vascular invasion, absence of extrahepatic disease, adequate hepatic functional reserve, and tumor considered anatomically resectable on the basis of imaging findings. Assessment of hepatic function was by the Child–Pugh classification. Selection for hepatic resection was based on this classification unless another test such as the indocyanine green clearance test was performed to further assess the safety of surgery on the hepatic function.

Surgical Technique

Patients undergoing hepatectomy were generally explored through a bilateral subcostal incision with vertical midline upward extension. After laparotomy, intraoperative ultrasound was routinely performed to detect any lesions in the contralateral lobe, any tumor invasion of portal vein or hepatic veins, and to define the relationship between the tumor and major intrahepatic vessels. The plane of transection or resection was then marked on the liver capsule using the diathermy pencil. Depending on the location, size, and bleeding risk of the patient, liver mobilization was performed to obtain total vascular control (portal vein, hepatic artery, hepatic vein, and inferior vena cava). Parenchymal transection was performed using an ultrasonic dissector. Hemostasis during hepatic transection was achieved by diathermy coagulation, argon beam coagulation, and fine suturing. Intermittent hepatic inflow occlusion was applied during hepatic transection if excessive bleeding was encountered. Intra-abdominal drains were placed in situ after resection and prior to laparotomy closure. Hepatic resection was classified as major if at least three Couinaud segments were resected and minor if fewer than three segments were removed.

Postoperative Management

All patients were admitted to the intensive care unit during the early postoperative period after surgery. Patients were commenced on oral intake when bowel function was regained and drain tubes were removed when output was low. All patients were followed prospectively at monthly intervals for the first 3 months and at six monthly intervals thereafter with measurement of the serum AFP level and CT of the liver. The diagnosis of recurrence was based on typical imaging studies that demonstrate development of hepatic tumor, and an eventual increment in AFP levels, or development of extrahepatic metastasis. Tumor biopsy was not performed to

confirm the diagnosis of a recurrence. Depending on decision from the multidisciplinary tumor board which was based on the patient's performance status, liver function, extent of hepatic disease, and concurrent extrahepatic disease, a management strategy was decided. Repeat hepatectomy was considered the treatment of choice for resectable recurrent tumors (based on the criteria described above). Alternatively, other non-surgical treatments include radiofrequency ablation, transarterial chemoembolization, selective internal radiation using Yttrium-90 Microspheres (SIR-Spheres®), percutaneous ethanol injection, or systemic chemotherapy. Best supportive care represents no attempt at active treatment of disease with a primary focus on symptomatic management and comfort care.

Data Collection

The following data were collected for each patient: demographics including age, sex, cause of chronic hepatitis, ethnicity and Child–Pugh score; treatment-related factors including extent of hepatic disease, number of segments resected, perioperative treatments, type of hepatic surgical procedure, requirement of vascular surgical procedures as part of hepatic resection, requirement of other visceral surgical procedures as part of hepatic resection, presence of ruptured tumor, and presence of extrahepatic disease; and pathological factors including AFP levels, number of lesions, focality of tumor, maximum size of the largest lesion, histological grade, presence of tumor necrosis, presence of tumor capsule, histological diagnosis of cirrhosis, vascular invasion, lymph node involvement, and margin status. Margin status were examined histologically and reported as R0 as free of tumor >1 mm from the resection margin, R1 being tumor present <1 mm from the resection margin, and R2 being tumor being present at the resection margin. Staging was performed based on current staging algorithm including American Joint Cancer Committee staging,[23] Barcelona Clinic Liver Cancer staging,[24] and Cancer Liver Italian Program staging.[25] In total, these 27 variables were examined as predictors for survival with both the time of hepatic resection to the time of disease recurrence (disease-free survival) and cancer-related death (overall survival) as endpoints. Follow-up data was obtained from the referring physicians and phone calls and/or emails from the patients.

Statistical Analysis

The data collected were analyzed using SPSS® for Windows version 15.0 (SPSS, Munich, Germany). The patient characteristics were reported using frequency and descriptive analyses. The Kaplan–Meier method was used to analyze survival. Univariate analysis (log-rank) was performed to determine the clinicopathological factors affecting survival. Multivariate analysis was performed on all factors $p<0.10$ using the Cox proportional hazards regression model. The median time to death was defined as the time where 50% of patients have died. Follow-up was calculated from the date of treatment of carcinomatosis to the date of last follow-up. $p\leq0.05$ was considered statistically significant.

Results

A total of 97 patients underwent hepatic resection for hepatocellular carcinoma. There were 22 females (23%) and 75 males (77%). The mean age was 61 (s.d.=14) years. Chronic hepatitis secondary to hepatitis B infection was present in 33 patients (34%), hepatitis C infection in 12 patients (12%), and from hemochromatosis in nine patients (9%). Sixty-five patients (67%) were of Caucasian background, 30 patients were of Asian decent (31%), and two patients (2%) were of other ethnic background.

The median AFP level was 31 (range, 1 to 239527). Eighty-two patients (85%) were classified as Child Pugh A, 14 patients (14%) as Child Pugh B, and one patient (1%) was a Child Pugh C. Thirty patients (31%) met transplant criteria (Milan/UCSF Liver Transplant Criteria).

Survival Outcomes

The median follow-up period was 19 (range, 1 to 188) months from the time of hepatic resection. During this time, 67 patients (69%) have developed recurrences and 46 patients (47%) have died. The median disease-free survival after hepatic resection was 17 months (95% CI, 9 to 24). The 1-, 2-, 3-, and 5-year recurrence-free survival rates were 57%, 40%, 37% and 22% respectively. The median overall survival was 41 months (95% CI, 17 to 64), with a 1-, 3-, 5-, and 10-year overall survival rate of 73%, 55%, 45%, and 27% respectively (Fig. 1).

Recurrences Following Hepatic Resection

In the 67 patients who developed recurrence, 39 patients developed intrahepatic recurrence, 21 patients developed intrahepatic and extrahepatic recurrence and seven patients developed extrahepatic recurrence. Fifteen patients received surgical treatments (repeat resection and/or ablation), 29 patients received non-surgical treatments, and 23 received best supportive care. In this group of patients, there were 46 deaths, the median overall survival was 21 months and the 1-, 3-, and 5-year survival rate was 61%, 40%, and 29% respectively.

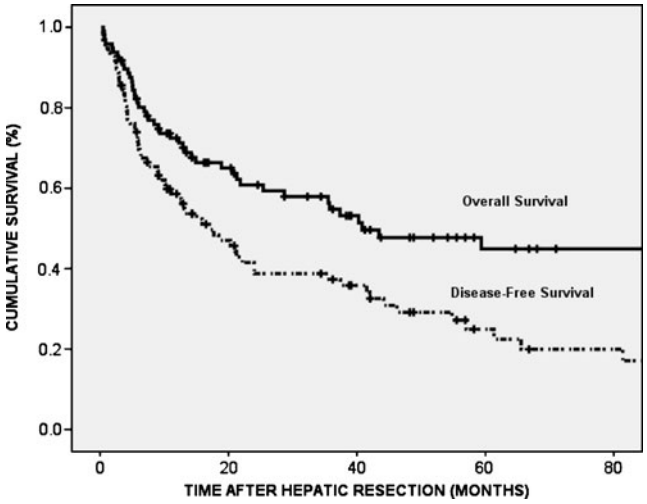

Fig. 1 Kaplan–Meier survival plots of disease-free (*broken lines*) and overall survival (*solid lines*) of 97 patients with hepatocellular carcinoma after undergoing hepatic resection.

Prognostic Factors for Survival

Eight clinical, eight treatment-related, and 11 histopathological factors were analyzed as prognostic determinants for disease-free and overall survival on univariate analysis (Tables 1, 2, and 3). Disease-free survival was influenced by 16 variables. These include sex (p=0.003), age (p=0.0038), the cause of chronic hepatitis (p=0.051), ethnicity (p=0.018), Child Pugh Score (p=0.013), American Joint Cancer Committee Stage (p=0.012), Barcelona Clinic Liver Cancer (p<0.001), Cancer Liver Italian Program (p<0.001), ruptured tumor (p=0.001), extrahepatic disease (p<0.001), AFP (p=0.029), histopathological grade (p<0.001), tumor necrosis (p=0.007), tumor capsule (p=0.051), histopathological diagnosis of cirrhosis (p<0.001), and vascular invasion (p<0.001).

Overall survival was influenced by 15 variables. These include sex (p=0.017), cause of chronic hepatitis (p=0.024), ethnicity (p=0.001), Child Pugh Score (p<0.001), American Joint Cancer Committee Stage (p=0.01), Barcelona Clinic Liver Cancer (p<0.001), Cancer Liver Italian Program (p<0.001), perioperative treatments (p=0.006), ruptured tumor (p=0.003), extrahepatic disease (p<0.001), AFP (p=0.004), histopathological grade (p<0.001), tumor necrosis (p=0.041), histopathological diagnosis of cirrhosis (p<0.001), and vascular invasion (p=0.01).

Variables p<0.10 in the univariate analysis were subjected to a Cox proportional hazards regression model for a multivariate analysis (Table 4). Independent predictors for disease-free survival include Child–Pugh score (hazard ratio (95% CI); 2.2 (1.0 to 5.0), p=0.045; Fig. 2a), histopathological grade (hazard ratio (95% CI); 3.1 (1.9 to 5.0, p<0.001) (Fig. 2b), histopathological diagnosis of cirrhosis (hazard ratio (95% CI); 3.9 (2.0 to 7.6), p<0.001; Fig. 2c), and vascular invasion (hazard ratio (95% CI); 2.6 (1.1 to 6.3), p=0.035; Fig. 2d). Independent predictors for overall survival include Child–Pugh score (hazard ratio (95% CI); 5.3 (1.9 to 14.4), p=0.001, Fig. 3a), perioperative treatments (hazard ratio (95% CI); 0.3 (0.2 to 0.6), p=0.001, Fig. 3b), AFP (hazard ratio (95% CI); 2.9 (1.1 to 7.8), p=0.031, Fig. 3c), focality (hazard ratio (95% CI); 2.8 (1.2 to 6.7, p=0.017, Fig. 3d), histopathological grade (hazard ratio (95% CI); 6.5 (3.3 to 13.1), p<0.001, Fig. 3e), tumor necrosis (hazard ratio (95% CI); 0.4 (0.2 to 0.9), p=0.034, Fig. 3f), and histopathological diagnosis of cirrhosis (hazard ratio (95% CI); 7.2 (3.1 to 16.8), p<0.001, Fig. 3g).

Discussion

The current study represents the largest analysis of the prognostic factors for overall survival and disease-free survival following surgical resection of HCC by an Australian institution. To date, there is a paucity of data from Australasian institutions examining this critical issue and the majority of published literature originates from Asian centers serving hepatitis B and C endemic populations or centralized North American and European institutions. In our Australian cohort, HCC has been shown to be equally contributed by chronic hepatitis secondary to hepatitis B/C viral infection and non-viral hepatitis, in particular alcoholic liver disease. A critical evaluation of the clinicopathological determinants for survival in this unique patient cohort is necessary to identify the patients who are most likely to benefit from surgical resection, and therefore, facilitate the patient selection process and tailoring of adjuvant therapies. This is particularly important given that a recent registry study has shown that the incidence of HCC in Australia doubled over 12 years, from 1.4/100,000 in 1990 to 2.8/100,000 in 2002 and the patient profile in Australia is different to other countries.[2]

The median disease-free survival and overall survival after surgical resection of HCC was 17 and 41 months, respectively, are comparable to other tertiary centers and concur with previous findings that resection enables a significant portion of patients with HCC to attain long-term survival.[5,7,9,19,20] Despite some series demonstrating encouraging results following local ablation, the only other treatment modality with comparable results for a curative treatment for HCC is orthotopic liver transplantation (OLT).[5,6,9,26–28] Theoretically, OLT may simultaneously cure the tumor and the underlying cirrhosis. It is the recommended first treatment for patients with small multinodular tumors (three nodules <3 cm) or those with advanced liver dysfunction; these patients can now expect a 5-year survival of 50–70% in specialized centers.[5,6,9,28] OLT as a treatment has also been shown to achieve longer

Table 1 Univariate Analysis of Clinical Factors Using the Log-Rank Test Anlaysis for Survival After Hepatic Resection of Hepatocellular Carcinoma

Patient characteristics	Analysis of disease-free survival			Analysis of overall survival		
	Patients (*n*)	Median disease-free survival (months)	Univariate analysis *p* value	Patients (*n*)	Median overall survival (months)	Univariate analysis *p* value
Sex			0.003*			0.017*
Male	75	13		75	10	
Female	22	55		22	52	
Age			0.038*			0.249
<62 years	49	22		49	102	
≥62 years	48	10		48	29	
Chronic hepatitis			0.051*			0.024*
Nil	43	21		43	102	
Hepatitis B	33	6		33	19	
Hepatitis C	12	36		12	40	
Hemochromatosis	9	42		9	NR	
Ethnicity			0.018*			0.001*
Caucasian	65	21		65	102	
Asian	30	9		30	19	
Others	2	–		2	–	–
Child–Pugh score			0.013*			<0.001*
A	82	21		82	102	
B	14	5		14	6	
C	1	22		1	36	
American Joint Cancer Committee (AJCC)			0.012*			0.010*
Stage 1	35	37		35	114	
Stage 2	24	21		24	59	
Stage 3	35	9		35	21	
Stage 4	3	6		3	7	
Barcelona Clinic Liver Cancer (BCLC)			<0.001*			<0.001*
A	18	57		18	102	
B	42	21		42	104	
C	37	6		37	12	
Cancer Liver Italian Program (CLIP)			<0.001*			<0.001*
0	25	37		25	NR	
1	34	24		34	102	
2	23	11		23	22	
3	13	4		13	6	
4	2	3		2	7	

disease-free survival, where Mazzaferro and colleagues report a 4-year recurrence-free survival rate of 83%.[6] In a similar cohort of early hepatocellular carcinoma treated by hepatic resection, Poon and colleagues report a 5-year disease-free survival rate of 36%.[29] In our series, the 5-year recurrence-free survival rate was 22%. Despite the long-term disease-free and overall survival possibility that OLT offers, OLT is limited by the severe shortage or donors. This leads to extensive waiting times and the consequent deterioration of liver function and/or progression of tumoral disease often result in formal contraindications for OLT or death in up to 30% of patients.[5] These issues are real in Australia where organ donor levels are the lowest among developed countries at 9/1,000,000 and transplants are rarely available for the treatment of malignancy.[30] Given these restrictions, aggressive surveillance of high-risk

Table 2 Univariate Analysis of Treatment Related Factors Using the Log-Rank Test for Survival After Hepatic Resection for Hepatocellular Carcinoma

Treatment-related factors	Analysis of disease-free survival			Analysis of overall survival		
	Patients (*n*)	Median disease-free survival (months)	Univariate analysis *p* value	Patients (*n*)	Median overall survival (months)	Univariate analysis *p* value
Extent of hepatic disease			0.788			0.819
Uni-lobar	82	17		82	40	
Bi-lobar	15	20		15	104	
Number of segments resected			0.993			0.931
≤ 2	53	15		53	40	
> 2	44	21		44	102	
Perioperative treatments			0.152			0.006*
No	49	10		49	21	
Yes	48	24		48	102	
Hepatic Surgical Procedure			0.419			0.205
Resection	77	19		77	114	
Resection and cryoablation	20	10		20	29	
Vascular surgical procedures			0.264			0.966
No	90	19		90	41	
Yes	7	8		7	NR	
Other visceral surgical procedures			0.409			0.775
No	85	19		85	41	
Yes	12	13		12	25	
Ruptured tumor			0.001*			0.003*
No	92	19		92	43	
Yes	5	3		5	5	
Extrahepatic disease			<0.001*			<0.001*
Absent	88	21		88	59	
Present	9	6		9	7	

populations (cirrhotics, HBV, HCV) and expert selection of candidates for resection is necessary to optimize patient outcomes.

We identified eight independent factors associated with disease-free survival and/or overall survival following resection of HCC. The Child–Pugh score assesses the severity of liver disease. It is used to guide patient selection at many institutions and generally only patients with Child's A or B are considered surgical candidates. As expected, the current series showed that patients with only minor liver dysfunction (Child's A) had a significantly better treatment outcome compared to other patients (OS p=0.001; DFS p=0.045). The level of AFP has been advocated by some investigators as a useful preoperative marker for long-term prognosis. Minagawa and colleagues,[18] analyzed data from a Japanese registry with 13,772 patients and showed an independent negative association between AFP levels and overall survival (p=0.0001). Our data showed a significant survival advantage in patients who had an AFP level <400 ng/ml (p=0.031). There is also evidence that AFP may predict disease recurrence although this was not evident in the current study.[21,31] The present study demonstrated the importance of tumor biology on outcome; patients with well-differentiated tumor had a significantly better prognosis than patients with moderately or poorly differentiated tumor (DFS p<0.001; OS p<0.001). Vascular invasion is a surrogate marker for advanced tumor biology and in some cases, indicates proximity to, or involvement of, major vascular structures. It has been consistently associated with a poorer outcome.[18,19,21] In the current study, vascular invasion was independently associated with poorer disease-free survival (p=0.035) although an association with poorer overall survival was less apparent. These data suggest that careful preoperative assessment of liver function, tumor markers, and tumor biology is necessary to optimize patient selection.

The efficacy of resection for the treatment of cirrhotic patients with HCC is disputed. Zhao and colleagues[32]

Table 3 Univariate Analysis of Pathological Factors Using the Log-Rank Test Anlaysis for Survival After Hepatic Resection Of Hepatocellular Carcinoma

Pathological factors	Analysis of disease-free survival			Analysis of overall survival		
	Patients (*n*)	Median disease-free survival (months)	Univariate analysis *p* value	Patients (*n*)	Median overall survival (months)	Univariate analysis *p* value
Alpha fetoprotein			0.029*			0.004*
< 400	67	24		67	102	
≥ 400	30	6		30	14	
Number of lesions			0.298			0.101
One	71	20		71	43	
More than one	26	9		26	15	
Focality			0.233			0.08
Unifocal	72	20		72	43	
Multifocal	25	9		25	15	
Maximum size of largest lesion			0.104			0.178
<8 cm	48	37		48	102	
≥8 cm	49	12		49	36	
Histopathological Grade			<0.001*			<0.001*
Well differentiated	30	85		30	NR	
Moderately differentiated	44	13		44	36	
Poorly differentiated	23	4		23	7	
Tumor necrosis			0.007*			0.041*
Absent	48	24		48	102	
Present	49	10		49	25	
Tumor capsule			0.051*			0.588
Absent	65	15		65	36	
Present	32	42		32	59	
Histological diagnosis of cirrhosis			<0.001*			<0.001*
Absent	63	24		63	104	
Present	34	8		34	11	
Vascular invasion			<0.001*			0.010*
Absent	56	44		56	102	
Present	41	9		41	21	
Lymph node involvement			0.891			0.705
Absent	93	17		93	41	
Present	4	10		4	29	
Margin evaluation			0.183			0.148
R0	67	20		67	102	
R1	13	13		13	36	
R2	17	9		17	13	

analyzed the prognostic features of 1,000 patients who underwent resection for small HCC at a large hepatobiliary unit in China. Their data showed that cirrhosis was independently associated with a poorer prognosis ($p=0.007$). In the multi-institutional series reported by Bilimoria and colleagues,[19] the absence of fibrosis/cirrhosis was the strongest predictor of 5-year survival ($p<0.01$). To this end, the authors argued that underlying disease rather than tumor factors are associated with long-term survival. Similarly, the current study showed that the overall survival of the 34 patients (35%) with cirrhosis at the time of resection was significantly worse than patients without cirrhosis (11 versus 104 months, $p<0.001$). However, more encouraging data has been shown by other centers. Poon and colleagues[8] compared the long-term prognosis after resection of 146 patients with HCC associated with

Table 4 Multivariate Analysis of Clinicopathological and Treatment-Related Variables ($p<0.10$ from univariate analysis) for Disease-Free and Overall Survival After Hepatic Resection for Hepatocellular Carcinoma (Only Significant Variables Displayed)

Variable	*p* value	Hazard ratio	95% Confidence interval
Disease-free survival			
Child–Pugh score	0.045	2.2	1.0 to 5.0
Histopathological grade	<0.001	3.1	1.9 to 5.0
Histological diagnosis of cirrhosis	<0.001	3.9	2.0 to 7.6
Vascular invasion	0.035	2.6	1.1 to 6.3
Overall survival			
Child–Pugh score	0.001	5.3	1.9 to 14.4
Perioperative treatments	0.001	0.3	0.2 to 0.6
Alpha-fetoprotein	0.031	2.9	1.1 to 7.8
Focality	0.017	2.8	1.2 to 6.7
Histopathological Grade	<0.001	6.5	3.3 to 13.1
Tumor Necrosis	0.034	0.4	0.2 to 0.9
Histological Diagnosis of Cirrhosis	<0.001	7.2	3.1 to 16.8

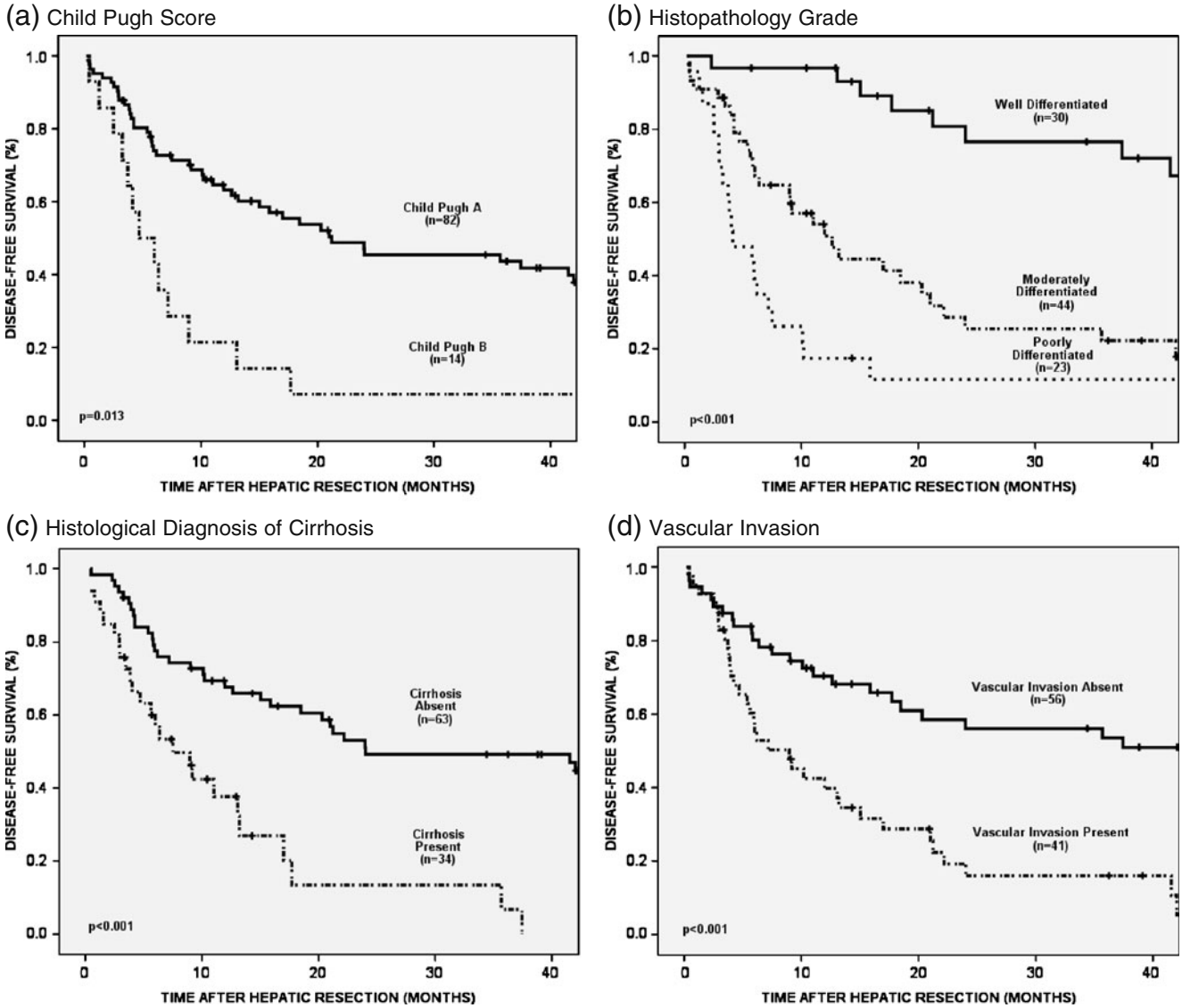

Fig. 2 Log-rank analysis demonstrating disease-free survival plots of patients with hepatocellular carcinoma after hepatic resection stratified according to independent prognostic factors: **a** Child–Pugh score, **b** histological grade, **c** histological diagnosis of cirrhosis, and **d** vascular invasion.

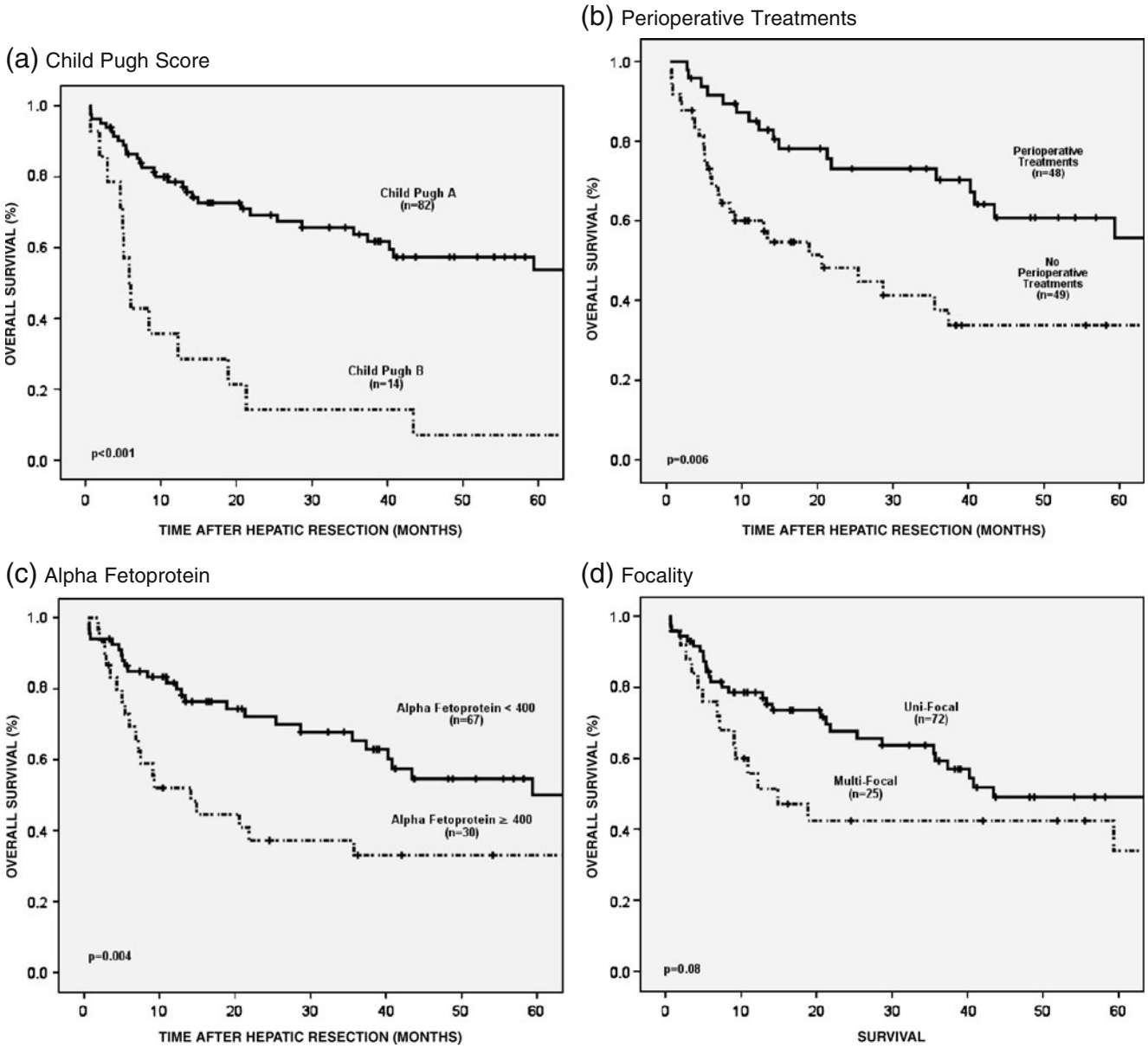

Fig. 3 Log-rank analysis demonstrating overall survival plots of patients with hepatocellular carcinoma after hepatic resection stratified according to independent prognostic factors: **a** Child–Pugh score, **b** perioperative treatments, **c** alpha fetoprotein, **d** focality, **e** histopathological grade, **f** tumor necrosis, and **g** histological diagnosis of cirrhosis.

hepatitis B-related cirrhosis with 155 noncirrhotic patients. The 5-year survival rates of cirrhotic and non-cirrhotic patients were comparable (44.3% versus 45.6%, $p=0.216$), even when stratified according to disease stage. In our experience of 15 patients with Child–Pugh B/C, there was one postoperative mortality, six patients dying of disease recurrence and progression, seven patients dying as a result of disease progression with development of liver decompensation, and one patient is currently still alive. Therefore, further evaluation is required to ascertain the value of resection in cirrhotic patients most particularly on the safety of the operation.

Given the need to optimize treatment outcome and improve survival, several adjuvant therapies for resection have been evaluated. Randomized trials evaluating adjuvant chemoembolization and/or chemotherapy have not shown that they are beneficial in preventing disease recurrence.[5,10,11,33,34] Internal radiation with 131-I-labeled lipiodol had a positive effect in a single randomized trial that was prematurely stopped after recruiting 43 patients.[12] A recent update by the authors confirmed that the group treated with 131-I-labeled lipiodol had a significantly better overall survival ($p=0.04$) and disease-free survival ($p=0.04$) than the control arm.[13] Several

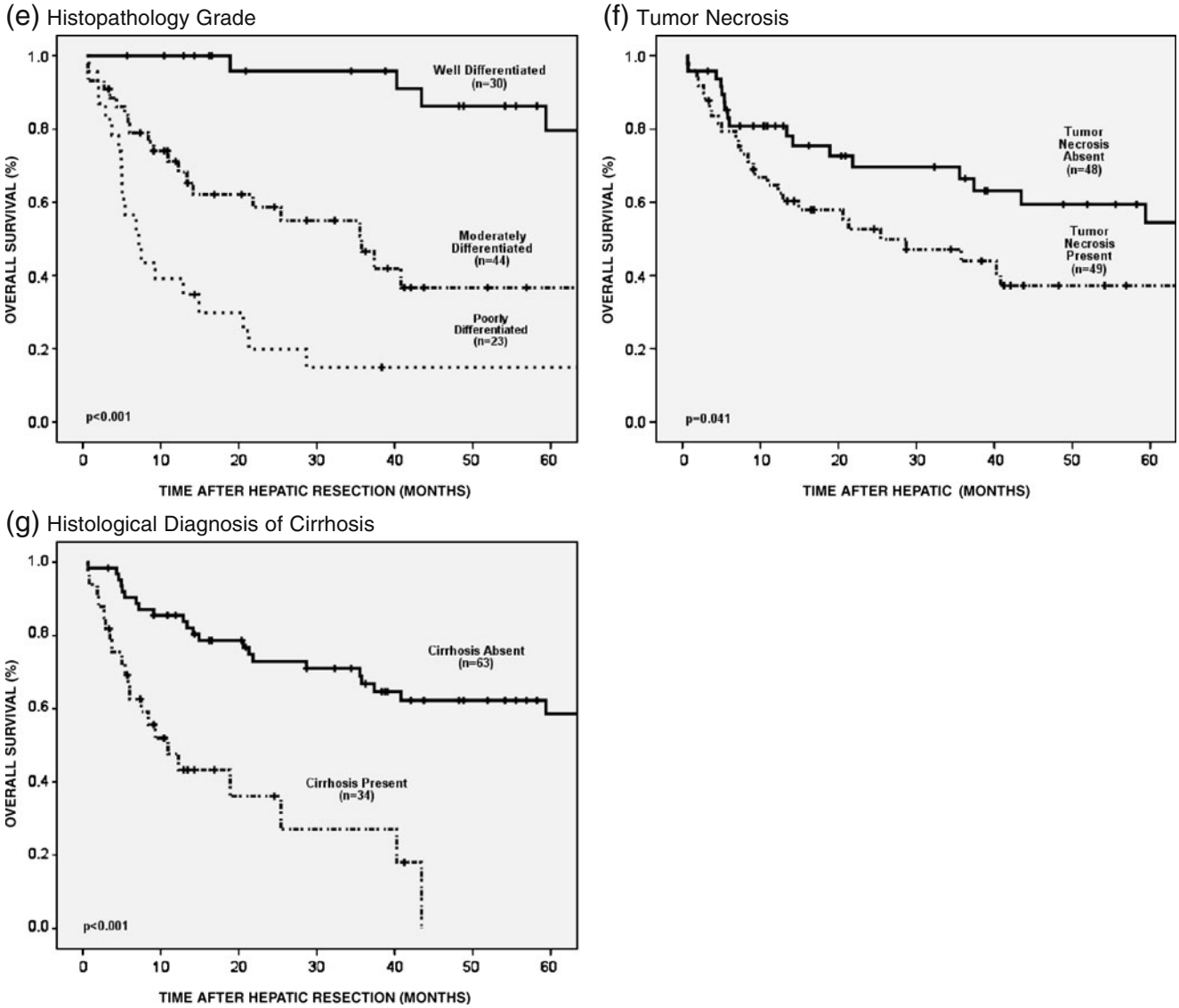

Fig. 3 (continued).

uncontrolled studies investigating this therapy have also been published, yielding promising results.[35] Adoptive immunotherapy by activated lymphocytes with interleukin-2 and antibody to CD3 reduced recurrence by 18% in a randomized trial of 150 patients after a median follow-up of 4.4 years.[17] Retinoid therapy was shown to reduce formation of a second primary tumor by a small randomized study.[16] Confirmatory trials are required to validate the results of these analyses. Interferon-alpha has shown positive results in some randomized trials, although the first trial from a Western institution showed overall negative results.[5] A novel molecular targeted agent, sorafenib, which has recently become a standard of care for advanced disease, may also be promising in an adjuvant setting to prevent early recurrence after curative surgery. Overall, although encouraging data have been reported with improvements in recurrence-free survival, there is no consensus regarding standard adjuvant therapy for resectable HCC. Therefore, expert selection of candidates based on identified risk factor remains fundamental to ensuring optimal treatment outcome.

In conclusion, the increased incidence of HCC in Western countries worldwide, in particular Australia mandates an effective treatment strategy for this malignancy. Surgical resection remains the mainstay of treatment given that liver transplantation is restricted by the scarcity of donors and conclusive evidence on the efficacy of adjuvant therapies is yet to be provided. Consequently, optimal patient selection based on prognostic features specific to a particular population is necessary and this may potentially tailor the use of adjuvant therapies as the evidence of its efficacy becomes available from randomized trials.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74–108.
2. Amin J, O'Connell D, Bartlett M, Tracey E, Kaldor J, Law M, et al. Liver cancer and hepatitis B and C in New South Wales, 1990-2002: a linkage study. Aust N Z J Public Health. 2007;31(5):475–82.
3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340(10):745–50.
4. Deuffic S, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. Lancet. 1998;351(9097):214–5.
5. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol. 2008;48(Suppl 1):S20–37.
6. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–9.
7. Nathan H, Schulick RD, Choti MA, Pawlik TM. Predictors of survival after resection of early hepatocellular carcinoma. Ann Surg. 2009;249(5):799–805.
8. Poon RT, Fan ST, Lo CM, Liu CL, Ng IO, Wong J. Long-term prognosis after resection of hepatocellular carcinoma associated with hepatitis B-related cirrhosis. J Clin Oncol. 2000;18(5):1094–101.
9. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology. 1999;30(6):1434–40.
10. Wu CC, Ho YZ, Ho WL, Wu TC, Liu TJ, P'Eng FK. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. Br J Surg. 1995;82(1):122–6
11. Yamasaki S, Hasegawa H, Kinoshita H, Furukawa M, Imaoka S, Takasaki K, et al. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res. 1996;87(2):206–11.
12. Lau WY, Leung TW, Ho SK, Chan M, Machin D, Lau J, et al. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. Lancet. 1999;353(9155):797–801.
13. Lau WY, Lai EC, Leung TW, Yu SC. Adjuvant intra-arterial iodine-131-labeled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial-update on 5-year and 10-year survival. Ann Surg. 2008;247(1):43–8.
14. Yamamoto M, Arii S, Sugahara K, Tobe T. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. Br J Surg. 1996;83(3):336–40.
15. Ono T, Nagasue N, Kohno H, Hayashi T, Uchida M, Yukaya H, et al. Adjuvant chemotherapy with epirubicin and carmofur after radical resection of hepatocellular carcinoma: a prospective randomized study. Semin Oncol. 1997;24(2 Suppl 6):S6-18–S6-25.
16. Muto Y, Moriwaki H, Saito A. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. N Engl J Med. 1999;340(13):1046–7.
17. Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet. 2000;356(9232):802–7.
18. Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg. 2007;245(6):909–22.
19. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol. 2002;20(6):1527–36.
20. Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg. 2009;249(4):617–23.
21. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol. 2003;38(2):200–7.
22. Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg. 2003;237(4):536–43.
23. Greene FL. The AJCC Cancer Staging Manual. Philadelphia: Lippinscott Raven Publisher; 2002.
24. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Sem Liv Dis. 1999;19:329–338.
25. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology. 1998;28(3):751–5.
26. Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology. 2005;234(3):961–7.
27. Ueno S, Sakoda M, Kubo F, Hiwatashi K, Tateno T, Baba Y, et al. Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within the Milan criteria. J Hepatobiliary Pancreat Surg. 2009;16(3):359–66.
28. Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology. 2001;33(5):1080–6.
29. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg. 2002;235(3):373–82.
30. Mathew T. The Australian experience in organ donation–2003. Ann Transplant. 2004;9(1):28–30.
31. Kumada T, Nakano S, Takeda I, Sugiyama K, Osada T, Kiriyama S, et al. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. Hepatology. 1997;25(1):87–92.
32. Zhou XD, Tang ZY, Yang BH, Lin ZY, Ma ZC, Ye SL, et al. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer. 2001;91(8):1479–86.
33. Kohno H, Nagasue N, Hayashi T, Yamanoi A, Uchida M, Ono T, et al. Postoperative adjuvant chemotherapy after radical hepatic resection for hepatocellular carcinoma (HCC). Hepatogastroenterology. 1996;43(12):1405–9.
34. Lai EC, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. Arch Surg. 1998;133(2):183–8.
35. Boucher E, Corbinais S, Rolland Y, Bourguet P, Guyader D, Boudjema K, et al. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. Hepatology. 2003;38(5):1237–41.

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ORIGINAL ARTICLE

Management of Type I Choledochal Cyst in Adult: Totally Laparoscopic Resection and Roux-en-Y Hepaticoenterostomy

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Abstract
Background/objective Choledochal cysts are congenital dilations of the biliary tree. The accepted mode of treatment is total excision with hepaticojejunostomy. In this retrospective study, we present our technique and results of laparoscopic choledochal cyst excisions.
Methods We retrospectively studied 45 patients who had undergone laparoscopic choledochal cyst excision in our institutes from September 2006 to August 2009. Data including age, gender, type of cyst, symptoms, surgical technique, conversion rate, morbidity, and mortality were analyzed.
Results There were type Ic (cystic) choledochal cysts in 31 patients (68.9%) and type If (fusiform) in 14 patients (31.1%). An anomalous pancreaticobiliary duct junction union was found in 66.7%. Forty percent (18 out of 45) and 37.8% (17 out of 45) cases had stones within the cysts and gallbladders, respectively. The average size of the cysts was 40.3±16.9 cm^2. The mean operative time was 307.7±58.0 min, the estimated operative blood loss was 252.3±162.5 ml, and the conversion rate was 8.9%. The mean hospital stay was 8.3±3.2 days. The overall morbidity rate was 17.1%, the reoperation rate was zero, and the mortality rate was also zero.
Conclusions Totally, laparoscopic management of type I choledochal cysts, although technically challenging, is safe and feasible in experienced hands.

Keywords Choledochal cyst · Laparoscopic · Operation · Adults

Introduction

The highest prevalence of choledochal cysts is found in Asian countries and is typically described as a congenital disease that mostly affects the pediatric population.[1] More than 60% of patients with choledochal cysts are diagnosed during the first decade of life. However, possibly as a result of improved non-invasive hepatobiliary imaging, adults with this disease are increasingly encountered. Extensive literature reviews on the prevalence of choledochal cysts according to type shows that type I cysts (solitary extra hepatic cyst) are most common (79%).[2]

The treatment of choice for a type I cyst is complete excision with creation of an anastomosis. Historically, this has been performed using an open surgical approach. However, choledochal cysts are more commonly diagnosed in young women. This group of patients is especially interested in cosmetic results as well as cure of the disease. In this report, we present our technique and results of totally laparoscopic choledochal cyst excision and biliary enteric reconstruction.

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Methods

Patients

This study took place in the Department of Biliary Surgery of Shengjing Hospital affiliated to China Medical University and Qianwei Hospital in Jilin Province, which maintain a prospective database of all choledochal cyst excisions performed. Forty-five patients with type I choledochal cysts according to the Todani classification scheduled to undergo laparoscopic excision from September 2006 to August 2009 were included in the study. The demographic data and preoperative status of the 45 patients are shown in Table 1. All patients underwent hematologic, liver function and other routine blood tests, chest radiograph, and electrocardiography as part of the preoperative routine workup. Abdominal computed tomography (CT), magnetic resonance cholangiopancreatography, or endoscopic retrograde cholangiopancreatography were performed to demonstrate the presence anomalous pancreaticobiliary duct junction union (APBDJU) and to determine the resection lines of the choledochal cyst and dissection planes. A laparoscopic approach was proposed for all patients after obtaining an informed consent. Prophylactic antibiotics (combination of a third generation cephalosporin with metronidazole) were administered immediately before induction of anesthesia and continued postoperatively for 5 to 7 days.

Operative Technique

General anesthesia was used. The patient was set in the supine position with a 15° reverse Trendelenburg's tilt and pneumoperitoneum created by a closed Veress needle technique through the umbilicus. The port position and team setup were as shown in Fig. 1. A 30° 10-mm telescope was used in all the procedures.

A general exploration of the abdomen was performed. Adequate exposure of the working area was achieved by cranial elevation of the liver and caudal traction of the transverse colon and duodenum.

Table 1 Demographic Data and Preoperative Status

Characteristics	Data
Age (years)	34.4±12.6
Gender	
Female, *n* (%)	33 (73.3)
Male, *n* (%)	12 (26.7)
Presenting symptoms	39 (86.7)
Abdominal pain, *n* (%)	28 (62.2)
Jaundice, *n* (%)	12 (26.6)
Cholangitis, *n* (%)	13 (28.8)
Pancreatitis, *n* (%)	5 (11.1)
None, *n* (%)	6 (13.3)

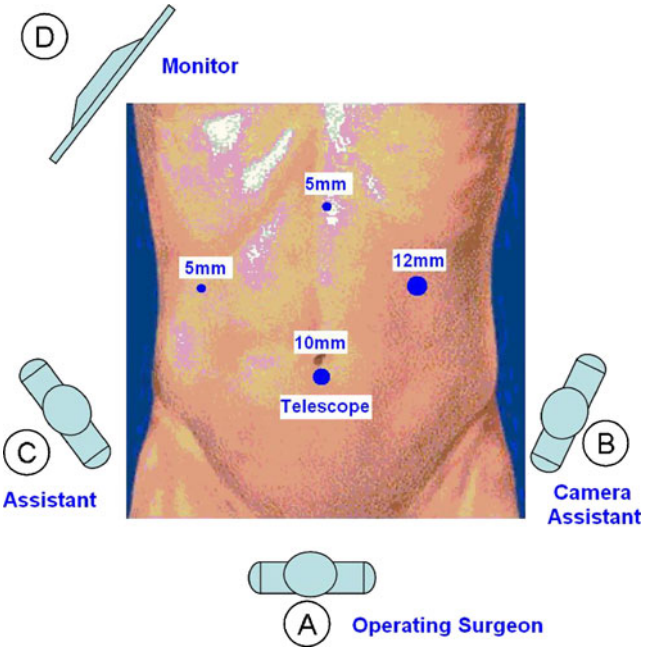

Fig. 1 The port position and team setup.

Resection of the Gallbladder and Choledochal Cyst

First, the fundus of the gallbladder was dissected from its bed toward the hepatic hilus. The cystic artery was identified, double-clipped, and divided. Then percutaneous aspiration was performed to confirm the cyst and bile specimen taken for analysis.

Method 1: Distal-End-First Resection Technique In the case of a medium size or small cyst, the serosa of the hepatoduodenal ligament was incised, and a dissecting plane developed around the choledochal cyst to free the cyst wall from the portal vein and hepatic artery. The duodenum was retracted downward using an intestinal grasper. The choledochal cyst was retracted upward, while the retroduodenal and intrapancreatic portions of choledochal cyst were dissected using ultrasonic shears. After the transition area of choledochal cyst at the head of the pancreas had been confirmed, choledochotomy was performed. In addition, to avoid pancreatic duct injury, intraoperative choledochoscopy was performed to identify the site at which the pancreatic duct joined the common bile duct. In patients with smaller cysts, the entire cyst was mobilized circumferentially without decompression. Once the distal transection line of choledochal cyst had been determined, the distal stump was ligated with ligatures or clipped with absorbable clips. In some patients, however, the pancreatic duct was inserted into the dilated duct. In

such cases, it was not possible to perform a complete excision of the cyst but rather remove the proximal part and leave the lower part attached to the pancreatic duct. With the distal portion of the choledochal cyst pulled upward, dissection was continued along the medial and posterior margin of choledochal cyst until the hepatic duct was identified. Transection of the distal end first allowed for easier dissection of the cyst from adjacent vascular structures. Elevation of the gallbladder and the cyst anteriorly facilitated the identification of small vessels from the hepatic artery and portal vein. Using a sharp edge of a harmonic scalpel, the cyst was then transected on the proximal edge at the hepatic duct. Frozen-section histology was performed in all patients to rule out the presence of malignancy (Fig. 2).

Method 2: Transverse Incision Technique In the case of a large cyst, a transverse incision was made on the anterior wall. The transverse incision over the anterior wall was enlarged toward the left and behind in order to dissect the medial and posterior cyst wall from the hepatic artery and portal vein. Blunt dissection with a suction nozzle was useful for this step of the operation. In our technique, this was achieved by medially and posteriorly extending the transverse incision on the cyst wall. The hepatic artery and portal vein were then separated from the entire length of the cyst. Then the proximal and distal edges of the posterior wall were retracted upward or downward with a grasper to aid in the dissection of the two parts of the cyst (Fig. 3).

Method 3: Lilly Technique Some patients suffered from recurrent attacks of cholangitis. In these cases, injury to the portal vein is possible if attempts are made to remove the entire posterior wall of the cyst especially when adhesions have formed between this wall and the portal vein. In these patients, the anterolateral part of the cyst can be resected and then resection or fulguration of the mucosal lining can follow, leaving a narrow rim of the posterior cyst wall on the portal vein and hepatic artery, as reported by Lilly[3] in 1978 (Fig. 4).

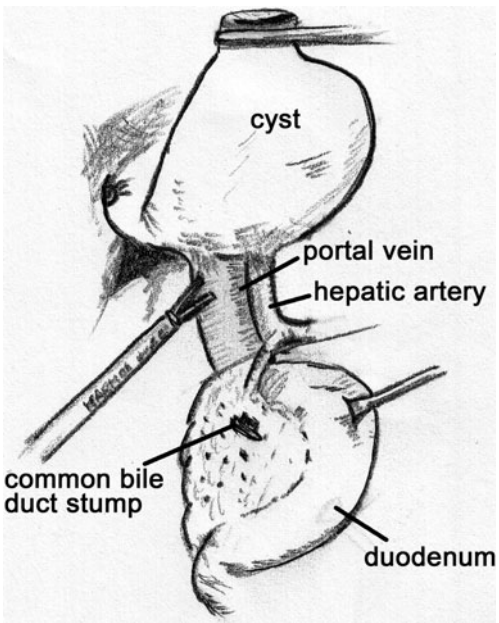

Fig. 2 Distal-end-first resection technique.

Roux-en-Y Loop Construction

After the ligament of Treitz had been identified, the jejunum, 15 cm distal to the duodenojejunal flexure, was transected with a stapler. Then the jejunal mesentery was divided with the harmonic scalpel to make a Roux-en-Y jejunal limb. At least 40 cm of the long limb was used for anastomosis with the proximal hepatic duct. The jejunojejunostomy was established by a side-to-side intracorporeal anastomosis using endostaplers. The Roux loop was constructed in a retrocolic fashion. The residual hole of the anastomosis was then closed with silk sutures (Fig. 5).

Hepaticojejunostomy

After approximation of the jejunum and hepatic duct, a small incision was made at the antimesenteric side of the jejunum for the anastomosis. The hepaticojejunostomy was performed in an end-to-side fashion by intracorporeal suturing. The anastomosis was performed in a single layer using continuous 4/0 Vicryl (Ethicon, US) sutures if the common hepatic duct diameter was more than 1.5 cm, while interrupted sutures were used if ducts were less than 1.5 cm. No decompression tube was placed in all patients. In some cases, the serosa of the jejunum near the anastomosis was fixed to the surface of the hepatic hilum using three or four intracorporeal sutures to reduce the tension of the anastomosis.

Results

Of the 45 patients, the choledochal cyst was of type Ic in 31 patients (68.9%) and type If in 14 patients (31.1%). The average size of the cysts was 40.3 ± 16.9 cm^2 (range 16 to 84 cm^2), and there were 30 (66.7%) patients with an anomalous pancreatobiliary junction. Forty percent (18 out of 45) and 37.8% (17 out of 45) cases had stones within the cysts and gallbladders, respectively (Table 2).

The conversion rate in our series was 8.9% (four of 45). Of the four patients, dense small vessels from the hepatic artery and portal vein resulted in massive bleeding more than 1,500 ml during the dissection of the cysts in three

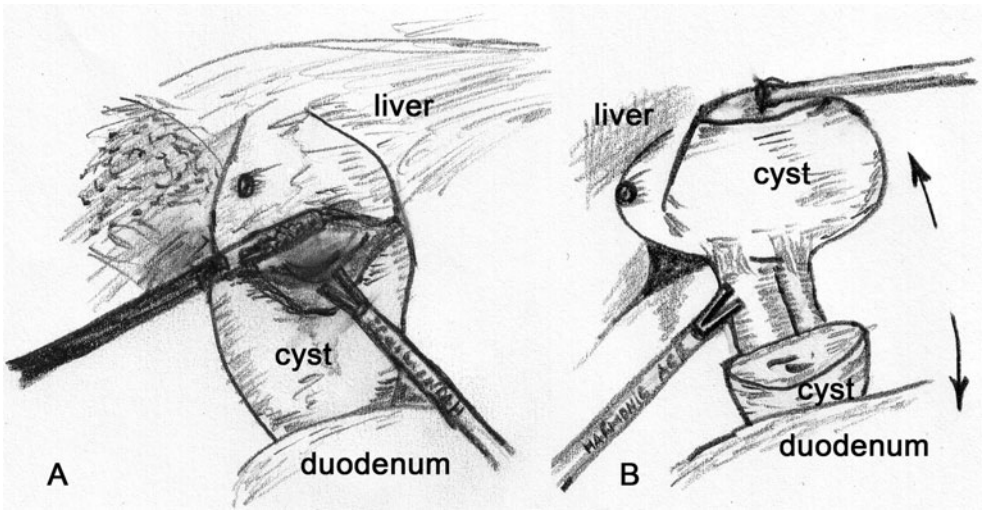

Fig. 3 Transverse incision technique.

patients, so conversions were done. The other patient had a conversion due to suspicion of malignancy, which was subsequently ruled out on histopathology. The remaining 41 patients were treated with the laparoscopic approach (Table 2).

Method 1 was adopted in 19 patients, while in six patients with large cysts, method 2 was adopted. In the rest of patients, the posterior wall of the cyst was so adherent because of previous episodes of cholangitis that method 3 (Lilly's technique) was adopted (Table 2).

In the 18 patients, the diameters of the common hepatic ducts were less than 1.5 cm; thus, hepaticojejunostomies were performed with interrupted sutures. In the other 23 patients with more than 1.5-cm-sized hepatic ducts, continuous sutures were adopted (Table 2).

The mean operative time was 307.7±58.0 min (range 150 to 420 min), and Fig. 6 showed that the operative times improved over the course of the series. The estimated operative blood loss was 252.3±162.5 ml (range 50 to 800 ml). The mean hospital stay was 8.3±3.2 days (range 4 to 20 days) (Table 2).

The overall morbidity rate was 17.1% (seven of 41), although no patients required reoperation. Five patients (12.1%) had self-limiting bile leak, and two patients (4.9%) had repeated episodes of cholangitis after operation. All five bile leaks occurred in patients with hepatic duct sizes less than 1.5 cm. Both patients with postoperative recurrent cholangitis recovered completely with conservative management. There was no mortality in all the patients (Table 2).

Discussion

The classic triad of intermittent jaundice, abdominal mass, and pain was originally described as the key features of

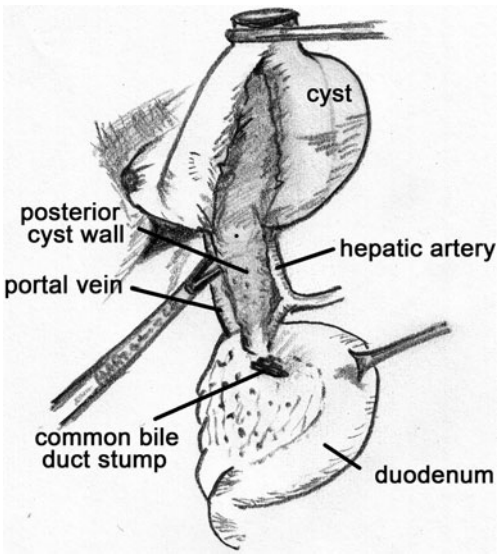

Fig. 4 Lilly technique.

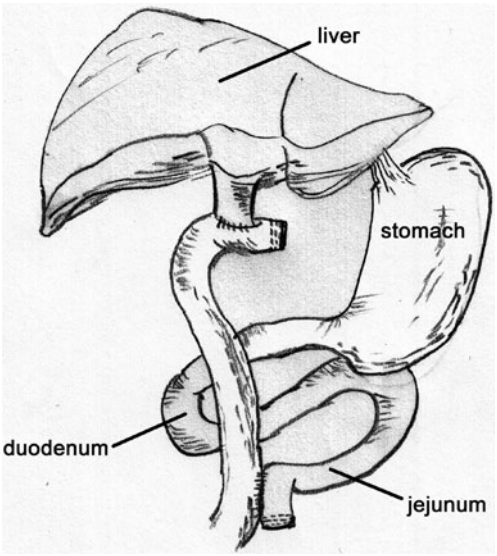

Fig. 5 Roux-en-Y loop construction and hepaticojejunostomy.

Table 2 Operative Characteristics

Characteristics	Data
Subtypes	
Cystic type (Ic), *n* (%)	31 (68.9)
Fuciform type (If), *n* (%)	14 (31.1)
Average size of cysts, cm^2 (range)	40.3 (16–84)
APBDJU, *n* (%)	30 (66.7)
Incidence of carcinoma, n(%)	0 (0)
Common hepatic duct size	
≤1.5 cm, *n*(%)	18 (43.9)
≥1.5 cm, *n* (%)	23 (56.1)
Operative technique	
Method 1: distal-end-first resection technique, *n* (%)	19 (46.3)
Method 2: transverse incision technique, *n* (%)	6 (14.6)
Method 3: Lilly's technique, *n* (%)	16 (39.1)
Operative time, min	307.7±58.0
Estimated blood loss, ml	252.3±162.5
Conversion, *n* (%)	4 (8.9)
Duration of postoperative stay, day	8.3±3.2
Postoperative complication, *n* (%)	7 (17.1)
Self-limiting bile leak, *n* (%)	5 (12.1)
Recurrent cholangitis, *n* (%)	2 (4.9)
Reoperation, *n* (%)	0 (0)
Perioperative death, *n* (%)	0 (0)

choledochal cysts in children but rarely seen in adults. In the present series, the presentation was usually nonspecific, comprising right upper abdominal pain, jaundice, pancreatitis, or cholangitis. Abdominal pain was the predominant feature in this series, and jaundice was more commonly observed in younger patients. In this study, the mean age of the patients presenting with jaundice was 18.6 years old. Such clinical presentations have been corroborated by other studies.[4,5] Pancreatitis may be one of the other major presentations of choledochal cyst in adults. Singham et al.[6] reported that 11% of adults suffered from pancreatitis. Similarly, 11.1% of the patients presented with pancreatitis in our study. Activation of pancreatic enzymes by bile reflux in association with APBDJU or stone obstruction at the common channel is thought to be involved in the pathogenesis of pancreatitis in such patients. Cystolithiasis and gallstones are a frequent accompanying conditions occurring in over 70% of adults with choledochal cyst.[7] In

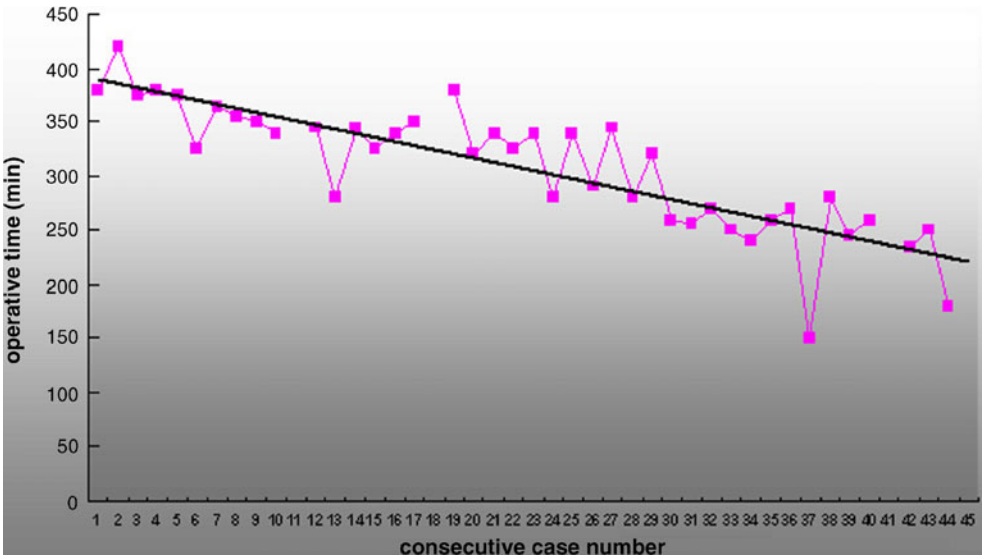

Fig. 6 The operative times improved over the course of the series.

this study, 40% and 37.8% adults had stones within the cyst and gallbladder, respectively, for which bile stasis is thought to be the primary etiologic factor.

Long-term complications such as suppurative cholangitis and cholangiocarcinoma have led to the evolution of the surgical management of choledochal cysts from simple internal or external drainage procedures to complete cyst excision with internal drainage of the biliary tree. At present, total excision of choledochal cysts (types I, II, and IV) with Roux-en-Y hepaticojejunostomy has been widely accepted as the procedure of choice. Laparoscopic surgery for choledochal cysts was first performed on a 6-year-old female child by Farello and colleagues[8] in 1995. Subsequently, in 1998, Shimura et al.[9] reported a case of laparoscopic choledochal cyst excision on a 19-year-old man with a type I cyst. Several published series have highlighted recent advances in laparoscopic resection of choledochal cysts with the Roux-en-Y hepaticojejunostomy in children[10–13] but is rarely seen in adult series.

In our series, we have found that the key principle to performing this procedure laparoscopically began with optimal port placement. This allows for increased maneuverability and the exposure of key structures. Port placement is based on where instruments need to be for safe dissection and ergonomic intracorporeal suturing during the creation of the hepaticojejunostomy. Some authors[9] have commented that the laparoscopic view of the hilum was poor using this technique. In our method, we use the gallbladder for retraction of the liver during the initial phase of the operation and perform cholecystectomy only at the end. This greatly enhances the vision in the hilar area for subsequent dissection.

In the case of large cysts, we recommend opening the cyst on its anterior wall for effective decompression, clearing of debris, and visualization of the mucosa of the cyst to identify malignancy and to aid dissection of the posterior wall of the cyst. Small or medium cysts need not be opened before excision. The conversion rates in published reports range from 0% to 37%,[12,14] and it was 8.9% in our series. The main limitation to completing the procedure laparoscopically is the presence of adhesions, which form as a result of recurrent cholangitis or pancreatitis, so that complete excision of the cysts is not always possible. Three of the four patients in this series who were converted to open surgery had dense inflammatory adhesions connecting the portal vein, hepatic artery, and posterior wall of the cyst, hindering our ability to delineate the surgical planes, which resulted in major bleeding that further obscured the operative field. Injury to the portal vein or hepatic artery was presumed unavoidable if dissection was to be attempted in this group of patients. In the patients with severe to moderate adhesions, we adopted "Lilly technique" to avoid conversion. However, it required due diligence to ensure a complete mucosal excision. It is worth noting that fulguration was safe only if the posterior layer of the cyst was thick from chronic inflammation; otherwise, there was danger of thermal injury to underlying structures. In our series, there was no incidence of portal vein or hepatic artery injury. We agree with other authors in thinking that injection of saline between the mucosa and the posterior wall may help raise the plane of dissection. Unfortunately, we did not apply this technique in our patients for the laparoscopic approach. Overzealous dissection of a densely adherent posterior cyst wall increases the likelihood of potentially deadly hemorrhage, so it should be discouraged, regardless of whether the operation is open or laparoscopic. The proper management of the posterior wall of the cyst and dissection of the distal part of the cyst from the head of the pancreas are the most difficult parts of the entire procedure.[15,16] The decision whether to excise the whole cyst including its posterior wall should be made intraoperatively**.** In our opinion, no attempt should be made to remove the posterior wall if it is adhered to the portal vein. The Kocher maneuver is suitable for mobilizing the head of the pancreas to expose the dilated bile duct located behind the pancreas. This will facilitate the dissection of the intrapancreatic bile duct laparoscopically. After the operation, imaging studies, preferably CT scan, are useful in determining the patency of the pancreatic duct.

Hepaticojejunostomy, choledochojejunostomy, and hepaticoduodenostomy are the common forms of reconstruction that follow laparoscopic choledochal cyst excision.[17–19] However, hepaticojejunostomy and Roux-en-Y anastomoses were recommended by most of the authors. Tanaka et al.[20] considered preservation of a proximal cuff of the choledochal cyst for easier anastomosis. We followed this principle in 18 patients with common hepatic duct size ≤1.5 cm. It has been shown that near complete excision rather than total excision of a cyst will have a negligible effect on the risk of cancer developing later.[21] We preferred placing the long limb of the Roux-en-Y loop in a retrocolic fashion for anastomosis because the length is shorter this way.

One of the commonest complications in the immediate postoperative setting was leakage of bile. Anastomotic leak rates range from 0% to 20%, as reported in a study.[22] A series of 100 patients by Ohi et al.[23] documented only one complication in the immediate postoperative setting—bile leakage at the hepaticoenterostomy, which closed without a reoperation. In our study, we had a self-limited hepaticojejunal anastomotic leak rate of 12.1%. The other relatively common postoperative complications include anastomotic strictures associated with intrahepatic cholelithiasis and cholangitis, liver abscess, and pancreatitis.[24–27] The absence of a normal epithelial lining in adults prevented a mucosa-to-mucosa anastomosis with the intestine; subsequent anastomotic stricture development was therefore not infrequent. In our series, two patients developed anasto-

motic strictures during follow-up. To prevent this complication, most investigators recommend a high-level anastomosis, beyond the relative stenosis in the common bile duct or a reconstructive operation at the junction of the intrahepatic ducts.[23,28] Miyano et al.,[29] however, did not report any problems in their experience of 171 subhilar hepaticoenterostomies. It seems that emphasis should be on achieving a wide, patent anastomosis. The incidence of malignancy after excision has been estimated at 0.7% in a comprehensive review.[30] In our series, no malignancy after operation was reported at 6- to 42-month follow-up. Chen et al.[31] reported a morbidity rate of 20% and a mortality of 3.3% in a series of 60 adult patients who underwent conventional surgery. The complication rate in our study was 17.1% with a 0% mortality rate. Although similar reports on long-term morbidity are sadly lacking in the laparoscopic approach, the short-term morbidity rates that have been published clearly show that the results are superior to those of the open procedures.[32] Nevertheless, the possibility of recurrent strictures and intrahepatic stone formation with malignant change cannot be excluded. Careful long-term follow-up is therefore mandatory.

In conclusion, laparoscopic excision of choledochal cysts, although technically challenging, is safe and feasible in experienced hands. It requires a greater degree of technical skill and dexterity, with adequate experience both in complex biliary operations and advanced laparoscopic surgery. Robotic surgery, with its promise of finer movements and flexible maneuvers, could perhaps improve on some of the challenges experienced during this procedure. The following advantages of the laparoscopic procedure are satisfying: excellent intraoperative visualization, great surgical accuracy, no early postoperative pain, no laparocele, prevention of adhesion, rapid resumption of peristalsis, reduced immunosuppression, excellent esthetics, and quicker resumption of activities. Despite the disadvantages of longer surgical time and higher cost, the overall benefits of this procedure to the patient cannot be underestimated.

References

1. Shi LB, Peng SY, Meng XK, Peng CH, Liu YB, Chen XP, Ji ZL, Yang DT, Chen HR. Diagnosis and treatment of congenital choledochal cyst: 20 years' experience in China. World J Gastroenterol 2001; 7:732–734.
2. Nagorney DM. Bile duct cysts in adults. In Blumgart LH, Fong Y, eds. Surgery of the liver and biliary Tract, vol. 2, 3rd ed. London: Saunders, 2000, pp 1229–1244.
3. Lilly JR.Total excision of choledochal cyst. Surg Gynecol Obstet 1978;146:254–256.
4. de Vries JS, de Vries S, Aronson DC, Bosman DK, Rauws EA, Bosma A, Heij HA, Gouma DJ, van Gulik TM. Choledochal cysts: age of presentation, symptoms and late complications related to Todani's classification. J Pediatr Surg 2002;37:1568–1573
5. Liu CL, Fan ST, Lo CM, Lam CM, Poon RT, Wong J. Choledochal cysts in adults. Arch Surg 2002;137:465–468
6. Singham J, Schaeffer D, Yoshida E, Scudamore C. Choledochal cysts: analysis of disease pattern and optimal treatment in adult and paediatric patients. HPB(Oxford) 2007; 9:383–387
7. Söreide K, Körner H, Havnen J, Söreide JA. Bile duct cysts in adults. Br J Surg 2004;91:1538–1548
8. Farello GA, Cerofolini A, Rebonato M, Bergamaschi G, Ferrari C, Chiappetta A. Congenital choledochal cyst: video-guided laparoscopic treatment. Surg Laparosc Endosc 1995;5:354–358.
9. Shimura H, Tanaka M, Shimizu S, Mizumoto K. Laparoscopic treatment of congenital choledochal cyst. Surg Endosc 1998; 12:1268–1271
10. Ure BM, Schier F, Schmidt AI, Nustede R, Petersen C, Jesch NK. Laparoscopic resection of congenital choledochal cyst, choledochojejunostomy, and extraabdominal Roux-en-Y anastomosis. Surg Endosc 2005;19:1055–1057.
11. Lee H, Hirose S, Bratton B, Farmer D. Initial experience with complex laparoscopic biliary surgery in children: biliary atresia and choledochal cyst. J Pediatr Surg 2004;39:804–807, discussion 804–807.
12. Aspelund G, Ling SC, Ng V, Kim PC. A role for laparoscopic approach in the treatment of biliary atresia and choledochal cysts. J Pediatr Surg 2007;42:869–872.
13. Martinez-Ferro M, Esteves E, Laje P. Laparoscopic treatment of biliary atresia and choledochal cyst. Semin Pediatr Surg 2005;14:206–215.
14. Liu DC, Rodriguez JA, Meric F, Geiger JL. Laparoscopic excision of a rare type II choledochal cyst: case report and review of the literature. J Pediatr Surg 2000;35:1117–1119.
15. Tan HL, Shankar KR, Ford WD. Laparoscopic resection of type I choledochal cyst. Surg Endosc 2003;17:1495.
16. Jang JY, Kim SW, Han HS, Yoon YS, Han SS, Park YH. Totally laparoscopic management of choledochal cysts using a four-hole method. Surg Endosc 2006;20:1762–1765.
17. Watanabe Y, Sato M, Tokui K, Koga S, Yukumi S, Kawachi K. Laparoscope-assisted minimally invasive treatment for choledochal cyst. J Laparoendosc Adv Surg Tech A 1999;9:415–418.
18. Vila-Carbó JJ, Lluna González J, Hernández Anselmi E, Nome Farbinger C, Ayuso González L, Marco Macián A. Congenital choledochal cyst and laparoscopic techniques. Cir Pediatr 2007;20:129–132.
19. Li L, Feng W, Jing-Bo F, Qi-Zhi Y, Gang L, Liu-Ming H, Yu L, Jun J, Ping W. Laparoscopic-assisted total cyst excision of choledochal cyst and Roux-en-Y hepatoenterostomy. J Pediatr Surg 2004;39:1663–1666.
20. Tanaka M, Shimizu S, Mizumoto K, Yokohata K, Chijiiwa K, Yamaguchi K, Ogawa Y. Laparoscopically assisted resection of choledochal cyst and Roux-en-Y reconstruction. Surg Endosc 2001;15:545–552
21. Jordan PH Jr, Goss JA Jr, Rosenberg WR, Woods KL. Some considerations for management of choledochal cysts. Am J Surg 2004;187:790–795.
22. Srimurthy KR, Ramesh S. Laparoscopic management of pediatric choledochal cysts in developing countries: review of ten cases. Pediatr Surg Int 2006;22:144–149.
23. Ohi R, Yaoita S, Kamiyama T, Ibrahim M, Hayashi Y, Chiba T. Surgical treatment of congenital dilatation of the bile duct with special reference to late complication after total excisional operation. J Pediatr Surg 1990;25:613–617.
24. Stain SC, Guthrie CR, Yellin AE, Donovan AJ. Choledochal cyst in the adult. Ann Surg 1995; 222:128–133.
25. Hewitt PM, Krige JE, Bornman PC, Terblanche J. Choledochal cysts in adults. Br J Surg 1995; 82:382–385.
26. Lipsett PA, Pitt HA, Colombani PM, Boitnott JK, Cameron JL. Choledochal cyst disease. A changing pattern of presentation. Ann Surg 1994; 220:644–652.

27. Chijiiwa K, Tanaka M. Late complications after excisional operation in patients with choledochal cyst. J Am Coll Surg 1994; 179:139–144.
28. Todani T, Watanabe Y, Urushihara N, Noda T, Morotomi Y. Biliary complications after excisional procedure for choledochal cyst. J Pediatr Surg 1995;30:478–481.
29. Miyano T, Yamataka A, Kato Y, Segawa O, Lane G, Takamizawa S, Kohno S, Fujiwara T. Hepaticoenterostomy after excision of choledochal cyst in children; a 30 year experience with 180 cases. J Pediatr Surg 1996;31:1417–1421
30. Watanabe Y, Toki A, Todani T. Bile duct cancer developed after cyst excision for choledochal cyst. J Hepatobiliary Pancreat Surg 1999;6: 207–212
31. Chen HM, Jan YY, Chen MF, Wang CS, Jeng LB, Hwang TL, Chen SC, Chao TC. Surgical treatment of choledochal cyst in adults: results and long-term follow-up. Hepatogastroenterology 1996;43:1492–1499.
32. Abbas HM, Yassin NA, Ammori BJ. Laparoscopic resection of type I choledochal cyst in an adult and Roux-en-Y hepaticojejunostomy: a case report and literature review. Surg Laparosc Endosc Percutan Tech 2006;16:439–444.

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ORIGINAL ARTICLE

Factors Predicting Failure Following High Bilio-enteric Anastomosis for Post-cholecystectomy Benign Biliary Strictures

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Abstract
Introduction Failures following Roux-en-Y hepatico-jejunostomy (HJ) for post-cholecystectomy benign bile duct strictures (BBS) pose significant challenge. This study was aimed to find out the factors predicting failure after surgical repair in patients with BBS.
Methods Between January 1989 and May 2007, 364 patients underwent Roux-en-Y HJ to the hilum for BBS. With a median follow-up of 61 (6–212) months, 334 (92%) patients had successful outcome and 30 (8%) had failure. A multivariate analysis was performed to find out the factors predicting failure.
Results Thirty patients who had failure became symptomatic after a median of 35 months (3 days–190 months) after surgical repair. Out of 30 patients, 11 (37%) were experiencing occasional episodes of cholangitis responding to antibiotics. All have patent anastomosis on nuclear scintigraphy and/or cholangiography. Cholangiogram demonstrated anastomotic stricture in 19/30 (63%) patients. Eighteen patients underwent re-intervention for re-strictures (nine — percutaneous balloon dilatation of the stricture, five — revision HJ, one — right hepatectomy, three — a combination of interventions). One patient refused to undergo a planned percutaneous balloon dilatation. Out of 18 patients, 12 (67%) had successful outcome following re-interventions. One patient who underwent revision HJ after a failed percutaneous balloon dilatation died in the immediate postoperative period. Preoperative bilirubin (p=0.001), attempted bilio-enteric anastomosis before referral (0.004), cirrhosis (0.006), portal hypertension (p=0.056), repair in the presence of external biliary fistula (0.000), and spontaneous bilio-enteric fistula (p=0.011) were the factors found to be predicting failure of surgical repair on multivariate analysis.
Conclusions Previous attempts of repair and delay in repair which predispose cirrhosis and portal hypertension may cause failure of surgical management in patients with BBS. In patients presenting with external biliary fistula, for a better outcome, surgical repair may be delayed till the fistula resolves.

Keywords Cholecystectomy · Bile duct injury · Stricture · Hepaticojejunostomy

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Introduction

Major bile duct injuries during cholecystectomy continue to be a concern, more so in the era of laparoscopic cholecystectomy. The incidence of bile duct injury during laparoscopic cholecystectomy is reported as 0.1–1%[1–4] compared to 0.04–0.2 %[3,5,6] in case of open cholecystectomy. Bile duct injury causes significant morbidity, prolongs hospital stay, and necessitates additional interventions. The management of a post-cholecystectomy bile duct injury costs 4.5 to 26 times that of a cholecystectomy.[7] A major bile duct injury leads to a benign biliary

stricture (BBS). Although excellent outcome can be achieved by Roux-en-Y hepatico-jejunostomy (HJ) in majority of patients with BBS, failure rates of up to 21% have been reported even from experienced centers.[8–10] Various factors have been blamed for the failure of HJ for BBS. We have reported our experience with repair of 300 patients with post-cholecystectomy BBS.[11] This study was aimed to find out the factors responsible for failure of HJ following surgical repair of post-cholecystectomy benign bile duct strictures (BBS) in a large group of patients.

Patients and Methods

Four-hundred and fifty-eight patients with post-cholecystectomy BBS underwent surgical repair from January 1989 to May 2009 at a 60-bed Surgical Gastroenterology Unit at a tertiary level referral hospital in northern India. Patients with acute bile duct injuries and those with BBS who were managed conservatively or with endoscopic or radiological intervention as definitive treatment were excluded from this analysis. All patients underwent ultrasonogram (US) of the abdomen. Stricture evaluation was done with percutaneous transhepatic cholangiography (PTC), magnetic resonance cholangiography (MRC), or endoscopic retrograde cholangiography (ERC). PTC was performed in 185 (40%) patients, ERC in 162 (35%), and MRC in 173 (38%). Some patients had multiple cholangiograms. Roux-en-Y HJ was the standard surgical repair. The anastomosis was extended to the left hepatic duct (Hepp–Couinaud approach)[12] to achieve a stoma size of preferably 20 mm. Anastomosis was stented in selected patients, depending upon the stricture type, technical difficulty at operation, and anticipated need for future percutaneous intervention.

Follow-up information was collected by outpatient visits, postal questionnaires, and telephonic interviews. Follow-up evaluation was done by clinical history and examination, liver function tests (LFT), and US. Patients who were eligible for a minimum follow-up of 2 years at the time of analysis (May 2009) were included in the study. Outcome of surgical repair was graded as per the categories suggested by McDonald et al.:[13] Grades A (asymptomatic, normal LFT), B (asymptomatic, mild LFT derangement or occasional episodes of pain or fever), C (pain, cholangitis defined as fever with jaundice, and abnormal LFT), and D (surgical revision or dilatation required). Patients with McDonald's grades A and B were classified as treatment successes. Patients with biliary symptoms or deranged LFT or abnormal US findings were further investigated with Mebrofenin nuclear scintigraphy. Cholangiogram (PTC or MRC) was done if there was biliary dilatation on US or delayed clearance and pooling of the radioactivity above the anastomosis on Mebrofenin scan. Those who had demonstrable stricture of the HJ at cholangiogram were offered re-intervention. Percutaneous balloon dilatation was the initial treatment for re-strictures. Revision repair was done if there was a favorable anatomy for a bilio-enteric anastomosis, or if balloon dilatation failed, or if the patient was not willing for anticipated repeated dilatations.

Patients with McDonald's grade C and D were classified as failures and were further analyzed and compared with those who had successful outcome to find out the factors predicting failure of surgical treatment. Analysis was done using SPSS 13.0 software. Results were expressed as percentages, mean, median, and range. Chi-square test, Fishers exact test, or Student's *t* test was used for univariate analysis, wherever appropriate. Binary logistic regression method was used for multivariate analysis. Significance was calculated at 95% confidence interval.

Results

Out of 458 patients, seven patients died in the immediate or early postoperative period because of surgery-related causes, and three patients died during the follow-up because of causes unrelated to their operation or the biliary disease. Out of the remaining 448 patients, 389 patients who were operated before May 2007 were included in the analysis to have a minimum eligible follow-up period of 2 years. Twenty five patients had a follow-up of less than 6 months and were considered as lost to follow up. The outcome after surgical repair in the remaining 364 patients was analyzed. Median follow-up was 61 (6– 212) months. Out of 364 patients, 334 (92%) had successful outcome [McDonald's grades A — 305 (84%) and B — 29 (8%)], and 30 (8%) patients were categorized as failures [McDonalds' grades C — 11 (3%) and D — 19 (5%)].

Among 30 failures, 23 (77%) were females and seven (23%) were males. Median age was 35 (19– 60) years. Twenty-eight patients had sustained the bile duct injury during open cholecystectomy and two following attempted laparoscopic cholecystectomy. Seven patients underwent emergency re-exploration to control bile extravasation. Out of 30 patients, nine (30%) were referred to us after an attempted repair of bile duct injury elsewhere (repair of the injury was attempted at the time of cholecystectomy in five patients and in four patients, stricture repair was attempted at a later date before referral to us). The first manifestation of bile duct injury was bile leak in 22 (73%) patients and cholangitis in eight (27%) patients. Stricture repair was done at our center after a median delay of 5 months (6 days–16 years) after cholecystectomy.

ERC was done in 14 patients, PTC in 19 patients, and MRC in four patients. Preoperative percutaneous trans-

hepatic biliary drainage (PTBD) was performed in four patients to control cholangitis. Median preoperative serum bilirubin was 4.6 (0.6–21.9) mg/dL and alkaline phosphatase was 486 (35–1862) IU/L. At operation, seven (23%) patients were found to have atrophy–hypertrophy complex (AHC) of the liver which was suspected on preoperative imaging also. Six (20%) patients had cirrhosis of the liver which was confirmed on histopathology, and five (17%) patients had portal hypertension. Thirteen (43%) patients had internal fistula to the duodenum.

Thirteen (43%) patients had low strictures (Bismuth's type I-4 and type II-9), and 17 (57%) had high strictures (Type III-11; Type IV-6). All patients underwent Roux-en-Y HJ. In three patients, right and left hepatic ducts were anastomosed separately to the Roux loop creating two stomas. Trans-anastomotic stents were used in ten patients. In the immediate postoperative period, five (17%) patients had bile leak from the anastomosis, two (7%) patients had intra-abdominal collection, and five (17%) had cholangitis. For intra-abdominal collections, percutaneous drainage was done in one patient, and the other was managed with one-time percutaneous aspiration. Cholangitis and bile leak were managed conservatively in all patients.

These 30 patients became symptomatic after a median of 35 months (3 days–190 months) after surgical repair. The re-stricture free survival is shown in Fig. 1. Eleven (37%) patients are experiencing occasional episodes of cholangitis and have been found to have raised serum bilirubin and/or alkaline phosphatase (McDonald's grade C). The nuclear scintigraphy and or cholangiography could not demonstrate anastomotic stricture in any of these patients. These patients are being managed with antibiotics during the episodes of cholangitis. Nineteen (63%) patients had cholangitis not responding to antibiotics and US demonstrated progressive dilatation of the intrahepatic ductal system. Mebrofenin nuclear scintigraphy demonstrated delayed clearance of radioactivity past the anastomosis. Cholangiogram demonstrated anastomotic strictures in all 19 patients. One patient refused to undergo a planned percutaneous balloon dilatation. This patient had Bismuth's type III stricture with atrophy of the right lobe, and separate stomas were constructed for the right and left ductal systems at the time of initial repair. The remaining 18 patients underwent re-intervention for re-strictures. The revision procedures performed in these 18 patients are described in Table 1. The patient who underwent right hepatectomy had atrophy of the right lobe of the liver 6 years after the initial HJ; she had a Bismuth's type IV stricture at the time of initial repair. One patient did not respond to percutaneous balloon dilatation, and she is still on external biliary drainage. Another patient had retained intrahepatic stone which could not be retrieved by percutaneous methods. The patient who underwent metallic stenting developed stone and sludge impaction 11 years after the stenting which is being managed by percutaneous balloon dilatation. One patient developed cirrhosis during follow-up. The patient who underwent revision HJ after a failed percutaneous balloon dilatation died in the immediate postoperative period because of sepsis. One patient was lost to follow up. The remaining 12/18 (67%) patients had successful outcome following re-interventions.

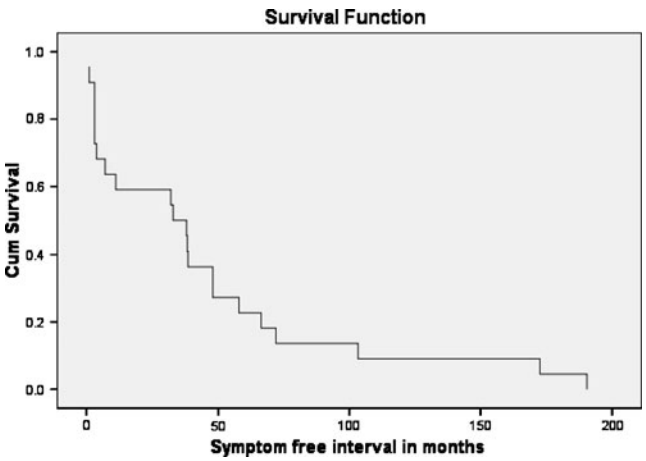

Fig. 1 Symptom-free survival in patients who had failure following initial surgical repair for post-cholecystectomy benign biliary strictures (n=30).

Patients who had successful outcome after the index repair at our center (n=334) were compared with those who had failure (n=30) to find out the predictors of failure following surgical repair of BBS. Factors which may have possible influence on the final outcome of the repair were subjected for univariate and multivariate analysis, and the results are given in Table 2. Among the preoperative parameters, only the total serum bilirubin level was found to be significantly affecting the outcome of repair. The Bismuth's type of stricture was not found to be a factor predicting the failure of repair. Twenty-four percent of patients who had failure had a history of attempted bilio-enteric anastomosis before referral to us compared to 7% in those who had successful outcome. Sixty percent of the

Table 1 Re-interventions in Patients who had Failure (McDonald's Grade D) Following Surgical Repair for Post-cholecystectomy BBS

Type of procedure	n=18
PBD	9
Metallic stenting followed by PBD	1
Revision HJ	5
PBD followed by revision HJ	1
Revision HJ followed by PBD	1
Right hepatectomy	1

HJ hepaticojejunostomy, *PBD* percutaneous balloon dilatation

Table 2 Factors Predicting Failure of Surgical Repair of Post-cholecystectomy Benign Biliary Strictures

Factor	Success: 334/364 (92%)	Failure: 30/364 (8%)	*P* Value (univariate analysis)	*p* Value (multivariate analysis)
Preoperative bilirubin (mean; mg/dL)	4.9	7.5	0.035	0.001
Attempted repair during index operation	18 (5%)	5 (17%)	0.009	0.263
Bilio-enteric anastomosis before referred to us	24 (7%)	7 (24%)	0.001	0.004
Cirrhosis	15 (5%)	7 (23%)	0.000	0.006
Portal hypertension	7 (2%)	5 (17%)	0.000	0.056
Repair in the presence of EBF	92 (28%)	18 (60%)	0.000	0.000
Bilio-enteric fistula	91 (27%)	13 (43%)	0.052	0.011
Atrophy-hypertrophy complex	36 (11%)	7 (23%)	0.021	0.459
Anastomotic leak	13 (4%)	5 (17%)	0.002	0.432

patients who had failure had persistent external biliary fistula (EBF) at the time of operation which also affected the final outcome of repair. Post-HJ anastomotic leak was a factor found to be significant in univariate analysis.

Discussion

Roux-en-Y HJ is the standard surgical treatment for post-cholecystectomy BBS. Addition of Hepp–Couinaud approach to the high bilio-enteric anastomosis has significantly increased the success rate of HJ.[12,13] Failure following HJ is a cause of concern even to an expert hepato-biliary surgeon. In series reporting high success rates following revision repair, initial repairs were mostly done at peripheral centers. Majority of these initial repairs, done at peripheral centers, are unlikely to be a high bilio-enteric anastomosis, and subsequent successful repairs can be performed by a high anastomosis because of the availability of the ductal system, especially the left hepatic duct, above the stricture. In contrast, failures following a high bilio-enteric anastomosis pose a challenging management problem because of the difficult anatomy of re-strictures. Failure rate as high as 50% was reported by Chapman et al.[10] for re-intervention for recurrent BBS following primary repair at the same center. Other large series have reported better success rates by judicious use of balloon dilatation and revision HJ.[8,14]

Out of 364 patients analyzed in this series, 55 (15%) patients were referred to us after failure of the bile duct injury repair done elsewhere. We noticed a significant difference in the repair–recurrence interval between patients who had recurrent strictures following repair elsewhere and those who failed after primary repair at our institution (median 1.6 vs. 35.0 months; $p=0.001$), indicating that most of the repairs done elsewhere had early failures, perhaps due to technical reasons.[14] The choice of subsequent intervention was mainly guided by the biliary anatomy. In patients with early (technical) failure and cholangiogram showing an intact left hepatic duct, surgical revision was the preferred option. Operative repair using the left hepatic duct showed high success rate in published series.[15] Patients referred to us with recurrent strictures following primary repairs done elsewhere had a 94% successful outcome after revision repair done by us. On the other hand, 12/18 (66%) patients who had failure following primary repair done by us had excellent outcome following a combination of interventions. Schmidt et al.[16] reported nine (17%) failures following HJ in 54 patients — five of this had a successful outcome after endoscopic/repeat surgical intervention. Chapman et al.[10] reported 25 (23%) failures following repair in 108 patients — 11/22 had a good final outcome after further intervention. The Johns Hopkins Group had 13 (9%) failures in 142 patients following repair of bile duct injury — ten had final successful outcome after subsequent interventions.[8]

Only a few studies have addressed the issue of causes of failures following surgical repair of BBS. Various risk factors have been suggested to influence the outcome of repair in these patients. Injury–repair interval, preoperative stenting, and duration of postoperative stenting were not found to influence the outcome of repair.[13,17] Our study also reports similar findings. Number of previous repairs was found to be a factor associated with the development of re-stricture in some reports.[10,18] Among the nine failures reported by Schmidt et al.,[16] five had undergone previous attempts at repair. But contradictory reports are also available.[8,13] Previous attempt at repair with a bilio-enteric anastomosis was found to be an independent predictor of poor outcome in our series. This may be because attempted repair by HJ near the hilum makes subsequent surgical repair difficult and challenging. Conversely, a low repair either by end-to-end bile duct anastomosis or choledochoduodenostomy (commonly performed procedure by general surgeons) leaves adequate stumps of untouched higher ducts for subsequent revision repairs.

Repair in presence of either external or internal biliary fistula was also a factor predicting poor outcome in our series. The presence of fistula does not allow the inflammation near the bile duct to settle completely. Moreover, the undilated ductal system makes the anastomosis technically difficult. These may be the causes for more unfavorable outcome in patients who present with continuing bile leak. Schmidt et al.[16] found the presence of peritonitis at the time of repair to be a risk factor for failure of HJ.

Repair in patients with strictures at or above the level of confluence of the left and right ducts (Bismuth's types III, IV, and V) has been found to be another risk factor for failure in some series.[10,16] Blumgart and others[19,20] have also emphasized the relationship between level of stricture and early and late results. We could not, however, find any difference in the outcome of repair between patients with low (Bismuth's type I and II) and high (Bismuth's type III, IV, and V) strictures.

Stricture repair in presence of cirrhosis and portal hypertension was another factor which affected the outcome of repair in our series. Portal hypertension has been found to be associated with higher mortality following stricture repair in one series.[10] Although preoperative portosystemic shunt has been advocated by some authors, we did not perform a shunt before HJ in any of our patients. AHC distorts the biliary anatomy which may result in misidentification of ducts at the time of repair. Presence of cirrhosis, portal hypertension, AHC, or a combination of any of these makes the performance of a high bilio-enteric anastomosis a tedious job for the surgeon.

Proper delineation of the biliary anatomy by a preoperative cholangiogram is of paramount importance for the planning of stricture repair. Presently, MRC is our preferred method of cholangiogram. Performance of stricture repair with a wide mucosa to mucosa bilio-enteric anastomosis is essential for getting optimal results in patients with BBS.[21] The bile duct heals by the mechanism of overhealing after an injury.[22] It is essential to achieve wide and adequate anastomosis at operation because the final stoma size after healing will be less than the original anastomosis diameter made at operation.

In this report, we have described our experience of surgical repair in patients with BBS in a large volume center with sufficient experience in managing complex biliary problems. One of the preventable factors for failure was a previous unsuccessful attempt at bilio-enteric anastomosis. It is, therefore, recommended that the first attempt at repairing a BBS should be made by an experienced biliary surgeon at a high volume center. Even in these centers some bilio-enteric anastomoses may fail (re-stricture). Successful outcome could be achieved in majority of patients with re-strictures following bilio-enteric anastomosis with judicious use of a combination of percutaneous balloon dilatation and revision surgery. Risk factors for failures may help the surgeon to identify patients who are likely to fail following a bilio-enteric anastomosis and to keep them under close follow up with LFT, US, isotope scan, and MRC to detect re-stricture early before cirrhosis — another factor for failure — sets in.

References

1. Deziel DJ, Millikan KW, Economou SG, et al. Complications of laparoscopic cholecystectomy: a national survey of 4292 hospitals and an analysis of 77604 cases. Am J Surg 1993; 165: 9–14.
2. Richardson MC, Bell G, Fullarton GM. Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: an audit of 5913 cases. Br J Surg 1996; 83: 1356–60.
3. Russell JC, Walsh SJ, Mattie AS, et al. Bile duct injuries, 1989–1993 — a state wide experience. Arch Surg 1996; 131: 382–88.
4. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991; 324: 1073–78.
5. Roslyn JJ, Binns GS, Hughes EFX, et al. Open cholecystectomy — a contemporary analysis of 42,474 patients. Ann Surg 1993; 218: 129–137.
6. Gilliland TM, Traverso LW. Modern standards for comparison of cholecystectomy with alternative treatments for symptomatic cholelithiasis with emphasis on long term relief of symptoms. Surg Gynecol Obstet 1990; 170: 39–44.
7. Savader SJ, Lillemoe KD, Prescott CA, et al. Laparoscopic cholecystectomy related bile duct injuries — a health and financial disaster. Ann Surg 1997; 225: 268–73.
8. Lillemoe KD, Melton GB, Cameron JL, et al. Post operative bile duct strictures: management and outcome in the 1990s. Ann Surg 2000; 232: 430–41.
9. Mercado MA, Chan C, Tielve M, et al. Iatrogenic injury to the bile duct — experience with repair in 180 patients. Rev Gastroenterol Mex 2002; 67: 245–49.
10. Chapman CW, Halevy A, Blumgart LH, et al. Post cholecystectomy bile duct strictures — management and outcome in 130 patients. Arch Surg 1995; 130: 597–604.
11. Sikora SS, Pottakkat B, Srikanth G, et al. Post cholecystectomy benign biliary strictures — long term results. Digest Surg 2006;23 (5–6):304–12.
12. Hepp J. Hepaticojejunostomy using the left biliary trunk for iatrogenic biliary lesions: the French connection. World J Surg 1985; 9: 507–11.
13. McDonald MI, Farnell MB, Nagorney D, et al. Benign biliary strictures: repair and outcome with a contemporary approach. Surgery 1995; 118: 582–91.
14. Pottakkat B, Sikora SS, Kumar A, et al. Recurrent bile duct stricture — causes and long term results of surgical management. J HPB Surg 2007;14(2):171–6.
15. Murr MM, Gigot JF, Nagorney D, et al. Long term results of biliary reconstruction after laparoscopic bile duct injuries. Arch Surg 1999; 134: 604–10.
16. Schmidt SC, Langrehr JM, Hintze RE, et al. Long-term results and risk factors influencing outcome of major bile duct injuries following cholecystectomy. Br J Surg 2005; 92: 76–82.
17. Pellegrini CA, Thomas MJ, Way LW. Recurrent biliary stricture — pattern of recurrence and outcome of surgical therapy. Am J Surg 1984; 147: 175–80.

18. Chaudhary A, Chandra A, Negi SS, et al. Reoperative surgery for post cholecystectomy bile duct injuries. Dig Surg 2002; 19: 22–27.
19. Blumgart LH, Kelly CJ, Benjamin IS. Benign bile duct stricture following cholecystectomy: critical factors in management. Br J Surg 1984; 71: 836–43.
20. Mathews JB, Blumgart LH. Benign biliary strictures. In Blumgart LH, editor. Surgery of the liver and the biliary tract. 2nd ed. London: Churchill Livingstone; 1994. p. 865–94.
21. Moosa AR, Mayer D, Stabile B. Iatrogenic injury to the bile duct — who, how, where? Arch Surg 1990; 125: 1028–30.
22. Geng ZM, Yao YM, Liu QG, et al. Mechanism of benign biliary stricture: a morphological and immunohistochemical study. World J Gastroenterol 2005; 11: 293–95.

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ORIGINAL ARTICLE

Binding Versus Conventional Pancreaticojejunostomy After Pancreaticoduodenectomy: A Case-Matched Study

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Abstract
Background Postoperative morbidity of pancreaticoduodenectomy remains high and is mainly related to postoperative pancreatic fistula. Peng et al. (J Gastrointest Surg 2003;7:898–900; Am J Surg 2002;183:283–285; Ann Surg 2007;245:692–298) recently described binding pancreaticojejunostomy and reported a zero percent rate of pancreatic fistula. The aim of this study was to compare postoperative outcome of binding pancreaticojejunostomy and conventional pancreaticojejunostomy after pancreaticoduodenectomy.
Methods Between June 2006 and June 2008, a case-control study was conducted, including all patients with binding pancreaticojejunostomy after pancreaticoduodenectomy. These patients were matched with similar patients with conventional pancreaticojejunostomy. Matching criteria were as follows: age, body mass index, pancreatic texture, and pancreatic main duct size. Postoperative mortality and morbidity were analyzed. Postoperative pancreatic fistula was defined according to the International Study Group of Pancreatic Surgery.
Results Twenty-two patients with binding pancreaticojejunostomy and 25 with conventional pancreaticojejunostomy were included. There was no difference concerning the rate of postoperative pancreatic fistula, but median delay for healing of postoperative pancreatic fistula was longer in the binding pancreaticojejunostomy group (29 vs. 9 days, $p=0.003$). Postpancreatectomy hemorrhage was more frequent in the binding pancreaticojejunostomy group (6/22 vs. 0/25, $p=0.023$).
Conclusion Results of this study showed that binding pancreaticojejunostomy after pancreaticoduodenectomy was not associated with lower postoperative pancreatic fistula and moreover seems to increase postpancreatectomy hemorrhage.

Keywords Pancreaticoduodenectomy · Binding pancreaticojejunostomy · Pancreatic fistula · Postpancreatectomy hemorrhage

Introduction

With recent improvement of postoperative mortality, indications for pancreaticoduodenectomy (PD) are increasing, recently adding benign neoplasms and nonneoplastic conditions to the classical periampullary cancer.[1,2] However, postoperative morbidity of PD remains high[3–5] and is mainly correlated with the occurrence of a leakage from the pancreatic anastomosis. Postoperative pancreatic fistula (POPF) is observed with an incidence ranging between 5% and 30%[3,6–10] after PD and, besides morbidity, largely contributes to mortality and longer hospital stay.[1,11]

Many risk factors for POPF have been identified including pancreatic parenchyma characteristics,[12–14] pancreatic main duct size,[12,13,15,16] and technical factors such as anastomosis technique.[1,13] Several techniques have been described for safe surgical management of the pancreatic remnant, including main duct stenting, pancreaticogastrostomy, and pancreaticojejunostomy with duct to mucosa anastomosis or intussusception, but none has a clearly proven superiority over the others and subsequently became widely accepted.[10,17–22]

Recently, Peng et al.[23,24] described a new anastomosis technique, called binding pancreaticojejunostomy (BPJ).

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The originality of this technique lies in an intussusception of the pancreatic stump inside the jejunum after destruction of the jejunal mucosa. In 2007, a randomized control trial comparing BPJ with conventional pancreaticojejunostomy (CPJ) in 217 patients reported an exceptional zero percent rate of pancreatic leakage after BPJ.[25]

Impressed by these results, we aimed to prospectively assess the operative results of this technique. To our knowledge, this study is the first report of BPJ after PD in a western high-volume center.

Methods

Patients

All patients undergoing a PD in our center are prospectively entered in a database.

Patients with a pancreatic reconstruction according to the Peng technique (BPJ) operated between June 2006 and June 2008 were identified and manually matched to all identical patients from the database with conventional end-to-side pancreaticojejunostomy (CPJ) and operated in the same period, according to the individual matching procedure published by Miettinen.[26] To avoid possible bias related to the learning curve of the technique, the six first cases performed from January 2006 to May 2006 were excluded from this study.

Matching criteria were age (±10%), body mass index (±10%), score of the American Society of Anesthesiologists (ASA), pancreatic texture (soft or hard, according to the intraoperative surgeon's assessment), and pancreatic main duct size (≤3 or >3 mm, defined on preoperative morphologic assessment or intraoperative observation). Investigators were blinded to the primary and secondary end points in both groups during manual matching to reduce bias.

Surgical Procedures

In both groups, after completion of the PD by the standard technique, hemostasis of the pancreatic transection margin, was achieved suturing all arterial and venous vessels with 4/0 and 5/0 nonabsorbable monofilament sutures.

BPJ was realized according to the original technique previously described by Peng et al.[23–25] The jejunal stump was everted for a length of 3 cm by applying two sutures to the jejunal cut edge. The jejunal mucosa was then destroyed using electrocautery. The remnant of the pancreas was mobilized for a distance of at least 3 cm from the pancreatic transection margin. Anastomosis was performed in two layers. First, the cut edge of the pancreatic stump and the everted jejunal mucosa were anastomosed using 4/0 polypropylene monofilament suture. Pancreatic duct was involved whenever technically possible (i.e., with sufficient dilatation). The everted jejunum was then restored to its normal position to wrap over the pancreatic stump, and the jejunal seromuscular layer was sutured to the pancreatic capsule with four interrupted monofilament sutures for fixation. Finally, a 3/0 polyglactine ligature was looped around the jejunum 1.5 to 2 cm from its cut edge, through a hole in the mesentery, and was tied just tight enough to allow the tip of a haemostatic clamp to pass underneath the ligature.

CPJ with end-to-side anastomosis was realized in a single layer using interrupted 4/0 polypropylene monofilament suture. Pancreatic duct was also involved whenever technically possible. The proximal jejunal stump was closed with a linear stapler.

Only two surgeons performed all pancreatic anastomoses.

After pancreatic reconstruction, an end-to-side hepaticojejunostomy and an end-to-side retrocolic gastrojejunostomy completed the reconstruction for both groups, performed on the same jejunal loop at 20 and 40 cm from the pancreaticojejunostomy, respectively.

At the end of the operation, a multichannel open passive silicone drain was placed close to the pancreatic and biliary anastomoses and pulled out through the right flank of the patient.

Octreotide (Sandostatine; Novartis, Rueil-Malmaison, France; 100 μg subcutaneously, three times per day) was given for 7 days in patients with soft pancreatic remnant as prophylaxis of POPF. Patients with hard pancreas did not receive octreotide.

Surgical drainage output was recorded daily. Serum amylase level and amylase level in drainage fluid were monitored on postoperative days 3, 5, 7, and 10. Computed tomography (CT) scan was systematically performed in case of complicated postoperative course.

Outcome Measures

Primary end point was the occurrence of a postoperative pancreatic fistula (POPF). Secondary end points were grade of POPF severity, duration of POPF, occurrence of delayed gastric emptying (DGE), occurrence of postpancreatectomy hemorrhage (PPH), occurrence of intraabdominal abscess, and length of hospital stay.

POPF was defined according to the International Study Group of Pancreatic Surgery (ISGPS) all inclusive definition as a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content more than three times the serum amylase activity.[27] Severity of POPF was staged according to its clinical impact into three grades: A (no clinical impact), B (minor adjustment on the clinical pathway), and C (major change in the clinical management) according to the ISGPS graduation system.[27] Duration of POPF was

calculated until there was no measurable volume of drainage fluid.

DGE was defined as either nasogastric tube decompression for 10 days, emesis after nasogastric tube removal, or failure to progress with diet at day 14.[28,29] Medical morbidity included cardiac, pulmonary, and renal complications not related to surgical complications.

PPH was defined according to the ISGPS as postoperative episode of hemorrhage[30] and was classified as early (<24 h after the end of PD) or late PPH (≥24 h after the end of PD).[30] Two groups of PPH were defined according to hemorrhage localization[30]: perianastomotic group included all intraluminal hemorrhages and all intraperitoneal hemorrhages from peripancreatic structures (all peripancreatic vessels, pancreatic cut surface, suture line of the pancreaticojejunostomy site, and the retroperitoneal area of resection). Distant hemorrhage group included all hemorrhages from distant structure to the anastomotic area (i.e., suture line of the gastrojejunostomy, gall bladder fossa after cholecystectomy, or any distant intraperitoneal structure). Origin of PPH was localized on CT scan with intravenous contrast injection, on angiography or at reoperation.

Statistical Analysis

Continuous data are presented as median (range) and were compared with the Mann–Whitney *U* test. Proportions are presented as number of cases/total number of patients and were compared with either the Pearson's χ^2 test or the Fisher's exact test, as appropriate. The level of statistical significance was set at $p<0.05$, and tests were always two-sided. Analysis was performed using Statistical Package for the Social Sciences (version 16.0; SPSS, Chicago, IL).

Results

Population and Preoperative Findings

Between June 2006 and June 2008, 139 patients had a PD in our institution. Among them, 22 patients had a pancreaticojejunostomy according to the Peng technique, constituting the BPJ group. These patients were matched to 25 identical patients with CPJ from the database, constituting the control group.

As described in Table 1, groups were comparable on the matching criteria: age ($p=0.654$), body mass index ($p=0.601$), ASA score ($p=0.773$), pancreatic texture ($p=0.920$), and distribution of pancreatic main duct dilatation ($p=0.861$)

There was also no statistical difference between the two groups concerning gender (12/22 of male in the BPJ group vs. 13/25 in the control group, $p=0.861$), distribution of malignancy (16/22 in the BPJ group vs. 19/25 in the control group, $p=0.797$), and preoperative biliary drainage (8/22 in the BPJ group vs. 8/25 in the control group, $p=0.753$).

Postoperative Mortality and Morbidity

Postoperative course in both groups is detailed in Table 2.

There was no significant difference between both groups concerning mortality (0/22 in the BPJ group vs. 1/25 in the control group, $p=0.343$). One patient died in the control group from acute hepatic failure developed on chronic liver disease after PD with portal reconstruction.

Overall morbidity, medical morbidity, and surgical morbidity showed no difference between both groups. Moreover, overall medical and surgical morbidities in the control group were also equivalent to those observed in the remaining 92 patients (data not shown).

The incidence of POPF was not different between BPJ and control groups with rates of 8/22 and 7/25, respectively. Severity of POPF showed no difference between both groups. POPF from the BPJ groups had a statistically longer median duration than the control group (29 [9–95] vs. 9 [7–30] days, respectively; $p=0.003$).

Management of POPF graded B or C included enteral nutrition (3/10), total parenteral nutrition (5/10), antibiotics (3/10), percutaneous drainage (1/10), and relaparotomy for POPF-induced sepsis (1/10).

PPH was significantly more frequent in the BPJ group (6/22 in the BPJ group vs. 0/25 in the control group, $p=0.023$). Moreover, all PPH occurred more than 24 h after the end of the PD (and were therefore considered as late PPH) and occurred from the peripancreatic region. PPH treatment included blood transfusion (5/6), angiography followed by arterial embolization (4/6), and relaparotomy for a severe PPH with hypovolemic shock (1/6). PPH occurred in two patients with POPF and in four patients without postoperative anastomotic leak. In these four latter patients, PPH was strictly intraluminal and CT scan localized its origin from the pancreatic stump.

The rate of reoperation did not differ between both groups. Incidence of abdominal abscess, DGE, and medical morbidity showed no difference between both groups. Postoperative hospital stay showed no difference between both groups concerning either intensive care unit stay or overall stay. Incidence of POPF, PPH, and reoperation also did not differ between the control group and the 92 remaining patients.

Discussion

POPF remains a major cause of postoperative morbidity after PD and contributes significantly to postoperative

Table 1 Preoperative Findings of 47 Patients Undergoing PD (Matching Criteria are in Bold Characters)

	BPJ group (n=22)	Control group (n=25)	*p*-value
Age (y)	**58 (19–77)[a]**	**60 (20–75)[a]**	**0.654**
Gender (male)	12 (55)[b]	13 (52)[b]	0.861
Body mass index	**22 (18–37)[a]**	**22 (18–39)[a]**	**0.601**
ASA score	**2 (1–3)[a]**	**2 (1–3)[a]**	**0.773**
Malignant disease	16 (73)[b]	19 (76)[b]	0.797
Preoperative biliary drainage	8 (36)[b]	8 (32)[b]	0.753
Hard pancreatic texture	**12 (55)[b]**	**14 (56)[b]**	**0.920**
Main pancreatic duct >3 mm	**10 (46)[b]**	**12 (48)[b]**	**0.861**

[a] Median (range)

[b] Number (percent) of patients

mortality. Surgical technique has been shown to be one of the important factors in the prevention of POPF, and therefore, several pancreatic reconstruction techniques have been proposed.[10,17–22] In our institution, the standard reconstruction technique was pancreaticogastrostomy for several years.[8,31] Peng et al.[23–25] have recently reported results of BPJ after PD in three studies and highlighted the low morbidity associated with this technique. Impressed by these results, we aimed to prospectively assess BPJ in order to improve postoperative outcome of PD. To our knowledge, the present study is the first report of the postoperative results of BPJ after PD in a western high-volume center.

In this case-control study of 22 patients with PD and BPJ according to Peng technique, POPF was observed in 8 of 22 of the patients with no statistical difference from the control group composed of 25 patients with PD and CPJ. Moreover, duration of POPF observed after BPJ, with a median duration of 29 days, were significantly longer than those observed in control group (median duration: 9 days). Third, BPJ was associated with a high rate of PPH (8/22), all from a peripancreatic origin. The results of BPJ in the present study compare unfavorably to those reported in the Peng's trial.

In the present study, BPJ was realized according to the technique reported by Peng et al.,[23–25] with only slight

Table 2 Postoperative Course of 47 Patients After PD

	BPJ group n = 22	Control group n = 25	*p*-value
Mortality	0	1 (4)[a]	0.343
Morbidity			
Post-operative pancreatic fistula (POPF)			
Overall	8 (36)[a]	7 (28)[a]	0.539
Grade of severity			
A	2 (25)[a]	3 (43)[a]	
B	4 (50)[a]	4 (57)[a]	0.336
C	2 (25)[a]	0	
Duration (days)	29 (9-95)[b]	9 (7-30)[b]	0.003
Post-pancreatectomy hemorrhage	6 (27)[a]	0	0.023
Biliary leak	0	1 (4)[a]	0.343
Abdominal abscess	5 (23)[a]	2 (8)[a]	0.157
Delayed gastric emptying	4 (18)[a]	3 (12)[a]	0.553
Medical morbidity	4 (18)[a]	10 (40)[a]	0.187
Total (patients with one or more complications)	*14 (64)[a]*	*15 (60)[a]*	*0.798*
Reoperation	*2 (9)[a]*	*3 (12)[a]*	*0.747*
Postoperative hospital stay			
Intensive care unit (days)	2 (1-60)[b]	2 (1-13)[b]	0.616
Total (days)	22 (12-100)[b]	20 (6-40)[b]	0.488

a: number of patients (percentage of patients)
b: median (range)

[a] Number (percent) of patients

[b] Median (range)

differences from its original description. Jejunal mucosa destruction was obtained using electrocautery, while Peng et al. favored chemical destruction in the most recent publication[25] but originally described the technique using both methods.[23,24] Furthermore, we did not routinely test the BPJ for watertight closure, as originally described.[23–25] However, all three safety measures described by Peng et al.[24] were carefully fulfilled: jejunal mucosa destruction, anastomotic sutures penetration of the only inner jejunal mucosa layer (to avoid injury of the muscular and serosal layer of the jejunum), and binding of the jejunum to the pancreatic remnant.

The high POPF rate (8/22) after BPJ following PD in this study contrasts with previous reports of this technique.[23,25] Peng et al. reported the results of 150 consecutive PD with BPJ with a 0% of POPF rate,[23] yet with a higher methodological quality than the present study. This result might be partially explained by the definition of POPF used. The present study considered the ISGPS all-inclusive definition as an "Output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than three times the upper normal serum value",[27] whereas Peng et al., in 2007, reported a 0% POPF rate using a narrower definition of POPF as "the drain fluid amylase level being 3 times or more the upper limit of the normal amylase level from the third postoperative day onward when the drain output was ≥10 mL",[25] potentially excluding some cases of POPF with low volume output. Such POPF is not frequently associated with major clinical impact and is commonly graded as A according to the ISGPS graduation system.[27] However, in the present study, 75% of the POPF observed in the BPJ group were graded B or C and therefore had a clinical impact on the postoperative course. Furthermore, two of eight on the POPF observed in the BPJ group were graded C, requiring CT scan-guided percutaneous drainage ($n=1$) or emergency reoperation ($n=1$), suggesting that BPJ is not, at least in our experience, able to suppress the lethal risk of POPF.

PPH was extensively described by the ISGPS,[30] which differentiated PPH into early (<24 h) and late (≥24 h) time of onset, assessing that early PPH may be caused by technical failure or unappropriate intraoperative hemostasis during PD. In the present study, no early PPH was observed. Late PPH was observed in six patients and was associated with POPF in only two, suggesting that POPF might not be the major cause of PPH after BPJ. Furthermore, all PPH observed issued from perianastomotic structures including four who originated from the pancreatic cut surface. Wente et al.[30] described the "pancreatic surface at anastomosis" as a possible cause of late PPH because of enzymatic digestion of the blood vessel wall by trypsin, elastase, and other pancreatic exocrine enzymes. As BPJ creates a large pancreatic cut surface inside the anastomotic jejunal lumen, we hypothesized that this technical specificity could explain the large number of PPH observed after PD with BPJ. A recent randomized study comparing invagination to duct to mucosa pancreaticojejunostomy did not reported specific results concerning PPH, but in this trial, the thickness of the pancreatic transection margin was included into the anastomosis in both techniques that could have decreased the risk of PPH originating from the pancreas.[17] Therefore, a particular attention is needed during the postoperative course of PD with BPJ, as, even with satisfying intraoperative hemostasis and absence of POPF, late PPH might be observed.

The absence of superiority of BPJ observed is also supported by the similar length of hospital stay in both groups (22 [12–100] days in BPJ group vs. 20 [6–40] days, respectively). The occurrence of POPF contributes to an increased hospital stay, but several studies have also highlighted relationship between POPF severity and duration of hospital stay.[3,8,11] In the present study, POPF observed after BPJ was not significantly less severe than those observed after CPJ, but it also needed a longer time for closure. Although some patients could be discharged before complete POPF closure, persistent POPF has a significant economic impact, requiring longer nursing care and wound management and also reducing short-term quality of life.

In our experience, BPJ failed to reduce the postoperative rate of pancreatic fistula after PD and was associated with a significant rate of PPH. Exceptional results reported by the initial reports were not reproduced, and therefore, BPJ was abandoned by our institution. Our results suggest that BPJ is not able to completely suppress the risk of POPF after PD.

References

1. Shrikhande SV, Qureshi SS, Rajneesh N, Shukla PJ. Pancreatic anastomoses after pancreaticoduodenectomy: do we need further studies? World J Surg 2005;29:1642–1649.
2. Barens SA, Lillemoe KD, Kaufman HS, Sauter PK, Yeo CJ, Talamini MA, Pitt HA, Cameron JL. Pancreaticoduodenectomy for benign disease. Am J Surg 1996;171:131–135.
3. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, Clavien PA. Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 2006;244:931–939.
4. Balcom JHt, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–398.
5. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML,

Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248–260.
6. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244:10–15.
7. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT. Risk factors for complications after pancreatic head resection. Am J Surg 2004;187:201–208.
8. Munoz-Bongrand N, Sauvanet A, Denys A, Sibert A, Vilgrain V, Belghiti J. Conservative management of pancreatic fistula after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg 2004;199:198–203.
9. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, Obertop H. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786–795.
10. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, Lillemoe KD, Pitt HA. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222:580–592.
11. Fuks D, Piessen G, Huet E, Tavernier M, Zerbib P, Michot F, Scotte M, Triboulet JP, Mariette C, Chiche L, Salame E, Segol P, Pruvot FR, Mauvais F, Roman H, Verhaeghe P, Regimbeau JM. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. Am J Surg 2008;197:702–709.
12. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, Nakeeb A, Zyromski NJ, Lillemoe KD. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg 2007;246:1058–1064.
13. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005;11:2456–2461.
14. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, Campbell KA, Choti MA. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232:419–429.
15. Hosotani R, Doi R, Imamura M. Duct-to-mucosa pancreaticojejunostomy reduces the risk of pancreatic leakage after pancreatoduodenectomy. World J Surg 2002;26:99–104.
16. Marcus SG, Cohen H, Ranson JH. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 1995;221:635–648.
17. Berger AC, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, Hyslop T, Schmidt CM, Rosato EL, Lavu H, Nakeeb A, Pitt HA, Lillemoe KD, Yeo CJ. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg 2009;208:738–747.
18. Kleespies A, Rentsch M, Seeliger H, Albertsmeier M, Jauch KW, Bruns CJ. Blumgart anastomosis for pancreaticojejunostomy minimizes severe complications after pancreatic head resection. Br J Surg 2009;96:741–750.
19. Poon RT, Fan S, Lo C, Ng K, Yuen W, Yeung C, Wong J. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg 2007;246:425–433; discussion 433–425.
20. Winter JM, Cameron JL, Campbell KA, Chang DC, Riall TS, Schulick RD, Choti MA, Coleman J, Hodgin MB, Sauter PK, Sonnenday CJ, Wolfgang CL, Marohn MR, Yeo CJ. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2006;10:1280–1290.
21. McKay A, Mackenzie S, Sutherland FR, Bathe OF, Doig C, Dort J, Vollmer CM, Dixon E. Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy. Br J Surg 2006;93:929–936.
22. Bassi C, Falconi M, Molinari E, Mantovani W, Butturini G, Gumbs AA, Salvia R, Pederzoli P. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. Surgery 2003;134:766–771.
23. Peng SY, Mou YP, Liu YB, Su Y, Peng CH, Cai XJ, Wu YL, Zhou LH. Binding pancreaticojejunostomy: 150 consecutive cases without leakage. J Gastrointest Surg 2003;7:898–900.
24. Peng S, Mou Y, Cai X, Peng C. Binding pancreaticojejunostomy is a new technique to minimize leakage. Am J Surg 2002;183:283–285.
25. Peng SY, Wang JW, Lau WY, Cai XJ, Mou YP, Liu YB, Li JT. Conventional versus binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg 2007;245:692–698.
26. Miettinen OS. Individual matching with multiple controls in the case of all-or-none responses. Biometrics 1969;25:339–355.
27. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.
28. Tani M, Terasawa H, Kawai M, Ina S, Hirono S, Uchiyama K, Yamaue H. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Ann Surg 2006;243:316–320.
29. van Berge Henegouwen MI, van Gulik TM, DeWit LT, Allema JH, Rauws EA, Obertop H, Gouma DJ. Delayed gastric emptying after standard pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy: an analysis of 200 consecutive patients. J Am Coll Surg 1997;185:373–379.
30. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Buchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20–25.
31. Gaujoux S, Sauvanet A, Vullierme MP, Cortes A, Dokmak S, Sibert A, Vilgrain V, Belghiti J. Ischemic complications after pancreaticoduodenectomy: incidence, prevention, and management. Ann Surg 2009;249:111–117.

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ORIGINAL ARTICLE

Sociodemographics and Comorbidities Influence Decisions to Undergo Pancreatic Resection for Neoplastic Lesions

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Abstract

Introduction Pancreatic resection is being performed with increasing frequency and safety. Technical outcomes and long-term survival for neoplastic lesions are well reported; however, reasons why patients do not undergo surgery for potentially resectable lesions are not well understood. The aim of this study was to determine the factors contributing to the decision not to operate for resectable pancreatic neoplasms.

Methods From 2004 to 2008, all patients with resectable pancreatic neoplasms at a single high-volume hepatopancreaticobiliary center were evaluated. The impact of patient factors, sociodemographics, medical comorbidities (Charlson combined comorbidity index (CCI) and ACCI), disease factors (tumor characteristics), and surgical factors (type of resection required) on the decision to undergo pancreatectomy were analyzed using univariate and multivariate binary logistic regression analysis.

Results Three hundred seventy-five patients with resectable pancreatic lesions were identified. The median age was 62 years (21–93); 203 out of 375 (54.1%) were males. Fifty-five (14.7%) did not undergo resection. On univariate analysis, age (odds ratio (OR) 1.116, $p<0.001$), non-English speaking background (NESB; OR 4.276, $p=0.001$), tumor type ($p=0.001$ increased for cystic neoplasms including intraductal papillary mucinous neoplasm), CCI score (OR 1.239, $p=0.001$), and ACCI score (OR 1.433, $p<0.001$) were associated with an increased risk of not undergoing resection. Gender, age, marital status, and urban residence were not predictive. On multivariate analysis, NESB ($p=0.018$) and the ACCI ($p=0.002$) remained predictive of not undergoing resection. The majority of patients did not undergo surgery because the patient declined in 25 out of 55 (45.5%), and resection was not offered in 15 out of 55 (27.3%). In the remainder, medical contraindications precluded surgery. Advanced age, tumor type, comorbidities (27.3%), age (21.8%), surgical risk (29.1%), frailty (18.2%), and uncertain diagnosis (5.5%) were cited as reasons for not proceeding with surgery.

Conclusion Patients with a higher ACCI and those from a NESB are less likely to undergo surgery for resectable neoplastic lesions of the pancreas. These factors must be taken into consideration in the decision-making process when considering surgery for patients with pancreatic neoplasms. Novel strategies should be employed to optimize access to surgery for patients with resectable pancreatic neoplasms.

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Introduction

Neoplastic lesions of the pancreas have variable biology and outcomes depending in the cell of origin. Pancreatic lesions are being identified with increasing frequency due to the wide availability of cross-sectional imaging. For most neoplasms, the treatment of choice is surgical resection either alone or in combination with multimodality therapy including chemotherapy and/or radiotherapy. Specifically, for pancreatic adenocarcinoma, the survival for patients who undergo surgical resection is superior to patients treated with nonsurgical methods with median survival ranging from 5 to 9 months[1–3] with nonsurgical treatment and from 15 to 24 months[4–8] for patients who undergo surgery with or without the addition of chemotherapy. Even for pancreatic neoplasms with less aggressive behavior, surgery is usually recommended for definitive management.

Over the past decade, there has been significant improvement in the perioperative outcomes following pancreatic surgery, particularly at institutions that perform a high volume of pancreatectomies.[9–11] This has led to an increasing number of patients with advancing age and comorbidities being offered pancreatic resection.[12,13] In the absence of other modalities with a potential for cure, it has been proposed that surgery should not be withheld on the basis of age and comorbidity alone.[14]

Several scoring systems have been developed which predict perioperative morbidity and mortality during major surgery.[15–17] The Charlson comorbidity index (CCI),[18] initially developed to predict mortality in longitudinal studies and later validated in combination with age—the combined comorbidity index (ACCI)—to predict perioperative complications,[19] has been used to aid operative decision making for both renal[20] and bladder[21] tumors. The ACCI gives a weighted score to comorbidities and age (Table 1) to provide the combined comorbidity index for an individual patient and was designed to evaluate long-term survival in patients undergoing general surgical procedures. To date, there have been no studies to determine whether the ACCI correlates with the decision to operate for patients with resectable pancreatic neoplasms.

In addition, sociodemographic factors have been associated with outcomes of many diseases including cancers.[22] Our patients come from diverse socioeconomic backgrounds and over a wide geographical region. It has been reported that patients who are from low socioeconomic and minority populations have worse health outcomes than patients from higher socioeconomic or nonminority populations.[23–25] For example, it has been reported that African-American patients with colorectal cancer, present at an earlier age, have a more advanced stage of disease at presentation and have a lower survival than Caucasians.[25] The factors that contribute to these differences are poorly delineated but are likely multifactorial and may be related to decreased access to care, external economic pressures in private market systems, and/or related comorbidities or inferior social supports. The objective of this study was to evaluate factors that impact surgical decision making for patients with resectable pancreatic neoplasia, specifically which factors were associated with patients not receiving surgery for potentially resectable pancreatic neoplasms.

Methods

The study population is made up of 375 patients with resectable pancreatic neoplasms identified from a comprehensive prospective database of all patients with pancreatic tumors seen at the University Health Network (University of Toronto, Canada) by a group of nine high-volume hepatobiliary surgeons. Supplemental information was obtained from a review of the charts. All patients diagnosed with a resectable pancreatic neoplasm between January 2004 and August 2008 were analyzed. Institutional ethics board approval was obtained (REB # 08-0701-CE).

For the purposes of the study, all patients with primary and secondary neoplastic lesions that met criteria for surgical resection were included in the study population. Patients with malignant tumors that were deemed unresectable due to either technical factors (e.g., encasement of major arteries) and/or the presence of metastatic disease were excluded from the study population. For patients with cystic neoplasms, only patients that met local criteria for resectability (i.e., main branch intraductal papillary mucinous neoplasms (IPMNs), large side branch IPMNs ≥3 cm, mucinous/solid pseudopapillary or indeterminant lesions) were included.

It is the practice at our institution to offer resection to all patients with localized pancreatic neoplasms who are deemed medically fit, have tumors which require surgery as definitive treatment, and have lesions which are technically resectable with clear margins. Patients with a need for celiac, superior mesenteric, or hepatic arterial resection to achieve an R0 margin were decided on a case-by-case basis. Prior to final determination of unsuitability for surgery, patients are discussed in a multidisciplinary forum involving nine hepatopancreaticobiliary (HPB) surgeons and a radiologist.

In order to identify the factors which influenced the decision making regarding surgery, information was collected on patient demographics, place of residence, religion, language spoken at home, American Society of Anesthesia

(ASA) score, comorbidities (individually and combined as the ACCI), type and location of tumor, and resection required. ACCI was calculated by attributing the appropriate score for each of the comorbidities and age (Table 1). In those patients with resectable lesions who did not proceed to surgery, further factors that informed the decision-making process, including reasons for patient refusal or surgeons recommending against surgery, were obtained from chart review. We chose the ACCI as a preoperative scoring system as it is simple to use, widely applicable, can be used with administrative databases,[26,27] and has been validated as a predictor of survival and complications in surgical patients.[16,21]

Statistical analysis was undertaken using SPSS v17.0 (SPSS Inc., Chicago, IL, USA). The analysis was considered statistically significant when the p value was <0.05. Continuous variables were compared using Student's t test or the Mann–Whitney U test as appropriate, while categorical variables were compared using chi-square or Fisher's exact test. The contribution of specific variables to preoperative decision making was determined using univariate binary logistic regression analysis; clinically and statistically significant variables ($p<0.1$) were then included in a multivariate binary logistic regression analysis, using forward stepwise regression. In creating the multivariate model, collinear variables (such as age and CCI) were not included. Subgroup analysis was undertaken for patients who did not proceed to surgery to determine which factors had the greatest contribution.

Table 1 Combined Comorbidity Index (ACCI)

Comorbidity	Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebral vascular disease	1
Dementia	1
Chronic obstructive pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes mellitus	1
Hemiplegia	2
Moderate to severe renal disease	2
Diabetes with end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
AIDS	6
For each decade over 40	1

Results

During the period January 2004 to August 2008, 375 patients with resectable pancreatic neoplasms were assessed at our institution. Two hundred three out of 375 (54.1%) were males. The mean age of the cohort was 62.5±13.1 years. Two hundred forty-six out of 375 (65.6%) patients were offered surgery for primary pancreatic adenocarcinoma; other diagnoses were IPMN (15.7%), neuroendocrine tumors (11.7%), and cystadenoma/carcinoma (5.3%). Uncommon and secondary tumors accounted for 1.6% of the cohort; 49.6% of the tumors were located in the head of pancreas, 20.9% in the tail, and 29.5% were periampullary. Over the same time period, a further 327 patients were assessed by the surgical team with unresectable pancreatic neoplasms or cystic lesions that did not meet criteria for resection.

Fifty-five out of 371 (14.7%) patients did not undergo pancreatic resection. Patient demographics are shown in Table 2. The patients who did not undergo resection were older ($p<0.001$), were more commonly from a NESB ($p=0.001$), and had a higher CCI ($p=0.001$) and ACCI ($p<0.001$). There were no between group differences in gender, place of residence, marital status, or ASA between those who did/did not receive surgery. The impact of various predictor variables on whether the patients received surgery was determined by binary logistic regression analysis the results of which are outlined in Table 3. On univariate analysis, the risk of not undergoing resection was increased in patients who were older (odds ratio (OR) 1.116; $p<0.001$), from a NESB (OR 4.276; $p=0.001$), had a diagnosis of IPMN (OR 2.654; $p=0.007$) or cystadenoma/carcinoma (OR 15.571; $p=0.002$), and a higher CCI (OR 1.239; $p=0.001$) and ACCI (OR 1.433; $p<0.001$). Multivariate analysis was then undertaken (without including age and CCI due to collinearity with ACCI). On multivariate analysis, patients from a NESB, with a diagnosis of IPMN and cystadenoma/carcinoma, and those with a higher ACCI remained at greater risk of not undergoing pancreatic resection.

In the group that did not have surgery, 15 out of 55 (27.3%) were not offered resection by the treating surgeon. Comorbidities (27.3%), age (21.8%), surgical risk (29.1%), frailty (18.2%), and uncertain diagnosis (5.5%) were cited as reasons for recommendation of nonsurgical management. However, in this group that did not undergo resection, there was no significant difference in these variables between patients who were offered surgery compared to those who were not offered resection. Surgeons stated that age was a

Table 2 Differences Between Those Who Received Surgery and Those Who Did Not

Patient characteristic	No surgery (%), n=55	Surgery (%), n=320	p value
Age	74	60.4	<0.001
Gender (male/female)	25:30 (12.3:17.4%)	178:142 (87.7:82.6%)	0.162
Non-English speaking background	9:46 (39.1:13.1%)	14:306 (60.9:86.9%)	0.001
Residence (urban/nonurban)	34:21 (16:13%)	179:141 (84:87%)	0.416
Marital status (married)	40 (12.6%)	277 (87.4%)	0.130
Diagnosis			<0.001
Pancreatic adenocarcinoma	28 (11.4%)	218 (88.6%)	
IPMN	15 (25.4%)	44 (74.6%)	
Neuroendocrine tumor	3 (6.8%)	41 (93.2%)	
Cystadenoma/carcinoma	4 (66.7%)	2 (33.3%)	
Other	5 (25%)	15 (75%)	
Tumor location			0.528
Head	23 (13.3%)	150 (86.7%)	
Tail	6 (8.2%)	67 (91.8%)	
Duodenum	12 (11.7%)	91 (88.3%)	
ASA (median)	3	3	0.798
CCI	1 (0–11)	0 (0–12)	0.001
ACCI	5 (0–14)	3 (0–14)	<0.001
Total	55 (14.7%)	320 (85.3%)	

contraindication to surgery in 40% of those not offered surgery compared with 15% in those offered surgery (p=0.046). There was no statistical difference in age for those not offered vs those offered resection in this group (77.13±10.7 vs 72.9±10.3, p=0.087).

Subgroup analysis was undertaken for patients with frankly malignant lesions to determine if the same relationships were maintained. On univariate analysis, the risk of not undergoing resection was increased in patients who were older (OR 1.116, p<0.001) and had a higher CCI (OR 1.296, p=0.09) or ACCI (OR1.422, p<0.001). Those patients from NESB had increased risk of not undergoing resection; however, this did not reach statistical significance (OR 3.136, p=0.66). No other factors were predictive of a

Table 3 Logistic Regression of Factors Predictive of Not Receiving Surgery

Patient characteristic	Odds ratio	95% Confidence interval	Univariate analysis	Multivariate analysis
Age	1.116	1.08–1.154	<0.001	–
Gender (male/female)	1.504	0.847–2.673	0.164	–
Non-English speaking background	4.276	1.751–10.444	0.001	0.02
Residence (urban/nonurban)	0.784	0.436–1.410	0.417	NS
Marital status (married)	0.523	0.224–1.225	0.136	–
Diagnosis				
Pancreatic adenocarcinoma			0.001	0.002
IPMN	2.654	1.310–5.376	0.007	
Neuroendocrine tumor	0.570	0.165–1.962	0.372	
Cystadenoma/carcinoma	15.571	2.727–88.928	0.002	
Other	2.595	0.876–7.687	0.085	
Tumor location				NS
Head			0.533	
Tail	0.584	0.227–1.5	0.264	
Duodenum	0.86	0.41–1.81	0.692	
ASA	1.691	0.085–33.606	0.731	NS
CCI	1.239	1.091–1.407	0.001	–
ACCI	1.433	1.261–1.628	<0.001	<0.001

decision not to undergo surgery on univariate analysis. On multivariate analysis, a higher ACCI remained predictive of an increased risk of not undergoing surgery.

The surgeon cited comorbidities as a contraindication in 55.3% of those not offered surgical resection vs 17.6% in those offered resection ($p=0.008$), but the mean CCI (2.6 vs 1.9; $p=0.325$) and the mean ACCI (5.8 vs 4.7; $p=0.163$) were nonsignificantly higher in those who did not get offered resection. Tumor type (0.685), type of surgery required ($p=0.422$), and the tumor location ($p=0.995$) were not significantly associated with the surgeon's decision to recommend surgery. There was no significant difference in the proportion of patients not offered surgery between different surgeons ($p=0.148$). Twelve out of 55 patients who refused surgery went on to alternative forms of treatment. Seven patients had chemotherapy alone, two had combined chemotherapy and radiotherapy, and three were enrolled into phase 1 trials (sorafenib and immunotherapy).

Twenty-five out of 55 (45.5%) patients refused surgery, making this the most frequent reason for not undergoing resection. The age of patients who refused surgery was not significantly different to those who did not (73.4±9.9 vs 74.5±11.1, $p=0.702$). Fourteen out of 25 (56%) patients had adenocarcinoma of the pancreas; this was not significantly different ($p=0.78$) compared to refusal with other diagnoses. In these patients, the most frequent reason given for refusing surgery was patient concern over perioperative morbidity vs. the perceived benefit of surgery. Others refused due to uncertain diagnosis and because the lesions had not changed over time. In the group of patients who did not proceed to surgery, there was no association between the patient refusing surgery and being married, having an urban vs rural residence, and being from a NESB. There was no significant difference in the type of surgery required ($p=0.189$), tumor location (0.131), and underlying pancreas pathology ($p=0.780$) between those patients who refused surgery and those who did not.

Discussion

Pancreatectomy is the only treatment which is able to confer long-term survival for patients with malignant neoplasms of the pancreas and is also the only treatment able to eliminate the malignant potential of premalignant lesions.[2,5,6,8,12,28] Moreover, it has been shown that pancreatectomy can be performed safely with low rates of morbidity and operative mortality. Over the last three decades, perioperative mortality has decreased to 1% and 5-year survival for resected adenocarcinoma which in node and margin negative patients has increased to 41%.[29] This is occurring despite an aging population with a greater number of comorbidities.[12,30] Laparoscopic distal pancreatectomy has further extended the boundaries of resection; it has been shown that equivalent resections can be performed compared to open resections (for a broad range of indications), with similar complication rates and shorter hospital stay.[31–33] Given the improvements in safety, introduction of new technology, and the absence of other curative treatment modalities, all patients with pancreatic lesions should be at least reviewed by a HPB surgeon and considered for surgery. Patients and surgeons should be armed with the best information possible to enable them to make informed treatment choices.

In addition to improvements in safety of pancreatectomy and more liberal selection criteria, more lesions are now being identified due to increased availability and improvements in cross-sectional imaging. Despite this, a recent analysis of the national cancer database by Bilimoria et al.[34] found that 71.4% of patients with stage 1 pancreatic adenocarcinomas did not undergo surgical resection for what is a potentially curative lesion. Moreover, 38.4% of these patients had no identifiable contraindications. In light of this, it was our intent to analyze the impact of patient, disease, and surgeon factors which contributed to the decision not to operate in patients with resectable pancreatic lesions.

In this study, we report that age, comorbidities, and poor English language proficiency are associated with a higher rate of not operating on resectable pancreatic lesions. Patient refusal was the commonest reason given for not proceeding with surgical treatment, specifically the patients who were concerned over surgical risk and diagnostic uncertainty. Surgeons did not offer resection predominantly because of concern over comorbidities and age. Only 14.7% of our patients did not undergo surgery, which is significantly lower than rates reported in previous studies,[34–36] even when accounting for patients treated in a high-volume cancer center, while the rates of resection from our center are not directly comparable to the population-based data in these studies, due to the differences in referral patterns and the inherent selection process that occurs when patients are referred for a surgical opinion. The patients in this study cohort are likely to have the best access to care, be motivated, fit enough to undergo resection, and also quoted low rates for the morbidity and mortality of surgery, and hence, the low no go rate that can be achieved when patients are managed in a high-volume center underestimates the rate when compared to the real world situation. Other reasons for differences may be due to the effect of the single center analysis, combined with overestimation from population-based registries due to incomplete or unavailable data.

Advanced age is a common reason given for not proceeding with major surgery. Withholding surgery based

upon age alone would deny large numbers of patient's potentially curative procedures. Major hepatobiliary resections can be undertaken safely in patients with advanced age,[14,37] with equivalent perioperative complication rates, and with short- and long-term survivals. In our series, advancing age on its own was predictive on univariate analysis of a decision not to operate; moreover, when combined with the patient's comorbidities as the ACCI, it was highly predictive of a decision not to proceed with surgery. Many studies have shown that pancreatectomies can be performed safely and with equivalent cost in older people[10,12,29,38,39]; however, these come mainly from single centers with large volumes, where perioperative morbidity and mortality may be lower than in the general population.[10,11,36,40–43] These results differ somewhat from population-based registry data[35,44] and may not be generalizable. In these studies, octogenarians had higher perioperative mortality, morbidity, used of extended care facilities, and a lower 5-year survival (11%). Elderly patients also have less physical reserve and experience a greater functional decline following major pancreatic surgery.[13] This may make an important contribution to the surgeon's recommendations regarding surgical treatment when faced with an elderly patient. In addition, elderly people, especially those with comorbidities, have a high rate of refusing medical treatment, up to 16%.[45] In a study by Rothman et al.,[45] elderly patients most commonly refused medical treatment due to fear of side effects and lack of efficacy. Advanced age should not be a contraindication to pancreatic resection; however, given the attendant risks involved for these patients, the operation should be done where the risk of perioperative morbidity and mortality can be kept low.

Several preoperative scoring systems have been developed to assess perioperative surgical risk and long-term outcomes with major operations.[15–17,20,21,46,47] The aim of these is twofold: first to help appropriately inform patients and second to guide management. What these scoring systems lack, however, is a measure of clinical experience and intuition. Woodfield et al.[48] found that surgeons were able to accurately predict perioperative risk for patients and that the surgeon's subjective clinical assessment improved the utility of the more objective perioperative scoring systems. In our series, 27.3% of patients did not undergo resection due to the surgeon not offering resection. Although there was a trend toward older age and increasing comorbidities in the group, they did not offer resection as this was not statistically significant suggesting that there is a yet to be measured variable or variables that informed the advice given to the patients. This is further supported by the fact that the surgeons stated that age and comorbidities were the most frequent contraindications to surgery despite there being no significant difference in age and comorbidities between the group that was offered and those who were not offered surgery.

The impact of comorbidities on long-term outcomes following pancreatectomy has been variably reported[13,38,44]; however, it has been reported that following surgery for other cancers patients with moderate and severe comorbidities had a lower 1- and 5-year survival and that the difference increased over time.[49] Individuals recognize the impact of their own comorbidities on their functional status and quality of life, and refusal of surgery may be a manifestation of this construct. Further, more detailed qualitative analysis in this group is warranted to identify the impact of comorbidities on the decisions made about resection.

Assessment of cumulative morbidity using the ACCI has been shown to be independently predictive of outcome for other cancers[16,20,21,47,50] and is able to help inform both patient and surgical decision making. In this study, the ACCI was predictive on univariate and multivariate analysis of the decision not to proceed with pancreatectomy. For every one point increase in ACCI, there was a 10% greater risk of not proceeding with pancreatectomy. There was a nonsignificantly higher ACCI in those patients who were not offered surgery. To date, there have been no studies determining whether ACCI is independently predictive of perioperative morbidity and mortality following pancreatic resections; it is, however, an independent predictor of morbidity, mortality, length of stay, and need for assisted care after other general surgical operations.[16] We used the ACCI as surrogates to define cumulative comorbidity as it relates to surgical decision making, and further studies focusing on outcomes after pancreas surgery are required to determine whether the relationships can be validated. Other scoring systems such as the P-POSSUM have been shown to estimate perioperative morbidity well but underestimate mortality[15] following pancreatectomy. This scoring system may not be widely applicable in the clinic setting because of its complexity and need for several laboratory results, whereas the ACCI is simple, easy to calculate, and is based on clinical history and physical examination.

Socioeconomic and demographic factors have implications in outcomes of patients with tumors such breast cancer and colon cancer, but in a population-based study, Baastrup et al.[51] found no consistent association between socioeconomic, demographic, and health variables and age-standardized relative survival for pancreatic cancer. The absence of a difference in these populations may be because of the low prevalence of disease in the study population and the generally poor outcomes. This study is in contrast to Glasgow et al.[10] who found that patients treated in the private sector had lower rates of perioperative morbidity and mortality. We found that those patients not proficient in

English had a four times greater risk of not undergoing surgery. The reasons for this are unclear from this study. In those who did not undergo resection, there was no association between language proficiency and refusal of surgery. This finding is consistent in several studies of pancreas as well as other cancers,[23,52] where those from minorities or NESB have a higher rate of not being offered surgery and also refusing surgery. This was carried throughout the different phases of their treatment.

It is essential when counseling patients with pancreatic neoplasms that they fully understand the implications of their decision; patients from minority groups and NESB may have an increased fear and fatalism when diagnosed with cancer.[53] In addition, health care professionals often feel they are unable to overcome cultural and language barriers,[54] making appropriate decision making difficult. Several studies in other disease groups have found that culturally appropriate education, focus groups, and appropriate use of interpreters are able to improve short-term health outcomes, uptake of screening procedures, and understanding.[53,55–57]

The limitations of our study include the relatively small number of patients; this makes definitive statements about reasons for not receiving surgery difficult; however, our results are similar and support the findings of other studies in this area focusing on pancreas as well as other organ pathology. In addition, there may be selection bias in our patients, as all the patients were referred to our center which is high volume and the surgeons are more comfortable with the decision to operate even in patients with significant comorbidities. This is supported by our no go rate which was lower than that reported in the other series. Not all of our data were collected prospectively, and this may lead to recall bias and also prevents the formulation of systematic qualitative questionnaires and hence makes it more difficult to identify the information used to make decisions (both for the doctor and patient) and what factors were important aside from the doctor–patient interaction. Despite these limitations, we were able to abstract data that informed both the surgeon and patient decisions about surgery.

Conclusions

Preoperative decision making in pancreatic surgery is complex. Decisions not to operate on patients with pancreatic neoplasms should be based on objective criteria and adjusted for local complication rates. In our cohort, those cases with more comorbidities and who were not proficient in English had a greater risk of not undergoing potentially curative surgery. Novel strategies should be developed to optimize the decision-making process for pancreatic surgery in order to ensure appropriate access to surgery for patients with respectable pancreatic neoplasms.

References

1. Azria D, Ychou M, Jacot W, et al. Treatment of unresectable, locally advanced pancreatic adenocarcinoma with combined radiochemotherapy with 5-fluorouracil and cisplatin. Pancreas 2002; 25(4):360–5.
2. Lavu H, Mascaro AA, Grenda DR, et al. Margin positive pancreaticoduodenectomy is superior to palliative bypass in locally advanced pancreatic ductal adenocarcinoma. J Gastrointest Surg 2009; 13:1937–1946.
3. Okamoto A, Tsuruta K, Karasawa K, et al. Resection versus palliation: treatment of stage III and IVA carcinomas of the pancreas employing intraoperative radiation. World J Surg 2003; 27(5):599–605.
4. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001; 358(9293):1576–85.
5. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2001; 234 (6):758–68.
6. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004; 350(12):1200–10.
7. Ramacciato G, Mercantini P, Petrucciani N, et al. Does portal-superior mesenteric vein invasion still indicate irresectability for pancreatic carcinoma? Ann Surg Oncol 2009; 16(4):817–25.
8. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. Jama 2008; 299(9):1019–26.
9. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. Jama 1998; 280(20):1747–51.
10. Glasgow RE, Jackson HH, Neumayer L, et al. Pancreatic resection in Veterans Affairs and selected university medical centers: results of the patient safety in surgery study. J Am Coll Surg 2007; 204 (6):1252–60.
11. Glasgow RE, Mulvihill SJ. Hospital volume influences outcome in patients undergoing pancreatic resection for cancer. West J Med 1996; 165(5):294–300.
12. Balcom 4th JH, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001; 136(4):391–8.
13. Lightner AM, Glasgow RE, Jordan TH, et al. Pancreatic resection in the elderly. J Am Coll Surg 2004; 198(5):697–706.
14. Petrowsky H, Clavien PA. Should we deny surgery for malignant hepato-pancreatico-biliary tumors to elderly patients? World J Surg 2005; 29(9):1093–100.
15. Tamijmarane A, Bhati CS, Mirza DF, et al. Application of Portsmouth modification of physiological and operative severity scoring system for enumeration of morbidity and mortality (P-POSSUM) in pancreatic surgery. World J Surg Oncol 2008; 6:39.
16. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. J Gastrointest Surg 2004; 8 (8):1061–67.

17. de Castro SM, Biere SS, Lagarde SM, et al. Validation of a nomogram for predicting survival after resection for adenocarcinoma of the pancreas. Br J Surg 2009; 96(4):417–23.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373–83.
19. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47 (11):1245–51.
20. O'Connor KM, Davis N, Lennon GM, et al. Can we avoid surgery in elderly patients with renal masses by using the Charlson comorbidity index? BJU Int 2008; 103:1492–1495.
21. Koppie TM, Serio AM, Vickers AJ, et al. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer 2008; 112(11):2384–92.
22. Dalton SO, Schuz J, Engholm G, et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: Summary of findings. Eur J Cancer 2008; 44(14):2074–85.
23. Clegg LX, Li FP, Hankey BF, et al. Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology, and End Results) Program population-based study. Arch Intern Med 2002; 162(17):1985–93.
24. Oliver MN. Access to prostate cancer care and implications for survival among minorities. J Urol 2009; 181(2):447–8.
25. Polite BN, Dignam JJ, Olopade OI. Colorectal cancer model of health disparities: understanding mortality differences in minority populations. J Clin Oncol 2006; 24(14):2179–87.
26. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol 1996; 49(12):1429–33.
27. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004; 57(12):1288–94.
28. Neoptolemos JP, Stocken DD, Tudur Smith C, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer 2009; 100(2):246–50.
29. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006; 244 (1):10–5.
30. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S.: utilization, outcomes, and the effect of hospital volume. Cancer 2007; 110(6):1227–34.
31. Fernandez-Cruz L, Blanco L, Cosa R, Rendon H. Is laparoscopic resection adequate in patients with neuroendocrine pancreatic tumors? World J Surg 2008; 32(5):904–17.
32. Casadei R, Ricci C, Zanini N, et al. Laparoscopic distal pancreatectomy in non-malignant pancreatic tumors. Jop 2008; 9 (1):71–3.
33. Eom BW, Jang JY, Lee SE, et al. Clinical outcomes compared between laparoscopic and open distal pancreatectomy. Surg Endosc 2008; 22(5):1334–8.
34. Bilimoria KY, Bentrem DJ, Ko CY, et al. National failure to operate on early stage pancreatic cancer. Ann Surg 2007; 246 (2):173–80.
35. Cress RD, Yin D, Clarke L, et al. Survival among patients with adenocarcinoma of the pancreas: a population-based study (United States). Cancer Causes Control 2006; 17(4):403–9.
36. Riall TS, Nealon WH, Goodwin JS, et al. Pancreatic cancer in the general population: improvements in survival over the last decade. J Gastrointest Surg 2006; 10(9):1212–23; discussion 1223–4.
37. Kondo K, Chijiiwa K, Funagayama M, et al. Hepatic resection is justified for elderly patients with hepatocellular carcinoma. World J Surg 2008; 32(10):2223–9.
38. Vickers SM, Kerby JD, Smoot TM, et al. Economics of pancreatoduodenectomy in the elderly. Surgery 1996; 120 (4):620–5; discussion 625–6.
39. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006; 10(9):1199–1210; discussion 1210–1.
40. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. Arch Surg 2003; 138(7):721–5; discussion 726.
41. Riall TS, Nealon WH, Goodwin JS, et al. Outcomes following pancreatic resection: variability among high-volume providers. Surgery 2008; 144(2):133–40.
42. Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. J Am Coll Surg 2008; 207(4):510–9.
43. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349 (22):2117–27.
44. Finlayson E, Fan Z, Birkmeyer JD. Outcomes in octogenarians undergoing high-risk cancer operation: a national study. J Am Coll Surg 2007; 205(6):729–34.
45. Rothman MD, Van Ness PH, O'Leary JR, Fried TR. Refusal of medical and surgical interventions by older persons with advanced chronic disease. J Gen Intern Med 2007; 22(7):982–7.
46. Gulbinas A, Barauskas G, Pundzius J. Preoperative stratification of pancreas-related morbidity after the Whipple procedure. Int Surg 2004; 89(1):39–45.
47. Wang CY, Lin YS, Tzao C, et al. Comparison of Charlson comorbidity index and Kaplan–Feinstein index in patients with stage I lung cancer after surgical resection. Eur J Cardiothorac Surg 2007; 32(6):877–81.
48. Woodfield JC, Pettigrew RA, Plank LD, et al. Accuracy of the surgeons' clinical prediction of perioperative complications using a visual analog scale. World J Surg 2007; 31(10):1912–20.
49. Iversen LH, Norgaard M, Jacobsen J, et al. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006—a population-based cohort study. Dis Colon Rectum 2009; 52(1):71–8.
50. Lubke T, Monig SP, Schneider PM, et al. Does Charlson-comorbidity index correlate with short-term outcome in patients with gastric cancer? Zentralbl Chir 2003; 128(11):970–6.
51. Baastrup R, Sorensen M, Hansen J, et al. Social inequality and incidence of and survival from cancers of the oesophagus, stomach and pancreas in a population-based study in Denmark, 1994-2003. Eur J Cancer 2008; 44(14):1962–77.
52. Merrill RM, Merrill AV, Mayer LS. Factors associated with no surgery or radiation therapy for invasive cervical cancer in Black and White women. Ethn Dis 2000; 10(2):248–56.
53. Dignan M, Michielutte R, Sharp P, et al. The role of focus groups in health education for cervical cancer among minority women. J Community Health 1990; 15(6):369–75.
54. Thomas V, Richardson A, Saleem T, et al. The efficacy of bilingual health advocacy in ethnic minority patients with cancer. Nurs Stand 2000; 14(26):32–3.
55. Alcaraz KI, Kreuter MW, Davis KL, et al. On linkages: increasing awareness of and interest in public health and cancer control careers among minority middle school students. Public Health Rep 2008; 123(4):533–9.
56. Gany FM, Herrera AP, Avallone M, Changrani J. Attitudes, knowledge, and health-seeking behaviors of five immigrant minority communities in the prevention and screening of cancer: a focus group approach. Ethn Health 2006; 11(1):19–39.
57. Hawthorne K, Robles Y, Cannings-John R, Edwards AG. Culturally appropriate health education for type 2 diabetes mellitus in ethnic minority groups. Cochrane Database Syst Rev 2008(3):CD006424.

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ORIGINAL ARTICLE

True Aneurysm of the Pancreaticoduodenal Arteries: A Single Institution Experience

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Abstract
Background True pancreaticoduodenal artery (PDA) aneurysm is a rare but potentially fatal disease. The aim of this study was to make recommendations for management of true PDA aneurysm.
Methods True aneurysms of the PDA were diagnosed at our institution between 1996 and 2007 and analyzed retrospectively, for clinical presentation, management, and outcome.
Results Eight patients were admitted to our institution for true aneurysms of the PDA. Five patients had aneurysmal rupture, and three were asymptomatic. In the rupture group, computed tomography (CT) showed the retroperitoneal hematoma around the pancreas and aneurysm, ranging from 5 to 25 mm (median, 12 mm). In the non-rupture group, CT revealed saccular aneurysm, ranging from 10 to 20 mm (median, 16 mm). The celiac axis was occluded in two patients, stenotic in four, and normal in two. Two patients underwent laparotomy, and we finally performed transcatheter arterial embolization in seven. All patients are alive, and there is no evidence of recurrence after median follow-up of 6 years.
Conclusions We recommend treatment of all true PDA aneurysms at the time of diagnosis. True PDA aneurysm with celiac artery stenosis or occlusion requires precise techniques for embolization to preserve blood flow in the celiac artery territory.

Keyword Pancreaticoduonenal artery aneurysm · Celiac axis stenosis · Embolization · Revascularization

Introduction

Aneurysms of the pancreaticoduodenal arteries (PDAs) are rare and account for <2% of all aneurysms in the visceral arteries.[1] The first case of PDA aneurysm was reported in 1895 by Ferguson.[2] True and false PDA aneurysms should be distinguished: the latter result from pancreatitis, abdominal trauma, or septic emboli, whereas the former are frequently associated with stenosis or occlusion of the celiac axis and rupture into the retroperitoneal space. In 1973, Sutton and Lawton first described this association.[3] Most of these aneurysms are asymptomatic, and they are seldom detected

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until rupture. However, non-ruptured PDA aneurysms are now being reported more often, which is a reflection of the increased use of imaging techniques, such as multidetector-row computed tomography (CT), multiplanar (MPR) imaging, reconstruction imaging, and CT angiography (CTA). The aim of this study was to assess retrospectively the clinical presentation, management, and outcome of patients with true PDA aneurysms.

Methods

We reviewed the medical records of all patients admitted to Okinawa Prefectural Chubu Hospital between 1996 and 2007, for true PDA aneurysms. Aneurysms associated with pancreatitis, abdominal trauma, or septic emboli were considered pseudoaneurysms and were excluded from this study. We treated the anterior/posterior superior pancreaticoduodenal artery and anterior/posterior inferior pancreaticoduodenal artery around the head of the pancreas as the pancreaticoduodenal artery because it was difficult to distinguish these four arteries exactly. Eight patients were identified: three women (mean age, 75 years; range, 64–82 years) and five men (mean age, 56 years; range, 45–68 years). Five patients were diagnosed after aneurysm rupture into retroperitoneal space or duodenum, and three patients were asymptomatic and incidentally diagnosed by means of enhanced CT for evaluation of other diseases. Two patients had a history of systemic hypertension, and another two had a history of chronic hepatitis. Neither of the latter had other systemic diseases, such as pancreatic or collagen disease. All cases were analyzed with regard to clinical presentation, diagnosis, therapeutic approach, and treatment outcome.

Results

We encountered eight patients with true PDA aneurysms between 1996 and 2007 at our institution. The characteristics of each patient are summarized in Table 1. Five patients had aneurysmal rupture (rupture group), and three were asymptomatic and did not have rupture (non-rupture group). In two patients in the non-rupture group, the aneurysm was diagnosed by enhanced CT, and in the other, the aneurysm surrounded the pancreas and was diagnosed by abdominal echography, which was used to follow the course of chronic hepatitis.

In the rupture group, four patients had sudden onset of epigastric pain with or without nausea and vomiting. On admission, three of these patients were hemodynamically stable, but under observation; eventually all four patients developed an unstable state of shock and required immediate resuscitation. One patient was admitted with only vomiting and diarrhea, and 10 days later, his aneurysm ruptured into the duodenum. On physical examination, mild diffuse, peri-umbilical tenderness was noted, without signs of peritonitis, and no bruit was audible.

Laboratory tests and abdominal radiography were unremarkable. One patient presented with slightly elevated serum amylase level, and contrast-enhanced CT also revealed retroperitoneal inflammation around the pancreas; thus, we initially presumed that the patient had acute pancreatitis.

Enhanced CT was performed in seven patients. In the non-rupture group, CT revealed saccular aneurysm around the head of the pancreas, which ranged from 10 to 20 mm in diameter (median, 16 mm). In four patients in the rupture group, CT showed a large retroperitoneal hematoma that surrounded the head of the pancreas and the duodenum. One typical CT image is shown in Fig. 1. On angiography, the aneurysm ranged from 5 to 25 mm in diameter (median, 12 mm). In two patients in the rupture group, selective angiography showed small irregular branches from the posterior inferior PDA (PIPDA), which was diagnosed as aneurysmal dilatation. The celiac axis was occluded in two patients, stenotic in four, and normal in two. The occlusion and stenosis of the celiac axis seemed to be caused by extrinsic compression (Fig. 2) and angiography also showed that retrograde blood flow from the gastroduodenal artery through the pancreatic arcade was supplied from the superior mesenteric artery (SMA; Fig. 3).

Table 1 Characteristics of Eight Patients with True PDA Aneurysm in Our Institution

Patient no.	Date	Age/sex	Status	Size of aneurysm (mm)	Celiac axis	Embolization	Surgery	Outcome
1	1996	45/M	R	5	Normal	Micro-coils		Alive
2	1998	68/M	R	25	Stenosis	Micro-coils	Exploratory laparotomy	Alive
3	2002	68/M	NR	18	Occlusion	Micro-coils		Alive
4	2004	50/M	R	Irregular aneurysmal dilatation	Stenosis	Micro-coils		Alive
5	2005	82/F	NR	10	Normal	Micro-coils		Alive
6	2005	64/F	R	5	Stenosis	NBCA		Alive
7	2006	47/M	R	Irregular aneurysmal dilatation	Stenosis	Micro-coils		Alive
8	2007	79/F	NR	20	Occlusion	–	Aneurysmectomy	Alive

R ruptured, *NR* non-ruptured, *NBCA* *N*-butyl-2-cyanoacrylate

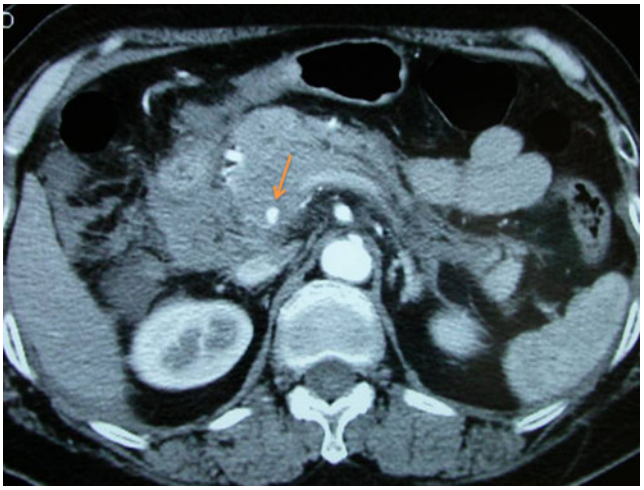

Fig. 1 Enhanced abdominal CT scan, showing a retroperitoneal hematoma and with suspicious aneurysm.

Management of PDA aneurysms consisted of transcatheter arterial embolization (TAE) and surgical revascularization. In the non-rupture group, two patients underwent TAE electively, using micro-coils or *N*-butyl-2-cyanoacrylate. One patient underwent resection of PIPDA aneurysm and anastomosis between the SMA and PIPDA. In the rupture group, four patients successfully underwent emergency TAE of the aneurysm after diagnosis by enhanced CT. One patient with aneurysm rupture into the duodenum underwent emergency laparotomy for uncontrolled upper gastrointestinal bleeding. At the time of laparotomy, we found a hard mass in the retroperitoneal space around the mesentery of the transverse colon; therefore, the patient was subjected to angiography. Selective angiography of the SMA showed pooling of contrast medium at the medial site of the duodenal C-loop from the branch of the inferior PDA, and contrast medium leaked into duodenum. After diagnosis of aneurysmal rupture from the inferior PDA, we performed TAE using micro-coils.

There was no perioperative or long-term mortality. All eight patients were discharged from our institution a few

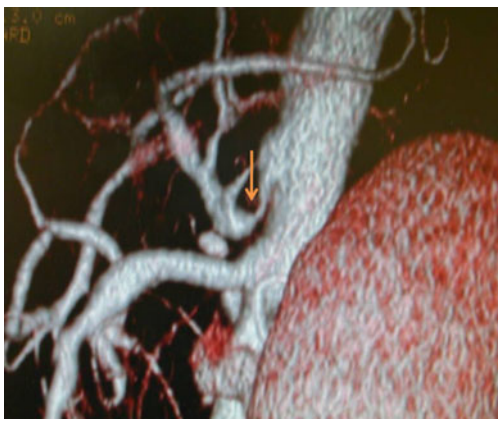

Fig. 2 3D CT reconstruction, showing the stenosis of celiac artery seemed to be extrinsic compression.

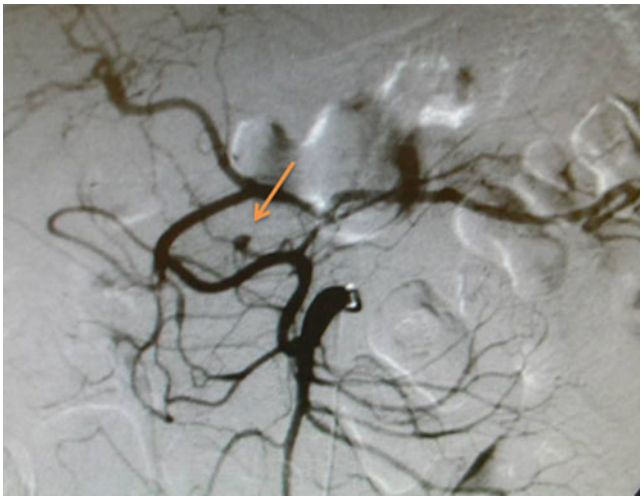

Fig. 3 Subtraction angiogram, showing a saccular aneurysm, arising from retrograde blood flow through the pancreatic arcade was supplied from SMA.

weeks after treatment, and no further hemorrhage was observed. There was no evidence of disease progression or recurrence of visceral artery aneurysm after a median follow-up of 7 years (range, 3–14 years).

Discussion

True PDA aneurysm is an uncommon vascular disease whose pathogenesis and natural history remain incompletely characterized. Nevertheless, its importance to the surgeon lies in its potential for rupture or erosion into an adjacent viscus, which results in life-threatening hemorrhage. Nearly 50% of reported true PDA aneurysms present with rupture, which results in a 26% mortality rate.[4]

Anatomically, the pancreatic head is encircled by the arteries that make up the peripheral pancreatic circulation. This arterial network comprises the anterior and posterior superior pancreaticoduodenal branches of the gastroduodenal artery and the inferior pancreaticoduodenal branches of the SMA. The inferior pancreaticoduodenal arteries arise directly from the SMA or from its first jejunal branch. These arteries connect the SMA system to the celiac artery system (Fig. 4).

Associated risk factors of true PDA aneurysm are numerous, and atherosclerosis may not be the main etiology of true aneurysms of the visceral arteries. We suppose that local hemodynamic events play an important role in the development of most true PDA aneurysms. On routine diagnostic catheter angiography, the pancreatic arcades are not usually visible in the absence of celiac artery or SMA stenosis. In the presence of celiac artery stenosis or occlusion, the arcades serve as a retrograde collateral pathway to provide flow to the liver, stomach, and spleen. During this process, the arteries enlarge and the arcades appear prominent on SMA arteriography.[6]

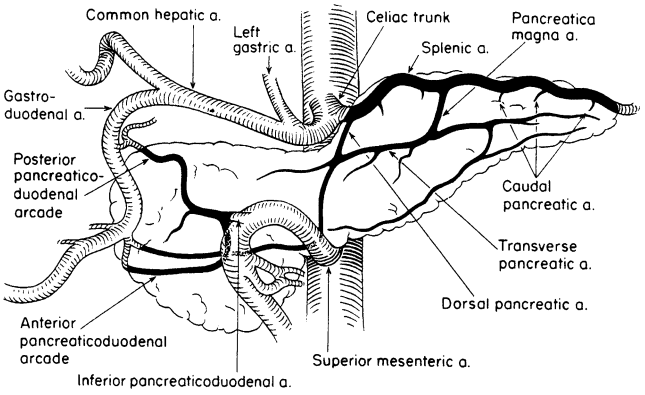

Fig. 4 Arterial supply to the pancreas.[5]

Visceral artery aneurysm is classified into two types: pseudoaneurysm and true aneurysm. Typically, aneurysms of the pancreaticoduodenal and gastroduodenal arteries evolve as complications of acute pancreatitis. Recently, hepatic artery aneurysm has also been frequently reported, which probably reflects the increasing use of percutaneous diagnostic and therapeutic biliary tract procedures[7] and chemotherapy infusion pump placement. This false aneurysm formation is caused by peripancreatic inflammation, such as pancreatitis, trauma, and iatrogenic injury. On the other hand, true isolated PDA aneurysm is believed to be caused mainly by hemodynamic change. Sutton and Lawton first described in 1973 that occlusion or stenosis of the celiac trunk appears to be the underlying cause of the true PDA aneurysm; increased blood flow in the peripancreatic arterial network provides collateral vessels for revascularization of the celiac trunk, thus dilating the vascular walls until an aneurysm develops.[3] De Perrot reported in 1999 that 63% of true PDA aneurysms, excluding pseudoaneurysms, were associated with a celiac trunk lesion.[4]

The cause of celiac axis stenosis is not clear in most of the reported cases. Of the 12 cases with a specified cause, nine were attributed to median arcuate ligament compression and three to atherosclerosis, thromboses, and agenesis of the celiac axis.[8–11]

As described in other series, the most common symptom is abdominal pain. The aneurysm usually ruptures into the retroperitoneal space around the pancreas, which causes acute abdominal pain. More rarely, if treatment is delayed, as in one of our cases, the aneurysm may finally rupture into the peritoneal cavity[12,13] or digestive tract,[14] which results in gastrointestinal bleeding.

Diagnosis at the acute stage has become possible due to advances in and increased use of imaging techniques, such as multidetector-row CT, MPR imaging, reconstruction imaging, and CTA. Plain CT shows that high absorption areas are seen around the head of the pancreas if there is a fresh hematoma. This is an important sign to distinguish between acute bleeding and acute inflammation, such as acute pancreatitis. Dynamic enhanced CT visualization of peripancreatic hematoma and aneurysm, and associated lesions of the celiac trunk, indicate the need for angiography to confirm the precise diagnosis and guide treatment.

As far as we are aware, no studies have described a definite relationship between aneurysm size and propensity to rupture. Suzuki et al. have reported that, in patients with aneurysm rupture, the diameter ranged from 4 to 70 mm (mean, 22.2 mm), whereas in those without rupture, it ranged from 5 to 42 mm (mean, 21.4 mm).[15] Therefore, the size of an aneurysm does not seem to be a determining factor for rupture, and we recommend treatment of all true PDA aneurysms, regardless of size, at the time of diagnosis.

Current treatment of PDA aneurysms consists of surgery, transcatheter occlusion of the aneurysm, and treatment of celiac trunk lesions, if present. The therapeutic options differ for each type of aneurysm and patient condition. A major goal in the treatment of these aneurysms is obliteration, treatment of any associated pathology, and preservation of blood flow in the territory of the celiac artery.

Over the past decade, the majority of these aneurysms have been managed through an open surgical technique that involves ligation, aneurysmectomy, or aneurysmorrhaphy. The first successful surgical treatment of a PDA aneurysm was reported in 1951 by Van Ouwerkerk and involved resection.[16] The mortality rate associated with surgery since 1980 has been 19%, yet surgery is still considered by many to be the initial and only definitive treatment for PDA aneurysm.[17] When these aneurysms are within the parenchyma of the pancreas, identification and isolation of the proximal and distal vessels can be difficult. In this regard, the optimal approach is to enter the aneurysm directly and suture/ligate the proximal and distal vessels.[7] However, pancreatic resection, such as pancreatoduodenectomy, may be required when the aneurysm cannot be visualized because of massive retroperitoneal hematoma.[4]

With the imaging techniques available today, the current standard management for all hemorrhagic syndromes related to visceral artery aneurysm rupture is TAE.[7,18–20] The 19% mortality rate associated with surgery of PDA aneurysm is significantly higher than that of embolization and nearly reaches statistical significance, despite the small number of cases reported.[17,18] Mandel et al. have reported a 79% success rate and no mortality linked to the procedure,[21] but the majority of these studies have investigated embolization of pseudoaneurysms caused by pancreatitis or trauma. True PDA aneurysm with celiac artery stenosis or occlusion requires precise and sophisticated techniques for embolization to preserve celiac artery territory blood flow.[4,22] There are risks of coil migration and unwanted embolization of other vessels, such as gastroduodenal or hepatic artery occlusion that leads to organ ischemia.[23] However, we suggest that transcatheter embolization should be considered as first-choice treatment in patients with ruptured aneurysm

because of the high mortality rate of surgery. The use of coil embolization offers the added features of radiopacity and palpability in the event that surgical exploration is required.[17]

There is no consensus whether we should treat the aneurysms and celiac axis stenosis at the same time. Some authors have recommended revascularization of the celiac territory to prevent aneurysm recurrence,[9,18,21] and resection of the median arcuate ligament has been performed in some cases.[4,15,18] Spontaneous resorption of the aneurysm after resection of the median arcuate ligament also has been reported.[24,25] Ducasse et al. has stated that direct celiac or hepatic artery bypass for revascularization seems an unnecessarily risky procedure in the absence of an associated multi-aneurysmal disorder.[18] Recently, endovascular treatment of the celiac trunk, by percutaneous transarterial angioplasty (PTA) using a stent, has been reported.[8] PTA may be used as initial treatment in patients with unruptured PDA aneurysms associated with celiac axis stenosis, to reduce the collateral blood flow in the aneurysmal artery and to prevent possible rupture, but no study has reported the recurrence of PDA aneurysms caused by residual celiac axis stenosis. Therefore, Suzuki et al. have stated that, if the risk of ischemic dysfunction of the liver and the duodenum is not high, additional treatment of celiac axis stenosis may not be required.[26] However, there are no guidelines as to when and in whom celiac axis revascularization should be undertaken. Moreover, the number of reported cases is limited, and there are no long-term results of treatment, therefore the optimal management of true PDA aneurysm with celiac axis stenosis is still a topic for discussion.

Conclusions

We recommend treatment of all true PDA aneurysms at the time of diagnosis. Selective angiography or multidetector-row CT is necessary to establish the diagnosis. Attention should be paid to organ blood flow and collateral circulation. True PDA aneurysm with celiac artery stenosis or occlusion requires precise techniques for embolization to preserve blood flow in the celiac artery territory.

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References

1. Stanley JC, Wakefield TW, Graham LM, Whitehouse WM Jr, Zelenock GB, Lindenauer SM. Clinical importance and management of splanchnic artery aneurysms. J Vasc Surg 1886; 3: 836–840
2. Ferguson F. Aneurysm of superior pancreaticoduodenal artery. Proc N Y Pathol Soc 1895; 24: 45–49
3. Sutton D, Lawton G. Celiac stenosis or occlusion with aneurysm of the collateral supply. Clin Radiol 1973; 24: 49–53
4. de Perrot M, Berney T, Deleaval J, Bühler L, Mentha G, Morel P. Management of true aneurysms of the pancreaticoduodenal arteries. Ann Surg 1999; 229: 416–420
5. Stewart R et al. Gastrointestinal Angiography vol. 1, 3rd ed. Philadelphia, Saunders 1986, p61
6. Kalva SP, Athanasoulis CA, Greenfield AJ, Fan CM, Curvelo M, Waltman AC, Wicky S. Inferior pancreaticoduodenal artery aneurysms in association with celiac axis stenosis or occlusion. Eur J Vasc Endovasc Surg 2007; 33: 670–675
7. Louis M, Messina, Charles J, Shanley. Visceral artery aneurysms. Surg Clini North Ame 1997; 77: 425–441
8. Yu Wen Tien, Hsien Li Kao, Hsiu Po Wang. Celiac artery stenting: a new strategy for patients with pancreaticoduodenal artery aneurysm associated with stenosis of the celiac artery. J Gastroenterol 2004; 39: 81–85
9. Quandalle P, Chambon JP, Marache P, Saudemont A, Maes B. Pancreaticoduodenal artery aneurysms associated with celiac axis stenosis. Ann Vasc Surg 1990; 4: 540–545
10. Ho KL. Aneurysm of pancreaticoduodenal artery: report of a case and review of the literature. Int Surg 1979; 64: 35–39
11. Partensky C, Descos L, Champetier P, Bretagnolle M, Bret PM. Aneurysm of an abnormal pancreatic arterial arch with agenesis of the celiac trunk. Gastroenterol Clin Biol 1987; 11: 260–261
12. Mariano EG, Giego R . Aneurysm of the pancreaticoduodenal artery. J Med Soc N J 1981; 78: 191–193
13. Bageacu S, Cuilleron M, Kaczmarek D, Porcheron J. True aneurysms of the pancreaticoduodenal artery: successful non-operative management. Surgery 2006; 139: 608–616
14. Kadir S, Athanasoulis CA, Yune HY, Wilkov H. Aneurysms of the pancreaticoduodenal arteries in association with celiac axis occlusion. Cardiovasc Radiol 1978; 1: 173–177
15. Suzuki K, Kashimura H, Sato M, Hassan M, Yokota H, Nakahara A et al. Pancreaticoduodenal artery aneurysms associated with celiac axis stenosis due to compression by median arcuate ligament and celiac plexus. J Gastroenterol 1998; 33: 434–438
16. Van Ouwerkerk LW. Aneurysm of the arteria pancreaticoduodenal. Arch Chir Netherlands 1951; 3: 2–7
17. David P, Ralph I, Morris D, Samuel Y et al. Aneurysms of the pancreaticoduodenal arteries: a change in management. Ann Vasc Surg 1998; 1: 286–291
18. Ducasse E, Roy F, Chevalier J, Massouille D, Smith M, Speziale F. Aneurysm of the pancreaticoduodenal arteries with a celiac trunk lesion: current management. J Vasc Surg 2004; 39: 906–911
19. Sandra C, William H, Robert L, Walter J, Albert A, James S. Current management of visceral artery aneurysm. Surgery 1996; 120: 627–634
20. Grego FG, Lepidi S, Ragazzi R, Iurilli V, Stramanà R, Deriu GP. Visceral artery aneurysms: a single center experience. Cardiovascular Surgery 2003; 11: 19–25
21. Mandel SR, Jaques PF, Mauro MA. Nonoperative management of peripancreatic arterial aneurysm. Ann Surg 1987; 205: 126–128
22. Uher P, Nyman U, Ivancev , Lindh M. Aneurysms of the pancreaticoduodenal artery associated with occlusion of the celiac artery. Abdom Imaging 1995; 20: 470–473
23. Trojanowski JQ, Harrist TJ, Athanasoulis CA, Greenfield AJ. Hepatic and splenic infarctions: complications of therapeutic transcatheter embolization. Am J Surg 1980; 139: 272–277
24. Mora JD, Obst D. Celiac axis artery stenosis with aneurismal calcification of the collateral supply. Aust Radiol 1976; 20: 252
25. Proud G, Chamberlain J. Aneurysm formation on the small pancreatic arteries in association with celiac axis compression. Ann R Coll Surg Eng 1978; 60: 294–297
26. Suzuki K, Tachi Y, Ito S, Maruyama K, Mori Y, Komada T, Matsushima M, Ota T, Naganawa S. Endovascular management of ruptured pancreaticoduodenal artery aneurysms associated with celiac axis stenosis. Cardiovasc Intervent Radiol 2008; 31: 1082–1087

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ORIGINAL ARTICLE

The Obstructed Pancreatico-biliary Drainage Limb: Presentation, Management, and Outcomes

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Abstract
Introduction Obstruction of the pancreatico-biliary (PB) drainage limb following major PB operations creates unique diagnostic and management dilemmas. We describe the etiology and prevalence, as well as diagnostic and therapeutic approaches for this challenging problem.
Methods Individuals with PB limb obstruction were identified from a cohort of 477 patients undergoing major PB resections or bypasses for benign and malignant (N=265) diseases from September 2000 to January 2010. Their presentation, management, short-term outcomes, and survival were analyzed.
Results Thirteen patients developed eventual PB limb obstruction with a mean time to presentation of 18.4 months (range 0.5–41.9), representing an overall adjusted incidence of 4%. Presenting symptoms were reflective of limb obstruction (elevated LFTs, jaundice, cholangitis, and pancreatitis). CT scans demonstrated dilation of the PB drainage limb in all 13 patients and evidence of intrahepatic biliary dilation in eight. Endoscopy was not valuable for either diagnostic or therapeutic purposes in the five patients evaluated in this manner. Percutaneous transhepatic biliary drainage (PTC) was pursued in six patients and provided definitive palliation in two, while three were temporized by this modality prior to a definitive operation, and it was employed postoperatively in another. Operative management occurred in 11 of 13 patients. Causative lesions were not accurately predicted by preoperative imaging and included adhesions, limb volvulus, abscess, malignant local recurrence, solitary metastatic disease, and carcinomatosis. Surgical interventions varied (five enteric bypasses, three adhesiolyses, two explorations, and one external limb venting). There were two perioperative mortalities, but limited morbidity otherwise (one myocardial infarction, one wound dehiscence, and one empyema from PTC placement). The median duration of postoperative hospital stay was 9 days, and no patient required readmission for further surgical management. No patients suffered subsequent recurrence of PB obstruction. In follow-up, nine of the remaining 11 patients are deceased with a median survival of 2.3 months (0.6–9.4 months). The other two are alive at a mean follow-up of 48 months.
Conclusion Although infrequent, PB limb obstruction occurs for a variety of reasons and most commonly in the setting of an original malignancy. Since numerous therapeutic modalities are available, an improved understanding of the condition is important in managing these complex patients. Decisive operative intervention accurately assesses the cause and extent of the problem and, for most presentations, provides definitive palliation with limited morbidity for this near-terminal event.

Keywords Biliary obstruction · Surgical palliation · Pancreatic cancer · Whipple's resection · Afferent limb obstruction

Introduction

The formation of an enteric drainage limb is necessary for reconstruction following many operations on the pancreatic

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and biliary systems for both benign and malignant conditions. Isolated blockage of this intestinal drainage channel is unique in that it causes insidious symptoms of biliary or pancreatic obstruction (jaundice, cholangitis, and pancreatitis) but seldom presents as obstruction of enteric transit with more overt evidence of nausea, distention, and vomiting.

Much is already known about the potential complications and optimal management of similar reconstruction conduits used in gastric surgical procedures. For instance, in bariatric surgery, drainage limb obstruction most commonly represents a technical problem in the early postoperative period or is otherwise evidence of an adhesive obstruction when presenting in a delayed fashion. In these circumstances, early operative management for relief of obstruction and correction of the underlying mechanical/technical problem is the standard of care.[1,2] Surgery also offers value in the management of small-bowel obstructions from metastatic malignancies.[3–5]

By contrast, little has been reported about this scenario in the context of prior major pancreato-biliary surgery. In the setting of gastric, duodenal, or periampullary malignancy, gastric outflow obstruction often portends a poor prognosis and high near-term mortality. Palliation for this problem is often performed through surgical means, even if no option for curative resection exists.[6] Alternatively, non-operative approaches to drainage limb obstructions have also been advocated.[7] For instance, Kiely et al. report a series of 30 patients with postoperative malignant gastric outlet obstruction treated with endoscopically placed metal enteric wall stents.[8] Furthermore, isolated postoperative obstructive strictures in the pancreatic or biliary systems have also been successfully treated using both endoscopic and percutaneous transhepatic approaches.[9] However, these have most commonly been applied to narrow-caliber ductal anastomotic strictures.[10]

Reconstruction with a drainage limb following pancreato-biliary procedures (PB limb) creates a unique circumstance in which there is potential for obstruction of pancreatic and biliary flow not only at the position of the ductal anastomoses but also through mechanical blockage of the drainage conduit itself. Luminal obstruction of the PB limb poses a challenging management dilemma due to the difficulty of accurately accessing the conduit through radiographic, endoscopic, or percutaneous approaches. Operative intervention is a viable option, but there is a paucity of literature on the topic to guide decision making. Our experience with this unique problem is analyzed, focusing on its incidence, management, short-term, and long-term outcomes.

Methods

Under an Institutional Review Board for Human Subjects Research approved protocol, the medical records of all patients undergoing major pancreato-biliary procedures at our institution between September 2000 and January 2010 were reviewed to identify patients who subsequently developed PB limb drainage obstruction. This period spans the time beginning with the index operation of the first patient to suffer obstruction until the presentation of obstruction in the last patient in the series. All operations (index and subsequent) were performed by one of two fellowship-trained, pancreato-biliary surgical specialists in a high-volume tertiary referral practice with the exception of one index case which was performed elsewhere.

Index operations consisted of both oncologic resections with curative intent for periampullary and biliary malignancies, as well as Roux-en-Y bilio-enteric bypass procedures performed for benign conditions (biliary stricture, chronic pancreatitis, etc.). These included pancreaticoduodenectomy, total pancreatectomy, pancreas-preserving duodenal resection, hepatico- and choledocho-jejunostomy, and lateral pancreaticojejunostomy (Puestow) procedures in which the same Roux limb was used to relieve biliary obstruction in a "jump" fashion. Biliary bypass procedures (often in conjunction with gastroenterostomy) performed with palliative intent in the setting of locally advanced PB malignancy were specifically excluded from evaluation due to the limited expectation of long-term survival in this particular scenario. The following operations using a Roux-en-Y conduit were also excluded as the biliary tree was not specifically drained: central pancreatectomy reconstructed with pancreaticojejunostomy, distal pancreatectomy with pancreaticojejunostomy (Duval procedure), cyst-jejunostomy for pancreatic pseudocysts, and Puestow procedures exclusively for pancreatic duct drainage. Choledochoduodenostomies were also not considered as an enteric drainage limb is not constructed.

For the vast majority (95%) of the initial pancreaticoduodenectomies, the method of reconstruction consisted of placement of the PB drainage limb behind the small-bowel mesenteric stalk. This conduit was situated to replicate the native anatomic position of the duodenum as it originally coursed through the ligament of Treitz canal. The other cases were managed through a retrocolic, trans-mesenteric alignment. All other bypass procedures consisted of Roux-en-Y conduits placed in a typical retrocolic, trans-mesenteric configuration.

Incidence calculations were derived by dividing cases of eventual obstruction by total index cases performed over the measured time period. A 2-year incidence rate also was calculated using only data from patients with 24 months' follow-up to account for lead time bias in the presentation of PB obstruction. Time to obstruction was defined as the period from the index operation to the establishment of a diagnosis of PB limb obstruction (either radiographically or operatively). Patient symptoms at the time of presentation with obstruction were annotated, as were laboratory and

imaging data. Duration of hospital stay and overall survival were calculated from the time of definitive intervention for the PB limb obstruction. Perioperative mortality is defined as any death occurring during the initial postoperative hospitalization or within 30 days of the operation.

To allow for an objective comparative analysis of outcomes, POSSUM scores were calculated to provide a metric for the measurement of expected outcomes based on the patient's physiologic condition at the time of presentation. The POSSUM scoring system uses a combination of physiologic and operative clinical variables to predict the rate of expected perioperative complications for a studied cohort. Physiologic and operative POSSUM scores for this series were individually calculated using the formula previously described by Copeland in 1991[11] and later validated in the setting of pancreatic surgery by Pratt et al. [12] Actual complications were identified and assigned clinical severity using the Clavien complication scale.[13] From this, an observed-to-expected (O/E) ratio was developed by dividing the rate of actual postoperative complications by the collective POSSUM score for the cohort. O/E ratios of 1.0 indicate on-par performance, while ratios <1.0 are an indication of better than expected performance, and those >1.0 suggest inferior performance.

Patient follow-up was conducted by the operating surgeon, and all survival data were based on documented patient visits for those still alive. For the remaining patients, their demise was verified by cross-referencing with the Social Security Death Index website (http://ssdi.rootsweb.ancestry.com/).

Results

Over the 112-month study period, 477 major pancreaticobiliary operations with PB limb creation meeting the inclusion criteria were performed. Of these, 265 were originally for a malignant pathology. From this group of index operations, 13 patients subsequently presented with obstruction of the PB drainage limb for an overall incidence of 2.7%. Malignancy was the underlying condition in 12 of the 13 obstructions, yielding a specific incidence in the setting of malignancy of 4.5% (12/265). The mean time from the index operation to presentation with obstruction was 18.4 months (range 0.5–41.9 months). Given this lead time bias, an adjusted 2-year incidence of PB obstruction would increase to 4% (12/303) if only patients with 24 months of follow-up are included. Table 1 presents the salient pre-, intra-, and postoperative features of the individual patients.

The most common initial presenting symptom was upper abdominal pain, seen in 11 patients (85%). Other commonly observed signs were reflective of pancreatic or biliary ductal obstruction: jaundice 69% (9/13), cholangitis 39% (5/13), and pancreatitis 23% (3/13). Elevations in transaminases were seen in 69% (9/13) with an elevation of alkaline phosphatase being universally present (13/13). Hyperbilirubinemia was evident in 62% (8/13), and 23% (3/13) had a hyperamylasemia. Leukocytosis was not regularly seen: four of 13 patients. All patients were initially evaluated by abdominal computed tomography scan. Obstructive dilation of the PB drainage limb was demonstrated in all 13 patients (Fig. 1), and intrahepatic biliary dilation was recognized in ten patients (77%). In those patients who were ultimately managed operatively, CT imaging correctly defined the full nature of the obstruction in fewer than half of the cases (five of 11).

Attempts at non-surgical management had limited efficacy. Endoscopy was not valuable for either diagnostic or therapeutic purposes in those four patients evaluated in this manner. In each case, these failures stemmed from the inability to effectively access the point of obstruction via the pancreato-biliary or Roux-en-Y drainage limb. Percutaneous transhepatic cholangiographic (PTC) drainage was pursued in six patients and constituted definitive treatment in two. In one case (patient no. 11), this transhepatic approach was used as a route for placement of an intraluminal metal enteric wall stent in the pancreato-biliary drainage limb, while in the other case, definitive short-term palliation was provided by external drainage alone (patient no. 12). Both of these patients were deemed not fit enough to endure an operative procedure with physiologic POSSUM scores of 14 and 38. Three patients (nos. 2, 9, and 10) were temporized by this modality prior to a definitive operation, and the last (no. 13) underwent a PTC for postoperative biliary decompression when an operative bypass was attempted but not technically possible (Table 1). In four of these six cases, internal wall stent placement was attempted across the obstruction after initial transhepatic percutaneous drainage, yet was not achieved on technical grounds.

Eleven patients went on to surgical exploration. Four cases were performed under emergent conditions. Causative lesions were not accurately predicted by preoperative imaging and included adhesions, limb volvulus, compressive abscess, malignant local tumor recurrence, solitary metastatic disease, and diffuse carcinomatosis. Surgical interventions varied: five enteric bypasses, three adhesiolyses, two explorations alone, and one external limb venting (Table 1).

Two patients expired in the postoperative period (Clavien Grade 5) for a mortality rate of 15%. On exploration, patient no. 10 had recurrent pancreatic adenocarcinoma infiltrating the root of the mesentery resulting in occlusion of the SMA with near-complete small-bowel necrosis—evident on neither preoperative CT imaging nor upper endoscopy. This led to infarction of the proximal aspect of the PB limb with resultant dilation. With such findings, there was no further operative recourse, and the patient was made "comfort measures only" and expired on POD 2. The other mortality (no. 13) occurred as a complication of the PTC intervention for biliary decompres-

Table 1 Presentation, Treatment, and Outcomes for Patients Indentified with PB Drainage Limb Obstruction

Demographics						Presenting symptoms					
Patient	Age	Gender	Original diagnosis	Original operation	Time interval (months)	Physiologic POSSUM score	Pancreatitis	Biliary obstruction	Intestinal obstruction	Cholangitis	PTC
1	82	F	Pancreatic CA	Whipple (classical)	35.7	31	No	Yes	Yes	No	No
2	73	F	Gallbladder CA	Roux-en-Y hepaticojejunostomy	7.6	27	No	Yes	Yes	Yes	Yes
3	63	M	Benign duodenal fibrosis	Whipple (classical)	8.3	27	Yes	No	Yes	No	No
4	58	F	Pancreatic CA	Whipple (pylorus preserving)	0.5	19	No	Yes	Yes	Yes	No
5	62	F	Pancreatic CA; chronic pancreatitis	Whipple (pylorus preserving)	41.9	19	No	No	Yes	No	No
6	78	F	Ampullary CA	Whipple (pylorus preserving)	19.1	27	Yes	Yes	Yes	No	No
7	50	M	Cholangio CA	R hepatectomy w/Roux-en-Y hepaticojejunostomy	14.2	28	No	Yes	Yes	No	No
8	80	F	Pancreatic CA	Whipple (pylorus preserving)	13.1	15	No	Yes	Yes	Yes	No
9	51	M	Ampullary CA	Whipple (pylorus preserving)	17.9	27	No	Yes	Yes	Yes	Yes
10	65	F	Pancreatic CA	Whipple (pylorus preserving)	19.7	37	No	Yes	Yes	No	Yes
11	67	M	Cholangio CA	Whipple (pylorus preserving)	10.4	14	No	Yes	Yes	No	Yes
12	68	M	Pancreatic CA	Whipple (pylorus preserving)	41.5	38	Yes	No	Yes	Yes	Yes
13	47	M	Pancreatic CA	Whipple (pylorus preserving) with portal reconst	9.9	21	No	Yes	Yes	No	Yes

sion. A hemothorax and subsequent biliary empyema developed, which required blood transfusion and eventual video-assisted thoracic surgery with external drainage (Clavien Grade 3B). The patient expired POD 26 after discharge to hospice care. A third patient was non-operatively managed due to poor functional status and expired in hospice care 21 days after PTC venting alone for an ischemic PB limb with evidence of pneumotosis. Beyond this, morbidity was limited, with only two other patients experiencing complications. One patient suffered a myocardial infarction in immediate recovery following emergent relief of a PB limb volvulus. This required urgent cardiac stenting with no functional sequelae (Clavien Grade 3a). The second complication was a wound dehiscence (Clavien Grade 4) in a patient preoperatively on bevacizumab therapy for recurrent cholangiocarcinoma. The median duration of postoperative hospital stay in this series was 9 days (range 1–42 days), and no patient required readmission for further surgical management.

The average physiologic acuity of this particular patient group according to physiologic POSSUM scoring was 25.4 (range 14–38). By comparison, the equivalent POSSUM score for our elective pancreatcobiliary surgical patient population over this same period is 19.2, emphasizing the considerably higher acuity of these patients when they presented with obstructed PB limbs. The average total POSSUM score, reflecting both the physiologic acuity and the operative/procedural conduct, is 70.9%, whereas for our overall elective population, it is 52.1%.[12,14,15] Application of the POSSUM scoring system to the 13 study patients predicts that roughly nine complications would be expected. We observed only five complications (discussed above), leading to a very acceptable O/E ratio of 0.54.

Table 1 (continued)

Therapeutic interventions			Operative outcomes					Survival	
Endoscopy	Operative exploration	Emergent	Procedure/operation	Operative findings	Predicted POSSUM morbidity (%)	Complications	Hospital stay (days)	Deceased	Survival (months)
No	Yes	Yes	Adhesiolysis	Adhesive band obstructing the PB limb	89	Myocardial interaction	7	Yes	4.2
No	Yes	No	PTC biliary venting; gastroenterostomy; bypass of proximal Roux limb to downstream Roux limb	Roux limb obstruction from tumor recurrence	75		7	Yes	5.1
Yes	Yes	No	Extended adhesiolysis; jejunal resection, revision of pancreato-jejunostomy	Stricture of pancreato-jejunostomy, adhesions obstructing the PB limb	71		8	No	57.9
No	Yes	Yes	Drainage of abscess; J-tube placement	Abscess obstructing PB limb	54		5	No	37.8
Yes	Yes	Yes	Enteric bypass; J-Tube	Tumor recurrence at root of mesentery obstructing the PB limb	40		9	Yes	1.7
No	Yes	No	Adhesiolysis; G/J-Tube placement; decompressing PB limb vent placement	Carcinomatosis	75		8	Yes	2.3
Yes	Yes	No	Bypass of Roux-en-Y (enter-enterostomy×2)	Tumor at root of mesentery obstructing Roux-en-y limb	92	Wound dehiscence	42	Yes	2.1
No	Yes	No	Bypass of PB limb (jejunojejunostomy)	Multifocal tumor recurrence obstructing enteric drainage	34		9	Yes	4.0
No	Yes	Yes	PTC biliary venting; bypass of PB limb (jejunojejunostomy); left colectomy	Retroperitoneal recurrence at base of SMA; obstructing sigmoid colon mass	78		15	Yes	6.3
Yes	Yes	No	PTC biliary venting; exploratory laparotomy	Panintestinal necrosis	49	Death (POD 1)	1	Yes	0.0
No	No	No	PTC with luminal wall-stent placement	N/A	93		11	Yes	9.4
No	No	No	PTC biliary venting	N/A	96	Death	17	Yes	0.7
No	Yes	No	Exploratory laparotomy; subsequent PTC with luminal wall-stent placement	Carcinomatosis	78	Empyema (S/P PTC placement) death (POD 26)	12	Yes	0.8

No patients have manifested recurrence of their PB obstruction. There are two long-term survivors, yielding an overall survival from presentation with PB obstruction of 15% at 3 years with a mean survival of 10.2 months (Fig. 2). Excluding the two immediate perioperative mortalities described above, there were nine deceased patients. Their mean survival from point of intervention was 2.3 months (0.6–9.4 months). This includes the two patients managed solely with palliative PTC decompression who survived 9.4 and 0.7 months. The two long-term survivors (nos. 3 and 4, both operatively managed) are alive at 58 and 38 months, respectively. While one patient had original benign duodenal

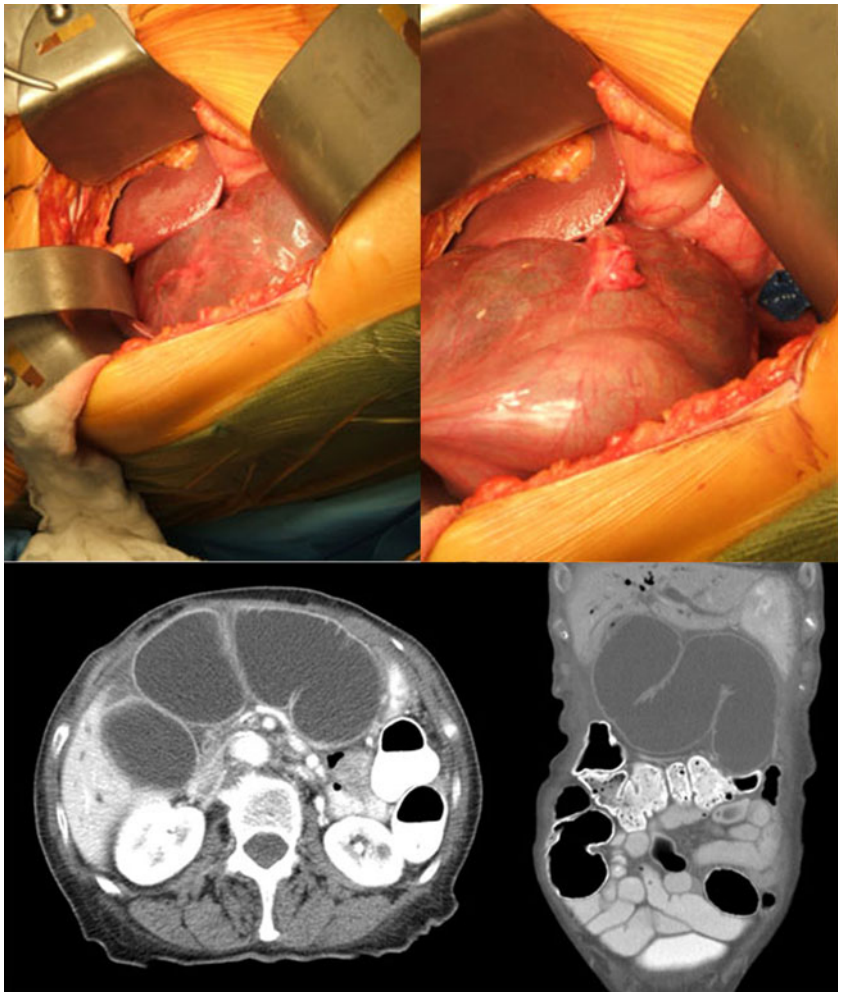

Fig. 1 Intra-operative findings of PB limb obstruction. This patient was seen to have diffuse carcinomatosis at the time of operative exploration, a finding not predicted by preoperative CT imaging studies.

fibrosis and the other pancreatic adenocarcinoma, neither had a malignant cause of PB limb obstruction (adhesion, abscess). Distinguishing demographic, radiographic, or laboratory characteristics at presentation were not identified between those patients who survived in follow-up and those who are deceased.

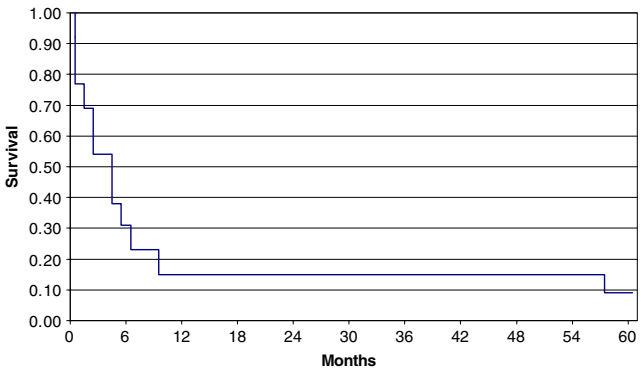

Fig. 2 Kaplan–Meier survival curve for 13 patients presenting with PB limb obstruction. Survival is documented from the time of diagnosis with PB limb obstruction.

Discussion

The problem of drainage limb obstruction following enteric reconstruction has been well characterized for conditions such as gastric resection and bariatric surgery. Given the acquired anatomic complexities of these cases, the value of operative intervention is well established. Surgery also plays an important role in the palliation of malignant small-bowel obstruction.[3–5] Conversely, complications pursuant to PB limb reconstruction are not well understood. Thus far, PB obstruction has been best characterized in regard to duct-to-enteric anastomotic strictures. Yet, luminal PB obstruction itself is poorly defined.

In this series of patients undergoing PB reconstruction for all causes, we found this presentation to be rare overall (2.7%). However, in the setting of an original resection for malignancy, it is twice as common (≈5%) and more troublesome in that it usually indicates a terminal phase. The initial surgical endeavor was usually for malignancy, which may make interpretation of subsequent imaging studies difficult as recurrent disease and postoperative adhesions may be indistinguishable from one another.

While de novo pancreato-biliary obstruction is traditionally managed with endoscopic approaches, in this particular clinical scenario, endoscopy is often limited by the distorted anatomy of the surgical reconstruction. Instead, our series indicates that an operative approach to this problem is reasonable, often necessary, and generally effective.

This series demonstrates the variety of possible causes of obstruction. This unpredictability underscores the value of surgical exploration as the ultimate diagnostic modality. Accurate characterization of the pathophysiology of the obstruction remains critical in the determination of the proper treatment plan for the patient. The numerous preoperative imaging tests combined (including luminal endoscopy) were able to accurately identify the true nature of the obstructive process in just half of the cases. While we found that CT was quite effective in determining the *presence* of obstruction, and defining it as the source of the symptoms, its ability to delineate malignant from functional processes was limited. As this particular distinction may influence discussion with the patient regarding on-going care and treatment options, the ability to determine the full extent of disease, short of exploration, is haphazard. Endoscopic evaluation was routinely unhelpful in these patients due to inability to access the point of obstruction in the PB drainage limb. This modality has previously been championed as a method of dealing with malignant postoperative gastric outlet obstruction. Kiely et al. reported a 90% success rate with this technique in a retrospective series with a median survival of 4.8 months in patients following biliary resections and 2.4 months following pancreatic surgery. However, this series dealt with patients who presented with symptoms related to poor gastric emptying and did not specifically address the effect of stenting on PB limb obstruction.

Transhepatic cholangiography has been well described as a method to delineate and treat anastomotic strictures and other causes of postoperative biliary obstruction.[16–19] However, as the epicenter of PB obstruction in our series involves the luminal portion of the drainage conduit, this modality did not prove to provide adequate palliation (2/6 successful in this cohort). In addition, this minimally invasive approach to management of PB limb obstruction is not without cost. One patient in our series suffered from significant bleeding and infectious complications from a PTC tube placed across the thoracic cavity, ultimately requiring operative evacuation of the pleural space and hastening his demise. While it may be argued that external biliary drainage alone is appropriate in a condition with a short-term survival and potential operative morbidity, we have found this to be impractical for two reasons. First, this management approach is suboptimal for fluid and nutritional management, often leading to prolonged hospitalization, need for home care services, and even readmission. Additionally, operative management affords the ability to ascertain a definitive diagnosis. Furthermore, while surgical attempts at PB limb decompression were not universally successful in our series, the success rate was much greater than that seen with percutaneous approaches and showed similar morbidity.

A range of operative interventions were required to successfully alleviate PB limb obstruction, and the ability to predict the nature of the operation preoperatively was limited. The various etiologies of obstruction encountered underscore the diagnostic value of operative exploration. Given typical CT findings of luminal obstruction, the causative lesions can be numerous; so, on-the-fly decision making is required. In several of these clinical scenarios, the conservative (i.e., non-operative) approach to therapy would likely have been unsuccessful as the initial assumptions with regard to etiology were erroneous. In this sense, operative management resulted in the delivery of more appropriate, timely, and targeted care to these patients. Yet, we acknowledge that in some cases, the prevailing clinical strategy favors non-operative management of intestinal or ductal obstruction in the background of recurrent malignancy based on the limited long-term survival with these diseases. However, this clinical rationale clearly does, and should, not apply in the less common setting of benign disease. We therefore propose an aggressive operative strategy in this scenario.

Definitive operative intervention in this series came with a low rate of postoperative complications. There was one in-hospital mortality—a woman with ischemic bowel which was not accurately diagnosed on preoperative CT scan (patient no. 10). In that case, the operation served a purpose in hastening clarity over the diagnosis and allowed for prompt decision making and, undoubtedly, resource conservation. The second postoperative death occurred in hospice at POD 26 as described above after PTC methods were employed to salvage a non-therapeutic laparotomy. Otherwise, there were only two complications. These outcomes were achieved in the setting of durable results from operative therapy as no patients required readmission for recurrent PB limb obstruction. This combination of limited short-term morbidity and quality-of-life improvement argues for the efficacy of an operative approach to the management of these patients.

When objectively comparing these outcomes using the POSSUM model, we see that surgical intervention in these patients indeed outperformed even what would be expected despite the high acuity of this patient population. In fact, the large differential in observed complications (44%) from those predicted (71%) is another indicator that surgical intervention in these patients can in fact be performed safely and may even decrease the risk to the patient cohort when compared with other approaches. This model, well tested in other fields of general surgery, has previously been validated by our group as a reliable metric for acuity in the realm of pancreatic resections.[14] In contrast with elective pancreatic resections, the patients with PB limb obstruction in this series have

significantly greater impairment in baseline function as indicated by their physiologic POSSUM score (mean 25.4 compared with 19.2 for elective resection). The markedly low observed/expected complication ratio in the surgical patients illustrates the point that surgical management can be not only useful to the clinician as a means of establishing a diagnosis and affecting therapy simultaneously but also that it may indeed result in improved patient outcomes when compared with non-operative palliative approaches or inaction.

It might be argued that the method of PB limb reconstruction regularly (approximately 95% of the time) employed by our group during pancreatoduodenectomy—a natural anatomic/retromesenteric limb placed in the native position of the resected duodenum—could potentially predispose to obstruction secondary to malignant recurrence in the lymphovascular tissue of the resection bed. Though a very valid consideration, we have not found this to be the case, with is only a single case in this review (denominator of 12 for malignancy) representing this particular scenario. Additionally, the alternative retrocolic approach to reconstruction may itself become a point of mechanical obstruction, internal herniation, or a fixed point for volvulus of the small bowel, as was seen in another patient.

In summary, pancreatico-biliary limb obstruction is a rare event following major PB operations with a consistent presentation despite a variety of etiologies. This often occurs in the setting of prior malignancy and generally portends a near-terminal phase of care for patients. While minimally invasive approaches are available for palliation, they are not often successful. Operative intervention more often yields diagnostic certainty and definitive palliation at a reasonable risk-benefit profile.

References

1. Koppman, J.S., Li, C., and Gandsas, A., *Small bowel obstruction after laparoscopic Roux-en-Y gastric bypass: a review of 9,527 patients.* J Am Coll Surg, 2008. **206**(3): p. 571–84.
2. Husain, S., Ahmed, A.R., Johnson, J., et al., *Small-bowel obstruction after laparoscopic Roux-en-Y gastric bypass: etiology, diagnosis, and management.* Arch Surg, 2007. **142**(10): p. 988–93.
3. Rosato, F.E., Jr. and Rosato, E.L., *Current surgical management of intestinal metastases.* Semin Oncol, 2008. **35**(2): p. 177–82.
4. Finan, P.J., Campbell, S., Verma, R., et al., *The management of malignant large bowel obstruction: ACPGBI position statement.* Colorectal Dis, 2007. **9 Suppl 4**: p. 1–17.
5. Helyer, L. and Easson, A.M., *Surgical approaches to malignant bowel obstruction.* J Support Oncol, 2008. **6**(3): p. 105–13.
6. Lillemoe, K.D., Cameron, J.L., Hardacre, J.M., et al., *Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial.* Ann Surg, 1999. **230**(3): p. 322-8; discussion 328–30.
7. Ripamonti, C.I., Easson, A.M., and Gerdes, H., *Management of malignant bowel obstruction.* Eur J Cancer, 2008. **44**(8): p. 1105–15.
8. Kiely, J.M., Dua, K.S., Graewin, S.J., et al., *Palliative stenting for late malignant gastric outlet obstruction.* J Gastrointest Surg, 2007. **11**(1): p. 107–13.
9. Smith, A.C., Dowsett, J.F., Russell, R.C., et al., *Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction.* Lancet, 1994. **344**(8938): p. 1655–60.
10. Bornman, P.C., Harries-Jones, E.P., Tobias, R., et al., *Prospective controlled trial of transhepatic biliary endoprosthesis versus bypass surgery for incurable carcinoma of head of pancreas.* Lancet, 1986. **1**(8472): p. 69–71.
11. Copeland, G.P., Jones, D., and Walters, M., *POSSUM: a scoring system for surgical audit.* Br J Surg, 1991. **78**(3): p. 355–60.
12. Pratt, W., Joseph, S., Callery, M.P., et al., *POSSUM accurately predicts morbidity for pancreatic resection.* Surgery, 2008. **143**(1): p. 8–19.
13. Dindo, D., Demartines, N., and Clavien, P.A., *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.* Ann Surg, 2004. **240**(2): p. 205–13.
14. Pratt, W., Callery, M.P., and Vollmer, C.M., Jr., *Optimal surgical performance attenuates physiologic risk in high-acuity operations.* J Am Coll Surg, 2008. **207**(5): p. 717–30.
15. Vollmer, C.M., Jr., Pratt, W., Vanounou, T., et al., *Quality assessment in high-acuity surgery: volume and mortality are not enough.* Arch Surg, 2007. **142**(4): p. 371–80.
16. House, M.G., Cameron, J.L., Schulick, R.D., et al., *Incidence and outcome of biliary strictures after pancreaticoduodenectomy.* Ann Surg, 2006. **243**(5): p. 571–6; discussion 576–8.
17. Lillemoe, K.D., *Benign post-operative bile duct strictures.* Baillieres Clin Gastroenterol, 1997. **11**(4): p. 749–79.
18. Lillemoe, K.D., Melton, G.B., Cameron, J.L., et al., *Postoperative bile duct strictures: management and outcome in the 1990 s.* Ann Surg, 2000. **232**(3): p. 430–41.
19. Lillemoe, K.D., Pitt, H.A., and Cameron, J.L., *Current management of benign bile duct strictures.* Adv Surg, 1992. **25**: p. 119–74.

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CASE REPORT

Left-sided Acute Appendicitis with Situs Inversus Totalis: Review of 63 Published Cases and Report of Two Cases

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Abstract
Background Situs inversus (SI) and midgut malrotation (MM) are uncommon anatomic anomalies that complicate diagnosis and management of acute abdominal pain.
Methods We present two cases of left-sided acute appendicitis with situs inversus totalis and a literature review of studies published in English language on left-sided acute appendicitis, accessed via Pubmed and Google Scholar database.
Results Sixty-three published cases of left-sided acute appendicitis were evaluated, and two patients (M:16 yr, F:17 yr) who presented to our clinic with left lower quadrant pain caused by left-sided acute appendicitis were reported. Thirty-five of the patients were male and 30 were female (including our patients) with age range from 8 to 63 years and median age of 26.7± 14.0 years. Fifty-three patients had situs inversus totalis (SIT), 8 had MM and two were with malrotation of the caecum. Thirty-eight patients had applied to the hospital with left lower quadrant pain, 12 with right and 6 with bilateral lower quadrant pain. Thirty patients were diagnosed as having SIT or MM, while the diagnosis in 12 patients was established during the intraoperative period. Eleven patients with SIT were aware of having this anomaly. Five of the patients underwent laparoscopic appendectomy and in two patients laparoscopic appendectomy and cholecystectomy were performed in one session. Preoperative diagnosis has been easier to achieve after 1985, when ultrasonography(USG) and computed tomography(CT) were introduced into the medical practice.
Conclussion SIT and MM should be taken into consideration in patients with findings of the physical examination suspicious for left-sided acute appendicitis. X-ray, USG, CT and diagnostic laparoscopy are beneficial in developing the differential diagnosis.

Keywords Situs inversus totalis · Midgut malrotation · Mirror image · Left-sided acute appendicitis · Diagnostic dilemma

Abbreviations

SIT	Situs inversus totalis
MM	Midgut malformation
USG	Ultrasonography
CT	computed tomography

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Introduction

Acute appendicitis remains the most frequent cause for emergency operations in gastrointestinal surgery and is usually relatively simple to diagnosis. Diagnostic uncertainty due to non-classical presentation of acute appendicitis may occur in cases of malposition of the appendix. The appendix is a vestigial organ located at the posterio-medial

aspect of the cecum, 2.5 cm below the ileocecal valve. It is the only organ in the body whose anatomic position is not constant. The various positions are retrocecal, pelvic, subcecal, preileal and postileal, while subhepatic, mesoceliac, intrahernial (femoral or inguinal), and left-sided are seen more rarely. Left-sided acute appendicitis occurs in association with two types of congenital anomalies: situs inversus (SI) and intestinal malrotation[1–17]. Between 1900 and 2010, a limited number of cases with left-sided appendicitis was published in the literature in English language[1–36]. While most of them were associated with SI, few of them occurred with midgut malrotation (MM). The purpose of this study is to present a brief review of the literature on this subject and to summarize two cases in which surgery has been performed.

Case Reports

Case 1

A 16-year-old male patient applied to the emergency unit with left lower quadrant pain which had started the previous morning. He had no previous history of any known illness. He was not aware of having situs inversus totalis. During physical examination, a significant sensitivity in the left lower quadrant was observed. The blood tests revealed no pathology, except for elevated leukocyte count (17,300 L/UL). Dextrocardia was observed on the chest X-ray; during ultrasonographic examination, SI and blind loop, consistent with acute appendicitis in the left lower quadrant were detected. The patient was taken to surgery and appendectomy was performed through left Mc Burney incision. He was discharged on the second day after surgery without any problem.

Case 2

A 17-year-old female patient applied to the emergency unit with nausea, loss of appetite, and left lower quadrant pain which started 2 days before. She described a pain, which initially developed in the epigastrium and migrated to the left lower quadrant in the morning of the day she came to the hospital. She had no history of any systemic disease and medication use. She was not aware of having situs inversus totalis (SIT). Rebound sensitivity in the left lower quadrant was detected during physical examination. Routine blood tests revealed normal liver and kidney functions, while leukocyte count was 13,500 K/UL. The chest X-ray showed dextrocardia (Fig. 1). During ultrasonographic examination, no abdominal pathology was observed, except for SI. The patient was operated on due to clinical findings consistent with acute appendicitis (Fig. 2). She was discharged on the first day after surgery.

Review of the Literature

The literature in English language published till January 2010 in PubMed and Google Scholar database was reviewed, and 34 articles concerning 63 patients with left-sided appendicitis were explored. The exclusion criteria of the study were insufficient patient clinical and demographic data. Table 1 summarizes the references of the study, publication year, age, sex, pain location, time of diagnosis, duration of symptoms, WBC count, diagnostic tools, abnormality, incision type, intraoperative or pathologic diagnosis, and surgical approach of those 63 patients and also includes the current two cases.

Table 1 contains information about a total of 65 patients, 35 (53.8%) male, 30 (46.2%) female, including our cases. The mean age of the patients was calculated as 26.7± 14.0 years (range: 8–63 years). Taking the type of anomaly into account, 53 (81.5%) patients had SIT, eight (12.3%) had MM, two were with malrotation of the cecum, one was with malposition of the colon and the small intestine; and in one case, the end of a long appendix running along the anterior side of the sacrum was found in the left side. According to the localization of the symptoms, 38 (58.4%) patients presented with left and 12 (18.4%) with right lower quadrant pain, six had bilateral lower quadrant pain, five had left upper quadrant pain, three were with periumblical and one was with pelvic pain. Regarding the diagnosis, it is observed that 30 (46.1%) patients were diagnosed during the pre-operative period, 11 (16.9%) patients were previously known to have the anomaly, the diagnosis in 12 (18.4%)

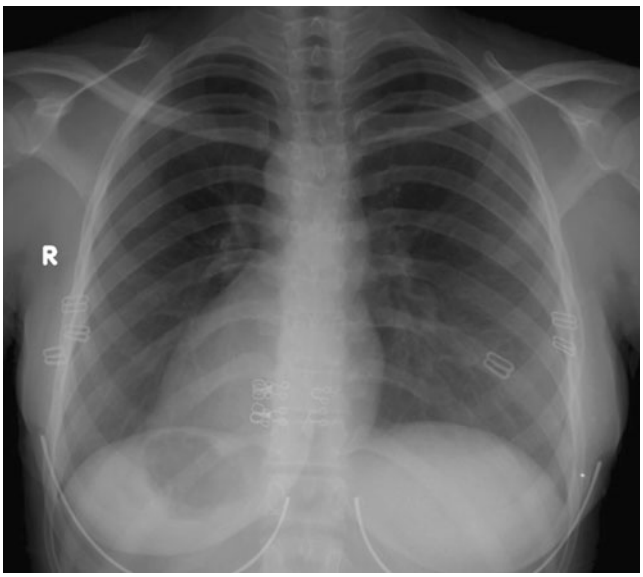

Fig. 1 X-ray of chest PA view. The apex of cardiac shadow is on the *right side*.

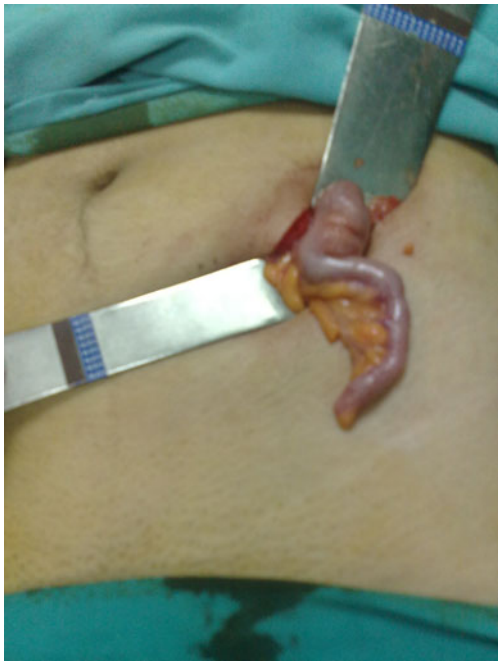

Fig. 2 Intraoperative photography view. Appendix located in the *left lower quadrant*.

patients was established during the intraoperative period and in four patients during the postoperative period. No information was given about eight (12.3%) patients. According to the studies published in the recent years, it is observed that in five patients, laparoscopic appendectomy and in two laparoscopic appendectomy with cholecystectomy were performed[7,10,12,13,17,25,30].

Willis et al.[18] investigated in their study published in 1925 a total of 16 cases of appendicitis with SI including their own cases. Eleven of them are summarized on Table 1, while no sufficient information was found in about five patients.

Block et al.[16] summarized in their study published in 1937 a total of 53 cases of appendicitis with SI, including their case of a 4-month pregnant woman. In one patient in the study, it was observed that the cecum and appendix were in the left iliac fossa, while the rest of the organs were in their normal location. In another case, the appendix migrated to the left of the mid-line, because the cecum was located in the mid-line and was adherent to the sigmoid colon. Therefore, there was no real SI in both cases. They reported that of the rest 51 cases, 12 had partial and 39 had total SI.

In the study published in 1949, Blegen et al.[19] summarized a total of 99 cases of appendicitis with SI, published until that date. In 77 of them, appendectomy and in three of them appendicular abscess drainage was performed; while in 14 patients, appendix could not be observed during the exploration and a clear information could not be obtained in five cases. Of those patients, 39 were diagnosed with SI in the preoperative, 24 in the intraoperative, and 10 in the postoperative period. No information was given about the rest of the cases. Thirty-two of the patients had a prominent pain in the left lower quadrant, 21 in right lower quadrant, and four bilaterally. Features of referred pain was observed in 15 of the patients with pain in the right lower quadrant. As a result of their study, they concluded that in one third the patients, due to referred pain, incisions at a wrong location were performed, necessitating a new incision or enlargement of the previous incision.

Discussion

Abdominal pain is one of the most common chief complaints seen in the surgical world; and among the diagnoses of abdominal pain, appendicitis is the most common surgical disorder. The diagnosis of appendicitis is based on well-established clinical symptoms, physical examination, and physician experience. Approximately one third of patients with appendicitis have pain localized outside the right lower quadrant, because the position of the appendix can vary considerably[3,8,17]. However, left lower quadrant pain as manifestation of appendicitis is relatively rare and misleading. The differential diagnosis of left lower quadrant abdominal pain in adult patients includes, among others, diverticulitis, renal colic, ovarian cyst rupture, Meckel's diverticulitis, epididymitis, incarcerated or strangulated hernia, bowel obstruction, regional enteritits, psoas abscess, and right- and left-sided appendicitis[5,20].

Left-sided appendicitis is a diagnostic dilemma because of its atypical clinical presentation. Left-sided appendicitis occurs in association with two types of congenital anomalies: SI and MM.

MM is a congenital anomaly, which may be attributed to either nonrotation or incomplete rotation of the primitive intestinal loop around the axis of the superior mesenteric artery during fetal development. The incidence of midgut malrotation anomalies reported in the literature varies from 0.03% to 0.5% in the live births[2,17]. While most cases of MM present in the first month of life with bilious vomiting, this anomaly is rarely seen in adulthood. MM was detected in eight (12.3%) of 64 left-sided appendicitis patients presented in our review of the literature[2,6,9,11,17,21–23]. Their age range was between 8 and 51 years (mean age: 31.57± 18.6 years). These results show that the first symptoms of MM may develop also in advanced ages.

SI, a very uncommon entity, is a rare autosomal recessive congenital defect characterized by the transposition of abdominal and/or thoracic organs. It was first

Table 1 The Summary of Clinico-Pathologic Characteristics of Patients with Left-sided Appendicitis Reported Between 1883 and 2010

No	References	Year	Age	Sex	Pain location	Time of diagnosis	Duration of symptom	WBC	Radiologic tools	Abnormality	Incision	Intraoperative finding	Outcomes
1	Perera[25]	2010	46	M	LLQ	Preop	1 day	NA	X-ray, CT	SIT	Laparoscopy	Appendicitis	Appendectomy
2	Uludag[1]	2009	29	M	LLQ	Preop	4 h	6,700	X-ray,USG, CT	SIT	Midline	Appendicitis	Appendectomy
3	Israelit[2]	2009	51	M	LUQ	Preop	1 day	12,200	CT	MM	Midline	Perforated Appendicitis	Appendectomy
4	Huang[26]	2008	60	F	LLQ	Known	1 day	9,000	X-ray, CT	SIT	Transvers incision, left	Appendicitis	Appendectomy
5	Welte[17]	2007	46	M	LLQ	Preop	4 days	18,100	X-ray,CT	MM	Laparoscopy	Perforated Appendicitis	Appendectomy
6	Ahmed[5]	2007	50	M	LLQ	Preop	2 days	11,600	X-ray,USG	SIT	Gridiron, left	Appendicitis	Appendectomy
7	Ucar[4]	2007	22	M	LLQ	Preop	8 h	14,700	X-ray,USG	SIT	Paramedian, left	Appendicitis	Appendectomy
8	Golash[7]	2006	40	M	LLQ	Preop	2 days	16,100	X-ray,USG, CT	SIT	Laparoscopy	Appendicitis	Appendectomy
9	Bielecki[28]	2006	16	F	LLQ	Known	2 days	Elevated	X-ray, USG	SIT	Pararectal, left	Gangrenous appendicitis	Appendectomy
10	Rodriguez[27]	2006	63	F	LLQ	Preop	2 days	NA	X-ray, CT	SIT	NA	Perforated Appendicitis	Appendectomy
11	Lee[6]	2006	43	M	LLQ	Preop	2 weeks	4,600	CT	MM	Midline	Periappendiceal abscess	Ileocecal resection with appendix
12	Hou[8]	2005	58	F	LLQ	Preop	1 day	12,700	USG,CT	**	McBurney	Appendicitis	Appendectomy
			48	M	LLQ	Preop	4 days	11,500	CT	SIT	Rockey Davis,Left	Perforated Appendicitis	Appendectomy
13	Kamiyama[9]	2005	14	M	LUQ	Preop	1 day	13,200	USG,CT	MM	Midline	Appendicitis	Appendectomy
14	Tiwari[29]	2005	30	F	LLQ	Known	4 days	19,000	USG	SIT	Transvers incision, left	Appendix	Right hemicolectomy
15	Song[10]	2004	32	F	Pelvic	Known	NA	NA	Not-performed	SIT	Laparoscopy	Appendicitis	Appendectomy + ablation of endometriotic implant
16	Hollander[11]	2003	9	M	LUQ	Preop	1 week	21,600	CT	MM	NA	Periappendiceal abscess	Appendectomy + drainage
17	Ratani[21]	2002	8	F	LLQ	Preop	2 days	17,000	X-ray, CT	MM	Midline	Appendicitis	Appendectomy
18	Bider[22]	2001	27	F	LLQ	Preop	1 week	12,000	USG,CT	MM	Midline	Perforated Appendicitis	Ileocecal resection with appendix
19	Franklin[12]	2001	25	F	LUQ	Preop	3 months	8,500	X-ray,USG	SIT	Laparoscopy	NA	Appendectomy + cholecystectomy
20	Nelson[20]	2001	42	M	LLQ	Preop	1 day	16,000	CT	SIT	NA	Appendicitis	Appendectomy
21	Djohan[13]	2000	20	F	LUQ	Preop	1 day	12,000	X-ray,USG	SIT	Laparoscopy	Appendix	Appendectomy + cholecystectomy
22	Contini[30]	1998	34	M	BLQ	Preop	1 day	14,000	X-ray,USG	SIT	Laparoscopy	Gangrenous appendicitis	Appendectomy
23	Prasad[31]	1992	34	M	LLQ	Postop	3 days	NA	Barium enema, USG	SIT	McBurney, left	Appendicitis	Appendectomy
24	Garg[23]	1991	17	M	RLQ	Postop	1 day	NA	Barium enema	***	McBurney, right	Appendix	Appendectomy
			50	M	LLQ	Preop	NA	NA	Barium enema	MM	Midline	Periappendiceal abscess	Appendectomy

25	Celik[36]	1986	16	F	LLQ	Preop	2 days	6,000	NA	SIT	NA	Periappendiceal abscess	Appendectomy + drainage
26	Du Toit[14]	1986	20	M	LLQ	Preop	2 days	NA	X-ray	SIT	Paramedian, Left	Appendix + omental abscess	Appendectomy + drainage
27	Steensel[32]	1985	29	M	LLQ	Known	1 day	17,000	X-ray, USG	SIT	Midline	Appendicitis	Appendectomy
28	Pillay[33]	1976	32	M	PU	Preop	3 days	NA	X-ray	SIT	Paramedian, Right	Perforated Appendicitis	Appendectomy
29	Holgersen[34]	1970	12	F	LLQ	Preop	1 day	12,950	X-ray	SIT	Gridiron, left	Appendicitis	Appendectomy
30	Winter[15]	1953	46	M	PU	Known	4 days	NA	NA	SIT	Paramedian, Left	Appendicitis	Appendectomy
31	Abel[35]	1949	14	M	PU	Known	1 day	13,750	X-ray,Barium	SIT	Gridiron, Left	Appendicitis	Appendectomy
32	Belmes[19]	1944	17	F	RLQ	Intraop	NA	NA	NA	SIT	Right Rectus	NA	Appendix not found
33	King[19]	1941	20	F	BLQ	Preop	4 days	NA	NA	SIT	Midline	Appendicitis	Appendectomy
34	Uehara[19]	1940	28	F	RLQ	Intraop	NA	NA	NA	SIT	Right rectus	Appendicitis	Appendectomy
35	Laurence[19]	1940	19	F	BLQ	Intraop	12 h	NA	NA	SIT	Right rectus	Appendicitis	Appendectomy
36	Simens[19]	1939	22	F	RLQ	Intraop	NA	NA	NA	SIT	Right rectus	NA	Appendix not found
37	Lucente[19]	1938	16	M	BLG	Intraop	NA	NA	NA	SIT	Midline	Appendicitis	Appendectomy
38	Hemple[19]	1937	9	F	RLQ	Intraop	1 day	NA	NA	SIT	Pararectal, right	Appendicitis	Appendectomy
39	Block[16]	1937	26	F	RLQ	Intraop	4 h	21,800	NA	SIT	McBurney, right	Appendicitis	Appendectomy
40	Votta[16]	1936	15	F	LLQ	Known	NA	NA	NA	SIT	Paramedian, left	Appendicitis	Appendectomy
41	Pol[16,19]	1935	21	F	LLQ	Intraop	NA	NA	NA	CM	Midline	Appendicitis	Appendectomny
			8	F	RLQ	Known	NA	NA	NA	SIT	McBurney, bilateral	Appendicitis	Appendectomy
42	Mason[16,19]	1933	13	F	LLQ	Preop	1 day	NA	NA	SIT	Paramedian, left	Gangrenous appendicitis	Appendectomy
43	Depol[16,19]	1933	35	M	RLQ	Known	NA	NA	NA	SIT	Pararectal, left	Gangrenous appendicitis	Appendectomy
44	Minne[16]	1933	12	M	LLQ	Postop	NA	NA	Barium enema	CM	McBurney, right	Appendicitis	Appendectomy
45	Scopinaro[16,19]	1932	30	M	BLQ	Intraop	NA	NA	NA	SIT	Midline	Appendicitis	Appendectomy
46	Courtney[16]	1931	21	F	RLQ	Intraop	NA	NA	NA	SIT	McBurney, right	Appendicitis	Appendectomy
47	Rush[19]	1928	18	M	RLQ	Preop	2 days	NA	NA	SIT	Right rectus	Appendicitis	Appendectomy
48	Pool[19]	1925	14	M	RLQ	Intraop	NA	NA	NA	SIT	Right rectus, Mc Burney, left	Appendicitis	Appendectomy
49	Willis[18]	1925	19	M	LLQ	Preop	NA	Normal	NA	SIT	McBurney, left	Appendicitis	Appendectomy
50	Bertone[19]	1923	13	F	RLQ	Intraop	NA	NA	NA	SIT	Right rectus	Appendicitis	Appendectomy
51	Franke[18]	1922	15	M	LLQ	NA	NA	NA	NA	SIT	NA	Appendicitis	Appendectomy
52	Jacobson[18]	1917	24	M	LLQ	NA	NA	NA	NA	SIT	McBurney, left	Periappendiceal abscess	Drainage
53	Christie[18]	1916	22	F	LLQ	NA	NA	NA	NA	SIT	Midline	Cronic Appendicitis	Appendectomy
54	St Clair[18]	1915	27	M	LLQ	NA	NA	NA	NA	SIT	Pararectal, right	Appendicitis	Appendectomy
55	Palamountain[18]	1915	18	F	LLQ	NA	NA	NA	NA	SIT	Midline	Appendicitis	Died secondary to peritonitis
56	Podevin[18]	1913	42	F	LLQ	NA	NA	NA	NA	SIT	NA	NA	No-performed
57	Muhsam[18]	1912	21	M	LLQ	Known	NA	NA	NA	SIT	McBurney, left	Appendicitis	Appendectomy

Table 1 (continued)

No	References	Year	Age	Sex	Pain location	Time of diagnosis	Duration of symptom	WBC	Radiologic tools	Abnormality	Incision	Intraoperative finding	Outcomes
58	Pool EH[18]	1912	14	M	BLQ	Postop	NA	31,000	X-ray	SIT	McBurney, bilateral	Appendicitis	Appendectomy
59	Hebblethwaite[18]	1907	16	M	LLQ	NA	NA	NA	NA	SIT	Midline	Appendicitis	Appendectomy
60	Landgraf[18]	1883	50	F	LLQ	NA	NA	NA	NA	SIT	NA	Necropsy	Died secondary to peritonitis
61	Present case 1	2009	16	M	LLQ	Preop	2 days	17,300	X-ray, USG	SIT	Mc Burney, left	Appendicitis	Appendectomy
	Present case 2	2009	17	F	LLQ	Preop	2 days	13,500	X-ray, USG	SIT	Mc Burney, left	Appendicitis	Appendectomy

LLQ left lower quadrant, *RLQ* right lower quadrant, *BLQ* bilateral lower quadrant, *CM* cecal malrotation, *PU* periumblical, *SIT* situs inversus totalis, *MM* midgut malrotation, *XX* the long swollen appendix, measuring about 12 cm in length with the tip pointing towards the presacral region, just across the midline of the lower abdomen, *XXX* colon located left side, small bowel in right side

reported by Fabricius in 1600. This condition may be complete, when the organs in both thoracic and abdominal cavities are transposed, or partial, when only one of these cavities is affected[24,25]. Incidence of situs anomalies reported in the literature varies from 0.001% to 0.01% in the general population[7,25]. The incidence of acute appendicitis asociated with situs inversus totalis is reported between 0.016% and 0.024%[25,26,32].

The diagnosis of SIT can be based on physical examination, electrocardiogram, chest X-ray, ultrasonography (USG) and computed tomography (CT) scan. In our cases, we diagnosed this anomaly by a chest radiography and an abdominal USG. Diagnosis of SIT or MM for the most of patients in preoperative period has been easier to achieve after 1985 when USG and CT were introduced into the medical practice, while in the previous years diagnosis was established on intraoperative findings or with postoperative barium enema studies in some patients; even enlargement of incision or a further incision was required[1,2,4–6,11–13,20–22,26–32]. In the light of these results, despite the fact that physicians' clinical suspicion is a gold standard, the risk for false diagnosis is considerably reduced with the effective use of radiological diagnostic methods.

After establishing the diagnosis of SIT, the surgical options are the same as for normal patients. According to the reviewed literature, we observed that many open or laparoscopic procedures have been performed. Many procedures such as cholecystectomy, appendectomy, sigmoidectomy, gastrectomy, Roux-en-Y gastric bypass, gastric banding, Nissen fundoplication, and hemicolectomy have been done laparoscopically. Left-handed surgeons are likely more advantageous during laparoscopy. Among the total of 64 patients presented in this study, appendectomy was performed in six of them, while two underwent cholecystectomy in the same session. Besides, Palanivelu et al.[3] denoted in their study published in 2007 that they performed appendectomy for total of nine patients, eight patients with MM and one with SIT. We also believe that laparoscopy is considerably beneficial both in the differential diagnosis and definitive surgery.

In conclusion, history of the patient, findings of the physical examination, and results of the radiological investigations should be evaluated altogether and congenital anomalies such as SIT or MM should be taken into consideration in the differential diagnosis in patients with pain in atypical localization suspicious for appendicitis due to its presentation.

Competing Interests The authors declare that they have no competing interests.

References

1. Uludag M, Citgez B, Ozkurt H. Delayed small bowel perforation due to blunt abdominal trauma and periappendicitis in a patient with situs inversus totalis: a report of a case. Acta Chir Belg 2009;109 (2):234–237.
2. Israelit S, Brook OR, Nira BR, Guralnik L, Hershko D. Left-sided perforated acute appendicitis in an adult with midgut malrotation: the role of computed tomography. Emerg Radiol 2009;16(3):217–218.
3. Palanivelu C, Rangarajan M, John SJ, Senthilkumar R, Madhankumar MV. Laparoscopic appendectomy for appendicitis in uncommon situations: the advantages of a tailored approach. Singapore Med J 2007;48(8):737–740.
4. Ucar AE, Ergul E, Aydin R, Ozgun YM, Korukluoglu B. Left-sided acute appendicitis ıth situs ınversus totalis. The Internet Journal of Surgery 2007; 12(2).
5. Ahmed JU, Hossain GMZ, Karim MM, Hossain ASMJ, Ahmed M, Bhuya MSA. Left sided acute appendicitis with situs inversus in an elderly—an unusual case JCMCTA 2007;18 (1):29–31.
6. Lee MR, Kim JH, Hwang Y, Kim YK. A left-sided periappendiceal abscess in an adult with intestinal malrotation. World J Gastroenterol 2006;12(33):5399–5400.
7. Golash V. Laparoscopic management of acute appendicitis in situs inversus. J Min Access Surg 2006;2(4):220–221.
8. Hou SK, Chern CH, How CK, Kao WF, Chen JD, Wang LM, Huang CI. Diagnosis of appendicitis with left lower quadrant pain. J Chin Med Assoc 2005;68(12):599–603.
9. Kamiyama T, Fujiyoshi F, Hamada H, Nakajo M, Harada O, Haraguchi Y. Left-sided acute appendicitis with intestinal malrotation. Radiat Med 2005;23(2):125–127.
10. Song JY, Rana N, Rotman CA. Laparoscopic appendectomy in a female patient with situs inversus: case report and literature review. JSLS 2004;8(2):175-7.
11. Hollander SC, Springer SA. The diagnosis of acute left-sided appendicitis with computed tomography. Pediatr Radiol 2003;33 (1):70–71
12. Franklin ME, Almeida JA, Perez ER, Michaelson RLP, Majarrez A. Cholesistectomy and appendectomy by laparoscopy in a patient with situs inversus totalis: A case report and review of the literature. Asociacion Mexicana de Cirugia Endoscopica 2001;2(3):150–153.
13. Djohan RS, Rodriguez HE, Wiesman IM, Unti JA, Podbielski FJ. Laparoscopic cholecystectomy and appendectomy in situs inversus totalis. JSLS 2000;4(3):251–254.
14. Du Toit DF, Greeff M.Acute abdomen in a patient with situs inversus. A case report.S Afr Med J 1986;69(3):201–202.
15. Winter B, Dyk M. Left-sided acute appendicitis. Can Med Assoc J 1953;68(3):278–279.
16. Block FB, Michael MA. Acute appendicitis in complete transpsition of viscera: report of case with symptoms referable to right side mechanism of pain in visceral disease. Ann Surg 1938;107 (4):511–516.
17. Welte FJ, Grosso M. Left-sided appendicitis in a patient with congenital gastrointestinal malrotation: a case report. J Med Case Reports 2007;1:92.
18. Willis BC. Appendicitis and transposition of the viscera. Ann Surg 1925;82(2):256–259.
19. Blegen HM. Surgery in Situs Inversus. Ann Surg 1949;129 (2):244–259.
20. Nelson MJ, Pesola GR. Left lower quadrant pain of unusual cause. J Emerg Med 2001;20(3):241–245.
21. Ratani RS, Haller JO, Wang WY, Yang DC. Role of CT in left-sided acute appendicitis: case report. Abdom Imaging 2002;27 (1):18–19.
22. Bider K, Kaim A, Wiesner W, Bongartz G. Acute appendicitis in a young adult with midgut malrotation: a case report. Eur Radiol 2001;11(7):1171–1174.
23. Garg P, Singh M, Marya SK. Intestinal malrotation in adults. Indian J Gastroenterol 1991;10(3):103–104.
24. Kobus C, Targarona EM, Bendahan GE, Alonso V, Balagué C, Vela S, Garriga J, Trias M. Laparoscopic surgery in situs inversus: a literature review and a report of laparoscopic sigmoidectomy for diverticulitis in situs inversus. Langenbecks Arch Surg 2004;389 (5):396–399.
25. Perera WR, Hennessy OF. An unusual case of appendicitis. Am J Surg 2010 Feb 25.
26. Huang SM, Yao CC, Tsai TP, Hsu GW. Acute appendicitis in situs inversus totalis. J Am Coll Surg 2008;207(6):954.
27. Rodriguez O, Avilés A, Aquino E, Pérez Arzola M, Cortés F, Monasterio J. Acute abdominal symptoms as the first presentation of a patient with mirror-image dextrocardia with situs inverus. Bol Asoc Med P R 2006;98(4):244–248.
28. Bielecki K, Gregorczyk M, Baczuk L. Visceral situs inversus in three patients. Wiad Lek 2006;59(9–10):707–709.
29. Tiwari A, MacMull S, Fox S, Jacob SA. Left sided abdominal pain in a patient with situs inversus. Clin Anat 2006;19(2):154–155.
30. Contini S, Dalla Valle R, Zinicola R. Suspected appendicitis in situs inversus totalis: an indication for a laparoscopic approach. Surg Laparosc Endosc 1998;8(5):393–394.
31. Prasad V. Left sided appendicitis and situs inversus. Indian J Gastroenterol 1992;11(1):44–45.
32. Van Steensel CJ, Wereldsma JC. Acute appendicitis in complete situs inversus. Neth J Surg 1985;37(4):117–118.
33. Pillay SP. Perforated appendix in situs inversus viscerum. A case report. S Afr Med J 1976;50(5):141–143.
34. Holgersen LO, Kuehner CR, Stanley-Brown EG. Acute appendicitis in a child with complete situs inversus. J Pediatr Surg 1970;5 (3):379–380.
35. Abel WG. Acute appendicitis with concomitant situs inversus; report of a case. N Engl J Med 1949;241(3):97.
36. Celik F, Gulec S, Gokcora IH. A case of acute appendicitis with situs inversus totalis simulating ureteral colic. Turkish Journal of Med Sci 1986;4(1–2):147–148.

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CASE REPORT

Transumbilical Single-Incision Laparoscopic Cholecystojejunostomy Using Conventional Instruments: The First Two Cases

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Abstract
Background/Aim Optimization of quality of life is an important goal in the management of patients with unresectable peri-ampullary cancer. Herein, we share our two cases to demonstrate the feasibility of scarless transumbilical single-incision laparoscopic cholecystojejunostomy using conventional instruments in the management of unresectable peri-ampullary cancer.
Cases and Methods Two 58-year-old patients (one male) underwent transumbilical single-incision laparoscopic cholecystojejunostomies: The male and female patients were diagnosed with duodenal papillary carcinoma and pancreatic cancer, respectively. The hepatocystic junction was confirmed patent preoperatively in both patients. A 2-cm periumbilical incision was made for the placement of three trocars. Conventional rigid laparoscopic instruments were solely used throughout the procedure, and operative techniques were carried out in the same fashion as for conventional laparoscopic cholecystojejunostomy.
Results The procedures were completed uneventfully in 190 and 155 min, respectively, with no complications, and the blood loss was estimated at 80 and 20 ml, respectively. Postoperative pain scores on postoperative day 1 were 4/10 and 3/10. The patients were discharged from the hospital on postoperative days 3 and 5 with resolving jaundice.
Conclusions Transumbilical single-incision laparoscopic cholecystojejunostomy appears to be a technically feasible alternative to standard laparoscopic procedure and can be performed using conventional laparoscopic instruments.

Keywords Laparoscopy · Single-incision surgery · Cholecystojejunostomy

Introduction

Surgical resection is generally accepted as having beneficial effects on the survival for patients with peri-ampullary carcinoma.[1] When curative treatment is unfeasible, careful selection of optimal palliation becomes of central importance in the management of peri-ampullary cancer. Furthermore, in contemporary management, optimization of quality of life in patients with unresectable disease is the most important goal.

Laparoscopic biliary bypass is associated with low operative risk, devoid of the hazards of endoscopic or radiologic stent placement, and allows for combination of staging and palliation in patients diagnosed with unresectable disease at laparoscopy.[2] Single-incision laparoscopic operations have recently emerged as a less invasive alternative to conventional laparoscopy.

The aim of this study was to describe our initial experience with single-incision laparoscopic cholecystojejunostomy in two patients with unresectable peri-ampullary cancer by using conventional instruments while leaving virtually no scars both physically and psychologically. To our knowledge, our report on the two cases of single-incision laparoscopic cholecystojejunostomy is the pioneer of its kind. We describe here the challenges we confronted and the details of our operative technique.

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Patients and Methods

Patients

Case 1 A 58-year-old man presented with a 4-week history of jaundice and loss of appetite. His past medical history was significant for congestive heart failure and chronic renal failure (End-Stage Renal Disease), which was unstable for curative managements. On physical examination, he had normal vital signs, and his abdominal examination was unremarkable. His body mass index was 25.5 kg/m^2. The relevant laboratory readings were significantly deranged as shown in Table 1. A computed tomography (CT) scan of the abdomen revealed a mass in the peri-ampullary region. There was no periportal lymphadenopathy. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) also confirmed these findings. Biopsies were determinate for malignancy.

Case 2 A 58-year-old woman presented with a 3-month history of weight loss and a 2-week history of jaundice. Her body mass index was 27.5 kg/m^2, and the laboratory readings were also significantly deranged (Table 1). A CT scan of the abdomen revealed a mass in the pancreatic head and two metastatic foci of the liver. There was no periportal lymphadenopathy, and MRCP and ERCP have confirmed these findings.

From the imaging studies, we were able to confirm the patency of the hepatocystic junction in both patients, and the junction of the cystic duct with the common hepatic duct was more than 1 cm away from the proximal extent of the tumors. A preoperative nasobiliary drainage tube was installed endoscopically in each patient for early palliation of jaundice.

Due to both patients' medical history and disease status, palliative surgical protocols were scheduled. The patients and next of kin were informed in detail of the nature of the surgical procedure and risks involved before consents were obtained.

Table 1 Preoperative and Postoperative Laboratory Readings for the Two Patients

	Case 1	Case 2
Liver function tests		
Total bilirubin (μmol/L); range 3.4~20.5	270.6 (140.3)	151.9 (52.6)
Direct bilirubin (μmol/L); range 0~8.6	220.3 (116.7)	125.2 (46.3)
Alkaline phosphatase (U/L); range 40~150	679 (208.0)	749 (323.6)
γ-Glutamyltransferase (U/L); range 9~64	1,266 (225.0)	1,014 (383.2)
Tumor marker		
CA19-9 XR (U/L); range 0~37	416.0	>1,000.0

Postoperative day5 values in parentheses

Operative Technique

The procedures were performed under general anesthesia with the patients in the reverse Trendelenburg's position at a 15° tilt to the left. The team set up as shown in Fig. 1. Pneumoperitoneum was established by using closed Veress needle technique through the umbilicus. After insufflation of CO_2 and maintaining the pressure at 13 mmHg, a 2-cm periumbilical incision was made for trocar access. Conventional trocars were used, including a 5-mm, a 10-mm standard trocar and an unbladed trocar (Xcel B12LT; Ethicon Endo-Surgery, Inc., US). The three ports were placed within the umbilical incision in an inverted equilateral triangular configuration, 1-cm apart, with the camera placed at the apex (Fig. 2). A 30° 10-mm rigid laparoscope (Stryker Endoscopy, US) was used throughout the procedures.

The procedure began with a general exploration of the abdomen, particularly to confirm the radiologically patent hepatocystic junction. The intention of the operative procedure was the same as with conventional laparoscopy: to create a surgical bypass for the management of biliary tract obstruction. A simple side-to-side cholecystoenterostomy was performed 40 cm from the ligament of Trietz using a laparoscopic intracorporeal stapler-cutting device (ATW45; Ethicon Endo-Surgery, Inc., US) with the stapler

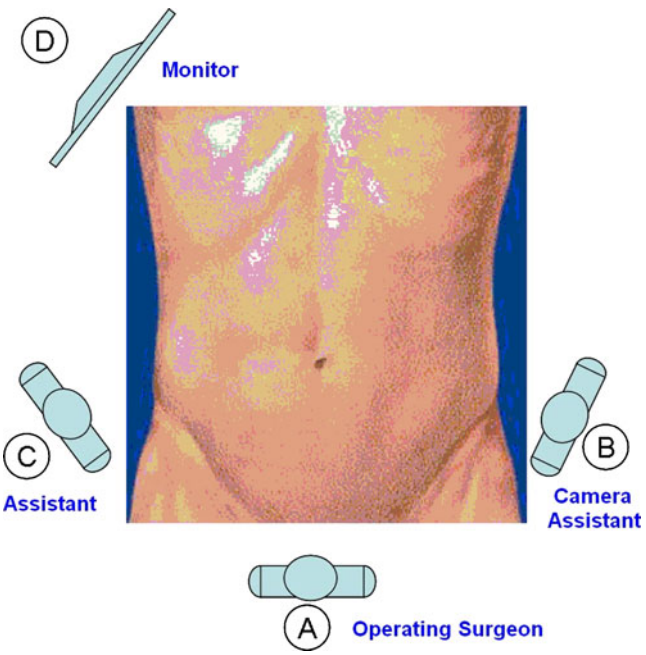

Fig. 1 The team setup.

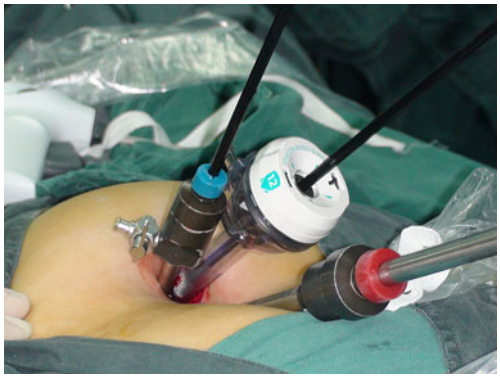

Fig. 2 The three ports placed within the umbilical incision in an inverted equilateral triangular configuration.

insertion sites made on the fundus of the gallbladder and jejunum, and the insertion openings were laparoscopically closed and tied in an intracorporeal fashion using simple running 3/0 absorbable Vicryl sutures (Ethicon, USA; Fig. 3a). This was followed by a side-to-side Braun's enteroenterostomy performed using intracorporeal linear stapler-cutting device (ATB45; Ethicon Endo-Surgery, Inc., US) with the stapler insertion sites made on the proximal and distal jejunal segments; finally, the insertion openings were also closed laparoscopically. The most challenging aspect of this technique was operating with the instruments that were crossing-over and clashing with each other. The three-port inverted triangular setup was the most ideal arrangement allowing for adequate range of motion for the 10-mm laparoscope to navigate between the work ports either inferiorly or superiorly.

Two percutaneous transfascial retraction sutures (3/0 Prolene; Ethicon, US) were placed at the right and left costal margins to achieve adequate exposure not only to facilitate anastomosis but also throughout the whole procedure. One suture was placed at one end of the anastomotic line between the fundus of the gallbladder and intestine (Fig. 3c), and the other was at one end of the anastomotic line between the two segments of the intestine (Fig. 3d). Completed anastomoses were inspected, and the abdomen was irrigated in the usual fashion. A 22-French sub-hepatic drainage tube was placed through the umbilicus (Fig. 4), and enlarged umbilical incision was closed under local anesthesia with 3/0-Vicryl sutures (Ethicon, US) after the drainage had been removed.

Results

The operations lasted 190 and 155 min, with a blood loss of 80 and 20 ml. No intraoperative complications had occurred. Both patients resumed oral diet 24 h after surgery at which they were also able to mobilize. The sub-hepatic drainage was removed on postoperative day2 for both patients, and patients were discharged from the hospital on

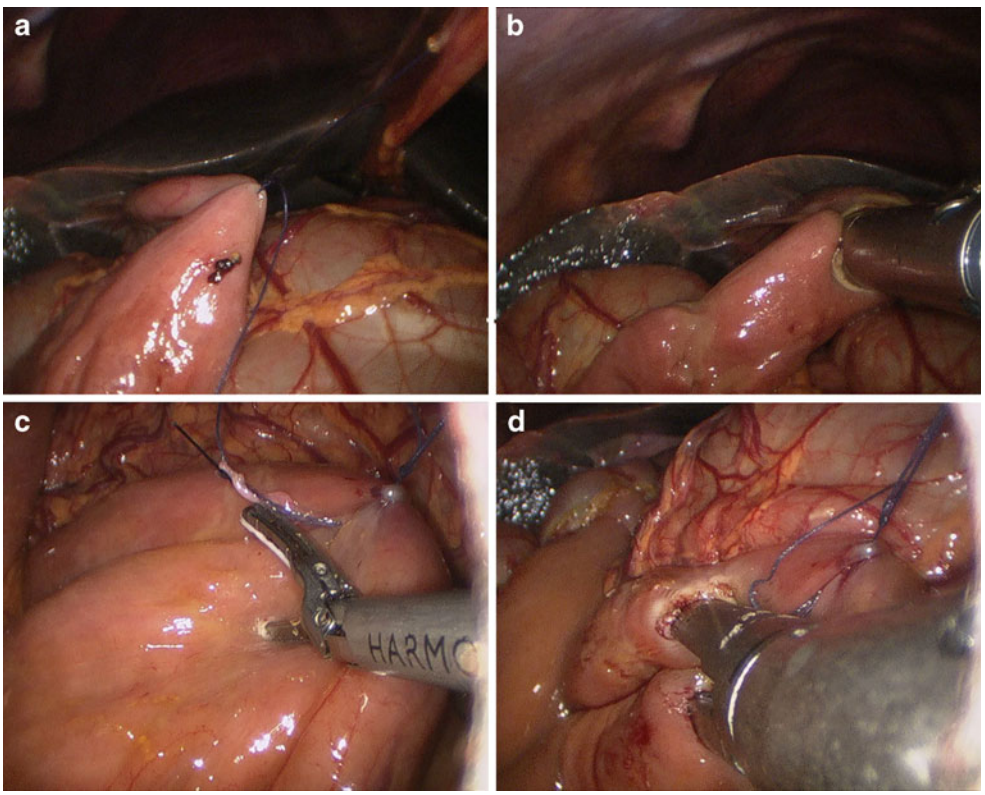

Fig. 3 **a** A simple intracorporeal, stapled, side-to-side cholecystoenterostomy was performed using a laparoscopic intracorporeal linear stapler-cutting device. **b** Intracorporeal, stapled, side-to-side Braun's enteroenterostomy was performed using intracorporeal linear stapler-cutting device. **c** One transfascial retraction suture was placed at one end of the anastomotic line between the fundus of the gallbladder and intestine to achieve adequate anastomotic region retraction. **d** One transfascial retraction suture was placed at one end of the anastomotic line between the two segments of intestine to achieve adequate anastomotic region retraction.

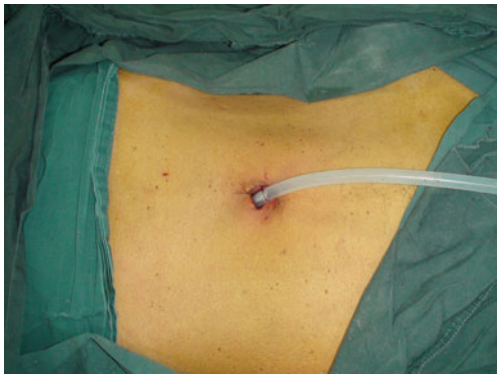

Fig. 4 A sub-hepatic drainage tube was placed through the umbilicus.

postoperative days 3 and 5. Postoperative pain was assessed by visual analog scale.[3] The postoperative pain scores of the patients on day 1 were 4/10 and 3/10 (Table 2). Liver function tests on postoperative day 5 showed trends of improvement (Table 1). The follow-up period for the two patients was 4–5 months; until now, no significant complication was reported.

Discussion

Laparoscopic surgery is a well-established alternative to open surgery across various disciplines. The evolution of minimally invasive techniques has further encouraged the surgical community to reduce the invasiveness of laparoscopic surgery. To this end, two recent innovations are being developed: natural orifice translumenal endoscopic surgery (NOTES™), which promises to eliminate abdominal incisions completely, and transumbilical single-incision or single-port laparoscopic surgery, which limits the number of abdominal incisions.[4] Transumbilical laparoscopic surgery can either be performed with three separate ports introduced through the same umbilical incision or one port having three working channels. The former technique is entitled single-incision laparoscopic surgery (SILS™), while the latter has been termed single-port access (SPA™).[5] The fundamental idea of SILS™ is to have all the work ports entering the abdominal cavity through the umbilicus, an embryonic natural orifice, wherein the surgical scar is virtually concealed. Potential benefits of SILS™ over conventional laparoscopy include less incisional pain with lower postoperative narcotic requirements, shorter hospital stays, faster return to work and routine activity, improved cosmesis, and ultimately higher patient satisfaction. This is similar to the anticipated benefits of NOTES™ procedures.[6] In contrast with NOTES™ and SPA™ procedures, SILS™ may use conventional laparoscopic instrumentation; it does not add any substantial increase in cost, making technical adaptation and mainstream acceptance more likely. To date, however, experience with SILS™ is still in its infancy, with a small amount of published cases reported for all indications and no cholecystojejunostomy cases.

The first reports of successful laparoscopic cholecystojejunostomy in unresectable peri-ampullary cancer appeared in 1992;[7–9] the three-port laparoscopic approach remains most favorable with minimal invasiveness. This study has shown that laparoscopic cholecystojejunostomy can be done using commercially available instruments without sacrificing the standard principles of cholecystojejunostomy, through a single umbilical incision. It appears to provide outcomes similar to standard laparoscopic cholecystojejunostomy. It remains to be proven if SILS™ will become a frequently chosen option for cholecystojejunostomy in selected patients. To our knowledge, this is the first SILS™ cholecystojejunostomy case reported in literature.

There were a few cautionary observations in this initial experience. SILS™ cholecystojejunostomy is technically more challenging than conventional laparoscopic procedure. The major drawback to such a surgical approach is that the concept of "triangulation" to which laparoscopic surgeons have grown accustomed to in terms of both the instruments and scope is compromised. All instruments are closely packed together, and clashing of instruments and the laparoscope are common. It will have a unique learning curve, principally in navigating the instruments within limited space, and needs significant coordination between the surgeon and the camera holder. The surgeon also has to adapt to counterintuitive movements due to frequent crossing of the instrument shafts at the point of entry into the abdominal cavity. In contrast to our expectation, these particular patients showed a trend toward a more severe, not less incisional pain (Table 2); this might be explained

Table 2 Comparison of Postoperative Pain Scores

Postoperative day	1	2	3	4	5
Case 1	4	5	3	–	–
Case 2	3	4	2	2	0
Conventional laparoscopic procedure[a]	2.2 ± 0.45	2.0 ± 0.71	2.6 ± 0.55	1.2 ± 0.45	0.25 ± 0.50

[a] Conventional laparoscopic procedure: a retrospective analysis of the postoperative pain scores of the last five non-complicated cases undergone conventional three-trocar laparoscopic cholecystoenterostomy dated before 1 Dec 2009

by the close placement of trocars in a confined space and stress exerted on the tissue by surgical instruments and laparoscope during the procedure. Also, a negative aspect of the single-incision technique is to have patients endure additional intervention of closing umbilical fascia under local anesthesia at the time of drainage removal, which may be of significant discomfort to the patients. In addition, the operative duration was longer than conventional laparoscopic procedure, which should however improve with further experience and advanced instrumentation.

New improvements in operative technique and instrumentation might facilitate SILS™ in the future. Novel single-port working platforms are being developed, such as the GelPort (Applied Medical), double-channel trocar (Applied Medical), Unix-X (Pnavel Systems), TriPort (Advanced Surgical Concepts), R-port (Advanced Surgical Concepts), or SILS™ port (Covidien). Merchant and colleagues[10] recently reported a novel technique of "flexible fulcrums" using the Gelport access device with conventional laparoscopic instruments and ports, which they have successfully applied to several laparoscopic procedures. This technique allows insertion and manipulation of up to four trocars with minimal clashing of instruments as it maintains pneumoperitoneum. New optical sources, such as the deflectable tip video laparoscope (Olympus) and the EndoEye laparoscope (Olympus), might improve visualization in a limited operative field. Elazary and colleagues[11] recently reported the use of a flexible therapeutic endoscope (Karl Storz) for successful SILS™ cholecystectomy in a porcine model. Use of the endoscope allowed for flexible visualization and the ability to use the endoscopic working port for retraction.

In conclusion, SILS™ cholecystojejunostomy appears to be a technically feasible alternative to standard laparoscopic procedure and can be performed with conventional laparoscopic instruments. However, increased incisional pain for the patients and technical difficulty of the procedure for the surgeons may argue otherwise to the application of the single-incision technique. Large randomized controlled trials are recommended to determine the true benefits of SILS™ cholecystojejunostomy compared to conventional laparoscopic approach.

References

1. Wagner M, Redaelli C, Lietz M, Seiler A, Friess H, Buchler W. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004;91:586–594.
2. Ammori BJ. Pancreatic surgery in the laparoscopic era. JOP 2003;4:187–192.
3. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990;13:227–236.
4. Raman JD, Cadeddu JA, Rao P, Rane A. Single-incision laparoscopic surgery: initial urological experience and comparison with natural-orifice transluminal endoscopic surgery. BJU Int 2008;101:1493–1496.
5. Hodgett SE, Hernandez JM, Morton CA, Ross SB, Albrink M, Rosemurgy AS. Laparoendoscopic single site (LESS) cholecystectomy. J Gastrointest Surg 2009;13:188–192.
6. Pearl JP, Ponsky JL. Natural orifice translumenal endoscopic surgery: a critical review. J Gastrointest Surg 2008;12:1293–1300.
7. Shimi S, Banting S, Cuschieri A. Laparoscopy in the management of pancreatic cancer: Endoscopic cholecystojejunostomy for advanced disease. Br J Surg 1992;79:317–319.
8. Fletcher DR, Jones RM. Laparoscopic cholecystojejunostomy as palliation for obstructive jaundice in inoperable carcinoma of pancreas. Surg Endosc 1992;6:147–149.
9. Hawasli A. Laparoscopic cholecysto-jejunostomy for obstructing pancreatic cancer: technique and report of two cases. J Laparoendosc Surg 1992;2:351–355.
10. Merchant AM, Cook MW, White BC, Davis SS, Sweeney JF, Lin E. Transumbilical gelport access technique for performing single incision laparoscopic surgery (SILS). J Gastrointest Surg 2009;13:159–162.
11. Elazary R, Khalaileh A, Zamir G, Har-Lev M, Almogy G, Rivkind AI, Mintz Y. Single-trocar cholecystectomy using a flexible endoscope and articulating laparoscopic instruments: a bridge to NOTES of the final form? Surg Endosc 2009;23:969–972.

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HOW I DO IT

Laparoscopic Fundoplication with or Without Pyloroplasty in Patients with Gastroesophageal Reflux Disease After Lung Transplantation: How I Do It

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Abstract
Introduction Several studies have confirmed that gastroesophageal reflux disease (GERD) in lung transplant patients is a risk factor for the development and progression of bronchiolitis obliterans syndrome (BOS), a form of rejection after lung transplantation. Moreover, numerous reports indicate that surgical correction of GERD may control the decline in lung function characteristic of BOS. Although laparoscopic fundoplication is an accepted treatment option for these patients with GERD, the surgical technique, which often includes a laparoscopic pyloroplasty, has not been standardized.
Methods The purpose of this article is to describe a step-by-step approach to the laparoscopic treatment of GERD in lung transplant patients. We also address specific technical concerns encountered in the surgical management of this high-risk patient population; we provide data on the safety of this operation; and we illustrate the evidence-based rationale for each technical step of the procedure.

Keywords Gastroesophageal reflux disease (GERD) · Laparoscopic antireflux surgery (LARS) · Gastroparesis · Pyloroplasty · Lung transplantation

Introduction

Despite improvements in immunosuppressive strategies, the median survival of patients after lung transplantation is only 5 years, still inferior to the transplantation of any other solid organ.[1–4] This low survival rate is largely due to the development of bronchiolitis obliterans syndrome (BOS).[5–7] Unfortunately, the pathophysiology of BOS is poorly understood, though evidence suggests that BOS might represent a non-immunologic aberrant response to a chronic stimulus injury.[7–9] Several reports have shown that GERD might be responsible for this chronic injury.[10] Indeed, some studies have confirmed that GERD in lung transplant recipients is a risk factor for the development or progression of BOS and that surgical correction of GERD may control the decline in lung function.[11–14] The purpose of this article is threefold: (1) to describe a step-by-step approach to the laparoscopic treatment of GERD in lung transplantation, illustrating the evidence-based rationale for each technical step; (2) to address specific technical concerns we have encountered in the management of this high-risk patient population; and (3) to provide the results of our approach in terms of perioperative safety and outcomes.

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Preoperative Evaluation

All lung transplant patients who are potential candidates for laparoscopic surgical correction of GERD undergo a preoperative assessment that includes a symptomatic evaluation, a barium swallow, an upper endoscopy, a gastric emptying nuclear scan, and esophageal manometry

with ambulatory pH monitoring. Each patient also undergoes rigorous pre-anesthesia testing, where critical anesthetic concerns are addressed (e.g., prevention of infection, airway trauma, fluid overload, respiratory depression, and pharmacological interaction between antirejection medications and anesthetic agents). Most important is the assessment of post-transplant pulmonary function. This predicts both the patient's ability to tolerate general anesthesia and the success of ventilator weaning and extubation after the procedure. If the patient has developed BOS since the lung transplant, fibrosis and obliteration of the small airways may produce severe airway obstruction and the inability to have sufficient pulmonary function to allow extubation after the anesthetic.

Operative Planning and Anesthesiologic Considerations

Before induction, the patient is positioned with a beanbag on the operative table. Pneumatic compression stockings are always used as prophylaxis against deep vein thrombosis. However, subcutaneous heparin is usually not administered preoperatively. Preoperative antibiotics are administered prior to skin incisions. No stress dose of hydrocortisone is routinely administered. In most patients, invasive monitoring with a central line or an arterial line is not employed to minimize the risk of infectious complications. A Foley catheter is always inserted to monitor the fluid status, as crystalloid infusions are minimized to prevent fluid overload. Then, the patient is intubated carefully to avoid trauma to the site of the tracheal anastomosis. A rapid and careful intubation also protects against regurgitation and aspiration of gastric contents. During transplantation, resection of one or both lungs results in disruption of tracheal innervation, and stimulation of the bronchial mucosa during intubation may not elicit a cough reflex. This places the patient at increased risk of aspiration. Moreover, the prevalence of gastroparesis in these patients is high (about one third in our series) and further poses them at risk for an aspiration event. Even if the patient has electively fasted for greater than 8 h prior to the procedure, a totally empty state can never be guaranteed, especially in those with gastric atony. Therefore, the anesthesiologist performs a rapid sequence intubation technique to rapidly secure the airway. Further measures are also employed to diminish gastric volume and increase the pH of gastric fluid. If a laparoscopic pyloroplasty is planned, the patient is asked to maintain a liquid diet for the preceding 2 to 3 days. It is also our practice to administer H_2 receptor blockers prior to surgery with 15–30 mL of a 0.3 M solution of sodium citrate 15–30 min before induction of anesthesia. After intubation, the beanbag is inflated and the lower extremities are placed in stirrups such that the surgeon stands between them. The abdomen is then prepped and draped and the patient is positioned in steep reverse Trendelenburg.

Operative Technique

Initial Access and Placement of Trocars

After complete neuromuscular paralysis is achieved, a 1-cm transverse midline incision is made in the skin 14 cm below the xiphoid process; the fascia is grasped with a Kocher clamp, pulled, and nicked with a #15 scalpel blade; the Veress needle is inserted, a water drop test is performed, and the abdomen is insufflated to 14 mmHg; then the Veress needle is removed and an 11-mm Kii Optical Fixation Trocars ™ (Applied Medical, Rancho Santa Margarita, CA) is inserted into the abdominal cavity under direct visualization with a 0° laparoscope. Maintaining the same alignment of the entry path, the introducer of the trocar is removed and the laparoscope is reinserted into the abdominal cavity to inspect the entry area, ensuring that no intrabdominal injuries were made upon entering the abdominal cavity. The 0° laparoscope is then exchanged for a 30° laparoscope, and the other trocars are placed under direct visualization in the order illustrated by Fig. 1. Port 2 is placed below the left costal margin in the mid-clavicular line and accommodates an 11-mm trocar. This is a working port through which the graspers, the laparoscopic Ligasure™ Vessel Sealing System (Valleylab, Boulder, CO), and the suturing instruments are introduced. This port is placed second in order, as it allows the introduction of an atraumatic grasper that facilitates the placement of the Nathanson retractor below the left lobe of the liver. Port 3 is inserted next and is placed in the epigastrium just to the left of the xiphoid process. A 5-mm incision is used to insert bluntly through the abdominal wall the tip of a Nathanson retractor. This retractor is placed to retract the left lobe of the liver away from the diaphragmatic hiatus and expose the gastroesophageal junction. The Nathanson retractor is then held in place by a self-retaining system attached to the operating table. Port 4 is placed below the right costal margin in the mid-clavicular line and holds an 11-mm trocar. This is a working port and is placed after retraction of the left lobe of the liver through the falciform ligament to achieve optimal exposure of the gastroesophageal junction. Port 5 is placed last, accommodates an 11-mm trocar, and is situated on the left anterior axillary line at the level of the optical port. It is used for (a) manipulation of a laparoscopic atraumatic Allis clamp; (b) a grasper, which will hold the Penrose drain once it has been placed around the esophagus; (c) the Ligasure™ to take down the short gastric vessels; and (d) to introduce a clip applier.

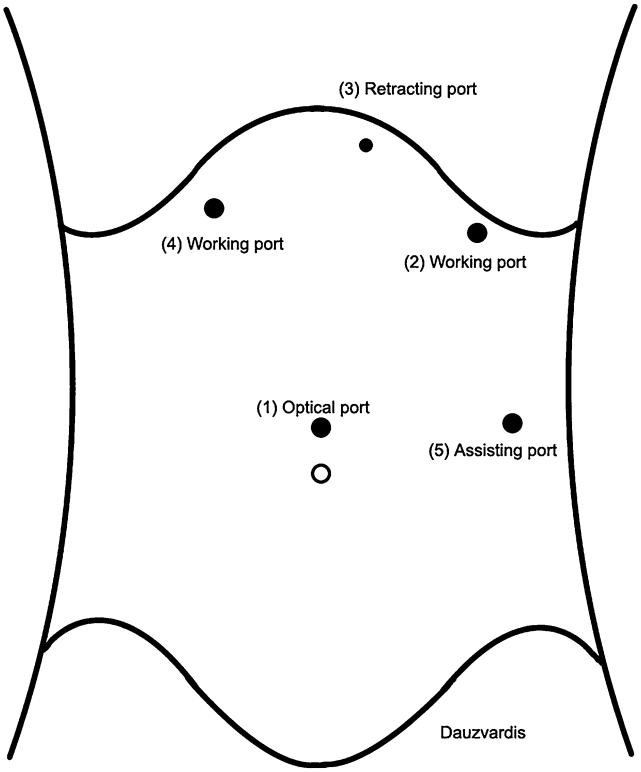

Fig. 1 Position of operative ports in order of placement: *(1) optical port*, 14 cm below the xiphoid process; *(2) left working port*, below the left costal margin in the mid-clavicular line; *(3) epigastric port* for the Nathanson retractor; *(4) right working port*, below the right costal margin in the mid-clavicular line; *(5) assisting port*, on the left anterior axillary line at the level of the optical port.

Identification and Dissection of the Esophagus

Once all ports are placed, the assistant inserts the laparoscopic atraumatic Allis clamp through port 5, places it onto the stomach just distal to the gastroesophageal junction, and applies gentle lateral traction to facilitate the surgeon's dissection. The surgeon uses ports 2 and 4 to start the dissection by dividing the gastrohepatic ligament with the Ligasure™ until the apex of the right diaphragmatic crus is identified. Subsequently, the phrenoesophageal ligament is divided anteriorly from the apex of the right crus to the apex of the left crus, and the anterior vagus nerve is identified. The esophagus is then bluntly dissected away from the right crus, and the posterior vagus nerve is identified. Finally, the right crus is dissected inferiorly toward the junction with the left crus.

Creation of the Retroesophageal Window

While the assistant maintains lateral and cephalad traction of the stomach just distal to the gastroesophageal junction with the laparoscopic Allis clamp, the surgeon creates a retroesophageal window by blunt dissection lateral to the left pillar of the crus, staying in the abdominal cavity, and not in the posterior mediastinum, and away from the mediastinal pleura. Through this window, a 1/4-in. Penrose drain, 6 in. long, is passed around the esophagus and the posterior vagus, and its tails are anchored with metal clips applied by a clip applier introduced through port 5. This drain is then used for the atraumatic traction of the gastroesophageal junction instead of the Allis clamp. This atraumatic traction onto the gastroesophageal junction helps in completing the dissection of the retroesophageal window which will later accommodate the fundoplication. This part of the dissection is completed only when the gastroesophageal junction is completely mobilized and freed from the attachments of the esophagus to the posterior mediastinum, and both borders of the diaphragmatic crura are cleared (when this step is completed, a classic "V", which is represented by the two diaphragmatic pillars, is always demonstrated). The goal is to obtain at least 1 in. of intra-abdominal esophagus around which the wrap is fashioned.

Division of Short Gastric Vessels

While the assistant applies medial traction on the greater curvature of the stomach with the Allis clamp through port 4, the surgeon applies countertraction with a grasper introduced through port 2 and divides the short gastric vessels with the Ligasure™ starting 10–15 cm distally to the angle of His. Then, the dissection continues upward until all short gastric vessels and the posterior gastric artery, which originates from the splenic artery and which gives blood supply to the upper portion of the posterior wall of the stomach, are divided. This last step assures that the posterior wall of the stomach, which will constitute the fundoplication, is completely mobilized and available for a floppy wrap.

Closure of the Diaphragmatic Hiatus

The diaphragmatic crura are always closed with two or three intracorporeally tied, interrupted, #0 silk sutures with an Endostitch™ (Covidien, Norwalk, CT). The first stitch is placed just above the junction of the crura. One or two additional stitches are placed above the first one, 1 cm apart, with the uppermost being placed 1 cm posterior to the esophagus to avoid excessive tightening of the diaphragmatic hiatus.

Fundoplication

A total 360° Nissen fundoplication is usually performed. A partial 240° posterior fundoplication is usually reserved for those patients with advanced-stage scleroderma with absent esophageal motility on preoperative esophageal manometry.

The surgeon gently grabs the gastric fundus and pulls it under the esophagus through the retroesophageal window with atraumatic graspers. A "shoeshine" maneuver is performed to ensure the adequate mobilization of the fundus of the stomach, especially its posterior wall. The left and right sides of the fundus are grabbed at the level of the stumps of the short gastric vessels and held together in place with the Allis clamp introduced through port 5. Then, three 2–0 silk sutures, spaced 1 cm apart, are placed to anchor the two ends of the fundoplication to each other and tied intracorporeally. None of these stitches include the esophagus. No bougie is passed. The Penrose drain is removed. Two stitches are then placed, one on each side of the fundoplication, to pexy the fundoplication and the esophagus to the diaphragm. These "apical" stitches incorporate the top of the fundoplication, the esophagus, and the uppermost portion of the crus (Fig. 2). Finally, one additional interrupted 2–0 silk suture is placed with the Endostitch™ between the posterior side of the fundoplication at the 6 o'clock position and the crura closed to fashion a posterior gastropexy (Fig. 2).

Laparoscopic Pyloroplasty

A laparoscopic Heineke–Mikulicz pyloroplasty is performed when severe gastric atony is preoperatively identified by dynamic scintigraphic nuclear medicine imaging in a symptomatic patient. Fig. 3 illustrates the port placement for the execution of the laparoscopic pyloroplasty. Port 6 is placed at the right mid-clavicular line at the level of the transverse umbilical line. This port holds an 11-mm optical trocar. Port 1 is then converted to a working port. Finally, a 5-mm working port (port 7) is placed at the right anterior axillary line, triangulating with Port 1 for combined manipulation of the suturing instruments. Special attention must be given to proper port placement, because if placed too high, the angle of suturing becomes too wide and suturing becomes difficult. Once the pylorus is identified, electrocautery is employed to score the anterior surface of the pylorus and first portion of the duodenum. The pylorus is then entered, and a 5-cm longitudinal enterotomy is carried distally in the duodenum and proximally in the antrum with the Ligasure™. Anchoring sutures are placed at the top and bottom of the enterotomy with interrupted 2–0 silk stitches with a V-20 needle intracorporeally. To prevent incorporation of the posterior wall of the pylorus during closure, a rolled piece of Gelfoam (created by placing 2–0 silk ties at both ends) is introduced into the lumen of the pylorus and left in place to later dissolve. The longitudinal enterotomy is then closed transversely in a single layer over the Gelfoam roll with interrupted 2–0 silk sutures. These are placed approximately 0.3–0.5 cm apart starting from the ends, progressing towards the middle, and tied intracorporeally. A Maryland dissector is then used to assess for gaps between sutures, and simple 2–0 silk stitches are placed where appropriate. Finally, two metallic clips are placed on the top and the bottom of the pyloroplasty to facilitate the location of the pyloroplasty on subsequent barium swallow.

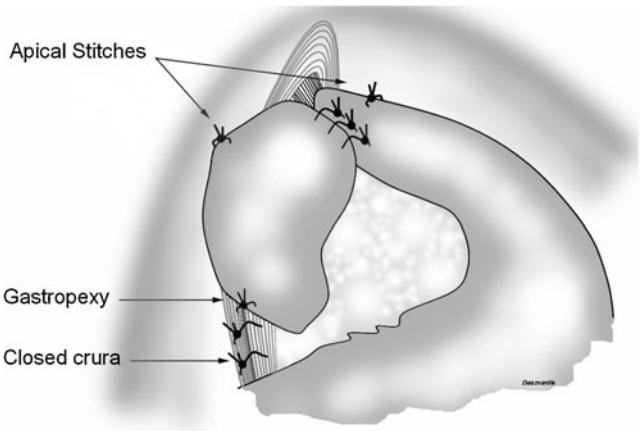

Fig. 2 Position of operative ports for the pyloroplasty.

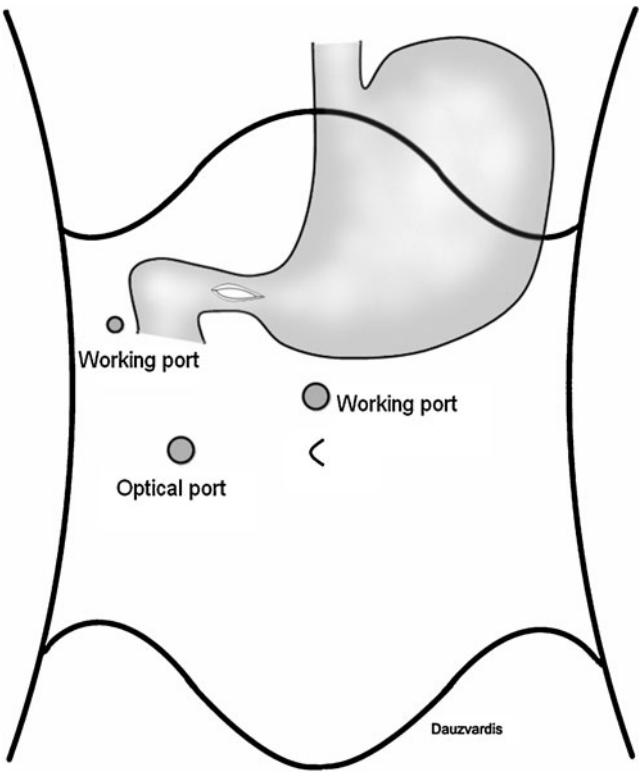

Fig. 3 Completed Nissen fundoplication with collar stitches, posterior gastropexy and pyloroplasty.

Closure of Port Sites and Termination of Anesthesia

After a final inspection, the Nathanson retractor and all trocars are removed under direct visualization. The pneumoperitoneum is completely evacuated and the midline fascial incision of port 1 is closed with a figure-of-eight 2–0 absorbable suture. Fig. 3 shows a completed fundoplication. During the entire procedure, the anesthesiologist rigorously maintains the peak airway pressure less than 40 cm H_20 and finally removes the endotracheal tube only when the patient is fully awake to minimize the risk of aspiration, as the cough reflex is impaired.

Postoperative Care

Postoperatively, all patients are closely monitored by both the surgical and the lung transplant teams in the Surgical Intensive Care (ICU) overnight. No chest X-ray is performed. They are started on a soft mechanical diet, the morning of postoperative day 1 and are asked to keep this dietary regimen for the first 2 weeks postoperatively and then to advance to more solid foods as tolerated. A barium swallow is never required before starting oral intake, unless a pyloroplasty is performed. In this case, a barium swallow is performed on postoperative day 1 to rule out a gastric leak. Patients are then discharged from the ICU after breakfast on postoperative day 1 and are able to resume regular activities in the next few days.

Specific Technical Concerns in the Lung Transplant Population

In our series of lung transplant patients with GERD who underwent laparoscopic antireflux surgery (LARS), we have noticed that the tissues of the esophagus and stomach are generally more friable and edematous, probably due to the use of steroids. Therefore, we advocate a very gentle handling of the organs. A perforation would have disastrous consequences and can be definitely avoided by handling the tissues with atraumatic graspers and by applying atraumatic traction of the gastroesophageal junction with a Penrose drain. This step of the operation should be accomplished early in the course of the procedure, as it will facilitate the remainder of the hiatal dissection. Moreover, we have found that the dissection of the esophagus from the posterior mediastinum can be challenging, as the pleura can be plastered to the esophagus, as a result of the previous lung transplantation. Therefore, if the mediastinal dissection is not carried out safely and meticulously, one may risk causing a unilateral or a bilateral pneumothoraces or even injuring the vagus nerves. This is especially true when the patient had a bilateral transplant or a re-transplant. In all cases, cautious dissection with the Ligasure™ has prevented symptomatic pneumothoraces and allowed for full esophageal mobilization, though we rarely encountered a hiatal hernia large enough to increase the difficulty of the dissection and the repositioning of the gastroesophageal junction to its proper anatomic location within the abdomen. We speculate that the rarity of a large hiatal hernia (we encountered only a small hiatal hernia in 24% of our series of 25 lung transplant) may be due to the adhesion of the pleura to the distal esophagus, which may prevent a hernia to develop after lung transplantation. Lastly, we noticed that when a replaced left hepatic artery is encountered (two patients, or 8%, in our series), a fundoplication is still feasible, and the aberrant vessel can always be preserved, although this may add time to the operation.

Results

Between November 2008 and February 2010, 25 consecutive lung transplant patients with GERD underwent laparoscopic Nissen fundoplication according to our standardized approach. A laparoscopic pyloroplasty was added in seven patients. The perioperative outcome of these lung transplant recipients was prospectively compared over the same time period to a control group of 23 patients without lung disease or transplantation (observational data submitted for publication). There was no in-hospital or 30-day mortality. The estimated blood loss, the duration of surgery, and length of hospital stay were similar between lung transplant patients and controls. There was no difference in complication or readmission rates after LARS between the lung transplant population and the control group despite the fact that these patients faced a significantly higher surgical risk (median ASA class, 3 vs. 2 for controls, $p<0.0005$). Overall, these results suggest that our approach to LARS is as safe for lung transplant patients as it is for the general population with GERD.

Discussion

Although laparoscopic fundoplication is an accepted treatment option for lung transplant patients with GERD, the surgical technique, which often includes a laparoscopic pyloroplasty, has not been standardized. The way we perform the operation takes into account several technical steps whose execution has proven successful in non-transplant patients. Such technical elements include a full mobilization of the esophagus with meticulous closure of the diaphragmatic crura, division of the short gastric

vessels, a non-tailored approach when performing the fundoplication, and the addition of a laparoscopic pyloroplasty in patients with symptomatic and severe gastric atony. Below, we illustrate the evidence-based rationale for the technical details for each step of the operation.

Esophageal Mobilization, Closure of the Diaphragmatic Crura, and Pexy of the Fundoplication

A meticulous esophageal mobilization, closure of the diaphragmatic crura, and pexy of the fundoplication are essential to obtain good results. Soper et al. demonstrated an advantage to complete esophageal mobilization followed by meticulous closure of the diaphragmatic crura.[15] They analyzed the outcomes of 290 patients who had undergone laparoscopic Nissen fundoplication over a 6-year period and found a significant difference in anatomic failure rate between those patients in whom the diaphragmatic crura were not routinely closed and those in whom the crura were routinely closed (19% vs. 4%; $p<0.05$). The most common cause of failure was intrathoracic wrap herniation. In addition, when the authors conducted a multivariate analysis, they identified large hiatal hernia size, postoperative emesis, diaphragmatic stressors, and early operative experience (at which time, the crura were not routinely closed) as factors predictive of failure. Horgan et al. also demonstrated the need of respecting important technical elements of the procedure in order to prevent failures.[16] They identified three types of failure. Type I failure was identified when the gastroesophageal junction was herniated through the hiatus, either with the fundoplication (type IA) or without it (type IB), resulting in a telescoping of the stomach through the fundoplication; Type II failure involved a redundant stomach; and Type III failure was attributed to defective position or construction of the fundoplication. The authors demonstrated that the following technical details may play a role in the success of the operation: mobilization of the esophagus and placement of the gastroesophageal junction into the abdomen, meticulous closure of the hiatus, suturing the fundoplication to the esophagus to avoid telescoping, and suturing the fundoplication to the closed crura (posterior gastropexy) to prevent its herniation into the chest.

Division of the Short Gastric Vessels

Although controversy still exists between advocates and opponents of dividing the short gastric vessels, we prefer to routinely divide them to allow for a tension-free and floppy fundoplication. Our approach is supported by the data of Bell et al. and Wu et al. Specifically, in the study by Bell et al., the non-division of the short gastric vessels accounted for almost two-thirds of operative failures ($p=0.045$).[17] In addition, Wu et al. noted a complete absence of wrap slippage into the chest in those patients in whom the division of the short gastric vessels was employed together with a posterior crural closure and pexy of the wrap to the crus.[18]

Type of Fundoplication

We prefer to perform a total 360° Nissen fundoplication, and we reserve a partial 240° posterior fundoplication for those patients with absent esophageal motility on preoperative esophageal manometry. Several trials have shown that the tailored approach provides less-than-optimal results. In a controlled trial from 2001, which 200 patients were stratified according to the presence or absence of esophageal dysmotility and randomized to either 360° (Nissen) or 270° (Toupet) fundoplication, Fibbe et al. showed that clinical outcome and reflux recurrence were similar (21% vs. 14%) in patients with and without dysmotility.[19] The authors concluded that esophageal dysmotility (1) does not affect postoperative clinical outcome, (2) that it is not corrected by fundoplication, regardless of the surgical procedure performed, and (3) that it does not require a tailored approach. Then, in 2004, Patti et al. conducted a retrospective study of 235 patients in whom a tailored approach was used between October 1992 and December 1999 (141 patients, partial fundoplication and 94 patients, total fundoplication).[20] They showed that heartburn from reflux on pH monitoring recurred in 19% of patients after partial fundoplication and in 4% after total fundoplication. They also showed that in 122 patients in whom a non-selective approach was used after December 1999 (total fundoplication regardless of quality of peristalsis), heartburn recurred in only 4% of patients after total fundoplication. In addition, this group found that the incidence of postoperative dysphagia was similar regardless of the procedure performed. The authors concluded that laparoscopic partial fundoplication was less effective than total fundoplication, and that, compared with a partial (240°) fundoplication, a total (360°) fundoplication was not followed by more dysphagia, even when esophageal peristalsis was weak (esophageal peristalsis was considered weak if the amplitude in the distal esophagus was equal or less than 40 mmHg). These results were confirmed in a multicenter retrospective review by Novitsky et al. in 2007 in which they showed that patients with severely disordered esophageal peristalsis (defined as an esophageal amplitude of 30 mmHg or less and/or 70% or more non-peristaltic esophageal body contractions) can safely undergo a laparoscopic total fundoplication with expected low rates of long term postoperative dysphagia (4%).[21]

Specific to lung transplantation, prior studies allow for minimal assessment of the operative approach to antireflux surgery. Most reports limit their discussion to the percent-

age of those undergoing total versus partial fundoplication as opposed to a focus on their respective technique and outcomes.[11–13,22] The study of Burton et al. in 2009 is one of the few, comparing partial to total fundoplication in lung transplant patients, demonstrating no difference in the chosen technique on gas bloat, satisfaction, or dysphagia score.[14] Though Burton et al. indicate a preference for partial fundoplication, other centers typically reserve a partial fundoplication for poor esophageal acid clearance or absent esophageal motility.[11,22]

Pyloroplasty

Gastroparesis is prevalent after lung transplantation. Studies from other lung transplant centers report a prevalence ranging from 23% to 92%.[22–28] Among lung transplant patients with GERD studied at our institution by nuclear medicine imaging, 36% had severe delayed gastric emptying. Because gastroparesis has been shown to be implicated in the pathogenesis of GERD and associated with aspiration and allograft compromise, we prefer to perform a pyloroplasty at the time of LARS in the lung transplant patient with objectively identified GERD and symptomatic and severe gastric atony (defined as when <30% of the radiolabeled gastric contents were emptied into the small bowel by 90 min).[27,28]

Conclusion

Laparoscopic surgical correction of reflux, with or without pyloroplasty, is accepted and safe in lung transplant patients and may preserve pulmonary function by preventing aspiration of gastroduodenal contents. The respect for specific anesthesiologic details and technical aspects of the operation in this high-risk patient population is essential. The important technical elements of the operation, including meticulous closure of the hiatus, division of the short gastric vessels, and a 360° fundoplication in all but those with absent esophageal motility, should be respected. This effort, in combination with the appropriate patient selection and a standardized management, may provide the lung transplant recipient an effective treatment for GERD and reduce their risk of aspiration.

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References

1. Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel A, Taylor DO, Kucheryavaya AY, Hertz MI. Registry for the International Society for Heart and Lung Transplantation: Twenty-fifth Official Adult Lung and Heart/Lung Transplantation Report. J Heart Lung Transplant 2008; 27(9):957–969.
2. Brown RS, Rush SH, Rosen HR, Langnas AN, Klintmalm GB, Hanto DW, Punch JD. Liver and intestine transplantation. Am J Transplant 2004; 4(Suppl 9):81–92.
3. Wynn JJ, Distant DA, Pirsch JD, Norman D, Gaber AO, Ashby VB, Leichtman AB. Kidney and pancreas transplantation. Am J Transplant 2004; 4(Suppl 9):72–80.
4. Pierson RN 3rd, Barr ML, McCullough KP, Egan T, Garrity E, Jessup M, Murray S. Thoracic organ transplantation. Am J Transplant. 2004; 4(Suppl 9):93–105.
5. Yousem SA, Berry GJ, Cagle PT, Chamberlain D, Husain AN, Hruban RH, Marchevsky A, Ohori NP, Ritter J, Stewart S, Tazelaar HD. Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: lung rejection study group. J Heart Lung Transplant 1996; 15(1 Pt 1):1–15.
6. Grossman EJ, Shilling RA. Bronchiolitis obliterans in lung transplantation: the good, the bad, and the future. Transl Res 2009;153(4):153-165.
7. Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, Mallory GB, Snell GI, Yousem S. Bronchiolitis obliterans syndrome 2001, an update of the diagnostic criteria. J Heart Lung Transplant 2002;21(3):297–310.
8. Valentine VG, Robbins RC, Berry GJ, Patel HR, Reichenspurner H, Reitz BA, Theodore J. Actuarial survival of heart–lung and bilateral sequential lung transplant recipients with obliterative bronchiolitis. J Heart Lung Transplant 1996;15(4):371–383
9. Nicod, LP. Mechanisms of airway obliteration after lung transplantation. Proc Am Thorac Soc 2006;3(5):444–449.
10. Li B, Hartwig MG, Appel JZ, Bush EL, Balsara KR, Holzknecht ZE, Collins BH, Howell DN, Parker W, Lin SS, Davis RD. Chronic aspiration of gastric fluid induces the development of obliterative bronchiolitis in rat lung transplants. Am J Transplant 2008;8(8):1614–1621.
11. Cantu E 3rd, Appel JZ 3rd, Hartwig MG, Woreta H, Green C, Messier R, Palmer SM, Davis RD Jr. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg 2004;78(4):1142–1151.
12. Lau CL, Palmer SM, Howell DN, McMahon R, Hadjiliadis D, Gaca J, Pappas TN, Davis RD, Eubanks S. Laparoscopic antireflux surgery in the lung transplant population. Surg Endosc 2002;16(12):1674–1678.
13. Davis RD Jr, Lau CL, Eubanks S, Messier RH, Hadjiliadis D, Steele MP, Palmer SM. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. J Thorac Cardiovasc Surg 2003;125(3):533–542.
14. Burton PR, Button B, Brown W, Lee M, Roberts S, Hassen S, Bailey M, Smith A, Snell G. Medium-term outcome of fundoplication after lung transplantation. Dis Esophagus 2009;22(8):642–648.
15. Soper NJ, Dunnegan D. Anatomic fundoplication failure after laparoscopic antireflux surgery. Ann Surg 1999;229:669–676; discussion 76–77.
16. Horgan S, Pohl D, Bogetti D, Eubanks T, Pellegrini C. Failed antireflux surgery: what have we learned from reoperations? Arch Surg 1999;134(8):809–815
17. Bell RC, Hanna P, Mills MR, Bowrey D. Patterns of success and failure with laparoscopic Toupet fundoplication. Surg Endosc 1999;13(12):1189–1194.
18. Wu JS, Dunnegan DL, Luttmann DR, Soper NJ. The influence of surgical technique on clinical outcome of laparoscopic Nissen fundoplication. Surg Endosc 1996;10(12):1164–1169; discussion 1169–1170.

19. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001;121(1):5–14
20. Patti MG, Robinson T, Galvani C, Gorodner MV, Fisichella PM, Way LW. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004;198(6):863–869; discussion 869–870.
21. Novitsky YW, Wong J, Kercher KW, Litwin DE, Swanstrom LL, Heniford BT. Severely disordered esophageal peristalsis is not a contraindication to laparoscopic Nissen fundoplication. Surg Endosc 2007;21(6):950–954.
22. Gasper WJ, Sweet MP, Hoopes C, Leard LE, Kleinhenz ME, Hays SR, Golden JA, Patti MG. Antireflux surgery for patients with end-stage lung disease before and after lung transplantation. Surg Endosc 2008;22(2):495–500.
23. Hadjiliadis D, Davis RD, Steele MP, Messier RH, Lau CL, Eubanks SS, Palmer SM. Gastroesophageal reflux disease in lung transplant recipients. Clin Transplant 2003;17(4):363–368.
24. Young LR, Hadjiliadis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. Chest 2003;124(5):1689–1693.
25. D'Ovidio F, Mura M, Ridsdale R, Takahashi H, Waddell TK, Hutcheon M, Hadjiliadis D, Singer LG, Pierre A, Chaparro C, Gutierrez C, Miller L, Darling G, Liu M, Post M, Keshavjee S. The effect of reflux and bile acid aspiration on lung allograft and its surfactant and innate immunity molecules SP-A and SP-D. Am J Transplant 2006;6(8):1930–1938.
26. Au J, Hawkins T, Venables C, Morritt G, Scott CD, Gascoigne AD, Corris PA, Hilton CJ, Dark JH. Upper gastrointestinal dysmotility in heart–lung transplant recipients. Ann Thorac Surg 1993;55(1):94–97.
27. Berkowitz N, Schulman LL, McGregor C, Markowitz D. Gastroparesis after lung transplantation. Potential role in postoperative respiratory complications. Chest 1995;108(6):1602–1607.
28. Sodhi SS, Guo JP, Maurer AH, O'Brien G, Srinivasan R, Parkman HP. Gastroparesis after combined heart and lung transplantation. J Clin Gastroenterol 2002;34(1):34–39.

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REVIEW ARTICLE

Extended Pancreaticoduodenectomy with Vascular Resection for Pancreatic Cancer: A Systematic Review

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Abstract
Objectives This systematic review objectively evaluates the safety and outcomes of extended pancreaticoduodenectomy with vascular resection for pancreatic cancer involving critical adjacent vessels namely the superior mesenteric-portal veins, hepatic artery, superior mesenteric artery, and celiac axis.
Methods Electronic searches were performed on two databases from January 1995 to August 2009. The end points were: firstly, to evaluate the safety through reporting the mortality rate and associated complications and, secondly, the outcome by reporting the survival after surgery. This was synthesized through a narrative review with full tabulation of results of all included studies.
Results Twenty-eight retrospective studies comprising of 1,458 patients were reviewed. Vein thrombosis and arterial involvement were reported as contraindications to surgery in 62% and 71% of studies, respectively. The median mortality rate was 4% (range, 0% to 17%). The median R0 and R1 rates were 75% (range, 14% to 100%) and 25% (range, 0% to 86%), respectively. In high volume centers, the median survival was 15 months (range, 9 to 23 months). Nine of 10 (90%) studies comparing the survival after extended pancreaticoduodenectomy with vascular resection versus standard pancreaticoduodenectomy reported statistically similar ($p>0.05$) survival outcomes. Undertaking vascular resection was not associated with a poorer survival.
Conclusions The morbidity, mortality, and survival outcome after undertaking extended pancreaticoduodenectomy with vascular resection for pancreatic cancer with venous involvement and/or limited arterial involvement is acceptable in the setting of an expert referral center and should not be a contraindication to a curative surgery.

Keywords Morbidity · Mortality · Postoperative complication · Pancreatic cancer · Pancreaticoduodenectomy · Whipple's operation · Roux-en-Y anastomosis · Vascular procedures

Introduction

The current curative treatment paradigm for pancreatic cancer entails a strategy of complete surgical resection combined with adjuvant chemotherapy or chemoradiotherapy. Randomized clinical trials have reported a median survival of approximately 22 months compared to 18 months in patients undergoing adjuvant therapy with gemcitabine chemotherapy after surgery compared to observation alone.[1,2] When chemotherapy is combined with radiation therapy as a radio-sensitizer, the survival benefit appeared to be more pronounced with the chemo-radiation group having a median survival of about 25 months compared to 19 months in patients undergoing observation alone.[3] Although these strategies have not shown a significant difference in overall survival, they may delay the time to recurrence and may, therefore, be useful in treating patients with a microscopically positive margin (R1). In patients with unresectable tumors otherwise termed locally advanced pancreatic cancer, gemcitabine in combination with oxaliplatin evaluated in the GERCOR and GISCAD phase-III trial yielded a median

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survival of 9 months.[4] When treated with chemoradiation, the median survival may increase to about 13 months as reported in the 2001-01 FFCD/SFRO study.[5] The survival disparity in nonresectable tumors as compared to resectable tumors in these trials emphasizes the positive impact of a complete surgical resection (R0) and a rationale towards undertaking aggressive curative surgery where possible.

A common contraindication for resection in the current clinical practice for patients with locally advanced tumors (T3/T4 tumors) is the presence of vascular involvement of the critical adjacent vessels. However, there is a recognized arbitrary state of borderline resectable pancreatic cancer where tumors involve the superior mesenteric-portal veins but may remain relatively resectable with additional vascular surgical procedure. Hence, the definition of resectability may vary between different treatment centers with varying level of expertise and willingness to undertake extended pancreaticoduodenectomy. The concept of a regional pancreatectomy as first described by Fortner[6] was an attempt to improve results of surgical resection of pancreatic cancer by performing a subtotal or total pancreatic resection which usually involves resection and reconstruction of the pancreatic segment of the portal vein, en bloc regional lymphadenectomy, and in highly selected cases resection and reconstruction of a major artery. Such extended pancreatectomy may facilitate resection in patients with tumors that are classified as T3/T4 and total clearance of the peripancreatic, hepatoduodenal, mesenteric, and celiac lymph nodes. The clinical benefit of extended pancreatic resections must, however, be balanced with the risk of the procedure. With regard to extended lymphadenectomy, its role as a routine procedure is no longer proven following evidence from randomized trials that showed no survival advantage and increased morbidity.[7,8] It has been shown that the prognosis in patients with lymph node involvement is related more so to the number of nodes involved than just the nodal status itself.[9] Therefore, lymphadenectomy may still have a role in the management of patients with nodal disease. Observations from a multicenter study of patients following R0/R1 pancreatectomy showed that patients with node positive disease are likely to benefit from adjuvant chemoradiation treatment.[10] With regard to vascular resection as part of an extended pancreatectomy procedure, it continues to remain controversial due to the procedural complexity, the safety and consequential morbidity imposed on the patient in a disease that portends a poor survival, and the lack of randomized evidence to demonstrate its efficacy.

A previous systematic review by Siriwardana and colleague failed to recognize the heterogeneity in survival outcomes that reflected the expertise of the treatment center, hence, leading to an overstated conclusion that did not reflect the current consensus of expert pancreatic surgeons.[11] More recently, a collective review of recent publications of pancreatectomy combined with superior mesenteric-portal vein resection concluded that the procedure was safe, feasible, and provides important survival benefits.[12] The objective of the current review serves to provide a systematic review with full tabulation of published studies with stratification of vessel (vein or artery) involvement and level of expertise (high- or low-volume centers) and to compare the extended pancreaticoduodenectomy with vascular procedure to a standard pancreaticoduodenectomy alone to thoroughly supplement and establish the current evidence in this field.

Methods

Literature Search Strategy

Original published studies on pancreaticoduodenectomy with vascular resection of both veins and arteries for pancreatic cancer were identified by searching the MEDLINE database (1995 to August 2009) and PubMed (January 1995 to August 2009) using the keywords: "pancreatectomy, pancreaticoduodenectomy, pancreatic cancer, vascular resection, portal vein, superior mesenteric vein, hepatic artery, celiac axis, and superior mesenteric artery." The search was limited to human articles published in the English language. The reference lists of all retrieved articles were manually reviewed to further identify potentially relevant studies. All relevant articles identified were assessed with application of a predetermined selection criterion.

Selection Criteria

Studies which specifically addressed pancreaticoduodenectomy with vascular resection and reported the complications, mortality, and survival outcomes were evaluated. Studies which reported vascular resection as a subset analysis in pancreatectomy without evaluating the mentioned endpoints of review or not comprehensively reported were excluded. To ensure that the sample size would not bias the reporting of the morbidity and mortality outcomes, only studies reporting more than 10 patients were included. For institutions reporting updated experiences, only the most recent or complete paper was selected for review. Studies were selected for evaluation if they were level I evidence: randomized controlled trials; level II evidence: nonrandomized controlled clinical trials or well-designed cohort studies; level III evidence: observational studies, as described by the US Preventive Services Task Force.

Data Extraction and Critical Appraisal

Two reviewers (T.C.C. and A.S.) independently critically appraised each article using a standard protocol. Data extracted include the methodology, quality criteria, perioperative variables, morbidity and mortality outcomes, and survival data. All data were extracted and tabulated from the relevant articles' texts, tables, and figures. Discrepancies were resolved by discussion and consensus. Following tabulation of the results, the morbidity, mortality, and survival outcomes were synthesized. Stratification was made based on whether the institution was considered as a high- or low-volume center by searching the literature for publications on pancreatectomy for pancreatic cancer. High-volume centers were assigned if prospective case series from the institution reported at least 20 pancreatic resection cases per year irrespective of the number of pancreatic surgeons in the institution. Meta-analysis was inappropriate because of the heterogeneous nature of the included studies and the lack of a controlled comparative arm.

Results

Quantity and Quality of Evidence

Literature search using the above-described search strategy through both MEDLINE and PubMed databases identified 182 articles. Through reviewing of the abstracts and references lists, 58 relevant articles were identified. The specific selection criteria were applied, and serial publications of papers reporting accumulating number of participants or increased length of follow-up were excluded with only the most recent and definitive update from each institution or the paper that fulfilled the specified endpoints of this review being included for appraisal and data extraction. In total, 28 articles were critically evaluated and tabulated (Table 1). The level of evidence from these studies was low (all level III). They comprised of retrospective observational studies. The 28 articles arose from institutions in the USA (n=7), Europe (n=11), and Asia (n=10). In total, 1,458 patients were evaluated.

Treatment Criteria

In selecting patients for treatment, 21 studies[13–33] reported the mode of investigations performed. This include computed tomography scans in all 21 institutions (100%), magnetic resonance imaging or magnetic resonance cholangiopancreatography in 12 institutions (57%), and angiography in nine institutions (43%). After treatment investigations, all studies (n=28) reported patients with pancreatic head tumors (100%), 12 studies (43%) included patients with pancreatic body tumors, and seven studies (25%) included patients with pancreatic tail tumors.

The priori basis of selecting patients for extended pancreaticoduodenectomy with vascular resection and reconstruction was reported in 21 studies (75%).[13–22,24,26–29,31,32,34–37] Among which, vein thrombosis was a reported contraindication to surgery in 13 of 21 studies (62%), and arterial involvement was a reported contraindication to surgery in 15 of 21 studies (71%) (Table 1).

Procedure of Extended Pancreaticoduodenectomy with Vascular Resection and Reconstruction

All 28 studies undertook resection of superior mesenteric-portal vein. Five of 28 studies (18%)[21,22,30,35,37] undertook resection of the celiac axis, six studies (21%)[21,22,30,31,35,37] undertook resection of the hepatic artery, and five studies (18%)[21,22,30,31,35] undertook resection of the superior mesenteric artery. One thousand, one hundred thirty-six patients (78%) underwent pancreaticoduodenectomy. In undertaking vascular resection, 23 of 28 studies (82%)[13–15,17–27,29–32,34–36,38,39] examined the resected vessel histologically. The histopathological analysis of the resected vessel indentified true neoplastic invasion in between 21% and 100% of cases with a median of 63%. The most common techniques of reconstruction after vascular resection include end–end anastomosis and graft reconstruction (using either an autologous vein graft or synthetic graft). The surgical procedure resulted in estimated blood loss that was reported in 18 of 28 studies (64%)[15–20,22–24,26–29,32,33,37,40] ranging between 700 and 3,083 mL with a median of 1,494 mL (Table 2).

Postoperative Complications and Mortality Outcome

The mortality rate was reported in 27 of 28 studies (96%)[14–40] and ranged from 0% to 17% with a median of 4%. The median rate of bleeding was 4% (range, 0% to 16%), rate of collection or abscess was 5% (range, 0% to 29%), rates of vascular thrombosis was 0% (range, 0% to 4%), rate of pancreatic fistula was 6% (range, 0% to 18%), rate of biliary leak was 0% (range, 0% to 16%), rate of pancreatic duct leak was 1% (range, 0% to 17%), and the reoperation rate was 9% (range, 0% to 25%). The median average length of hospital stay was 17 days (range, 11 to 69 days; Table 3).

Treatment Efficacy

Twenty-one of 28 studies (75%)[13–19,22–25,27–29,31–34,36–40] reported margin status after extended pancreaticoduodenectomy with vascular resection. Microscopically clear margin

Table 1 Characteristics of the Studies from the Various Institutions

First author	Institution city/ country	Year published	Patients (*n*)	Preoperative imaging			Tumor location	Contraindications	
				Computed tomography	Magnetic resonance imaging	Angiography		Vein thrombosis (Y/N)	Arterial involvement (Y/N)
Kaneoka [19]	Ogaki, Japan	2009	42	Y	Y	Y	Head	N	Y
Martin [22]	Louisville & Atlanta, USA	2009	36	Y	Y	N	Head	N	N
Muller [23]	Heidelberg, Germany	2009	110	Y	Y	N	Head	NR	NR
Yekebas [31]	Hamburg, Germany	2009	136	Y	N	N	Head, Body, Tail	Y	Y
Illuminati [18]	Rome, Italy	2008	29	Y	N	N	Head, Body, Tail	Y	Y
Stitzenberg [37]	Philadelphia, USA	2008	12	NR	NR	NR	Head, Body, Tail	N	N
Wang [30]	Wuhan, China	2008	80	Y	Y	Y	Head	NR	NR
Al-Hadad [13]	Jacksonville, USA	2007	22	Y	Y	Y	Head, Body, Tail	N	Y
Riediger [25]	Freiburg, Germany	2006	53	Y	Y	Y	Head	NR	NR
Nakao [35]	Nagoya, Japan	2006	200	NR	NR	NR	Head, Body, Tail	N	N
Carrere [16]	Cedex, France	2006	45	Y	Y	Y	Head	Y	Y
Shimada [27]	Tokyo, Japan	2006	86	Y	Y	Y	Head, Body	N	Y
Jain [33]	Athens, Greece	2005	48	Y	Y	Y	Head	NR	NR
Zhou [32]	Shanghai, China	2005	32	Y	Y	N	Head, Body	Y	Y
Koniaris [20]	Various, USA	2005	11	Y	N	N	Head	N	NR
Li [21]	Xiamen, China	2004	79	Y	Y	N	Head	N	N
Poon [24]	Hong Kong, China	2004	12	Y	N	N	Head	Y	Y
Tseng [28]	Houston, USA	2004	141	Y	N	N	Head	Y	Y
Nakagohri [39]	Kashiwa, Japan	2003	33	NR	NR	NR	Head, Body, Tail	NR	NR
Capussotti [15]	Torino, Italy	2003	24	Y	N	N	Head	Y	Y
Howard [17]	Indianapolis, USA	2003	13	Y	N	N	Head	Y	Y
Kawada [34]	Sapporo, Japan	2002	28	NR	NR	NR	Head	Y	NR
Bachellier [14]	Strasbourg Cedex, France	2001	31	Y	Y	Y	Head	Y	Y
Shibata [26]	Sendai, Japan	2001	28	Y	N	Y	Head, Body	Y	Y
Van Geenen [29]	Amsterdam, Netherlands	2001	34	Y	N	N	Head	Y	Y
Launois [38]	Saint Gregoire, France	1999	14	NR	NR	NR	Head	NR	NR
Harrison [40]	New York, USA	1996	58	NR	NR	NR	Head, Body, Tail	NR	NR
Roder [36]	Hamburg, Germany	1996	21	NR	NR	NR	Head, Body	Y	Y

(R0) rates ranged from 14% to 100% with a median of 75%. The rate of margins that were grossly clear but microscopically involved (R1) ranged from 0% to 86% with a median of 25%. The median survival in studies reporting vein resection was 13 months (range, 5 to 23 months), with a median 1-year survival rate of 56% (range, 23% to 88%), median 3-year survival rate of 18% (range, 0% to 49%), and median 5-year survival rate of 12% (range, 0% to 25%). The median survival in studies reporting both vein and artery resection was 18 months (range, 3 to 20 months), with a median 1-year survival rate of 65% (range, 26% to 83%), median 3-year survival rate of 13% (range, 0% to 35%), and median 5-year survival rate of 0% (range, 0% to 20%; Table 4).

Outcomes in High-Volume Centers

Sixteen high-volume centers each reporting more than 20 pancreatectomy procedures per annum were identified, and their outcomes were reported separately in Table 5.[14,16,18,22,23,25,27–33,36,37,40] In these centers, 10 of 16 studies (63%)[14,16,18,22,25,27,28,31,36,40] reported a com-

Table 2 Vascular Surgical Procedures

First author	Vascular involvement					Patients with true vessel Invasion (%)	Type of pancreatic resection			Reconstruction techniques	Estimated blood loss (ml)
	Portal vein	Superior mesenteric vein	Celiac axis	Hepatic artery	Superior mesenteric artery		PD (*n*, %)	TP (*n*, %)	DP (*n*, %)		
Kaneoka [19]	Y	Y	N	N	N	60	42 (100)	0	0	End–end Graft reconstruction	1,280
Martin [22]	Y	Y	Y	Y	Y	67	36 (100)	0	0	End–end Patch Interposition Venorrhaphy	700
Muller [23]	Y	Y	N	N	N	78	110 (100)	0	0	Venorrhaphy Patch End–end Interposition	1,182
Yekebas [31]	Y	Y	N	Y	Y	57	92 (68)	34 (25)	10 (7)	Primary closure Patch End–end Interposition	NR
Illuminati [18]	Y	Y	N	N	N	76	17 (59)	2 (7)	7 (24)	Primary closure Patch End–end Interposition	700
Stitzenberg [37]	Y	Y	Y	Y	N	NR	6 (50)	4 (33)	2 (17)	End–end Graft reconstruction	1,250
Wang [30]	Y	Y	Y	Y	Y	71	80 (100)	0	0	NR	NR
Al-Hadad [13]	Y	Y	N	N	N	64	19 (86)	2 (9)	1 (5)	End–end Graft reconstruction	NR
Riediger [25]	Y	Y	N	N	N	60	49 (92)	4 (8)	0	Primary closure Patch End–end	NR
Nakao [35]	Y	Y	Y	Y	Y	57	NR	NR	NR	End–end Graft reconstruction	NR
Carrere [16]	Y	Y	N	N	N	NR	45 (100)	0	0	End–end Graft reconstruction	812
Shimada [27]	Y	Y	N	N	N	67	81 (94)	5 (6)	0	NR	1,686
Jain [33]	Y	Y	N	N	N	NR	48 (100)	0	0	Venorrhaphy End–end	700
Zhou [32]	Y	Y	N	N	N	63	32 (100)	0	0	End–end Graft reconstruction	1,420
Koniaris [20]	N	Y	N	N	N	100	11 (100)	0	0	End–end Graft reconstruction Interposition	2,090
Li [21]	Y	Y	Y	Y	Y	42	79 (100)	0	0	End–end Graft reconstruction Interposition	NR

Table 2 (continued)

First author	Vascular involvement					Patients with true vessel Invasion (%)	Type of pancreatic resection			Reconstruction techniques	Estimated blood loss (ml)
	Portal vein	Superior mesenteric vein	Celiac axis	Hepatic artery	Superior mesenteric artery		PD (*n*, %)	TP (*n*, %)	DP (*n*, %)		
Poon [24]	Y	N	N	N	N	50	12 (100)	0	0	End–end	800
Tseng [28]	Y	Y	N	N	N	NR	141 (100)	0	0	End–end Interposition	1,675
Nakagohri [39]	Y	Y	N	N	N	52	27 (82)	6 (18)		NR	NR
Capussotti [15]	Y	Y	N	N	N	82	24 (100)	0	0	End–end	2,100
Howard [17]	Y	Y	N	N	N	100	13 (100)	0	0	Venorrhaphy End–end Interposition	1,567
Kawada [34]	Y	Y	N	N	N	75	23 (82)	5 (18)	0	Venorrhaphy End–end Interposition	3,083
Bachellier [14]	Y	Y	N	N	N	67	10 (48)	11 (52)	0	End–end Graft reconstruction Venorrhaphy	NR
Shibata [26]	Y	Y	N	N	N	43	23 (82)	3 (11)	2 (7)	End–end Patch	1,583
Van Geenen [29]	Y	Y	N	N	N	44	34 (100)	0	0	End–end Graft reconstruction Interposition	1,800
Launois [38]	Y	Y	N	N	N	21	14 (100)	0	0	End–end Graft reconstruction Venorrhaphy	NR
Harrison [40]	Y	Y	N	N	N	NR	42 (72)	8 (14)	8 (14)	End–end Venorrhaphy	1,900
Roder [36]	Y	Y	N	N	N	61	26 (84)	5 (16)	0	End–end Graft reconstruction	NR

PD pancreaticoduodenectomy, *TP* total pancreatectomy, *DP* distal pancreatectomy

parison of survival between patients who underwent extended pancreaticoduodenectomy with vascular resection versus standard pancreaticoduodenectomy. Nine of 10 (90%) studies reported statistically similar survival outcomes.[14,16,18,22,25,28,31,36,40] The median survival of patients undergoing extended pancreaticoduodenectomy with vascular resection was 15 months (range, 9 to 23 months).

In the analysis of prognostic factors after extended pancreaticoduodenectomy with vascular resection, 11 studies[14,16,18,22,27–29,31,32,36,37] reported univariate analysis of clinicopathological factors associated with survival. There were no consistent adverse factors associated with a poor survival. Venous tumor infiltration was commonly identified as having no effect on survival. Seven studies[14,16,23,25,28,36,40] reporting a combined univariate analysis of patients undergoing both extended pancreaticoduodenectomy with vascular resection and standard pancreaticoduodenectomy reported that undergoing vascular resection was not associated with a poorer survival (Table 5).

Discussion

Surgery remains the only curative option for pancreatic cancer. It is commonly performed in selected patients with localized disease of the pancreas (T1 and T2 tumors). In the past, this procedure has been morbid with mortality rates of up to 25% in early series. However, improved techniques and training in the last decade have led to improved operative

Table 3 Complications of Extended Pancreaticoduodenectomy with Vascular Resection and Reconstruction

First author	Mortality (*n*, %)	Bleeding (*n*, %)	Collection/ abscess (*n*, %)	Thrombosis (*n*, %)	Pancreatic fistula (*n*, %)	Biliary leak (*n*, %)	Pancreatic duct leak (*n*, %)	Reoperation (*n*, %)	Average length of hospital stay (day)
Kaneoka [19]	2 (5)	NR	NR	NR	2 (5)	1 (2)	NR	0	NR
Martin [22]	0	0	3 (8)	0	0	0	1 (3)	0	11
Muller [23]	4 (4)	3 (3)	3 (3)	NR	4 (4)	NR	NR	10 (9)	18
Yekebas [31]	5 (4)	6 (4)	NR	3 (2)	9 (7)	9 (7)	NR	NR	NR
Illuminati [18]	1 (3)	1 (3)	0	0	1 (3)	0	2 (7)	0	16
Stitzenberg [37]	2 (17)	1 (8)	1 (8)	0	0	0	2 (17)	3 (25)	21
Wang [30]	1 (1)	3 (4)	0	3 (4)	14 (18)	2 (3)	NR	4 (5)	16
Al-Hadad [13]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Riediger [25]	2 (4)	4 (8)	4 (8)	NR	4 (8)	NR	NR	4 (8)	16
Nakao [35]	10 (5)	NR	NR	NR	NR	NR	NR	NR	NR
Carrere [16]	2 (4)	7 (16)	2 (4)	2 (4)	3 (7)	7 (16)	NR	10 (22)	23
Shimada [27]	1 (1)	5 (6)	2 (2)	0	14 (16)	1 (1)	0	2 (2)	44
Jain [33]	0	3 (6)	0	1 (2)	0	0	0	4 (8)	12
Zhou [32]	0	0	2 (6)	0	0	0	0	2 (6)	NR
Koniaris [20]	1 (9)	1 (9)	1 (9)	0	1 (9)	0	0	1 (9)	16
Li [21]	4 (5)	3 (4)	NR	0	0	0	0	NR	NR
Poon [24]	0	1 (8)	1 (8)	0	0	0	1 (8)	0	15
Tseng [28]	3 (2)	9 (6)	8 (6)	NR	NR	NR	2 (1)	4 (3)	13
Nakagohri [39]	2 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Capussotti [15]	0	0	0	0	1 (5)	0	0	3 (13)	26
Howard [17]	1 (8)	0	2 (15)	0	2 (15)	0	0	2 (15)	14
Kawada [34]	1 (4)	2 (7)	8 (29)	NR	NR	NR	NR	NR	69
Bachellier [14]	1 (3)	1 (3)	1 (3)	0	1 (3)	0	0	3 (10)	22
Shibata [26]	1 (4)	NR	1 (4)	NR	NR	NR	1 (4)	NR	NR
Van Geenen [29]	0	3 (9)	3 (9)	NR	NR	NR	3 (9)	3 (9)	15
Launois [38]	0	NR	NR	NR	NR	NR	NR	NR	NR
Harrison [40]	3 (5)	NR	NR	NR	NR	NR	NR	10 (17)	22
Roder [36]	0	1 (3)	0	0	NR	NR	5 (16)	3 (10)	28

results and long-term survival outcomes for patients with pancreatic cancer following pancreaticoduodenectomy, hence leading to a renewed interest in the surgical oncologic management of this disease.[41] Through cumulated experience in the operative and perioperative management of patients undergoing pancreatic surgery, the criteria for resectability has gradually expanded. Extended pancreaticoduodenectomy with vascular resection has been offered in various institutions to treat patients with tumors that has involved or invaded the adjacent blood vessels. This would represent a large number of patients as the siting of the pancreas and its relationship with the adjacent critical blood vessels make these structures a common site of tumor involvement through direct invasion. Performing vascular resection during pancreaticoduodenectomy would often be the goal of a surgeon who seeks to attempt a total resection. With now established safety, it appears that such a procedure may be considered given the grim outlook of patients with unresectable tumors even after treatment. It is unlikely that the conduct of a randomized trial to determine if extended pancreaticoduodenectomy with vascular resection versus a comparator group such as a standard pancreaticoduodenectomy with adjuvant chemoradiation to treat the remnant tumor burden or a treatment of chemoradiation alone would be feasible given the known prognosis of incomplete resections. Therefore, a systematic review that critically examines the important aspects of this procedure, namely the safety, survival outcomes in relation to the resection of involved vessels in the context of expert centers, would be invaluable in achieving consensus and acceptance of this procedure.

Results from this review show that vascular resection is commonly performed in patients with venous only involvement. The median mortality rate of 4% of extended pancreaticoduodenectomy with vascular resection, the similar rates of postoperative complications that occur, and a median average length of hospital stay of 17 days suggest that the

Table 4 Survival Outcomes After Extended Pancreaticoduodenectomy with Vascular Resection and Reconstruction

First author	R0 resection (%)	R1 resection (%)	Median survival (months)	1-Year survival rate (%)	3-Year survival rate (%)	5-Year survival rate (%)
Kaneoka [19]	76	24	VR=12	NR	NR	17
Martin [22]	78	22	VAR=18	58	8	0
Muller [23]	49	49	VR=15	55	14	NR
Yekebas [31]	88	12	VAR≈20	72	35	20
Illuminati [18]	100	0	VR=19	76	17	17
Stitzenberg [37]	50	50	VAR=17	83	17	0
Wang [30]	NR	NR	VR=13	VR=56	VR=19	VR=13
			AR=7	AR=16	AR=0	AR=0
Al-Hadad [13]	NR	NR	VR=10	48	20	NR
Riediger [25]	69	31	VR=22	62	21	12
Nakao [35]	NR	NR	VR=9	VR=40	VR=9	VR=4
			VAR=3	VAR=26	VAR=0	VAR=0
Carrere [16]	82	18	VR=15	63	22	18
Shimada [27]	62	38	VR=14	65	20	12
Jain [33]	100	0	VR=40[a]	NR	NR	18
Zhou [32]	84	16	VR=17	59	16	NR
Koniaris [20]	NR	NR	VR=16	NR	NR	NR
Li [21]	NR	NR	NR	NR	49	16
Poon [24]	92	8	VR=20	88	45	0
Tseng [28]	78	22	VR=23	86	33	25
Nakagohri [39]	76	24	VR=15	58	9	9
Capussotti [15]	NR	NR	NR	NR	NR	NR
Howard [17]	75	25	VR=13	83	NR	NR
Kawada [34]	36	64	VR=11	41	9	9
Bachellier [14]	62	38	VR=12	54	NR	NR
Shibata [26]	NR	NR	VR=6	31	13	9
Van Geenen [29]	47	53	VR=14	55	NR	NR
Launois [38]	14	86	VR=5	23	15	0
Harrison [40]	73	27	VR=13	55	22	10
Roder [36]	32	68	VR=9	28	0	0

VR vein resection, *AR* artery resection, *VAR* vein and artery resection

[a] Mean

perioperative outcome is similar to that of a standard pancreaticoduodenectomy. In 16 centers which were classified as high-volume centers where at least 20 pancreatectomy procedures were performed per annum, the median survival of patients undergoing extended pancreaticoduodenectomy with vascular resection was 15 months. These survival results when compared with their independent cohorts who underwent standard pancreaticoduodenectomy procedures were not different. Studies that analyzed prognostic factors showed that undergoing vascular resection was not associated with a poorer survival. A 75% chance of a clear margin (R0) rate after this radical procedure further supports the rationale of undertaking extended pancreaticoduodenectomy with vascular resection when total resection of a locally advanced tumor is achievable.

Pancreatic cancer involvement of key vessels on preoperative imaging may not necessarily imply vascular invasion of the tumor into macroscopic vessels. It is not easy to determine definitively based on imaging the texture of the tumor and its associated adherence. Intraoperatively, the involvement or encasement that is present may occur as part of a peritumoral inflammatory reaction of the peripancreatic stromal tissue that leads to fibrotic change that may mimic tumor.[42] However, even in instances when there is true tumor involvement after histopathological examination of the resected vessel, venous tumor infiltration was not identified to affect survival. This may lead to a proposal for a change in surgical approach in patients with venous involvement on preoperative imaging scans and when examined at laparotomy. An en bloc vascular resection after adequate mobilization of proximal

Table 5 Critical Analysis of Outcomes from High Volume Centres Performing Extended Pancreatectomy with Vascular Resection

First author	Comparison of median survival (months)		$p<0.05$ (Y/N)	Analysis of prognostic factors (PVR/PVR & P)	Prognostic factors for survival after extended pancreatectomy with vascular resection
	Vascular resection	No vascular resection			
Martin [22]	VAR=18	19	N	PVR	Adverse factors: lymph node positive disease, body and tail location of tumors, no adjuvant therapy
					No effect: venous tumor infiltration
Muller [23]	VR=15	NR	NR	PVR & P	Adverse factors: operating time >420 minutes, age >70, occurrence of postoperative complications
					No effect: venous tumor infiltration, tumor size, blood loss, lymph node status, lymph node ratio, neoadjuvant treatment, technique of reconstruction, preoperative CA 19-9, CEA, ASA
Yekebas [31]	VAR≈20	16	N	PVR	Adverse factors: lymph node positive disease, poorly differentiated tumors
					No effect: venous tumor infiltration, sex, age, tumor size, margin status
Illuminati [18]	VR=19	21	N	PVR	Adverse factors: nil
					No effect: tumor differentiation, lymph node status, retroperitoneal margin status, tumor location
Stitzenberg [37]	VAR=17	NR	NR	PVR	Adverse factors: neoadjuvant chemoradiation
					No effect: age, sex, lymph node status, preoperative CA 19-9, margin status, undergoing arterial resection
Wang [30]	VR=13 AR=7	NR	NR	NR	NR
Riediger [25]	VR=22	15	N	PVR & P	Adverse factors: R1 margin status, poorly differentiated tumors
					No effect: undertaking venous resection, venous tumor infiltration
Carrere [16]	VR=15	20	N	PVR & P	Adverse factors: R1 margin status, reoperation, tumor diameter >30 mm, lymph node positive disease, perioperative blood transfusion
					No effect: age, sex, ASA, preoperative CA 19-9, undertaking venous resection, age, sex, perineural invasion, neoplastic intravascular embolism, tumor grade, adjuvant therapy
				PVR	No effect: venous tumor infiltration, type of venous resection
Shimada [27]	VR=14	35	Y	PVR & P	Adverse factors: undertaking venous resection, CA 19-9>240, tumor size >35 mm, serosal invasion, duodenal invasion, portal vein invasion, extrapancreatic nerve plexus invasion, node positive disease, R1 margin status, intraoperative radiation therapy
					No effect: age, sex, retropancreatic tissue invasion, bile duct invasion, tumor grade, peritoneal cytology, adjuvant chemotherapy
				PVR	Adverse factors: CA 19-9>240, tumor size >35 mm
					No effect: venous tumor infiltration
Jain [33]	VR=40[a]	NR	NR	NR	NR
Zhou [32]	VR=17	NR	NR	PVR	Adverse factors: R1 margin status
					No effect: venous tumor infiltration
Tseng [28]	VR=23	27	N	PVR & P	Adverse factors: lymph node positive disease
					No effect: undertaking venous resection
				PVR	No effect: venous tumor infiltration

Bachellier [14]	VR=12	15	N	PVR & P	No effect: undertaking venous resection
				PVR	No effect: venous tumor infiltration
					Adverse factors: venous tumor infiltration
Van Geenen [29]	VR=14	NR	NR	PVR	No effect: margin status, type of venous resection
Harrison [40]	VR=13	17	N	PVR & P	No effect: undertaking venous resection
Roder [36]	VR=9	12	N	PVR & PPVR	No effect: undertaking venous resection

PVR & P pancreatectomy with vascular resection and pancreatectomy, *VAR* vein and artery resection, *VR* vein resection, *AR* artery resection

[a] Mean

and distal ends to facilitate an end to end or graft reconstruction may be performed instead of an attempted dissection along the superior mesenteric-portal vein that risk injuring the thin and friable venous intima.

Clearly, the key of a successful surgical treatment arises from appropriate patient selection that preoperatively determines the extent of venous or arterial involvement, nodal disease, and absence of distant metastatic sites together with a patient's overall performance status and fitness for surgery. The majority of studies (71%) performing vascular resections reported arterial involvement as a contraindication to surgery. However, in centers such as that reported by Martin et al.,[22] Yekebas et al.,[31] and Stitzenberg et al.,[37] with expertise in en bloc resection of the hepatic artery, superior mesenteric artery, or even the celiac trunk itself, this may be performed with equivalent survival outcomes with median survival of 18, 20, and 17 months reported, respectively. In contrast, less experienced centers who have undertaken this procedure have shown poorer outcomes following arterial resection than after venous only resection.[35]

Improved survival in pancreatic cancer has evolved from standard pancreatectomy to extended pancreatectomy in selected patients in the setting of an expert referral center through increasing the resectability rates in borderline resectable patients after careful selection and achieving high R0 resection rates. Vascular resection and reconstruction of the adjacent vein and in some highly selected instances, the arteries appear to be feasible, without compromising R0 resection rates, and allow for patients with "unresectable tumors" to undergo a curative procedure for a chance at having long term survival. Presently, further surgical advancement to resect pancreatic cancer in patients with nonlocalized disease is unlikely to be beneficial. To improve the survival from now, the search for an effective systemic chemotherapeutic agent and testing of these agents in trials of neoadjuvant and/or adjuvant therapy with radiotherapy as well as with immunotherapy is necessary to complement the oncological benefit achieved after a complete surgical resection.

References

1. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–277.
2. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of adjuvant therapy for pancreatic cancer. Br J Cancer 2009;101:908–915.
3. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC

gastrointestinal tract cancer cooperative group.[see comment]. Ann Surg 1999;230:776–782; discussion 782–774.
4. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncology 2005;23:3509–3516.
5. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol 2008;19:1592–1599.
6. Fortner JG. Regional resection of cancer of the pancreas: a new surgical approach. Surgery 1973;73:307–320.
7. Michalski CW, Kleeff J, Wente MN, et al. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007;94:265–273.
8. Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618–628; discussion 628–630.
9. House MG, Gonen M, Jarnagin WR, et al. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. J Gastroint Surg 2007;11:1549–1555.
10. Merchant NB, Rymer J, Koehler EAS, et al. Adjuvant chemoradiation therapy for pancreatic adenocarcinoma: who really benefits? J Am Coll Surg 2009;208:829–838; discussion 838–841.
11. Siriwardana HPP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer.[see comment]. Br J Surg 2006;93:662–673.
12. Ramacciato G, Mercantini P, Petrucciani N, Giaccaglia V, Nigri G, Ravaioli M, Cescon M, Cucchetti A, Del Gaudio M. Does portal-superior mesenteric vein invasion still indicate irresectability for pancreatic carcinoma? Ann Surg Oncol 2009;16(4):817–825
13. Al-Haddad M, Martin JK, Nguyen J, et al. Vascular resection and reconstruction for pancreatic malignancy: a single center survival study. J Gastrointest Surg 2007;11:1168–1174.
14. Bachellier P, Nakano H, Oussoultzoglou PD, et al. Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg 2001;182:120–129.
15. Capussotti L, Massucco P, Ribero D, et al. Extended lymphadenectomy and vein resection for pancreatic head cancer: outcomes and implications for therapy. Arch Surg 2003;138:1316–1322.
16. Carrere N, Sauvanet A, Goere D, et al. Pancreaticoduodenectomy with mesentericoportal vein resection for adenocarcinoma of the pancreatic head. World J Surg 2006;30:1526–1535.
17. Howard TJ, Villanustre N, Moore SA, et al. Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. J Gastrointest Surg 2003;7:1089–1095.
18. Illuminati G, Carboni F, Lorusso R, et al. Results of a pancreatectomy with a limited venous resection for pancreatic cancer. Surg Today 2008;38:517–523.
19. Kaneoka Y, Yamaguchi A, Isogai M. Portal or superior mesenteric vein resection for pancreatic head adenocarcinoma: prognostic value of the length of venous resection. Surgery 2009;145:417–425.
20. Koniaris LG, Staveley-O'Carroll KF, Zeh HJ, et al. Pancreaticoduodenectomy in the presence of superior mesenteric venous obstruction. J Gastrointest Surg 2005;9:915–921.
21. Li B, Chen FZ, Ge XH, et al. Pancreatoduodenectomy with vascular reconstruction in treating carcinoma of the pancreatic head. Hepatobiliary Pancreat Dis Int 2004;3:612–615.
22. Martin RCG 2nd, Scoggins CR, Egnatashvili V, et al. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. Arch Surg 2009;144:154–159.
23. Muller SA, Hartel M, Mehrabi A, et al. Vascular resection in pancreatic cancer surgery: survival determinants. J Gastrointest Surg 2009;13:784–792.
24. Poon RT, Fan ST, Lo CM, et al. Pancreaticoduodenectomy with En Bloc Portal Vein Resection for pancreatic carcinoma with suspected portal vein involvement. World J Surg 2004;28:602–608.
25. Riediger H, Makowiec F, Fischer E, et al. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. J Gastrointest Surg 2006;10:1106–1115.
26. Shibata C, Kobari M, Tsuchiya T, et al. Pancreatectomy combined with superior mesenteric-portal vein resection for adenocarcinoma in pancreas. World J Surg 2001;25:1002–1005.
27. Shimada K, Sano T, Sakamoto Y, Kosuge T. Clinical implications of combined portal vein resection as a palliative procedure in patients undergoing pancreaticoduodenectomy for pancreatic head carcinoma. Ann Surg Oncol 2006;13:1569–1578.
28. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004;8:935–949; discussion 949–950.
29. van Geenen RC, ten Kate FJ, de Wit LT, et al. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. Surgery 2001;129:158–163.
30. Wang C, Wu H, Xiong J, et al. Pancreaticoduodenectomy with vascular resection for local advanced pancreatic head cancer: a single center retrospective study. J Gastrointest Surg 2008;12:2183–2190.
31. Yekebas EF, Bogoevski D, Cataldegirmen G, et al. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 2008;247:300–309.
32. Zhou GW, Wu WD, Xiao WD, et al. Pancreatectomy combined with superior mesenteric-portal vein resection: report of 32 cases. Hepatobiliary Pancreat Dis Int 2005;4:130–134.
33. Jain S, Sacchi M, Vrachnos P, Lygidakis NJ. Carcinoma of the pancreas with portal vein involvement - our experience with a modified technique of resection. Hepatogastroenterology 2005;52:1596–1600.
34. Kawada M, Kondo S, Okushiba S, et al. Reevaluation of the indications for radical pancreatectomy to treat pancreatic carcinoma: is portal vein infiltration a contraindication? Surg Today 2002;32:598–601.
35. Nakao A, Takeda S, Inoue S, et al. Indications and techniques of extended resection for pancreatic cancer. World J Surg 2006;30:976–982; discussion 983–974.
36. Roder JD, Stein HJ, Siewert JR. Carcinoma of the periampullary region: who benefits from portal vein resection? Am J Surg 1996;171:170–174; discussion 174–175.
37. Stitzenberg KB, Watson JC, Roberts A, et al. Survival after pancreatectomy with major arterial resection and reconstruction. Ann Surg Oncol 2008;15:1399–1406.
38. Launois B, Stasik C, Bardaxoglou E, et al. Who benefits from portal vein resection during pancreaticoduodenectomy for pancreatic cancer? World J Surg 1999;23:926–929.
39. Nakagohri T, Kinoshita T, Konishi M, et al. Survival benefits of portal vein resection for pancreatic cancer. Am J Surg 2003;186:149–153.
40. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? Ann Surg 1996;224:342–347; discussion 347–349.
41. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244:10–15.
42. Wilentz RE, Hruban RH. Pathology of cancer of the pancreas. Surg Oncol Clin N Am 1998;7:43–65.

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REVIEW ARTICLE

Fundoplication After Laparoscopic Heller Myotomy for Esophageal Achalasia: What Type?

Marco G. Patti · Fernando A. Herbella

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Abstract Because of the high success rate of minimally invasive surgery, a radical shift in the treatment algorithm of esophageal achalasia has occurred. Today, a laparoscopic Heller myotomy is the preferred treatment modality for achalasia. This remarkable change is due to the recognition by gastroenterologists and patients that a laparoscopic Heller myotomy gives better and more durable results than pneumatic dilatation and intrasphincteric injection of botulinum toxin injection, while it is associated to a short hospital stay and a fast recovery time. While there is agreement about the need of a fundoplication in conjunction to the myotomy, some questions still remain about the type of fundoplication: Should the fundoplication be total or partial, and in case a partial fundoplication is chosen, should it be anterior or posterior? The following review describes the data present in the literature in order to identify the best procedure that can achieve prevention or control of gastroesophageal reflux after a myotomy without impairing esophageal emptying.

Keywords Esophageal achalasia · Laparoscopic Heller myotomy · Laparoscopic fundoplication

Esophageal achalasia is a primary esophageal motility disorder of unknown origin characterized by lack of esophageal peristalsis and inability of the lower esophageal sphincter (LES) to relax properly in response to swallowing. The goal of treatment is to relieve the functional obstruction caused by the LES, therefore allowing emptying of food into the stomach by gravity. A laparoscopic Heller myotomy is considered today the most effective and long-lasting treatment modality to achieve this goal (Table 1). However, a myotomy may cause reflux of gastric contents into the aperistaltic esophagus, with risk of developing complications such as strictures, Barrett's esophagus, and even adenocarcinoma.[11–14] While there is agreement about the need for a fundoplication in conjunction with the myotomy, there is no consensus about the type of fundoplication that should performed.

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The following review describes the data present in the literature in order to identify the best procedure that allows prevention or control of gastroesophageal reflux after a myotomy, without impairing esophageal emptying.

The Evolution of Minimally Invasive Surgery for Achalasia

In 1992, we described our initial experience with a thoracoscopic Heller myotomy.[15] We performed a left thoracoscopic myotomy (with the guidance of intraoperative endoscopy), which extended for only 5 mm onto the gastric wall. The rationale for the short myotomy was to relieve dysphagia while trying to avoid postoperative reflux. The long-term follow-up in the first 30 patients who underwent a left thoracoscopic Heller myotomy confirmed the excellent outcome of the initial report:[16] Almost 90% of patients had relief of dysphagia, the hospital stay was short, the postoperative discomfort was minimal, and the recovery was fast. However, some shortcomings of the thoracoscopic technique soon became apparent, particularly a very high incidence of postoperative reflux. We found, in fact, that a thoracoscopic myotomy was associated to reflux in 60% of patients studied postoperatively by pH monitoring. In

Table 1 Outcomes of Laparoscopic Heller Myotomy

Author/year	Type of study	Samples	Dysphagia relief (%)	Postoperative gastroesophageal reflux (%)	Follow-up	Note	Oxford Center for Evidence-Based Medicine Levels of Evidence
Meta-analysis							
Wang et al. 2009[1]	Meta-analysis	NR	82–84	NR	NR	LHM superior to pneumatic dilatation and botulinum toxin injection	1
Campos et al. 2009[2]	Meta-analysis	3,086	89	15	35 months	LHM superior to pneumatic dilatation and botulinum toxin injection	2
Studies with follow-up >10 years							
Cowgill et al. 2010[3]	Case series	47	92	NR	10.6 years	All patients over 10 years of follow-up	4
Jeansonne et al. 2007[4]	Case series	17	47	NR	11.2 years	All patients over 10 years of follow-up	4
Studies with follow-up >5 years							
Kilic et al. 2009[5]	Case series	46	80	NR	6.4 years	All patients over 5 years of follow-up	4
Studies with $n>100$							
Patti et al. 2001[6]	Case series	102	89	NR	25 months	Dor fundoplication	4
Zaninotto et al. 2008[7]	Case series	400	87	6	30 months	Dor fundoplication. 45% followed up >60 months	4
Wright et al. 2007[8]	Case series	115	90	19 (Dor)/50 (Toupet)	45 months	Dor or Toupet fundoplication	4
Khajanchee et al. 2005[9]	Case series	121	84	33	9 months	Toupet fundoplication	4
Perrone et al. 2004[10]	Case series	100	96	NR	26 months	Toupet fundoplication	4

NR not reported, *LHM* laparoscopic Heller myotomy

addition, we were unable to correct the reflux, which was already present in some patients secondary to pneumatic dilatation. Other centers also documented a high incidence of postoperative reflux after thoracoscopic myotomy.[17,18]

Other studies showed that a laparoscopic myotomy alone was also associated to a high incidence of reflux.[19,20] Kjellin and colleagues found abnormal reflux by pH monitoring in eight of 14 (57%) patients after laparoscopic myotomy without fundoplication.[19] Similarly, Burpee and colleagues documented reflux (by pH monitoring or endoscopy) in 18 of 30 patients (60%) after laparoscopic Heller myotomy without fundoplication.[20] The findings of these retrospective studies were confirmed by two prospective trials, which showed that a myotomy alone is associated to a high incidence of reflux, while a fundoplication decreased significantly this problem.[21,22] In 2003, Falkenback and colleagues reported the results of a prospective randomized trial comparing myotomy alone versus myotomy and Nissen fundoplication.[21] Postoperative reflux was present in 25% of patients who had a myotomy and fundoplication but in 100% of patients who had a myotomy alone. Twenty percent of the patients in the latter group developed Barrett's esophagus. In 2004, Richards and colleagues reported the results of a prospective randomized trial comparing laparoscopic myotomy alone versus laparoscopic myotomy and Dor fundoplication.[22] Postoperative ambulatory pH monitoring showed reflux in 48% of patients after myotomy alone but in only 9% of patients when a Dor fundoplication was added to the myotomy. The incidence and the score of postoperative dysphagia were similar in the two groups, suggesting that the addition of a partial fundoplication did not impair esophageal emptying (Table 2).

Which Fundoplication? Partial Versus Total Fundoplication

It has been shown that a laparoscopic total (360°) fundoplication is the procedure of choice in patients with

Table 2 Outcome of Laparoscopic Heller Myotomy Alone or Laparoscopic Heller Myotomy and Fundoplication

Author/year	Type of study	Samples	Dysphagia relief (%)	Postoperative gastroesophageal reflux (%)	Follow-up	Note	Oxford Center for Evidence-Based Medicine Levels of Evidence
Campos et al. 2009[2] LHM	Meta-analysis	579	90	31	NR		2
LHMF		2,507	90	9			
Richards et al. 2004[22] LHM	RCT	21	NR	48	6 months		1
LHMF		22	NR	9		Dor fundoplication	
Falkenback, et al. 2003[21] LHM	RCT	10	70	13	8 years		1
LHMF		10	70	0.1		Nissen fundoplication	

NR not reported, *RCT* randomized clinical trial, *LHM* laparoscopic Heller myotomy, *LHMF* laparoscopic Heller myotomy+fundoplication

gastroesophageal reflux disease. When compared to a partial fundoplication, a total fundoplication determines a better control of reflux without a higher incidence of postoperative dysphagia, even when esophageal peristalsis is weak.[23] In esophageal achalasia, however, the pump action of the esophageal body is completely missed, as there is no peristalsis. Therefore, a total fundoplication might determine too much of a resistance at the level of the gastroesophageal junction, impeding the emptying of food from the esophagus into the stomach by gravity and eventually causing persistent or recurrent dysphagia. Albeit some groups still claim good results adding a total fundoplication after a myotomy[21,24,25] (Fig. 1), others have abandoned this procedure and switched to a partial fundoplication. This switch was based on the results of long-term studies that showed that esophageal decompensation and recurrence of symptoms eventually occur in most patients.[26–30] For instance, Duranceau and colleagues initially reported excellent results with a Heller myotomy and total fundoplication.[28] Ten years later, however, they noted that symptoms had recurred in 14 of 17 patients (82%), five of whom required a second operation.[29] They felt that a total fundoplication determines over time a progressive increase in esophageal retention with poor emptying and recurrence of symptoms. They were able to avoid this problem by performing a partial fundoplication.[30] These findings have been recently confirmed by a prospective and randomized trial comparing a Dor to Nissen fundoplication after Heller myotomy.[31] While the incidence of clinical or instrumental reflux was low and similar in the two groups, 15% of patients after Nissen fundoplication had dysphagia at a 5-year follow-up, as compared to only 2.8% after Dor fundoplication.

Based on this evidence, it is reasonable to state that a laparoscopic Heller myotomy with partial fundoplication should be considered today the procedure of choice for esophageal achalasia, as it attains the best balance between relief of dysphagia and prevention of reflux (Table 3).

Partial Fundoplication: Anterior Versus Posterior

There are no published prospective randomized trials comparing a partial posterior (Toupet, Fig. 2) versus an anterior (Dor, Fig. 3) fundoplication in association to a Heller myotomy in patients with achalasia. Some groups

Figure 1 Heller myotomy and Nissen (total) fundoplication.

Table 3 Swallowing Status and Incidence of Postoperative Reflux After Laparoscopic Heller Myotomy and Total Fundoplication and Laparoscopic Heller Myotomy and Partial Fundoplication

Author/year	Type of study	Samples	Dysphagia relief (%)	Postoperative GERD (%)	Follow-up	Note	Oxford Center for Evidence-Based Medicine Levels of Evidence
Rebecchi et al. 2008[31] LHMT	RCT	67	85	0	125 months		1
LHMP		71	97	3		Dor fundoplication	
Studies with LHMT							
Falkenback et al. 2003[21]	RCT	10	70	0.1	8 years		1
Frantzides et al. 2004[24]	Case series	48	92	2	3 years		4
Rossetti et al. 2005[25]	Case series	195	98	0	83 months		4
Donahue et al. 2002[27]	Case series						4
Studies with LHMP							
Patti et al. 2001[6]	Case series	102	89	NR	25 months	Dor fundoplication	4
Zaninotto et al. 2008[7]	Case series	400	87	6	30 months	Dor fundoplication. 45% followed up >60 months	4
Wright et al. 2007[8]	Case series	115	90	19 (Dor)/50 (Toupet)	45 months	Dor or Toupet fundoplication	4
Khajanchee et al. 2005[9]	Case series	121	84	33	9 months	Toupet fundoplication	4
Perrone et al. 2004[10]	Case series	100	96	NR	26 months	Toupet fundoplication	4

NR not reported, *RCT* randomized clinical trial, *LHMT* laparoscopic Heller myotomy+total fundoplication, *LHMP* laparoscopic Heller myotomy+partial fundoplication

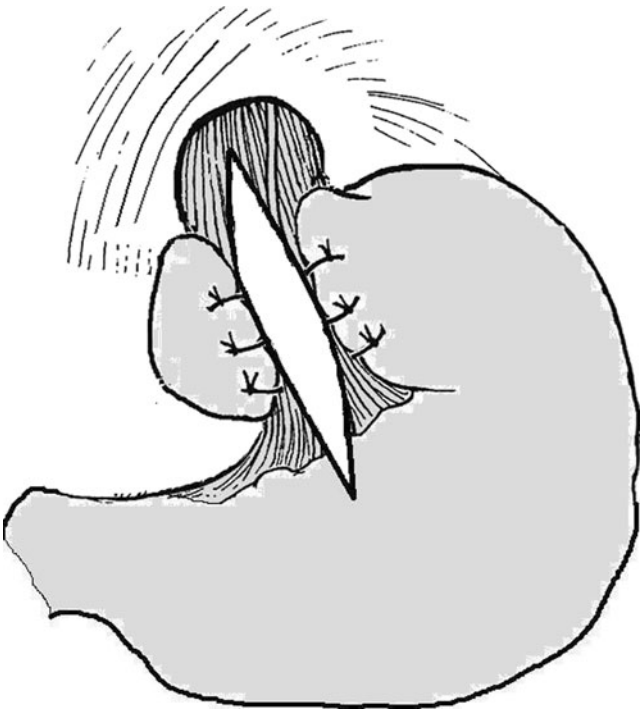

Figure 2 Heller myotomy and Toupet (partial anterior) fundoplication.

Figure 3 Heller myotomy and Dor (partial posterior) fundoplication.

Table 4 Swallowing Status and Incidence of Postoperative Reflux After Laparoscopic Heller Myotomy and Toupet and Laparoscopic Heller Myotomy and Dor Fundoplication

Author/year	Type of study	Samples	Dysphagia relief (%)	Postoperative gastroesophageal reflux (%)	Follow-up	Note	Oxford Center for Evidence-Based Medicine Levels of Evidence
Patti et al. 2001[6]	Case series	102	89	NR	25 months	Dor fundoplication	4
Zaninotto et al. 2008[7]	Case series	400	87	6	30 months	Dor fundoplication. 45% followed up >60 months	4
Wright et al. 2007[8]	Case series	115	90/90	19 (Dor)/50 (Toupet)	45 months	Dor or Toupet fundoplication	4
Khajanchee et al. 2005[9]	Case series	121	84	33	9 months	Toupet fundoplication	4
Perrone et al. 2004[10]	Case series	100	96	NR	26 months	Toupet fundoplication	4

feel that a posterior fundoplication is better procedure as it keeps the edges of the myotomy separated, and it may be a more effective antireflux operation.[32–34] Others, however, prefer a Dor fundoplication as it is simpler to perform (no need for posterior dissection), and it adds the advantage of covering the exposed mucosa[7,22,35–38] (Table 4).

SAGES is presently conducting a prospective, randomized, and multicenter study comparing laparoscopic Heller myotomy and Dor to laparoscopic Heller myotomy and Toupet fundoplication. The technique of the two procedures has been standardized.[9,39] The end point of the study will be the incidence of postoperative reflux as measured by pH monitoring and relief of dysphagia.

Our philosophy during the last 15 years has been to perform a laparoscopic Heller myotomy and Dor fundoplication.[39] The myotomy is about 9 cm in length and extends for about 2–2.5 cm onto the gastric wall. Intraoperative endoscopy is helpful at the beginning of a surgeon's experience to gauge the extent of the myotomy onto the gastric wall in respect to the squamous-columnar junction, as seen by endoscopy. However, once the surgeon has gained experience with the anatomy from a laparoscopic perspective, it can be omitted. After the short gastric vessels are divided, an anterior 180° fundoplication (Dor) is performed. There are two rows of sutures, one right and one left. The left row has three stitches: The first stitch incorporates the stomach, the esophagus, and the left pillar of the crus. The second and the third stitch incorporate only the stomach and the esophageal wall. Subsequently, the fundus is folded over the exposed mucosa, so that the greater curvature of the stomach is next to right pillar of the crus. Similar to the left the row, the right row has three stitches, placed between the fundus of the stomach and the right pillar of the crus. Finally, two or three additional stitches are placed between the superior aspect of the fundoplication and the anterior rim of the esophageal hiatus (Fig. 3).

Conclusions

The last decade has witnessed a radical change in the treatment of esophageal achalasia due to the adoption of minimally invasive techniques. Because of the high success rate of a laparoscopic Heller, surgery has in fact become the preferred treatment modality of most gastroenterologists and other referring physicians. During the last 5 years, we have noted a 15-fold increase in the number of patients referred for surgery every year. In addition, the gradual increase in the number of referred patients has been paralleled by an increase in the number of patients referred without previous treatment.[40] This remarkable change has followed documentation that laparoscopic myotomy outperforms balloon dilatation and botulinum toxin injection.[41,42]

References

1. Wang L, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. Dig Dis Sci 2009;54 (11):2303–2311.
2. Campos GM, Vittinghoff E, Rabl C, Takata M, Gadenstätter M, Lin F, Ciovica R. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg 2009;249(1):45–57.
3. Cowgill SM, Villadolid D, Boyle R, Al-Saadi S, Ross S, Rosemurgy AS 2nd. Laparoscopic Heller myotomy for achalasia: results after 10 years. Surg Endosc. 2009;24: 2644–2649.
4. Jeansonne LO, White BC, Pilger KE, Shane MD, Zagorski S, Davis SS, Hunter JG, Lin E, Smith CD. Ten-year follow-up of laparoscopic Heller myotomy for achalasia shows durability. Surg Endosc 2007;21(9):1498–1502.

5. Kilic A, Schuchert MJ, Pennathur A, Gilbert S, Landreneau RJ, Luketich JD. Long-term outcomes of laparoscopic Heller myotomy for achalasia. Surgery 2009;146(4):826–831.
6. Patti MG, Molena D, Fisichella PM, Whang K, Yamada H, Perretta S, Way LW. Laparoscopic Heller myotomy and Dor fundoplication for achalasia: analysis of successes and failures. Arch Surg 2001;136(8):870–877.
7. Zaninotto G, Costantini M, Rizzetto C et al. Four hundred laparoscopic myotomies for esophageal achalasia: a single center experience. Ann Surg 2008;248:986–993.
8. Wright AS, Williams CW, Pellegrini CA, Oelschlager BK. Long-term outcomes confirm the superior efficacy of extended Heller myotomy with Toupet fundoplication for achalasia. Surg Endosc 2007;21(5):713–718.
9. Khajanchee YS, Kanneganti S, Leatherwood AE, Hansen PD, Swanström LL. Laparoscopic Heller myotomy with Toupet fundoplication: outcomes predictors in 121 consecutive patients. Arch Surg 2005;140(9):827–833. discussion 833-834.
10. Perrone JM, Frisella MM, Desai KM, Soper NJ. Results of laparoscopic Heller-Toupet operation for achalasia. Surg Endosc 2004;18(11):1565–1571.
11. Ellis FH, Jr, Crozier RE, Gibb SP. Reoperative achalasia surgery. J Thorac Cardiovasc Surg 1986;92:859–865.
12. Ellis FH Jr. Oesophagomyotomy for achalasia: a 22-year experience. Br J Surg 1993;80:882–885.
13. Malthaner RA, Todd TR, Miller L, Pearson FG. Long-term results in surgically managed esophageal achalasia. Ann Thorac Surg 1994;58:1343–1347.
14. Devaney EJ, Iannettoni MD, Orringer MB, Marshall B. Esophagectomy for achalasia: patient selection and clinical experience. Ann Thorac Surg 2001;72:854–858.
15. Pellegrini CA, Wetter LA, Patti MG et al. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. Ann Surg 1992;216:291–296.
16. Patti MG, Arcerito M, De Pinto M et al. Comparison of thoracoscopic and laparoscopic Heller myotomy for achalasia. J Gastrointest Surg 1998;2:561-566.
17. Lindenmann J, Maier A, Eherer A et al. The incidence of gastroesophageal reflux after transthoracic esophagocardiomyotomy without fundoplication: a long term follow-up. Eur J Cardiothorac Surg 2005;27:357–360.
18. Stewart KC, Finley RJ, Clifton JC et al. Thoracoscopic versus laparoscopic modified Heller myotomy for achalasia: efficacy and safety in 87 patients. J Am Coll Surg 1999;189:164–170.
19. Kjellin AP, Granqvist S, Ramel S, Thor KBA. Laparoscopic myotomy without fundoplication in patients with achalasia. Eur J Surg 1999;165:1162–1166.
20. Burpee SE, Mamazza J, Schlachta CM et al. Objective analysis of gastroesophageal reflux after laparoscopic Heller myotomy: an anti-reflux procedure is required. Surg Endosc 2005;19:9–14.
21. Falkenback D, Johansson J, Oberg S et al. Heller's esophagomyotomy with or without a 360 degrees floppy Nissen fundoplication for achalasia. Long-term results from a prospective randomized study. Dis Esophagus 2003;16:284–290.
22. Richards WO, Torquati A, Holzman MD et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg 2004;240:405–412.
23. Patti MG, Robinson T, Galvani C et al. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004;198:863–869.
24. Frantzides CT, Moore RE, Carlson MA et al. Minimally invasive surgery for achalasia: a 10-year experience. J Gastrointest Surg 2004;8:18–23.
25. Rossetti G, Brusciano L, Amato G et al. A total fundoplication is not an obstacle to esophageal emptying after Heller myotomy for achalasia: results of a long-term follow up. Ann Surg 2005;241:614–621.
26. Donahue PE, Schlesinger PK, Sluss KF et al. Esophagocardiomyotomy-floppy Nissen fundoplication effectively treats achalasia without causing esophageal obstruction. Surgery 1994;116:719–724.
27. Donahue PE, Horgan S, Liu KJ, Madura JA. Floppy Dor fundoplication after esophagocardiomyotomy for achalasia. Surgery 2002;132:716–722.
28. Duranceau A, LaFontaine ER, Vallieres B. Effects of total fundoplication on function of the esophagus after myotomy for achalasia. Am J Surg 1982;143:22–28.
29. Topart P, Deschamps C, Taillefer R, Duranceau A. Long-term effect of total fundoplication on the myotomized esophagus. Ann Thorac Surg 1992;54:1046–1051.
30. Chen LQ, Chugtai T, Sideris L et al. Long-term effects of myotomy and partial fundoplication for esophageal achalasia. Dis Esophagus 2002;15:171–179.
31. Rebecchi F, Giaccone C, FArinella E et al. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia. Ann Surg 2008;248:1023–1030
32. Hunter JG, Trus TL, Branum GD, Waring JP. Laparoscopic Heller myotomy and fundoplication for achalasia. Ann Surg 1997;225:655–664.
33. Vogt D, Curet M, Pitcher D et al. Successful treatment of esophageal achalasia with laparoscopic Heller myotomy and Toupet fundoplication. Am J Surg 1997;174:709–714.
34. Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. Arch Surg 2003;138:490–495.
35. Yamamura MS, Gilster JC, Myers BS et al. Laparoscopic Heller myotomy and anterior fundoplication for achalasia results in a high degree of patient satisfaction. Arch Surg 2000;135:902–906.
36. Finley RJ, Clifton JC, Stewart KC et al. Laparoscopic Heller myotomy improves esophageal emptying and the symptoms of achalasia. Arch Surg 2001;136:892–896.
37. Ackroyd R, Watson DI, Devitt PG, Jamieson GG. Laparoscopic cardiomyotomy and anterior partial fundoplication for achalasia. Surg Endosc 2001;15:683–686.
38. Chapman JR, Joehl RJ, Murayama KM, et al. Achalasia treatment: improved outcome of laparoscopic myotomy with operative manometry. Arch Surg 2004;139:508–513.
39. Patti MG. Minimally invasive esophageal procedures. Chapter 35, pages 378–392, in ACS Surgery. Principles and Practice, 6th Edition, 2005.
40. Patti MG, Fisichella PM, Perretta S et al. Impact of minimally invasive surgery on the treatment of esophageal achalasia. A decade of change. J Am Coll Surg 2003;196:698–703.
41. Eckardt VF, Gockel I, Bernhard G. Pneumatic dilation for achalasia: late results of a prospective follow up investigation. Gut 2004;53:629–633.
42. Zaninotto G, Annese V, Costantini M et al. Randomized controlled trial of botulinum toxin versus laparoscopic Heller myotomy for esophageal achalasia. Ann Surg 2004;239:364–370.

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GI IMAGE

Cystic Lymphangioma of the Mesocolon

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Abstract A 46-year-old gentleman presented to our hospital with a short story of abdominal pain and distension. On examination, gross ascites was noted and confirmed on subsequent imaging with no other notable features. CT scan after ascitic drainage showed a cystic mass extending from the lower pole of the spleen to the left iliac fossa in keeping with an intraperitoneal cyst. At laparatomy, a cystic lymphangioma was resected. Lymphangiomas are rare benign tumours and are reported to occur preferentially in the neck of axilla in children. Abdominal lymphangiomas are extremely rare particularly in adults but important to recognise due to a potential for serious consequences.

Keywords Cystic · Lymphangioma · Abdomen · Distension

A 46-year-old gentleman presented to our hospital with a 2-week history of abdominal pain and distension associated with dark coloured urine, pale stools and a reduced appetite.

His past medical history was unremarkable, there was no recent history of foreign travel and he had no lifestyle or behavioural risk factors for chronic liver disease.

On examination, he was febrile (temperature 38.9 C) but haemodynamically stable with bilateral pitting oedema up to the knees. The abdomen was distended with dullness on percussion suggesting ascites and digital rectal examination was normal.

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Blood tests revealed a mild leucocytosis, ALT at 41, alkaline phosphatase 302, albumin 23 and CRP elevated at 317. Blood cultures and aetiological liver screen were negative. A chest radiograph was normal. Ascitic fluid showed no organisms but 982/mm^3 polymorphs and 614/mm^3 lymphocytes.

He was treated with broad spectrum intravenous antibiotics and underwent an abdominal ultrasound scan, thoraco-abdominal CT and ascitic fluid drainage followed by a further abdominal CT.

Abdominal ultrasound (Fig. 1) with Dopplers showed gross septate ascites but no other diagnostic features abdomino-pelvic computed tomography (CT; Fig. 2) showed gross ascites but no other significant abnormalities. CT scan after drainage of ascites (Fig. 3) showed a mesenteric cystic mass (20×10 cm) extending from the lower pole of the spleen to the left iliac fossa in keeping with an intraperitoneal cyst.

At laparotomy a cystic lymphangioma as described above (Fig. 4) was resected. The patient made an uneventful recovery.

Lymphangiomas are uncommon, occurring typically in children and most frequently reported in the neck or axilla.[1] Intra-abdominal lymphangiomas comprise less than 1% of all lymphangiomas,[2] the most common location being the mesentery of the small bowel.[3]

They probably occur as a result of a congenital abnormality of the lymphatic system causing sequestration of lymphatic tissue during embryological development.[2]

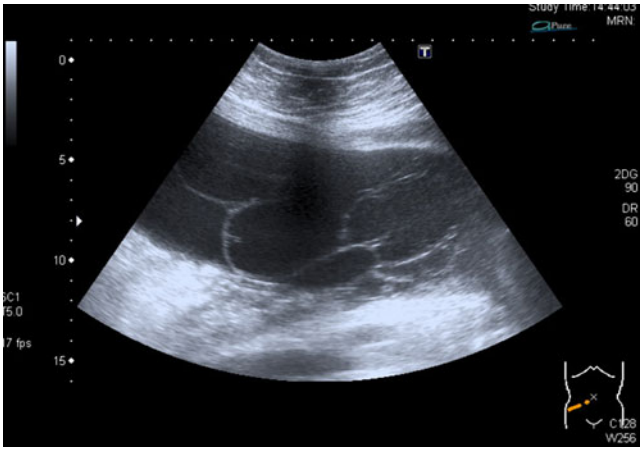

Fig. 1 Abdominal ultrasound with Dopplers at initial presentation.

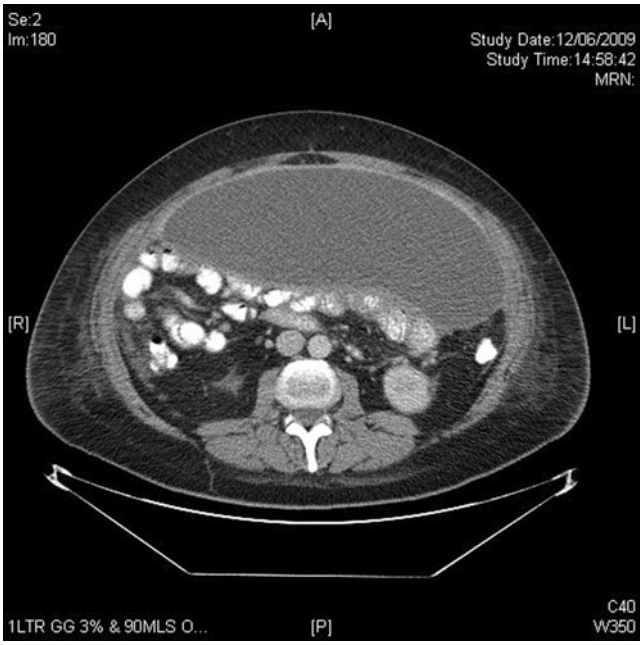

Fig. 3 CT scan after drainage of ascites.

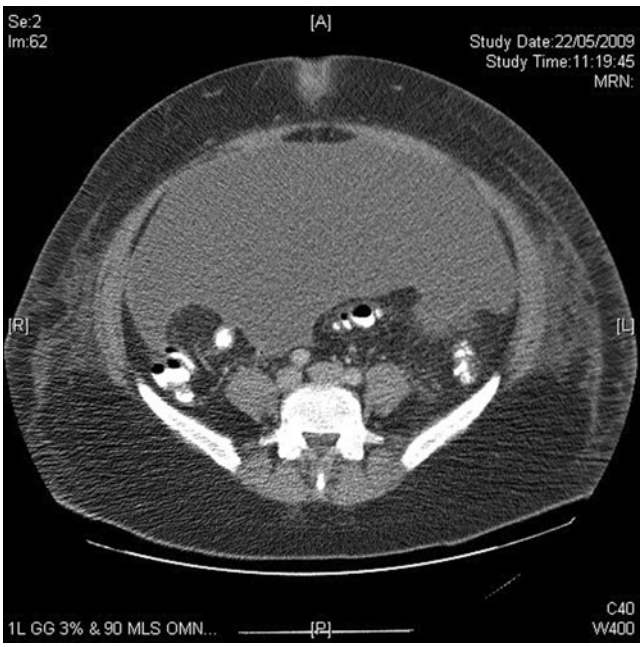

Fig. 2 Abdomino-pelvic computed tomography at initial presentation.

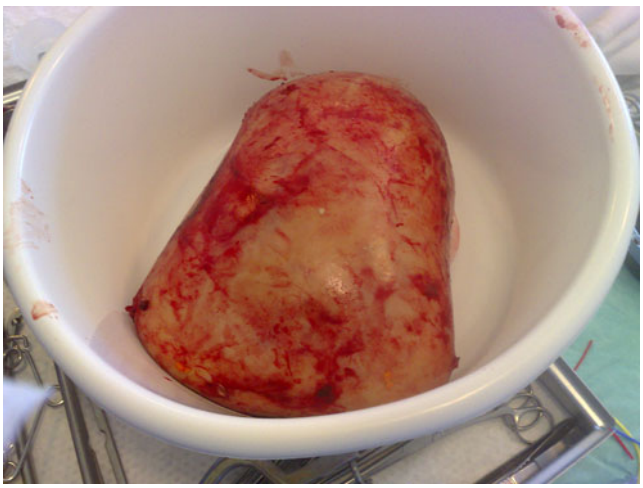

Fig. 4 A cystic lymphangioma as described above.

Abdominal trauma, inflammatory processes, lymphatic obstruction, radiation, or surgery can lead to the secondary formation of such a tumour.[4]

They are classified as simple, cavernous and cystic.[4]

Although usually asymptomatic, complications such as abdominal pain with distension, infection, haemorrhage and obstruction can occur[5] with significant morbidity or mortality due to compression of adjacent structures. Surgical resection is the treatment of choice.[5]

Mesenteric lymphangiomas should be considered in the differential diagnosis of cystic retroperitoneal masses and acute abdominal pain.

References

1. Hanagiri T, Baba M, Shimabukuro T, et al. Lymphangioma in the small intestine: report of a case and review of the Japanese literature. Surg Today 1992;22(4):363–367.
2. Roisman I, Manny J, Fields S, et al. Intra-abdominal lymphangioma. Br J Surg 1989;76 (5):485–489.
3. Chin S, Kikuyama S, Hashimoto T, et al. Lymphangioma of the jejunal mesentery in an adult: a case report and a review of the Japanese literature. Keio J Med 1993;42(1):41–43.
4. Chen CW, Hsu SD, et al. Cystic lymphangioma of the jejunal mesentery in an adult: a case report. World J Gastroenterol 2005;11(32):5084–5086.
5. Ha TK, Paik SS, Lee KG. Cystic lymphangioma arising from mesocolon. Clin Gastroenterol Hepatol 2009;7(3):e14–e15.

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GI IMAGE

A Bifid Neck of the Pancreas

Chad G. Ball · Christian Max Schmidt · Keith D. Lillemoe

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Abstract A 68 year-old male with a bifid pancreatic neck is described in the context of a common head during pancreatoduodenectomy.

Keywords Bifid pancreas · IPMN · Steatorrhea

A 68-year-old male was referred to our center with a recent history of weight loss (15 lb) and pancreatic insufficiency (steatorrhea). He also disclosed remote alcohol induced pancreatitis and lymphoma treated with chemotherapy. Computed tomography and magnetic resonance cholangiopancreatography revealed a 10-cm cystic structure in the head of his pancreas and a bifid pancreatic duct (Fig. 1). Subsequent endoscopic ultrasound identified both thick septi and a large soft tissue component within the cyst. The pancreatic duct was also dilated (1 cm) in the neck, body, and tail of the gland. The working diagnosis was a mixed type intraductal papillary mucinous neoplasm with possible malignant transformation.

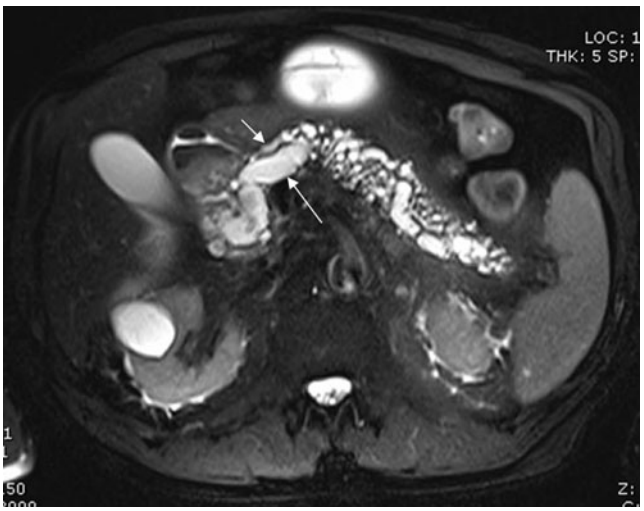

Fig. 1 Magnetic resonance cholangiopancreatography displaying a bifid pancreatic duct.

Subsequent operative exploration and pancreatoduodenectomy identified a concurrent bifid neck of the pancreas (Fig. 2). Bifid ductal anatomy was confirmed via intraoperative probing and direct visualization. A standard duct-to-mucosa pancreaticojejunostomy was employed to restore entero-pancreatic continuity. This was made possible by resection of the smaller cephalad pancreatic neck and direct suture closure of the associated ductal orifice. Microscopic examination of this specimen

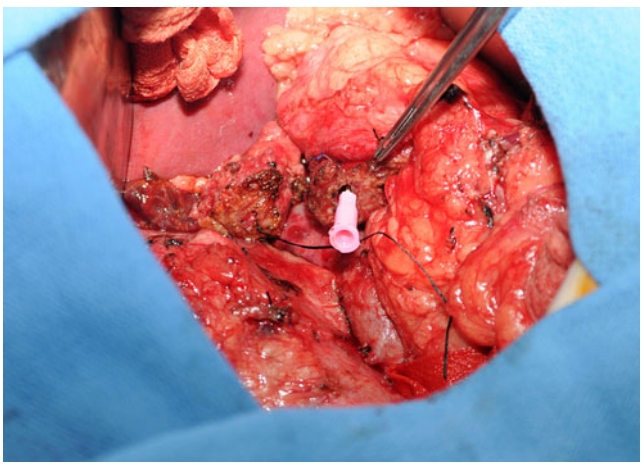

Fig. 2 Bifid neck of the pancreas. *Pink* angiocatheter in the main pancreatic duct. *Silk stitch* in the bifid pancreatic duct.

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also confirmed the presence of both pancreatic and ductal tissue.

Although a bifid pancreas is rare, glandular developmental abnormalities are not uncommon. These include pancreas divisum, annular pancreas, pancreatic hypoplasia, and aberrant pancreas. Furthermore, although descriptions of bifid tails of pancreas, as well as bifid pancreatic ducts within a unified gland have been previously reported,[1–3] this report is the first description of a bifid pancreatic duct in the context of distinct and separate pancreatic necks with a common head.

References

1. Tajima Y, Adachi T, Kuroki T, Tsuneoka N, Mishima T, Kosaka T, Kanematsu T. Intraductal papillary mucinous neoplasm of the pancreas with a bifid pancreatic duct. J Hepatobiliary Pancreat Surg 2009;16:865–868.
2. Dinter D, Lohr JM, Neff KW. Bifid tail of the pancreas: benign bifurcation anomaly. AJR Am J Roentgenol 2007;189:W251–W253.
3. Kikuchi K, Nomiyama T, Miwa M, Harasawa S, Miwa T. Bifid tail of the pancreas: a case presenting as a gastric submucosal tumor. Am J Gastrtoenterol 1983;78:23–27.

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LETTER TO THE EDITOR

Are We Moving Towards a New Era in Minimally Invasive Thoracic Surgery?

Jalal Assouad · Dominique Grunenwald

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We read with big interest the paper by Swanstrom et al.[1] in which authors described the use of a flexible endoscope in oesophageal surgery through a cervical incision.

Swanstrom et al. demonstrated here the feasibility of oesophageal mobilisation and dissection in a para-oesophageal plane using a flexible endoscope through a small cervical incision. Authors emphasised the inescapable help provided by positive pressure CO_2 mediastinoscopy in the creation and dissection of tissue planes in the mediastinum. They also mentioned a severe cardiopulmonary derangement in one animal due to mediastinum high pressure.

The para-oesophageal plan is located in the same anatomical space than the para-tracheal plane which is bordered by the mediastinal pleura. The creation of a communication between the para-tracheal space and the pleural cavity through the mediastinal pleura (pleurotomy) offers a good access to pleural cavities through a cervical incision.[2,3]

Our questions to doctor Swanstrom are the following: before the step of oesophageal dissection using gas inflation, do you think that the creation of a communication between the latero-tracheal space and the pleura using classical mediastinoscopic instruments, which did not necessitate any gas inflation, could offer a better control of the mediastinal inflation pressure during the following oesophageal dissection? And do you think that this communication helped by a simple intercostal needle to evacuate supplementary pressure could diminish the cardiopulmonary derangement due to mediastinal inflation?

The creation of a communication between the mediastinum and pleural cavity through a cervical incision has already been described using classical thoracoscopic tools.[2,3] Unfortunately, the rigidity of classical instruments did not allow a large exploration of the pleural cavity.

Using flexible endoscope property through validated and classical cervical access (mediastinoscopy) seems to be more adapted for thoracic specificities and could avoid major mediastinal complications than in N.O.T.E.S. approaches. In addition, it could afford large applications in the pleural cavity through single cervical incision.

More experimental studies are needed to assess the role of flexible endoscope in the exploration of the mediastinum and pleura through a cervical incision using a flexible endoscope.

References

1. Swanstrom, L L, Dunst CM, Spaun, GO (2010) Future applications of flexible endoscopy in esophageal surgery. J Gastroint Surg 14:127-32
2. Chamberlain MH, Fareed K, Nakas A, Martin-Ucar AE, Waller DA (2008) Video-assisted cervical thoracoscopy: a novel approach for diagnosis, staging and pleurodesis of malignant pleural mesothelioma. Eur J Cardiovasc Surg 34:200-3
3. Fowkes L, Lau KK, Shah N, Black E. A cervical approach to investigating pleural disease. Ann Thorac Surg 88:315-7.

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LETTER TO THE EDITOR

Response: Letter to Editor

Lee L. Swanstrom · Christy M. Dunst · Georg Spaun

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We would like to thank Doctors Assouad and Grunenwald for their kind response and comments on our paper "Future applications of flexible endoscopy in esophageal surgery".

They accurately point out that there is a rich history of innovation in mediastinoscopy that spans nearly a century. Unfortunately, most of these efforts used rigid instruments and optics which have always limited their application. Nonetheless, we, as do all innovators, function only by "standing on the shoulders of giants" who have gone before. We hope that the new generation of flexible endoscopes being developed will stimulate a renaissance in mediastinal surgery.

We did consider gasless standard approaches but felt that it would be difficult to achieve our goals of accessing the complete length of the mediastinum without both insufflation and flexible instrumentation. Unfortunately, our porcine animal model is uniquely sensitive to mediastinal or pleural space insufflation even with CO_2. As Dr. Assoud points out, simple needle decompression of the pleural space corrects the problem of capnothorax. If the mediastinal pleura is not violated, care must be taken to keep the insufflation pressures low (<8 mmHg). Fortunately, humans are much more resilient and easily tolerate both capnothorax and mediastinal insufflation.

We like the concept of transcervical thoracoscopy with flexible endoscopes that Drs. Assouad and Grunenwald propose and encourage them to pursue their ideas.

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LETTER TO THE EDITOR

High-Resolution and Conventional Manometry in the Assessment of the Lower Esophageal Sphincter Length

Fernando A. M. Herbella · Fernando P. P. Vicentine · Jose C. Del Grande

Received: 18 January 2010 / Accepted: 15 June 2010 / Published online: 1 July 2010

Dear Editor:

High-resolution manometry (HRM) is a revolutionary tool in the field of esophageal function tests. It is a valuable and incomparable instrument to assess the esophageal sphincters and segmental defects of esophageal body peristalsis due to a "panoramic" and simultaneous view from the pharynx to the stomach. Furthermore, it is quicker, more comfortable, and does not share some of the limitations of conventional manometry such as motion artifacts.

Ayazi et al.[1] from DeMeester group recently presented an elegant paper on the value of HRM in the assessment of the lower esophageal sphincter (LES) in comparison to the conventional manometry. The authors reported an overestimation of the LES length with HRM. The paper raises two questions: (1) Which manometry is better to evaluate LES length?; (2) How should HRM assess LES length?

When two methods are compared, the choice for which one should be considered the gold standard test may be sometimes difficult. Period of existence is not a guarantee that the older method is better. Ayazi et al.[1] concluded in their study that HRM is associated to errors in the evaluation of the borders of the LES leading to detriment of accuracy in LES assessment. As a new method, HRM should be interpreted with open mind and new eyes. Old concepts must not necessary be valid for its interpretation.

In regards to the evaluation of the borders of the LES and consequently of its length, motion artifacts must be carefully taken in consideration. It is known that LES is mobile with respiration (Fig. 1). This mobility is easily seen on HRM contours. It appears that the LES has a synchronous movement with the diaphragm, descending in average 0.85 cm during inspiration[2]. Two points can explain the overestimation of the LES found. First, the borders of the LES must be defined in a fixed point, ignoring the oscillation seem on the HRM contours. If the borders are defined by the distance between its maximum and minimum amplitude, the amplitude of movement will be counted twice, as noticed on Fig. 3 of the referred paper. Second, this very group from the University of Southern California has educated all of us that the LES is defined by a constant rise in baseline of at least 2 mmHg[3]. If we look at the area where the LES is intermittently present, a conventional manometry plot will not show a plateau of basal pressure expected for a sphincter, and it will not be incorporated in the calculation for the LES length (Fig. 2).

In regards to pH catheter placement, also a concern of the authors, we recommend the use of the upper border of the area where the LES is constantly present

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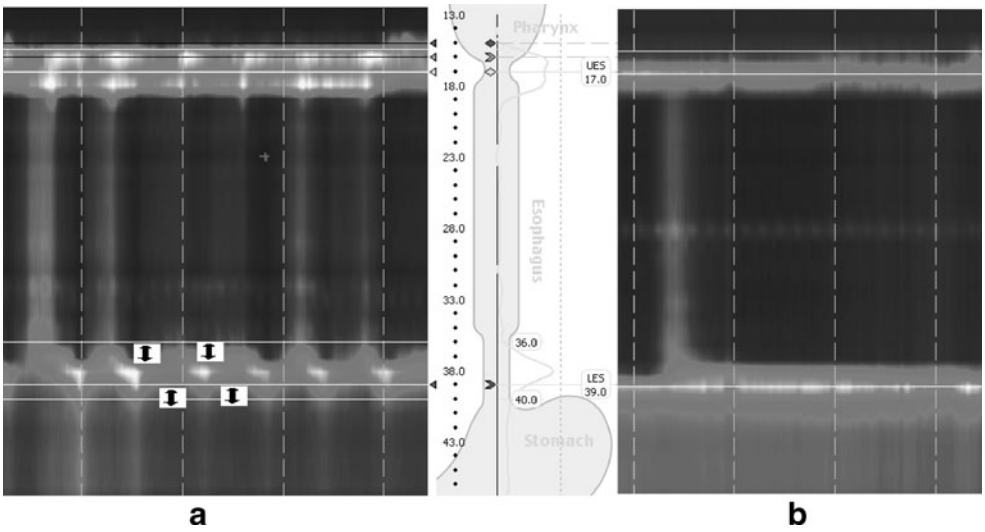

Fig. 1 Lower esophageal sphincter mobility. The sphincter excursionates 1 cm with calm breathing in this patient (**a**), but is immobile during apnea (**b**). This distance corresponds to the area where the sphincter is intermittently present both superiorly and inferiorly (*arrows*). This distance must be counted only once for the sphincter length calculation.

(Fig. 2). This point corresponds to the upper border of the LES according to conventional manometry. Thus, the reference for pH catheter placement created by this group and used for decades[4] will be kept and adapted to this new technology.

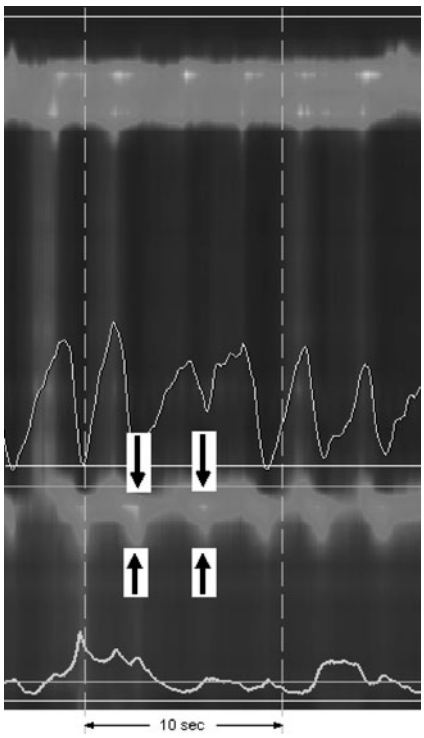

Fig. 2 High-resolution and conventional manometry view of the area where the lower esophageal sphincter is intermittently present due to its mobility; note the absence of a rise in baseline used for sphincter definition in conventional manometry. The *arrow* points to the spots to be considered the upper and lower borders of the sphincter.

In conclusion, HRM is probably the best method for the assessment of the LES, and the borders of the LES must be determined by the upper border of the area where the LES is constantly present to the lowest point of the high pressure zone.

References

1. Ayazi S, Hagen JA, Zehetner J, Ross O, Wu C, Oezcelik A, Abate E, Sohn HJ, Banki F, Lipham JC, Demeester SR, Demeester TR. The Value of High-Resolution Manometry in the Assessment of the Resting Characteristics of the Lower Esophageal Sphincter. J Gastrointest Surg. 2009 13: 2113–2120.
2. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol. 2006 May;290(5):G1033–G1040.
3. Bremner CG, DeMeester TR, Bremner RM, Mason RJ. Esophageal Motility Testing. Informa Healthcare, 2003.
4. Herbella FA, Nipominick I, Patti MG. From sponges to capsules. The history of esophageal pH monitoring. Dis Esophagus. 2009;22 (2):99–103.

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DOI 10.1007/s11605-010-1270-3

LETTER TO THE EDITOR

Re: High-Resolution Manometry and Lower Esophageal Sphincter Length

Shahin Ayazi · Jeffery A. Hagen · Joerg Zehetner · Steven R. DeMeester · John C. Lipham · Tom R. DeMeester

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Dear Editor,

We appreciate the interest in our manuscript[1] by Herbella and colleagues and thank them for their detailed questions. We share some of the authors' enthusiasm about high-resolution manometry (HRM). It is indeed faster to perform, more comfortable for the patient, and reduces some of the motion artifacts associated with conventional manometry. Further, the "panoramic" view of the pressure profile of the entire esophagus and its sphincters also has many advantages.[2] We do not however believe that the current body of literature on HRM is sufficient to declare this a revolution in the field of esophageal function testing. In particular, little data exist in regard to assessment of the lower esophageal sphincter (LES) resting characteristics.

We disagree with their implication that conventional manometry is not the gold standard. Time and experience in patients with esophageal disorders have shown that it is a reliable method to evaluate the LES. Until HRM was introduced, conventional manometry was not only the "gold standard" but the only standard for measuring resting characteristics of the LES. Herbella et al. are correct in suggesting that the "period of existence" of a test is not a guarantee that it is superior. Only the detailed analysis of new technology such as HRM and an evaluation of its clinical utility will determine if conventional manometry will be replaced.

Herbella and colleagues questioned the methods we used to measure LES length on HRM. Both explanations they provided for the overestimation of LES length that we observed appear to be based on a misunderstanding of the methods that we used to measure LES length. Their explanations imply that we included movement of the LES with respiration. We did not define the top of the LES as the highest point at end expiration on the landmark tracing as they have implied in Fig. 1 of their letter. Likewise, the bottom of the LES was not defined as the lowest point at end inspiration. Rather, to eliminate the effect of respiratory motion on LES lengths, all measurements were obtained at a fixed point in time at mid-respiration. This point was identified by a red vertical line in Figs. 1, 2, and 3 in the electronic version of our previously published manuscript (1), which unfortunately was not clearly evident on the black and white illustrations published in the journal. As a result, measurement errors related to motion of the LES with respiration was avoided in our study.

Herbella and colleagues specifically mentioned measurements made in the "pressure profile" mode illustrated in Fig. 3 of our manuscript. Confusion may have occurred because the upper and lower borders marked as horizontal dotted lines on the pressure profile appear to correspond visually to the highest and lowest points of the LES with respiration in the "spatiotemporal" plot on the left side of Fig. 3. This "spatiotemporal" plot was depicted only to indicate the point in time of mid-respiration that corresponds to the pressure profile shown on the right and was not used to measure LES length. Rather, the lower and upper borders of the LES were defined by the locations where the pressure profile tracing on the right rose above and dropped below the gastric baseline.

Accurate identification of the upper border of the LES is of significance with regard to positioning of the pH sensor given the clear relationship between the distance from the LES and the amount of acid measured.[3] As a result particular attention must be paid to this measurement. The

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standard methods for assessing the borders of the LES on conventional manometry specify that the upper border of the LES is defined as the point where the pressure tracing is constantly below the gastric baseline throughout the respiratory cycle. This does not correspond to the location indicated by the upper arrows in Fig. 2 from the letter of Herbella and colleagues. The end-inspiratory point indicated by their arrows corresponds to the point where the tracing is intermittently below the gastric baseline on conventional manometry. If the standard definition for the location of the upper border of the LES on conventional manometry is applied to HRM, the upper border of the LES would be at the top of the oscillation of the high pressure zone. Based on the work of Pandolfino et al., the LES moves an average of 0.85 cm with respiration, but this oscillation does not change the length of the LES; indeed, it remains identical.[4]

It remains to be determined whether HRM is equivalent to or better than conventional manometry in the evaluation of the resting characteristics of the LES. What can be said at this point is that the values obtained differ. In part these differences reflect the methods of determining lengths with the two techniques. Until definitions are standardized and published series are available that correlate the results of HRM with patient outcome as was done with conventional manometry,[5] it is impossible to conclude which test is superior.

References

1. Ayazi S, Hagen JA, Zehetner J, Ross O, Wu C, Oezcelik A, Abate E, Sohn HJ, Banki F, Lipham JC, Demeester SR, Demeester TR. The Value of High-Resolution Manometry in the Assessment of the Resting Characteristics of the Lower Esophageal Sphincter. J Gastrointest Surg. 2009 13: 2113-2120.
2. Ayazi S, Crookes PF. High-resolution esophageal manometry: using technical advances for clinical advantages. J Gastrointest Surg. 2010; 14 Suppl 1:S24-32.
3. Mekapati J, Knight LC, Maurer AH, et al. Transsphincteric pH Profile at the Gastroesophageal Junction. Clin Gastroenterol Hepatol 2008; 6(6): 630-634.
4. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol. 2006 May; 290(5):G1033-40.
5. Zaninotto G, DeMeester TR, Schwizer W, et al. The lower esophageal sphincter in health and disease. American Journal of Surgery 1988; 155(1):104-11.

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LETTER TO THE EDITOR

The Need of a Severity Scoring System for Postoperative Pancreatic Fistulas

Sergio Pedrazzoli · Alen Silvio Canton · Cosimo Sperti

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To the Editors:

Postoperative pancreatic fistulas (POPF) remain the major contributor to morbidity and mortality after pancreatic resection even in high volume centers.[1–3] We read with great interest the article by Fryerman et al[4] on the impact of grade C[5] POPFs on surgical outcome after pancreatic resections. The application of the International Study Group on Pancreatic Fistula (ISGPF) classification[5] to 483 patients who underwent pancreatic resection allowed the authors to confirm that the mortality due to POPF was confined to grade C POPFs (5/29). However, the authors stated that ISGPF classification is susceptible to bias in treatment selection due to its post hoc character, and does not provide a guideline for the timely treatment of POPF in an individual patient.

We recently reported a reoperation rate of 4.3% and a mortality rate of 0% for 70 POPFs diagnosed between 1993 and 2007.[6] We reviewed further 174 patients (83 pancreaticoduodenectomy, 53 distal pancreatectomy, nine central pancreatectomy, eight Frey procedures, six cystojejunostomy, six enucleation, five DPPHR, one triple derivative, one remaking pancreaticojejunostomy, one middle preserving pancreatectomy and one fistulogastrostomy) who underwent pancreatic surgery between September 1, 2007 and March 31, 2010. According to the ISGPF classification we registered 24 grade A, 13 grade B, and 21 grade C pancreatic fistulas for an overall fistula rate of 33.3% and a clinically significant (grade B and C) fistula rate of 19.5%. Two patients underwent reoperation for POPF, and one of them died of hemorrhagic shock. Another patient with a high output POPF died of septic shock 10 days after a central pancreatectomy. Therefore our overall reoperation and mortality rate for clinically significant POPFs was 4.8% (5/104) and 1.9% (2/104). These results compare favorably with the reoperation and mortality rate reported by Vin et al[1] (16.5% and 5%), Veillette et al[2] (6.7 and 9.3%), Fuks et al[3] (25.0% and 20.6%), and Frymerman et al[4] (31.2% and 6.5%). If these results are due to the aggressive treatment of the fistula track by our interventional radiologists or to other factors, it is impossible to be settled, due to the actual absence of a severity score during the early phase of a POPF. Frymerman et al[4] propose a high drain lipase activity on postoperative day 3, together with a soft pancreatic consistency, as predictors for the development of POPF grade C.

We propose that the definition of an early severity scoring system should be made by the ISGPF, to compare the different treatments of POPFs on the basis of their predicted severity and not on a post hoc basis.

In our experience,[6] one of the main factors responsible for the wide difference in outcome of patients with POPFs, was the fistula track, whose characteristics differ widely from patient to patient. In some the rapid walling off of the surgical drain(s) that, however, continue to drain the leak, allows the fistula track to evolve quickly in an almost straight communication between the pancreas and the skin, without stagnation of the pancreatic fluid. This pattern corresponds well to a grade A POPF. In some the walling off of the surgical drain(s) is incomplete, and the fistula track communicates with one or more collections that allow stagnation and, eventually infection of the pancreatic fluid. In some others, the walling off is too rapid and complete, preventing the pancreatic juice from being efficiently drained. An irregular fluid collection or a pancreatic abscess can develop, needing percutaneous drainage by an

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interventional radiologist. According to the severity of stagnation and/or infection we can have a grade B or a grade C POPF. Preventing stagnation and subsequent infection is therefore mandatory to prevent severe complications from a POPF. Inserting an appropriate drain through the fistula into the bowel's lumen, or as close to a disrupted pancreatic duct as possible,[6] and putting at least one catheter into every collection seen at fistulogram may help in preventing reoperation and death.

References

1. Vin Y, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan MF, Allen PJ. Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005.J Am Coll Surg 2008;207:490–498.
2. Veillette G, Dominguez I, Ferrone C, Thayer SP, McGrath D, Warshaw AL, Fernández-del Castillo C. Implications and management of pancreatic fistulas following pancreaticoduodenectomy: the Massachusetts General Hospital experience. Arch Surg. 2008;143:476–481.
3. Fuks D, Piessen G, Huet E, Tavernier M, Zerbib P, Michot F, Scotte M, Triboulet JP, Mariette C, Chiche L, Salame E, Segol P, Pruvot FR, Mauvais F, Roman H, Verhaeghe P, Regimbeau JM. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. Am J Surg. 2009;197:702–709.
4. Frymerman AS, Schuld J, Ziehen P, Kollmar O, Justinger C, Merai M, Richter S, Schilling MK, Moussavian MR. Impact of postoperative pancreatic fistula on surgical outcome–the need for a classification-driven risk management. J Gastrointest Surg 2010;14:711–718.
5. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.
6. Pedrazzoli S, Liessi G, Pasquali C, Ragazzi R, Berselli M, Sperti C. Postoperative pancreatic fistulas: preventing severe complications and reducing reoperation and mortality rate. Ann Surg. 2009;249:97–104.

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DOI 10.1007/s11605-010-1276-x

LETTER TO THE EDITOR

Comments of Prof. Pedrazzoli "Impact of Postoperative Pancreatic Fistula on Surgical Outcome—the Need for a Classification-Driven Risk Management"

Mohammed Reza Moussavian · Martin K. Schilling

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We appreciate the interest of Prof. Pedrazzoli in our work as well as his comments, which are largely in line with our understanding of the causes and the clinical course of postoperative pancreatic fistula after pancreatointestinal anastomosis.

In our experience, the correct placement of a drain posterior to the pancreatojejunal anastomosis leaving the abdominal cavity at the lowest point and running straight at the lower border of the pancreas hardly ever results in a fistula to the laparotomy especially in patients who had an orthotopic reconstruction and a closed retroperitoneum (Kollmar et al., submitted for publication). When we do see pancreatoincisional fistulas, it is due to a false placement of that drain.

We do agree that, in those cases, aggressive intervention is mandatory. Mortality in our experience, however, is largely confined to patients who had extensive vascular, mostly arterial reconstructions, and subsequently develop type C fistulas.

The fact that the current ISGPF classification is a post hoc classification does not reduce its importance; however, due to that characteristic, it does not help as an early postoperative treatment algorithm. We do agree with Pedrazzoli and his coworkers that an improved classification should be proposed by an international group of experts and that it should include early clinical or biochemical markers to aid in the treatment of pancreatic fistula.

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LETTER TO THE EDITOR

Needlescopic Splenectomy: A Safer Alternative to Single Incision Laparoscopic Splenectomy (SILS)

Michel Gagner

Received: 19 November 2009 / Accepted: 15 June 2010 / Published online: 2 July 2010

Sir,

I read with interest the article authored by Barbaros and Dinccag on "Single Incision Laparoscopic Splenectomy: The first two cases."[1] The authors claimed that current efforts aimed at reducing morbidity associated with minimally invasive surgery have been due to two "recent innovations" being developed, including transumbilical surgery with one very large port having three working channels, or three ports within the umbilicus, called single incision laparoscopic surgery (SILS).

The authors may have been unaware of the interim development of needlescopic surgery in the mid-90s, in which a major umbilical trocar of 12 mm is used for vision, stapling, clipping, energy sources, and extraction sites, whereas 2 mm or less instruments are used in the periphery (i.e., subcostal left for a splenectomy) for retraction.[2] A needlescopic endoscope was used when the umbilical channel was used for major work. This concept is the same as the transumbilical endoscopic surgery or SILS used in many recent publications, with the exception that additional needlescopic instruments used permits triangulation in surgical complex tasks, conferring a safer surgical dissection. Even in many publications of SILS nowadays, needlescopic instruments are often added to complement the surgical tasks. Indications for splenectomy of this type remain most likely in the domain of smaller spleens, benign disorders, and cysts. Splenic cysts can be marsupialized nicely with only a 12- or even 5-mm umbilical trocars with two or three (2–3 mm) trocars in the left subcostal area.[3]

My personal experience of needlescopic splenectomy, which started at the Cleveland Clinic in 1996, has demonstrated that in five cases (torsion, ITP, cyst, hereditary spherocystosis, and lymphoproliferative disorder), the mean operative time was 90 min compared to 186 min in 29 laparoscopic conventional splenectomies, the estimated blood loss had been reduced by a magnitude of fivefold, followed by a faster oral intake and shorter hospital stay (1.0 versus 5.5 days). The scar after needlescopic surgery is very negligible and non-existent after 12 months, achieving similar cosmetic results to SILS (even better if the umbilical scar in SILS has been extended in the periumbilical sphere).[4]

Further, I would argue that pain scores (no narcotics necessary!) maybe the same or better than SILS, due to higher trauma to the periumbilical area in single port surgery using diameters reaching >20 mm.[5] Finally, the long-term herniation risks in the periumbilical area will be exponential to the diameter of umbilical destruction (much higher in SILS) and will require a mesh repair at a later time. This mesh repair will, undoubtedly, prevent another SILS in the future.

References

1. Barbaros U, Dinccag A: Single Incision Laparoscopic Splenectomy: The first two cases. J Gastrointest Surg 2009; 1520–23
2. Gagner M, Garcia-Ruiz A: Technical Aspects of Minimally Invasive Abdominal Surgery Performed with Needlescopic Instruments. Surg Lap & Endosc, 1998;8(3):171–179.
3. Seshadri PA, Poulin EC, Mamazza J, Schlachta CM : Needlescopic decapsulation of a splenic epithelial cyst. Can J Surg. 2000 43 (4):303–5.
4. Mamazza J, Schlachta CM, Seshadri PA, Cadeddu MO, Poulin EC: Needlescopic surgery. A logical evolution from conventional laparoscopic surgery. Surg Endosc. 2001 15(10):1208–12.
5. Tagaya N, Rokkaku K, Kubota K: Splenectomy using a completely needlescopic procedure: report of three cases. J Laparoendosc Adv Surg Tech A. 2002; 12(3):213–6

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The authors were given the opportunity to respond to this Letter to the Editors, and declined.

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LETTER TO THE EDITOR

Revising the Atlanta Classification of Acute Pancreatitis: *Festina Lente*

Maxim S. Petrov

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To The Editor:

I read with interest the article by Dr. Harrison et al.[1] published in a recent issue of the *Journal*. The authors conducted an audit of all patients with pancreatic necrosis who underwent debridement over a 10-year period (1999–2008). While there is already a substantial file of retrospective studies on characteristics and outcomes of patients with acute pancreatitis after surgery,[2–4] the distinct feature of the study by Dr. Harrison and colleagues is that the proposed revision of the Atlanta classification[5] has been used to categorize the study outcomes. To the best of my knowledge, this is the first published study of its sort in the literature, and this deserves reflection.

The Atlanta classification of acute pancreatitis[6] has been serving the surgical and gastroenterological community well for nearly two decades. However, in recent years, its shortcomings became obvious, and a call for revision of the original Atlanta classification has been made.[7–9] One of the limitations is that the Atlanta classification is suboptimal in describing morphological changes in the (peri)pancreatic tissues that are seen on computed tomography (in fairness, it should be mentioned that the Atlanta classification was never meant to be used to interpret computed tomography scans).[10] This has been shown in the interobserver agreement study[11] in which five radiologists from The Netherlands categorized peripancreatic collections on computed tomography using the original Atlanta classification. The interobserver agreement among the radiologists was poor. As a consequence, a new set of morphologic terms was formulated and tested in another interobserver agreement study, which demonstrated a good interobserver agreement.[12] These two studies formed a basis for incorporation of the imaged-based classification in the revision of the Atlanta classification.

It is worth noting that, to date, the clinical and prognostic importance of the proposed imaged-based classification has never been evaluated. The study by Harrison et al.[1] is the first study that has done this. In a cohort of 73 patients who underwent debridement for pancreatic necrosis, the authors have found no significant association between the type of necrosis (according to the proposed revision of the Atlanta classification) and clinical outcomes (in-hospital mortality; infectious, pulmonary, renal, gastrointestinal, coagulopathic, and neurologic morbidity). In addition, it has been shown that the type of necrosis does not correlate with the type of operation performed. Certainly, these findings have to be interpreted with caution because of the possible limitations of the study, which include the retrospective nature of the investigation, relatively small sample size and somewhat simplistic approach to the statistical analysis (no attempt has been made to adjust for possible confounders). On the other hand, it cannot be ruled out that the imaged-based classification in the proposed form is of limited clinical importance and does not influence the surgical decision-making process.

There is no doubt that certain morphological characteristics of the pancreas and peripancreatic tissues are useful prognostic indicators of outcome in acute pancreatitis. Balthazar and colleagues were the first who demonstrated that pancreatic enlargement and (peri)pancreatic inflammation are associated with only 4% morbidity and 0% mortality as opposed to 54% morbidity and 14% mortality

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in patients with peripancreatic fluid collections and/or retroperitoneal air.[13] This was subsequently confirmed in a number of other studies.[14,15] Recently, Takeda et al. proposed a new computed tomography grading system for acute pancreatitis that assesses the degree of extrapancreatic progression of inflammation and the extent of the poorly enhanced area.[16] The authors found that the mortality rate was 0% in cases of grade 1, 14.3% in cases of grade 2, and 15.4% in cases of grade 3. The rate of complications also differed markedly between the groups (4.3% in cases of grade 1, 42.9% in cases of grade 2, and 46.2% in cases of grade 3).

There is also a good example of how new clinical (moderate and critical) categories of severity in acute pancreatitis have been justified. The justification for the moderate category of acute pancreatitis derived from the study by Vege et al. that demonstrated a significant difference in terms of the total length of hospital and ICU stay between the patients with and without local pancreatic complications in the absence of organ failure.[17] It was noted that the former patients required an average stay in ICU of 5 days and a total hospital stay of 28 days, which are longer than expected for patients with mild acute pancreatitis. The justification for the critical category of acute pancreatitis derived from the meta-analysis of 14 studies comprising 1,478 patients with acute pancreatitis.[18] It was found that patients with organ failure and infected pancreatic necrosis had a significantly higher risk of death in comparison with patients with organ failure and no infected pancreatic necrosis (relative risk 1.94; 95% confidence interval 1.32 to 2.85) and in comparison with patients with infected pancreatic necrosis and no organ failure (relative risk 2.65; 95% confidence interval 1.30 to 5.40). These have become a strong foundation for four severity categories of clinical classification of acute pancreatitis.[19]

To this end, though it may be tempting to ratify the proposed revision of the Atlanta classification as soon as possible, it appears that some of its aspects have to be supported by more solid evidence before wide-spread implementation into routine clinical practice. In particular, more studies are acutely needed to assess the clinical relevance of the proposed imaged-based classification and to establish how generalizable the new morphological terms are. Before that, it should be remembered what was said in ancient Rome: *Festina lente*!

References

1. Harrison S, Kakade M, Varadarajula S, Parden J, Morgan D, Christein J. Characteristics and outcomes of patients undergoing debridement of pancreatic necrosis. J Gastrointest Surg 2010;14:245–51.
2. Kingham TP, Shamamian P. Management and spectrum of complications in patients undergoing surgical debridement for pancreatic necrosis. Am Surg 2008;74:1050–1056.
3. Loveday BP, Mittal A, Phillips A, Windsor JA. Minimally invasive management of pancreatic abscess, pseudocyst, and necrosis: a systematic review of current guidelines. World J Surg 2008;32:2383–2394.
4. Navaneethan U, Vege SS, Chari ST, Baron TH. Minimally invasive techniques in pancreatic necrosis. Pancreas 2009;38:867–75.
5. Acute Pancreatitis Classification Working Group. Revision of the Atlanta classification of acute pancreatitis (3rd revision). www.pancreasclub.com/resources/AtlantaClassification.pdf Accessed February 01, 2010.
6. Bradley EL 3 rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993;128:586–90.
7. Vege SS, Chari ST. Organ failure as an indicator of severity of acute pancreatitis: time to revisit the Atlanta classification. Gastroenterology 2005;128:1133–1135.
8. Pandol SJ, Saluja AK, Imrie CW, Banks PA. Acute pancreatitis: bench to the bedside. Gastroenterology 2007;132:1127–1151.
9. Forsmark CE, Baillie J. AGA Institute Clinical Practice and Economics Committee, AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022–2044.
10. Bradley EL 3 rd. Confusion in the imaging ranks: time for a change? Pancreas 2006;33:321–322.
11. Besselink MG, van Santvoort HC, Bollen TL, van Leeuwen MS, Laméris JS, van der Jagt EJ, Strijk SP, Buskens E, Freeny PC, Gooszen HG. Describing computed tomography findings in acute necrotizing pancreatitis with the Atlanta classification: an interobserver agreement study. Pancreas 2006;33:331–335.
12. van Santvoort HC, Bollen TL, Besselink MG, Banks PA, Boermeester MA, van Eijck CH, Evans J, Freeny PC, Grenacher L, Hermans JJ, Horvath KD, Hough DM, Laméris JS, van Leeuwen MS, Mortele KJ, Neoptolemos JP, Sarr MG, Vege SS, Werner J, Gooszen HG. Describing peripancreatic collections in severe acute pancreatitis using morphologic terms: an international interobserver agreement study. Pancreatology 2008;8:593–599.
13. Balthazar EJ, Ranson JH, Naidich DP, Megibow AJ, Caccavale R, Cooper MM. Acute pancreatitis: prognostic value of CT. Radiology 1985;156:767–772.
14. Casas JD, Díaz R, Valderas G, Mariscal A, Cuadras P. Prognostic value of CT in the early assessment of patients with acute pancreatitis. AJR Am J Roentgenol 2004;182:569–574.
15. Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. Radiology 2002;223:603–613.
16. Takeda K, Yokoe M, Takada T, Kataoka K, Yoshida M, Gabata T, Hirota M, Mayumi T, Kadoya M, Yamanouchi E, Hattori T, Sekimoto M, Amano H, Wada K, Kimura Y, Kiriyama S, Arata S, Takeyama Y, Hirota M, Hirata K, Shimosegawa T. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. J Hepatobiliary Pancreat Surg 2009;17:37–44
17. Vege SS, Gardner TB, Chari ST et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include "moderately severe acute pancreatitis". Am J Gastroenterol 2009;104:710–715.
18. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010; Jun 8 [Epub ahead of print].
19. Petrov MS, Windsor JA. Classification of the severity of acute pancreatitis: how many categories make sense? Am J Gastroenterol 2010;105:74–76.

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LETTER TO THE EDITOR

Fertility Preservation for Young Women with Rectal Cancer—A Combined Approach from One Referral Center

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It was with great interest that we read the publication by Elizur et al.[1] regarding fertility preservation in young female patients with rectal and anal cancer. Five patients with rectal cancer and one with squamous cancer of the anal canal underwent combined fertility preservation techniques of laparoscopic ovarian transposition, ovarian tissue cryopreservation, and in vitro maturation and vitrification of oocytes and embryos, prior to adjuvant chemoradiation therapy. Of note, the fertility techniques employed were performed at a second operative procedure.

The authors are to be commended for utilizing a multidisciplinary approach in offering a solution to a problem (female fertility and colorectal cancer) for which very little data exist in the literature. However, we have two comments to make.

Firstly, we noted that one rectal cancer patient conceived spontaneously, leading to subsequent childbirth. This demonstrates that ovarian transposition alone was successful. Ovarian transposition can be performed synchronously with primary tumor resection,[2] thus sparing the patient a second operation. A valid question to the authors would be whether ovarian re-transposition (a third procedure) was required or performed in any of the patients.

Secondly, all patients underwent postoperative chemoradiation. In the current era, neo-adjuvant chemoradiation for advanced rectal cancer is advocated due to the advantage it provides in local control of the disease.[3] It would be interesting to find out if neo-adjuvant chemoradiation was an option for treatment of rectal cancer at the authors' institution, and if the patients in their series had any role in choosing the mode of therapy (adjuvant vs. neoadjuvant).

Young female patients with rectal cancer need to be informed about the effects of the disease and its treatment on fertility. There is very little data regarding the efficacy of current fertility preservation options in female patients with rectal cancer. Moreover, decisions regarding the choice of adjuvant therapy may be affected by the effects of therapy on fertility.[4] Nevertheless, Elizur et al. have made a very important contribution to the literature, and we await further results of their series of fertility preservation techniques in female rectal cancer patients with anticipation.

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References

1. Elizur SE, Tulandi T, Meterissian S, et al. Fertility preservation for young women with rectal cancer-a combined approach from one referral center. J Gastrointest Surg 2009;13:1111-1115
2. Spanos CP, Mamopoulos A, Tsapas A, et al. Female fertility and colorectal cancer. Int J Colorectal Dis 2008;23:735-743
3. Sauer R, Becker H, Hohenberger W, et al. German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740
4. Maltaris T, Boehm D, Dittrich R, et al. Reproduction beyond cancer: a message of hope for young women. Gynecol Oncol 2006; 103: 1109-1121