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On-table Endoscopy Following Laparoscopic Fundoplication

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Abstract
Background Laparoscopic fundoplication represents the gold standard in the surgical management of gastro-esophageal reflux disease (GERD). The achievement of long-lasting symptomatic and physiological control of reflux is the goal of therapy, as well as the minimization of troubling sequelae, in particular, dysphagia. On-table endoscopy after fundoplication was introduced in this Unit as a quality initiative in an attempt to minimize dysphagia and technical errors, and the aim of this study is to report the experience to date, and compare outcomes with the previous 100 cases performed by an experienced team.
Methods Eighty patients who underwent laparoscopic Rosetti-Nissen fundoplication and on-table endoscopy (group 2) were compared with 100 consecutive prior cases (group 1). Patients were prospectively evaluated and had pre- and postoperative symptom scoring and analysis of complications (all patients), and manometry and 24-h pH testing in 120 patients (60 in each group).
Results Both groups were similar with respect to demographics, esophagitis, pH score, and dysmotility. No bougie was used in either group. On-table endoscopy resulted in technical modifications in 4 (5%) patients. Early grade 2 or 3 dysphagia was evident in 4 (5%) patients in group 2, compared with 15 (15%) in group 1 ($p<0.001$). Late dysphagia was evident in one patient (1.5%) in group 2 compared with 7 (7%) in group 1 ($p<0.05$). Dilatation was performed in four patients (5%) in group 2, compared with 11 (11%) in group 1 ($p<0.05$).
Conclusions These data suggest that on-table endoscopy may be a useful quality assurance adjunct in laparoscopic anti-reflux surgery, in particular, reducing the incidence of dysphagia and reinterventions.

Keywords Fundoplication · Laparoscopy · Dysphagia

Introduction

The first fundoplication in man was performed by Rudolph Nissen in 1956.[1] The magnitude of the operative insult, the complication of gas-bloat relating to a long fundoplication, and the problem of persistent dysphagia resulted in poor acceptance among many, in particular, medical gastroenterologists. De Meester modified the open technique, and in a seminal paper in 1986 reported three modifications that were associated with excellent long-term control of reflux and a reduction of persistent dysphagia from 21% to 3%: a short wrap, reduced from 4 cm to 1–2 cm, division of the short gastric vessels, and use of a large esophageal bougie (60 Ch).[2] The short wrap principle helped simplify the laparoscopic approach, first reported in 1991,[3,4] and, despite the widespread availability of proton pump inhibitors, the years succeeding these reports has seen an enormous increase in anti-reflux surgery. The laparoscopic approach is well proven with respect to control of reflux, quality of life, short hospital stay, and cost savings, but the complication of dysphagia remains, and further technical improvements in the laparoscopic approach largely aim to minimize this risk. [5–8]

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In this tertiary Unit, the standard approach in the open and laparoscopic era has been the Rosetti modification of the Nissen fundoplication, with a short wrap, no division of the short gastric vessels, and selective hiatal repair.[9] We have previously reported the clinical and physiologic effectiveness of this approach.[10] No bougie is utilized. On-table endoscopy was introduced as a quality initiative aimed at assessment of the wrap at the completion of the procedure, noting in particular accurate wrap position, looseness, and lack of angulation. The goal was to further standardize the technical end result of the procedure, and to help understand and manage postoperative symptoms where they arise. This report of 80 cases, compared with 100 prior consecutive cases, highlights the positive impact of this assessment.

Patients and Methods

Study Population and Design A prospective database in the Esophageal Unit at St. James's Hospital includes clinical features, endoscopic and pathological grade of esophagitis, quality of life (QOLRAD), pH studies and manometry, and surgical details and complications. This study reports on 180 consecutive patients, from January 2001 to March 2005. The first 100 cases were treated by the laparoscopic operation that was standard in the Unit since 1997, and the two senior surgeons (JVR, NR) had performed 175 procedures before this analysis commenced.[10] On-table endoscopy was introduced in late 2003 as a quality assurance measure, in particular to identify factors that may relate to technical failures or result in postoperative dysphagia and reinterventions. The patients were divided into two groups: group 1 had no on-table endoscopy, and Group 2 had endoscopy on completion of what appeared laparoscopically to be a satisfactory result. Patients were followed up symptomatically at 1 month and at 6 months, and by pH studies at 6 months. All patients included in this report were followed up for a minimum of 6 months.

Operation and Indications Laparoscopic Rosetti-Nissen fundoplication was the technique employed in all cases.[11] In brief, after dividing the phrenoesophageal ligament, the diaphragmatic crura are dissected, a Penrose drain is passed behind the esophagus and anterior to the posterior vagus, and a generous posterior window is created. The fundus is mobilized and freed posteriorly, but the short gastric vessels and the gastrosplenic omentum are left undisturbed. A judgment is made by the operating surgeon as to the need for hiatal repair, and, if required, one or two sutures are used to close posteriorly the diaphragmatic crura. Thereafter, a fold of the anterior fundus is brought behind the esophagus, and a loose 360° wrap is created with two to three interrupted nonabsorbable sutures (0 Ethibond, Ethicon, Dublin, Ireland) over a length of 2 cm. No bougie is used, and the "floppiness" of the wrap is deemed satisfactory by both surgeons before closure. Postoperatively, free fluids are permitted on day 1, and a soft diet from day 2, and most patients are discharged on the second or third postoperative day.

In patients in group 2, an endoscopy was performed after the procedure was completed. Several features were noted: the ease of passage of the endoscope into the stomach, viewed both endoscopically and on the laparoscopic monitor; the presence of any stomach above the wrap; and, at J-maneuver, whether the "stack of coils" were parallel, a lack of alignment suggesting a rotated or angulated fundoplication. Any element considered unsatisfactory was corrected.

Esophageal Function Studies This was performed on all patients preoperatively. At 6 months postoperatively patients were invited to have the test repeated.

A stationary perfused esophageal manometry was carried out using a four-lumen esophageal catheter (Mui, Ontario, Canada) with side holes at 5 cm apart and orientated at 90° from each other. The catheter was passed per nares and positioned in the stomach. It was then withdrawn in 1 cm increments to document the lower esophageal sphincter pressure. Lower esophageal sphincter pressure (LESP) was measured as end expiratory pressure at the point of respiratory reversal. Three proximal sensors were placed in the esophageal body and the fourth sensor was positioned within the sphincter. Esophageal body function was assessed by measuring the presence of peristalsis in the esophageal body in response to 5-ml boluses of water. Manometry traces were analyzed according to the criteria of Castell [12] and colleagues and classified as normal motility or dysmotility. Dysmotility, defined as evidence of hypocontraction in the distal esophagus with at least 30% of wet swallows exhibiting any combination of the following abnormalities: (1) distal esophageal peristaltic wave amplitude <30 mm Hg, (2) simultaneous contractions with amplitudes <30 mm Hg, (3) failed peristalsis in which the peristaltic wave did not tranverse the entire length of the distal esophagus, or (4) absent peristalsis.[13] No modification of the operative approach was performed in patients with dysmotility.

Twenty-four hour pH monitoring was carried out by positioning an antimony pH probe 5 cm above the proximal border of the LOS and connecting it to a Mark III Digitrapper (Medtronics, Denmark). All patients discontinued proton pump inhibitors for a minimum of 10 days and other antireflux medications for at least 48 hours before the study. The DeMeester composite acid score was computed using EsopHogram software (Medtronics, Copenhagen), abnormal intraesophageal pH was defined as a score higher than 14.7.

Symptom Assessment Symptomatic outcome was assessed by completion of standardized reflux and quality of life questionnaires. Severity of GERD symptoms and dysphagia were assessed preoperatively, when off medication, according to the self-completed modified DeMeester Scoring System.[14] For heartburn, 0=none, 1=occasional (<3/week) brief episodes controlled by antacids, 2=frequent (3–5/week) and 3=daily. For regurgitation 0=none, 1=mild, occasional episodes, mostly postprandial and not predictable, 2=moderate, frequent episodes (3–5/week), predictable by posture, and 3=severe, daily, and interfering with work and social activities. Dysphagia was graded from 0 to 3, with 0=no symptoms, 1=occasional transient sensation of food sticking, 2=episodes of dysphagia requiring liquids to clear, and 3=severe dysphagia requiring medical attention, the need for dilatation or bolus obstruction requiring liquids to clear.

The need to resume medical treatment for acid symptoms was also documented. Patients ranked the outcome of surgery using a modified Visick [15] grading (1–4) and were also asked to score the outcome as excellent, good, fair, or poor. Excellent was defined as complete recovery, good as major improvement with only minor problems, fair as major improvement but with significant problems or adverse effects, and poor as minor or no improvements or deterioration. All questionnaires were completed in the presence of the principal investigator (NR), mostly at the Esophageal Clinic, and the remainder by telephone.

Reflux esophagitis as well as inflammation within the Barrett's segment was graded endoscopically according to the LA Classification.[16] Esophagitis was graded histologically based on the presence of basal layer hyperplasia and papillary elongation using the criteria of Ismail-Beigi and colleagues.[17] Esophagitis within a segment of Barrett's was graded histologically according to the Sydney grading system for inflammation.[18]

Statistical Analysis Nonparametric data were analyzed using Fisher's exact test for 2 × 2 contingency tables and the Mann–Whitney *U* test. For parametric data, an unpaired *t* test was used for comparison of differences between means in two groups. Statistical significance was ascribed to a *p* value of less than 0.05. All data are reported as medians and ranges unless otherwise stated.

Results

Demographics, including endoscopic grading, and preoperative symptom scores, are shown in Table 1. There was no difference between groups, and the majority of patients in each group had severe heartburn and regurgitation. A dysphagia score of 2 or 3 was present preoperatively in 13 patients (13%) in group 1 and nine patients (11%) in group 2, and a score of 1 was reported in 14% and 19% in groups 1 and 2, respectively. All patients were on proton pump inhibitors at the time of surgery, and over 90% of patients in each group were on treatment for more than 12 months.

Table 1 Demographics and Preoperative Characteristics

	Group 1 (n=100) %	Group 2 (n=80) %
Male/Female	71/29	51/29
LA Classification		
0	32 (32)	19 (24)
A	22 (22)	19 (24)
B	13 (13)	19 (24)
C	9 (9)	11 (14)
D	4 (4)	3 (4)
Barrett's Dysphagia Score	21 (21)	21 (26)
0	73 (73)	58 (73)
1	14 (14)	13 (16)
2	8 (8)	7 (9)
3	5 (5)	2 (3)
Regurgitation Score		
0	4 (4)	7 (9)
1	8 (8)	15 (19)
2	26 (26)	18 (23)
3	62 (62)	40 (50)
Heartburn Score		
0	2 (2)	2 (3)
1	1 (2)	3 (4)
2	4 (4)	14 (18)
3	93 (93)	61 (76)

In group 1, 15 patients (15%) had grade 3 or 4 esophagitis, compared with 15 (19%) in group 2, and 26 (26%) in group 1 had B, C, or D esophagitis, compared with 33 (41%) in group 2.

Surgery and Intraoperative Modifications

Hiatal closure was performed in 62 patients (62%) in group 1 and 51 (64%) in group 2. In group 2, four patients had modifications of the wrap performed based on endoscopic assessment. In two cases, this was caused by angulation and torsion of the wrap, and the wrap was taken down and refashioned. In one case, the wrap was judged to be too tight, and the wrap was refashioned, and in one case the hiatus was judged to be too tight and a suture was removed.

Postoperative Dysphagia

The reported prevalence of early (within 1 month) and late (at 6-month assessment) dysphagia, and the need for endoscopic or surgical reintervention is shown in Table 2.

Table 2 Postoperative Dysphagia and Reinterventions

	Group 1 (n=100) %	Group 2 (n=80) %
Early Dysphagia		
0	70 (70)	61 (76)
1	15 (15)	15 (19)
2	7 (7)	2 (3)
3	8 (8)	2 (3)
Late Dysphagia		
0	73 (73)	75 (94)
1	20 (20)	4 (5)
2	4 (4)	1 (1)
3	3 (3)	0
Reintervention		
None	87 (87)	75 (94)
Dilatation	11 (11)	4 (5)
Reoperation	2 (2)	1 (1)

An occasional transient sensation of dysphagia (score 1) was reported by 15% in group 1 and 20% in group 2. Early grade 2 or 3 dysphagia was evident in 15 in group 1 compared with four patients in group 2 ($p<0.001$). Late dysphagia was evident in seven patients (7%) in group 1 compared with one patient (1.3%) in group 2 ($p<0.05$). In all late cases, this was new-onset dysphagia.

Reintervention, either dilatation or reoperation was performed in five patients (6%) in group 2, compared with 13 (13%) in group 1 ($p<0.05$). This was not required in the four patients who had technical modifications at the time of surgery. In group 1, 11 patients (11%) underwent endoscopy and dilatation, eight on one occasion and three more than once, and two underwent reoperation (at 3 weeks and 2 months), where in both cases excessive fibrosis and scarring of the wrap to a repaired hiatus was evident. In group 2, four patients had dilatations on one occasion within 1 month of surgery, one of these patients needed two subsequent dilatations. One patient needed a reoperation in the first week for a slipped fundoplication. In those requiring dilatation, two patients in each group had grade 3 dysphagia preoperatively.

Symptomatic Outcome

At a minimum follow-up of 6 months, 88% of patients in group 1 and 95% in group 2 had no symptoms or had minor symptoms not interfering with quality of life or requiring medication. Ninety three percent compared with 100% in groups 1 and 2, respectively, considered the outcome to be excellent or good. Ten percent of patients in group 1 reported grade 2 or 3 heartburn, compared with none in group 2.

Manometry and pH Studies

The median preoperative acid reflux score was similar in groups 1 and 2 (Table 3). Postoperatively 60 patients in both groups agreed to undergo repeat studies, and these cohorts included all patients who had dysphagia or recurrent symptoms. Postoperatively there was a significant reduction in the DeMeester score in both groups, from 37 (18–146) to 2.5 (0.2–55) in group 1, and 42 (19–196) to 4.2 (0.3–8.8) in group 2 ($p<0.001$ pre vs post; p=ns, group 1 vs 2). Lower esophageal sphincter pressure increased significantly in both groups, as well as the amplitude of contractions. Esophageal dysmotility, present in 31% of group 1 patients and 36% of group 2 patients preoperatively, was still evident in 15% and 17%, respectively, at 6 months follow-up.

Discussion

In both the open and laparoscopic era, this Unit has favored the Rosetti modification of the Nissen fundoplication. This technique as originally described uses an anterior fold of fundus for the right limb of the fundoplication, rather than the posterior wall of the fully mobilized fundus as per the

Table 3 Manometry and pH Data

Manometry	Group 1		Group 2	
	Preoperative	Postoperative	Preoperative	Postoperative
LOSP, mmHg	6 (5–15)	14 (5–40)*	6 (3–8)	13 (7–23)*
Amplitude, mmHg	54 (30–277)	71 (35–153)*	59 (10–131)	73 (16–155)*
Dysmotility, %	31	15	36	17
Ph data				
Acid Score	37 (18–146)	2.5 (0.3–55)*	42 (19–196)	4.2 (0.3–8.8)*
Total, %	11 (3–42)	0.4 (0–15.5)*	13 (4–59)	0.7 (0–4.5)*
Upright, %	13 (2.5–44)	0.7 (0–12)*	15 (1.7–53)	1.2 (0–3.9)*
Supine, %	6.4 (0.1–65)	0 (0–16.7)	8.7 (0–67)	0 (0–2.4)
Postprandial, %	17 (4.2–63)	0.5 (0–24.9)*	22.5 (2.5–95)	0.7 (0–16)*

*Preoperative vs postoperative, $P<0.05$

Nissen approach.[9,19] The procedure does not require division of the short gastric vessels, utilizes selective hiatal repair, and no sutures are inserted in the esophagus as the risk of wrap migration is low. The outcomes of the Rosetti-Nissen in this and other reports[10] confirm effective symptomatic and physiological control of reflux consistent with benchmarks from the open and laparoscopic literature. The focus has shifted to try and simplify and perfect a technique that minimizes early and late postoperative problems, in particular dysphagia, and the need for dilatation or reoperation. In this report, a sequential prospective nonrandomized study, the value of the adjunct of on-table endoscopy at the completion of fundoplication resulted in a significant improvement in the achievement of this primary goal compared with the Unit standard in 100 previous cases. The outcomes in these 100 patients are similar to a prior cohort of approximately 200 cases previously performed by the authors (data not shown). Moreover, esophageal bougies have not used in this Unit for approximately 10 years, consistent with other series.[20]

There are several qualitative assessments achievable through on-table endoscopy. First, the endoscope must pass easily into the stomach, without obstruction or angulation at the level of the wrap, or at the cardia, and either event requires refashioning of the wrap. Second, retroversion of the endoscope in the stomach, the J maneuver, allows for visualization of the swirl pattern of folds, the so-called stacked coils appearance, which should be in precise alignment along the long axis of the endoscope.[21,22] If the alignment is incorrect, it may infer oblique angulation across the cardia, and should be corrected, as in two cases in this series. In this latter scenario, a redundant gastric fundus may be observed above the fundoplication.

The study of dysphagia is relatively complex, for several reasons.[6,8,23] First, the symptom of dysphagia may be present in many patients before surgery, reported to some degree in 27% of patients in this report, more commonly associated with esophagitis and acquired dysmotility. Second, published reports may also be imprecise with respect to the definition of dysphagia, the grading of symptoms, and the timing of study, and studies frequently use different assessment methods for dysphagia. Early postoperative dysphagia is common and almost invariably temporary, with no identifiable cause, perhaps relating to edema, stretching, or hypomotility. Identifiable causes include a tight fundoplication, a slipped fundoplication, hiatal stenosis, or paraesophageal herniation.[23] In this study, where early defined within the first month after surgery, some element of dysphagia was reported in 49 of 180 (27%) patients, with grade 2 or 3 dysphagia reported in 11% of patients.

Long-term dysphagia, most commonly assessed beyond 3 months, and in this study at 6 months, is reported in between 5 and 30% of cases.[8,23,24] In addition to persistence of identifiable mechanical factors that commonly are evident early after surgery, and occasional persistence of severe esophagitis or stricturing, fundoplication may also predispose to dysphagia by increasing lower esophageal sphincter pressure, both resting and residual pressure on swallowing, impaired lower esophageal sphincter (LOS) pressure on swallowing, impaired esophageal emptying, promoting retrograde competence in the presence of gastric distension, and inhibition of transient LOS relaxation.[22,24] In one report, patients with preexisting normal LOS pressures had a higher incidence of postoperative dysphagia than patients with reduced sphincter pressure.[25] In this study, grade 2 or 3 dysphagia was evident in 8/180 (4%) of patients, consistent with the lower end of the reported series, and in all cases this was new-onset dysphagia. If grade 1 is included, this rises to 32/180 (18%), but whether the occasional transient sensation of food sticking justifiably comes under the umbrella of dysphagia as a complication rather than an occasional sequelae of a fundoplication is a moot point.

In this sequential prospective study, we have shown that the addition of on-table endoscopy post fundoplication has significantly impacted on the problem of dysphagia and on the need for reintervention. Early dysphagia, grade 3 in 10% of the no endoscopy group, and in 2% of the study group, was markedly reduced, and the need for postoperative dilatation, required in 11 patients in the control group, with early reoperation in two, was significantly reduced in the study group. Persistent dysphagia of grade 2 or 3 was reduced from 7% to 1.5%. In terms of symptom control, quality of life and physiological assessment of acid reflux and manometry, there was little difference between the groups, with a significant decrease was evident in acid reflux, an increase in lower esophageal sphincter pressure, an increase in esophageal pressure amplitude, and in many cases preexisting esophageal dysmotility was reversed.

There are elements of the study open to critical comment. First, it is not a randomized trial, and although each surgeon had performed over 100 procedures before this analysis and were beyond the learning curve,[26] it is acknowledged that qualitative improvement with experience may be a continuous process. Second, as only the group 2 cohort represents the study group, bias in technical elements within this study cohort is possible. Third, the rate of reintervention in the study group was low, reflecting in large part the reduced incidence of dysphagia, but the confidence gained from completely satisfactory on-table endoscopy may increase the threshold for endoscopic dilatation in this group and may be a factor with respect to the frequency of reinterventions in the study group. Finally, as we do not utilize a bougie, in contrast to many groups,[27] it is possible that some of the benefit of

endoscopy in this prospective consecutive series may essentially substitute for a bougie, as may have been the case in two patients in this series. This is acknowledged, but we suggest that the combination of laparoscopic and endoscopic assessment of the wrap encompasses any advantage from a bougie as well as many quality assurance benefits unique to this approach.

Notwithstanding these issues, the significant decrease in early and late dysphagia over two study periods, and the very low incidence of dysphagia and reinterventions in the study group supports consideration of on-table endoscopy as an adjunct in the qualitative assessment of technical elements of laparoscopic fundoplication. Although we assume that the adjustments made in four patients prevented significant dysphagia and failure, the data suggest that other factors must be important in achieving the low dysphagia rate, and this merits further investigation. It may be that endoscopic knowledge of lack of tightness, angulation, and redundant fundus may have added benefit in decision-making in the management of all patients with significant postoperative dysphagia. We encourage evaluation of this approach in randomized trials compared with Unit standards and benchmarks.

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Effect of Obesity on Technical Feasibility and Postoperative Outcomes of Laparoscopy-Assisted Distal Gastrectomy—Comparison with Open Distal Gastrectomy

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Abstract
Objective The aim of this study was to compare outcomes between laparoscopy-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) in obese and non-obese patients.
Methods Subjects comprised 248 consecutive patients who underwent distal gastrectomy for gastric cancer between January 1999 and December 2005. Patients with body mass index (BMI)≥25 kg/m^2 were defined as obese, and patients with BMI< 25 kg/m^2 were defined as non-obese. Parameters analyzed included patients characteristics, tumor characteristics, operative details, postoperative outcomes, and prognosis.
Results For LADG, 35 patients were considered obese, and 106 patients were non-obese. For ODG, 25 patients were considered obese, and 82 patients were non-obese. Mean operative times in each procedure were significantly longer for the obese group than for the non-obese group (ODG: 241.4 min vs. 199.5 min, $p<0.0001$; LADG: 279.6 min vs. 255.3 min, $p=0.03$). Blood loss was significantly higher for the obese group than for the non-obese group in ODG (*300 ml vs. 400 ml*, $p=0.024$), but no significant differences were observed between obese and non-obese groups for LADG. Incidence of major postoperative complications, number of retrieved lymph nodes, and disease-free survival rates were similar in obese and non-obese groups for each procedure.
Conclusions Our analysis revealed that LADG can be safely performed in obese patients, with complication rates and operation outcomes similar to those for non-obese patients.

Keywords Laparoscopic gastrectomy · Gastric cancer · Obesity · Complication · Body mass index

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Introduction

Obesity is defined as excessive enlargement of the total quantity of fat or excessive accumulation of body fat. This represents a common condition in the USA, with a rising prevalence in recent years up to 31.1% of the total population of American adults.[1] In Japan, the prevalence of obese people, defined as body mass index (BMI)≥25 kg/m^2, has increased to 23% over the last 20 years,[2] and the rate of high BMI patients developing gastric cancer increased from 9.2% in 1971 to 22.9% in 2001.[3] Previous reports of open gastrectomy have shown that obesity increases the risk of postoperative complications.[4,5] Furthermore, Dhar et al.[6] showed that a higher BMI hampers regional lymph node dissection in gastric cancer patients and represents an independent predictor of cancer recurrence.

Laparoscopy-assisted distal gastrectomy (LADG) has recently seen increasing use in Japan for the treatment of

gastric cancer to improve quality of life in the early postoperative phase.[7] LADG represents a less-invasive surgical technique in terms of reduced postoperative morbidity, rapid return of gastrointestinal function, shortened hospital stay after operation, reduced adhesions, and better cosmetic results.[8,9]

Obesity has been generally regarded as a contraindication for laparoscopic surgery because of associated technical difficulties. Several reports of laparoscopic surgery have suggested obesity as a key risk factor in conversion rates.[10–12] However, the impact of obesity on the outcome of laparoscopic gastrectomy remains a controversial matter. Noshiro et al.[13] have shown that LADG for heavier patients is associated with the disadvantages of a longer operation time and delayed recovery of bowel activity. Conversely, a recent study of LADG in high BMI (≥23 kg/m^2) patients compared to normal BMI (<23 kg/m^2) patients identified no significant differences in operative parameters.[14]

Few studies have investigated the feasibility and safety of laparoscopic surgery for gastric cancer in obese patients. The present study reviewed operative outcomes in obese and non-obese patients who underwent LADG and open distal gastrectomy (ODG).

Patients and Methods

Between January 1999 and December 2005, a total of 256 consecutive patients with preoperatively diagnosed early gastric carcinoma underwent curative distal gastrectomy in our institute. Patients were assigned to undergo one of two procedures based on the depth of wall invasion as estimated by preoperative gastroscopy and endoultrasonography: LADG for tumors restricted to the mucosa and ODG for tumors invading the submucosa. After gastric cancer treatment guidelines were issued by the Japanese Gastric Cancer Association (JGCA) in 2001, all patients except those requesting ODG were assigned to the LADG group.

These patients were enrolled retrospectively in the present study, after excluding eight patients with simultaneous operations for other cancers. Extent of lymph node dissection was D1 plus alpha or beta, as defined by the JGCA guidelines. Electrocardiography, chest radiography, spirometry, and blood analysis were routinely performed for all patients. Additional assessments (e.g., echocardiography and coronary angiography) were performed selectively if physiological findings had been identified during preoperative workup. The following parameters were recorded: patient age and gender, American Society of Anesthesiologists physical status classification (ASA-PS), tumor characteristics, operative time, estimated blood loss, number of dissected lymph nodes, white blood cell count (WBC), serum C-reactive protein (CRP) level, postoperative complications, time to first flatus, time to fever resolution, postoperative hospital stay, and prognosis. Postoperative complications were defined as any event that required specific medical or surgical treatment. Patients were monitored by physical examination, blood test, and computer tomography at least every 6 months. Because obesity was defined as BMI≥25 kg/m^2 according to World Health Organization (WHO) definitions,[15] each operated patient was classified on the basis of BMI as obese (BMI≥25 kg/m^2) or non-obese (BMI<25 kg/m^2).

Surgical Procedures for LADG

Anatomical distribution and numbering of regional lymph nodes was based on the *Japanese Classification of the Gastric Carcinoma* (second English edition).[16]

The procedure for LADG has been described in our previous report.[17] Briefly, the patient was placed in the reverse Trendelenburg position. A five-trocar technique was used for laparoscopic procedures. Pneumoperitoneum was maintained at an insufflation pressure of 10 mmHg. Lymph nodes along the left gastric artery, common hepatic artery, and celiac axis were dissected in addition to D1 lymph node dissection. The procedure began with division of the omentum 3 cm from the gastroepiploic vessels to harvest lymph nodes (No. 4d) using ultrasonically activated coagulating shears (laparoscopic coagulating curved shears [LCS]; Ethicon Endo-Surgery, Cincinnati, OH, USA). The main root of the left gastroepiploic vessels was divided using double clips, then lymph nodes along these vessels were harvested (No. 4sb). Roots of the right gastroepiploic vein were identified and secured with clips. The right gastroepiploic artery was then isolated and divided at the origin. Through this procedure, the infrapyloric lymph nodes (No. 6) were dissected. The duodenum was transected using an endoscopic liner stapler (Endo-GIA; United States Surgical, Norwalk, CT, USA). The right gastric vessels were divided, and suprapyloric lymph nodes (No. 5) were dissected. Lymph nodes along the anterior common hepatic artery (No. 8) were dissected toward the celiac artery by LCS. Lymph nodes along the left gastric artery (No. 7) and celiac artery (No. 9) were stripped from the left gastric artery, which was divided using double clips. Right paracardial lymph nodes (No. 1) were dissected using the LCS, and lymph nodes along the lesser curvature (No. 3) were dissected distal to the resection line.

In the reconstruction phase, a small midline upper abdominal incision 4–5 cm in length was made. The stomach was externalized through the incision and dissected with the linear stapling device at least 1 cm proximal to the site of the tumor. The reconstruction was performed extracorporeally. In Billroth-I (B-I) reconstruction, the

duodenum and remnant stomach were externalized through the incision and sutured using the Albert–Lembert technique. In Billroth-II (B-II) reconstruction, gastrojejunostomy was performed by hand suture with Braun anastomosis extracorporeally. In Roux-en-Y (R-Y) reconstruction, after the remnant stomach was returned into the abdominal cavity, the jejunum was externalized through the incision, and the mesentery and jejunum were divided at a portion 25 cm distal to the ligament of Treitz. Extracorporeal anastomosis of the proximal end of the jejunum to the distal jejunum was created 30 cm distal from the jejunal division using the Endo-GIA (45 mm, white cartridge). The common entry hole was closed with a one-layer running suture. After the jejunum was returned to the abdominal cavity, the jejunal loop was brought up through the antecolic route, and isoperistalsis gastrojejunostomy was performed with side-to-side anastomosis using the Endo-GIA (60 mm, blue cartridge). The common entry hole was closed using a one-layer running suture.

A drain was placed at Winslow's foramen through the right inferior wound, and the operation was completed.

Statistical Analysis

All values except estimated blood loss are expressed as mean±standard deviation (SD), and comparisons among the four groups were made using the χ^2 test and Student's t test. Estimated blood loss is expressed as median±median absolute deviation (MAD), and comparisons among the four groups were made using the Mann–Whitney U test. Disease-free survival was calculated using the Kaplan–Meier estimation and examined by the log-rank test. Values of $p<0.05$ were considered statistically significant. Statistical analysis was performed using StatView software (Abacus Concepts, Berkeley, CA, USA).

Results

LADG was performed in 141 patients, whereas ODG was used for 107 patients. In LADG, 35 patients were considered obese (BMI: 27.0±2.4 kg/m^2), and 106 patients were non-obese (BMI: 21.7±2.0 kg/m^2). For ODG, 25 patients were identified as obese (BMI: 27.7±2.4 kg/m^2), and 100 patients were non-obese (BMI: 21.3±2.4 kg/m^2). Patient characteristics are given in Table 1. Age, gender, and ASA-PS did not differ significantly between obese and non-obese groups for each procedure. No significant differences were noted between obese and non-obese groups in terms of concurrent illness, with the exception of hypertension and liver dysfunction in LADG ($p=0.024$ and $p=0.018$, respectively).

Pathological examination revealed no significant differences in macroscopic type, tumor size, depth of tumor invasion, or cancer staging between obese and non-obese group for each procedure (Table 2).

Table 1 Patient Characteristics

	LADG ($n=141$)		p	ODG ($n=107$)		p
	Nonobese ($n=106$)	Obese ($n=35$)		Nonobese ($n=82$)	Obese ($n=25$)	
BMI* (kg/m^2)	21.7±2.0	27.0±2.4	<0.0001	21.3±2.4	27.7±2.4	<0.0001
Gender (male/female)	74/32	26/9	0.613	60/22	20/5	0.491
Age* (years)	63.5±9.9	64.7±8.9	0.529	64.9±12.2	64.3±10.8	0.838
Concurrent illness (n)						
IHD	4	1	0.799	4	1	0.856
Hyper tension	9	8	0.024	3	2	0.368
COPD	3	2	0.424	3	1	0.937
Diabetes	7	3	0.694	4	3	0.207
Liver dysfunction	1	3	0.018	4	2	0.553
Renal failure	1	0	0.564	2	1	0.679
Cerebral disease	1	0	0.564	2	1	0.679
Arrhythmia	5	0	0.191	2	1	0.679
Heart failure	1	0	0.564	1	0	0.579
ASA-PS (n)						
1	78	19	0.068	61	16	0.596
2	24	15		16	7	
3	4	1		5	2	

ODG Open distal gastrectomy; *LADG* laparoscopy-assisted distal gastrectomy; *BMI* body mass index; *IHD* ischemic heart disease; *COPD* chronic obstructive pulmonary disease; *ASA-PS* American Society of Anesthesiologists physical status classification
*Values represent mean±SD.

Table 2 Clinicopathological Findings

	LADG (n=141)		p	ODG (n=107)		p
	Nonobese (n=106)	Obese (n=35)		Nonobese (n=82)	Obese (n=25)	
Macroscopic type (elevated/depressed)	32/74	7/28	0.243	21/61	6/19	0.871
Tumor size* (mm)	31.9±20.6	33.7±22.6	0.652	38.3±20.5	43.8±25.9	0.298
Depth of invasion (n)						
T1	100	30	0.099	58	16	0.558
T2	6	5		15	7	
T3	0	0		9	2	
Stage (n)						
IA	96	28	0.368	51	14	0.936
IB	7	4		13	5	
II	2	2		9	3	
IIIA	1	1		4	2	
IIIB	0	0		5	1	

ODG Open distal gastrectomy; *LADG* Laparoscopy-assisted distal gastrectomy
*Values represent mean±SD.

Surgical outcomes for all 248 patients are given in Table 3. No patients required conversion to laparotomy. Reconstruction and number of retrieved lymph nodes were similar between obese and non-obese groups for each procedure. In each procedure, mean operative time was significantly longer in the obese group compared with the non-obese group. Mean operative time was significantly longer for LADG than for ODG in both obese and non-obese groups (non-obese group: 255.3±56.0 min vs. 199.5± 40.3 min, $p<0.0001$; obese group: 279.6±61.5 min vs. 241.4±57.3 min, $p=0.018$, respectively). In ODG, estimated blood loss was significantly greater in the obese group than in the non-obese group ($p=0.024$), whereas no significant difference was observed between obese and non-obese groups in LADG. Estimated blood loss was significantly less for LADG than for ODG in each group (non-obese group: 50±50 ml vs. 300±103 ml, $p<0.0001$; obese group: 80±70 ml vs. 400±196 ml, $p<0.0001$).

Regarding the incidence of major postoperative complications, no significant differences were seen between the two groups for LADG (Table 4). Anastomotic leakage occurred in five patients with LADG. One patient from the obese LADG group with a history of previous duodenal ulcer developed leakage from the duodenal stump requiring additional surgery after B-II reconstruction. The other four patients were treated conservatively after B-I reconstruction. Intra-abdominal abscess required image-guided drainage in one obese patient and two non-obese patients for

Table 3 Surgical Outcomes

	LADG (n=141)		p	ODG (n=107)		p
	Nonobese (n=106)	Obese (n=35)		Nonobese (n=82)	Obese (n=25)	
Reconstruction (n)						
Billroth-I	55	11	0.068	75	20	0.251
Billroth-II	10	7		5	3	
Roux-en-Y	41	17		2	2	
Retrieved LN* (number)	30.7±13.9	26.3±11.6	0.905	24.2±10.7	23.0±14.6	0.651
Operation time* (min) (range)	255. 3±56.0 (163–412)	279.6±61.5 (178–441)	0.031	199.5±40.3 (68–333)	241.4±57.3 (140–388)	<0.0001
Estimated blood loss** (ml) (range)	50±50 (0–600)	80±70 (0–400)	0.177	300±103 (50–1460)	400±196 (120–2000)	0.024

ODG Open distal gastrectomy; *LADG* Laparoscopy-assisted distal gastrectomy; *LN* lymph node
*Values represent mean±SD.
**Values represent median±MAD.

Table 4 Postoperative Complications of LADG

	Nonobese (n=106)	Obese (n=35)	p
Complication (n)			
Anastomotic leakage	3	2	0.423
Intraabdominal abscess	2	1	0.730
Anastomotic stricture	3	1	0.993
Wound infection	4	1	0.799
Pneumonia	1	0	0.564
Pancreatic juice leakage	2	0	0.413

LADG Laparoscopy-assisted distal gastrectomy

LADG after B-I reconstruction. Anastomotic stricture requiring balloon dilatation occurred in four patients in LADG. One patient in the obese LADG group developed small bowel obstruction secondary to bowel herniation through the laparoscopic trocar site on postoperative day 2. Immediately after diagnosis by computer tomography, the bowel was reduced, and then, the defect was primarily repaired with interrupted sutures.

WBC and CRP level on postoperative days 1, 3, and 7 were similar in obese and non-obese groups for each procedure. In the non-obese group, WBC and CRP on postoperative day 1 were significantly lower after LADG than after ODG (WBC: 95.4±27.5 vs. 111.1± 26.7, p=0.0002; CRP: 6.8±2.7 vs. 8.6±3.6, p=0.046, respectively).

No significant differences in time to first flatus or time to fever resolution (<37°C) were noted between obese and non-obese groups after each procedure. However, time to first flatus was significantly shorter for LADG than for ODG in both obese and non-obese groups (non-obese: 3.0±1.3 days vs. 4.0±1.1 days, p=0.0058; obese: 2.8±0.8 days vs. 3.5±0.9 days, p=0.0068, respectively). Length of postoperative hospital stay did not differ significantly between obese and non-obese groups for each procedure.

The 30-day postoperative mortality rate was 0.8% (2/248). One patient in the non-obese ODG group died of congestive heart failure on postoperative day 5, and one patient in the non-obese ODG group died of pneumonia on postoperative day 15.

Follow-up was available in 246 of 248 patients (2 postoperative hospital deaths were excluded). Cancer recurrence occurred in 12 patients during the median follow-up period of 45 months (range, 8–118 months). Port-site metastasis was observed in neither obese nor non-obese LADG groups. No significant differences in disease-free survival rate (non-obese group, 98.1%; obese group, 97.1%; p=0.714) or recurrence pattern were seen between obese and non-obese LADG groups.

Discussion

Over the last decade, the number of LADGs has rapidly increased, and the indications for LADG have been extended to include advanced cancer.[18] With advances in instrumentation and technique, various complex laparoscopic operations have been performed safely.[19] However, in general, surgeons consider laparoscopic surgery as difficult for obese patients because of limited visualization of surgical fields with cumbersome fat tissue, and surgeons are thus apt to hesitate about selecting laparoscopic surgery for a corpulent patient. Furthermore, LADG with systemic lymphadenectomy is considered technically more complicated than other laparoscopic procedures, as numerous great vessels must be identified and extensive lymph node dissection is necessary for radical gastrectomy.

Coincident with reports regarding open gastrectomy,[4] operation time and blood loss correlated with BMI in our study. As for LADG, although obesity significantly increased operation time, no significant differences were found in total blood loss between obese and non-obese patients. Our results resemble those of previous reports on LADG.[13,20] In open gastrectomy for a corpulent patient, the operative procedure becomes difficult because the operative field is deepened by the thick abdominal wall. Furthermore, the well-developed omentum and fat tissue around the intestinal tract of the obese patient impair exposure of the operation field. Conversely, sufficient extra space in the abdominal cavity is produced by pneumoperitoneum, and rotation of the operative table keeps the extra fat tissue distant from the stomach despite obesity, so the field of vision is not overly obstructed by intra-abdominal adipose tissue during LADG. In most obese patients, physiological adhesions attributable to excessive adipose tissue make anatomy unclear, particularly around the right gastroepiploic vein. Dissecting physiological adhesions is important for precise lymph node dissection and preventing intraoperative complications in LADG. We consider that extra time is required to dissect adhesions and excess fat tissue around the vessels, but LADG can be performed as safely in obese patients as in non-obese patients.

Obesity in laparoscopic colectomy has been reported to raise the risk of conversion to laparotomy.[10,11] However, Noshiro et al.[13] reported no significant difference between obese and non-obese patients in terms of conversion rates following LADG, and no cases of conversion were encountered in our 267 consecutive LADG series, including D2 lymph node dissection cases. Gervaz et al.[21] reported that obesity and inflammation were correlated with higher rate of conversion during laparoscopic colorectal resection. Patients with diverticular disease or inflammatory bowel disease were evaluated alongside patients with cancer in most studies regarding the risk for

conversion of laparoscopic colectomy.[10,11,22,23] This fact may have resulted in a high conversion rate in comparison with LADG.

Obesity can lead to serious health problems such as diabetes mellitus, hypertension, coronary heart disease, and cancer.[24–26] Given the high rate of comorbidities, obesity is often thought to represent a major risk factor for complications after surgery. Some reports of conventional open gastrectomy for gastric cancer have revealed postoperative complications correlating with BMI.[4,5,27] Conversely, Gretschel et al.[28] reported no significant correlation between BMI and complications in standard D2 lymph node dissection for gastric cancer. In a large cohort study, Dindo et al.[29] revealed that obesity does not represent a risk factor for postoperative complications in open surgery. However, the details of gastric surgery (e.g., type of gastrectomy, extent of lymph node dissection, and type of reconstruction) were not mentioned. More cases and information are needed for convincing data regarding postoperative complications after open gastrectomy. The incidence of complications after laparoscopic surgery for obese patients is controversial. Several reports of laparoscopic colectomy have suggested that obesity increases the risk of pulmonary complications and anastomotic leakage rates.[10,11] Other reports have revealed that no significant difference exists between obese and non-obese patients undergoing laparoscopic surgery for hysterectomy or cystectomy, in terms of postoperative complication rates.[30,31] Previous investigations of LADG have shown that postoperative complications are no more frequent in obese patients than in non-obese patients.[20] In our study, major complications and wound infection rates after LADG were comparable between obese and non-obese patients, and incidences of complications were similar in LADG and ODG. However, incisional hernia occurred in one obese patient at a lateral trocar site along with intestinal obstruction caused by ileal loop incarceration (Richter's hernia). To prevent port-site hernia, we employ a non-bladed trocar to reduce tissue damage and close the fascia of the abdominal wall after 12-mm trocar insertion. In laparoscopic surgery for obese patients, as the omentum and viscera can herniate through the thick preperitoneal space even with complete closure of the fascia, closing both the fascia and peritoneum is necessary to avoid port-site hernia.

Patients with BMI≥30 are considered obese in Western countries. However, the relationship between BMI and body fat varies among ethnic groups, and Asian people tend to have more fat for a given BMI than Caucasians.[32] The WHO, the International Obesity Task Force, and the International Association for the Study of Obesity have proposed lower cut-off points for overweight (BMI=23.0 kg/m^2) and obesity (BMI=25.0 kg/m^2) in Asian and Pacific Island populations.[33]

The extracorporeal approach with a small incision is generally accepted for reconstructions in LADG. Intra-abdominal anastomosis is a technically demanding and time-consuming procedure that requires a very skilled and experienced surgeon. We previously performed the anastomosis intracorporeally, but an incision of at least 3.5 cm is required to externalize the resected stomach from the abdominal cavity, and extracorporeal reconstruction can be accomplished using a 4-cm incision, so we perform anastomosis using the small incision to save operation time. When B-I reconstruction is performed extracorporeally with the small incision, the duodenum is hard to externalize in obese patients, because of the thick abdominal wall. To reduce extending the incision for safe reconstruction, we have performed reconstruction using the R-Y method since 2002. The jejunum is easily externalized regardless of obesity, and R-Y reconstruction does not produce tension at the gastroenteric anastomosis. Roux stasis syndrome reportedly develops in 16% of patients who receive R-Y gastrojejunostomy.[34] However, Roux stasis syndrome was not recognized in any of our 58 patients who underwent R-Y reconstruction with our original procedure after LADG.

Obesity has been shown to correlate with the poor prognosis of gastric carcinoma.[6,35] Dhar et al.[6] reported that the number of lymph nodes removed in D2 dissections was significantly lower in overweight patients than in non-overweight patients, and the failure to totally resect regional lymph node might be responsible for shorter recurrence-free survival in overweight patients with T2/T3 tumors. In this study, numbers of retrieved lymph nodes and disease-free survival rates were similar in obese and non-obese groups for each procedure. However, the prognosis of patients with early gastric cancer is known to be excellent, with 5-year survival rates ≥90%.[36] Multivariate analysis has shown that lymph node metastasis is the only significant predictive factor for recurrence of early gastric cancer.[37] Several studies have found that the extent of lymph node metastasis in patients with early gastric cancer is associated with tumor size and depth of invasion.[38,39] According to the German Gastric Cancer Study Group, 25 lymph nodes are necessary to obtain valid information about lymph node status.[40] In LADG, the number of retrieved lymph nodes was 30.7 in the non-obese group and 26.3 in the obese group, representing no significant difference between groups. Our results suggest that lymph node dissection in LADG can be performed precisely regardless of obesity.

As the Japanese medical insurance system is structured quite differently from that in Western countries, length of hospital stay could not be estimated correctly based solely on surgical aspects. After adopting the clinical pathway for

gastrectomy in our department, hospitalization for almost all patients who underwent LADG and ODG was approximately 6 and 8 days postoperatively, respectively.

Conclusion

In conclusion, we have demonstrated in this study that obesity does not adversely affect outcomes of LADG and ODG with respect to postoperative complications. Although operations take significantly longer, obesity should not be seen as a contraindication for LADG. As for operative outcome, blood loss correlated with obesity in ODG, but no such relationship was observed in LADG. LADG can thus be performed with equal safety in both obese and non-obese patients. A randomized control study is needed to assess whether LADG is superior to ODG for treating obese patients with gastric cancer. This retrospective study was preliminary but informative, suggesting that LADG on obese patients is not accompanied by more surgical difficulties compared with non-obese patients.

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Positive VEGF Immunostaining Independently Predicts Poor Prognosis in Curatively Resected Gastric Cancer Patients: Results of a Study Assessing a Panel of Angiogenic Markers

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Abstract Angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) contribute to gastric cancer aggressiveness by up-regulating the expression of proteases. We evaluated the expression and the prognostic significance of angiogenic factors and proteases in 148 patients with R0-resected gastric cancer. Expression of VEGF, Ang-2, cyclooxygenase-2 (COX-2), urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1, matrix metalloproteinases (MMP)-1 and -9 were assayed by immunohistochemistry. After a mean of 63±4 months, 81 out of 148 patients had died due to disease. The probability of being free of recurrence was 62, 48, and 42% at 2, 5, and 10 years, respectively. Single bivariate analysis identified VEGF, Ang-2, COX-2, PAI-1, and MMP-9 expression, along with several clinicopathological parameters (grade of curability, lymph node ratio, pTNM, pT, pN), as variables associated with both decreased disease-specific survival and recurrence. On multivariate analysis, after adjusting for significant clinical covariables, positive VEGF immunostaining was the primary prognostic factor, and no other tumor marker variable could add any significant improvement for the prediction, for both disease-specific survival (p=0.001; HR, 3.27; 95% CI, 1.76 to 6.10) and tumor recurrence (p=0.002; HR, 2.81; 95% CI, 1.48 to 5.35). Our study suggests that VEGF alone may be clinically useful for establishing therapeutic decisions in gastric cancer patients.

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Introduction

Gastric cancer (GC) is the second leading cause of death from cancer worldwide, being responsible for 10% of all cancer-related deaths.[1] The overall negative outcome for this neoplasia in western countries has not significantly improved over the last decades, with a 5-year survival rate estimated at 10–30%.[2] Despite new adjuvant therapies, surgical resection still remains the only potentially curative treatment for this condition.[3,4] Identification of prognostic and predictive factors that reflect the biology of GC (tumor spread and metastasis) is important for refining our assessment of prognosis and the selection of patients who may benefit from adjuvant systemic therapy.[5]

Angiogenesis, the formation of new blood vessels that develops from preexisting blood vessels, is a fundamental process in tumor growth and metastasis,[6,7] and the vascular endothelial growth factor (VEGF) has been identified as the most potent and specific promoter of tumor angiogenesis, being secreted by almost all solid cancers.[8] Among other pro-angiogenic factors, angiopoietin-2 (Ang-2) is a destabilization factor, rendering vasculature more amenable to sprouting under the influence of VEGF.[9] Inhibition of VEGF and Ang-2 suppress angiogenesis and tumor growth in *in vivo* models.[10,11] Moreover, proteolytic degradation of the basement membrane surrounding vascular endothelial cells with remodeling of the extracellular matrix (ECM) can allow endothelial cells to migrate and invade the surrounding stroma. The matrix metalloproteinases (MMPs) and the urokinase-type plasminogen activator (uPA) system are strongly implicated in this process.[12]

In gastric cancer, a positive correlation between VEGF expression and lymphatic invasion, lymph node metastasis, venous invasion, and patient outcome has been described by several groups;[13–16] however, the association between Ang-2 and patient prognosis remains less well studied.[17,18] We have previously reported that VEGF expression had an independent prognostic value with respect to tumor recurrence and overall survival in curatively resected gastric cancer patients.[16] Several studies assessing protein expression have found that increase in the plasminogen activator (PA) components uPA and PAI-1 are associated with either aggressive tumor characteristics or a poor prognosis in gastric cancer.[19,20] A recent *in vitro* study by Etoh et al.[17] demonstrated that Ang-2 derived from Ang-2-transfected MKN-7 gastric cancer cells in the presence of VEGF up-regulated the expression of uPA, MMP-1, and MMP-9 in endothelial cells. Although previous studies have demonstrated up-regulation in the expression of these angiogenic factors and proteases in gastric cancer, most of these clinical studies analyzed only a few factors simultaneously, the study groups were frequently limited in number, and were heterogeneous (R0 vs R1–R2), and the follow-up of patients was usually short (less than 30 months). Taking all these clinical and experimental data together, it is unclear which of these molecular parameters is the most relevant to patient outcome.

In the present study, we therefore examined the expression of the pro-angiogenic factors VEGF, Ang-2, COX-2, and the proteases uPA, PAI-1, MMP-1, and MMP-9 in a large series of patients with homogeneous management (all were R0) and with extended follow-up (>5 years) and have correlated the immunohistochemical findings and clinicopathologic parameters with patient survival.

Patients and Methods

Study Population

We studied 148 patients with histologically verified primary gastric adenocarcinoma who underwent a curative (R0) resection between 1984 and 1999 at the Hospital Clínic, Barcelona, Spain. None of the patients entered into the study had evidence of distant metastases or had received neoadjuvant therapy. The study protocol was approved by the Ethics Committee of the Hospital Clinic.

Immunohistochemical expression of angiogenic factors (VEGF, Ang-2, COX-2) and proteases such as uPA, PAI-1, MMP-1, MMP-9, and microvessel density (MVD) in the gastric tumor was assessed. Sixteen epidemiological (age, gender), therapeutic (extent of gastrectomy, extent of lymphadenectomy, grade of curability, adjuvant therapy), and tumor-related (presence of signet-ring cell type, Lauren's classification, degree of differentiation, lymphatic invasion, microvascular invasion, perineural invasion, ratio of involved to resected lymph nodes, pT, pN, and pTNM stage) variables were also evaluated.

The surgical procedure included a complete resection of the primary tumor and its lymphatic drainage. Based on the decision of the surgeon, 48 (32%) patients had a D1 lymphadenectomy, including the first-level lymph nodes (paracardial, major and minor curvature, supra-, and infrapyloric), and 100 (68%) patients had a D2 lymphadenectomy, in which the second-level nodes (left gastric artery, hepatic artery, celiac trunk, splenic hilum, and splenic artery) were also excised. The spleen and tail of the pancreas were resected only when required because of tumor invasion. To detect free abdominal tumor cells, analysis of abdominal fluid obtained by irrigation of the abdominal cavity immediately after laparotomy was routinely performed.

Tumors were classified according to the 2002 tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC).[21] After histological examination of the resected specimens, the operation was classified as R0 resection if the microscopical evidence indicated complete tumor removal, with no involvement of distant lymph nodes or distant metastases, and no malignant cells in the abdominal-washing fluid. The curability grade, defined by the Japanese Gastric Cancer Association,[22] divides the curative resection patients into two groups, A and B. Group A patients (no evidence of residual disease with high probability of cure) had tumor stage T1 or T2; N0 treated with lymphadenectomy D1 or D2 or N1 treated with D2; M0, no malignant cells in the abdominal-washing fluid; and margins of resection > 10 mm. Group B patients also had no evidence of residual disease, but had D1 lymphadenectomy in the presence of N1 or had margin resection < 10 mm). Group C patients, with residual disease, were not included in the study.

Follow-Up

Postoperative chemotherapy (mitomycin-C, 10 mg/m^2, intravenously on day 1 and Tegafur, 400 mg/12 h, orally, for a 6-week cycle, until four cycles were completed) was administered in 75 (51%) patients in the context of investigational protocols.[23] To investigate time to recurrence and disease-specific survival, two of the investigators evaluated all patients in a prospective manner every 3 months during the first 2 years and every 6 months thereafter. Histological confirmation of tumor recurrence was sought in all cases. Whenever follow-up was not complete, patients or their families were contacted by telephone, and death certificates were obtained from the Civil Register of the Barcelona Council. The final follow-up date was December 15, 2005.

Immunohistochemical Staining

Paraffin-embedded tissue blocks of formalin-fixed surgically resected samples were processed for conventional histological study and for immunohistochemical analysis. We used the automated immunohistochemical system TechMate 500 + Dako with the EnVision system (Dako). Briefly, 4-μm-thick sections were deparaffinised and hydrated through graded alcohol to water. Peroxidase was blocked for 7.5 min in ChemMate peroxidase-blocking solution (Dako S2023). Then, the slides were incubated with the primary antibodies for 30 min and washed in ChemMate buffer solution (Dako K5006). The peroxidase-labeled polymer, anti-rabbit (Dako K4011) or anti-mouse (Dako K4007) was then applied for 30 min. After washing in ChemMate buffer solution, the slides were incubated with the diaminobenzidine substrate chromogen solution (Dako K3468), washed in water, counterstained with hematoxylin, washed, dehydrated, cleared, and mounted in micromount (Surgipath 01730). Details of primary antibodies and antigen-retrieval techniques used in this investigation are given in Table 1.

Assessment of Immunohistochemical Staining

Expression of VEGF, Ang-2, COX-2, uPA, PAI-1, MMP-1, and MMP-9 was based on the intensity of staining and was assessed in the malignant epithelial cells (Fig. 1). Staining of endothelial, fibroblastic, or other stromal cells was not considered. All these factors were analyzed in the invasive front of the tumor away from the tumor center. Smooth muscle cells were used as positive internal controls for VEGF immunoreactivity,[24] and endothelial cells of tumor-associated vessels were positive controls for Ang-2.[25] The degree of expression of VEGF was classified into one of three categories according to the percentage of immunore-

Table 1 Details of the Primary Antibodies Used in this Study

Antibody	Type, clone and source	Antigen retrieval	Optimum dilution
CD 34	Monoclonal QBEnd/10 (Novocastra, Newcastle-upon-Tyne, UK)	No	1:200
VEGF	Polyclonal Rabbit A-20 (Santa Cruz Biotechnology, Santa Cruz, CA, USA)	Pressure cooker/EDTA, 2 min	1:300
Ang- 2	Polyclonal Goat SC-7015 (Santa Cruz Biotechnology, Santa Cruz, CA, USA)	Pressure cooker/EDTA, 2 min	1:100
COX-2	Polyclonal Mouse 160112 (Cayman, Ann Arbor, MI, USA)	Pressure cooker/EDTA, 2 min	1:200
uPA	Polyclonal Mouse AD-3689 (American Diagnostica, Greenwich, CT, USA)	Trypsin 0,05%+ TX100 0.5%, 37°C, 20 min	1:500
PAI-1	Polyclonal Mouse AD-3785 (American Diagnostica, Greenwich, CT, USA)	Trypsin 0.05%+ TX100 0.5%, 37°C, 20 min	1:50
MMP-1	Polyclonal Rabbit RB-1536-P1 (NeoMarkers, Fremont, CA, USA.)	Pressure cooker/citrate, 5 min	1:50
MMP-9	Polyclonal Rabbit RB-1539-P (NeoMarkers, Fremont, CA, USA.)	No	1:400

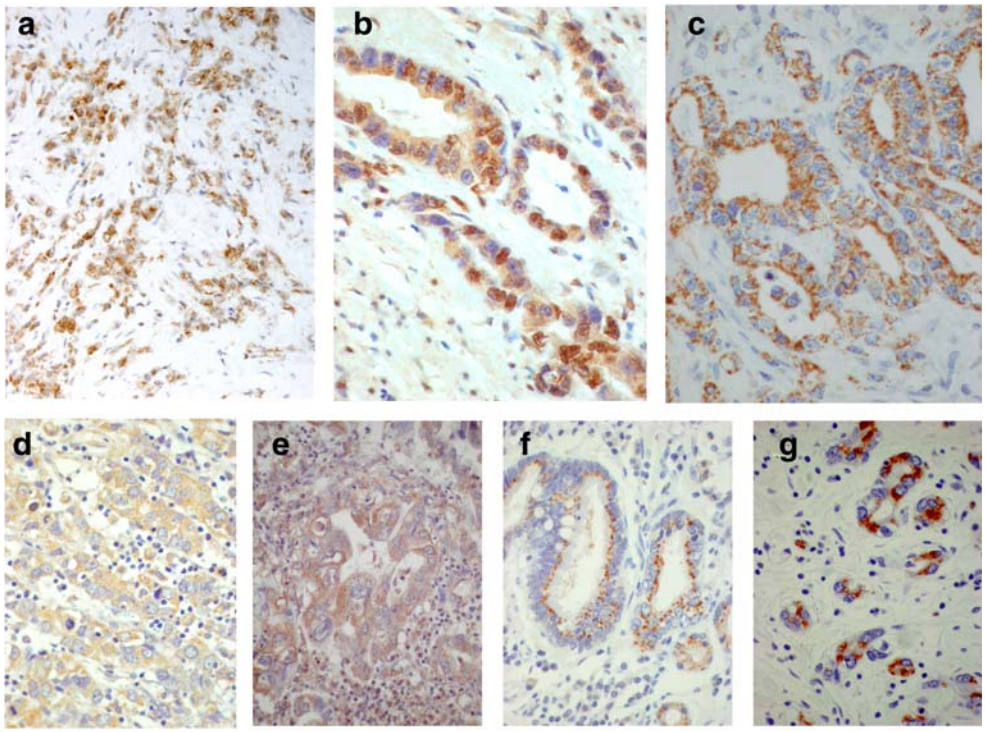

Figure 1 Representative examples of **a** VEGF, **b** Ang-2, **c** COX-2, **d** uPA, **e** PAI-1, **f** MMP-1, and **g** MMP-9 immunostaining in gastric adenocarcinoma of intestinal type. Positive VEGF immunoreactivity is detected in the cytoplasm of cancer cells in the invasive front of invasion (**a**). Strong cytoplasmic immunostaining of Ang-2 in tumor cells within the malignant gland (**b**). Intense COX-2 immunoreactivity is observed in the perinuclear region and cytoplasm of the malignant cells (**c**). Moderate and weak immunostaining for uPA and PAI-1, respectively, is present in the cytoplasm of tumor cells (**d–e**). Strong granulose-type cytoplasmic MMP-1 staining is detected in the luminal part of tumor cells within the malignant gland (**f**). Strong cytoplasmic and cell membranous staining for MMP-9 is seen in the tumor cells (**g**). Original magnifications: ×40 (**a**) and ×100 (**b–g**).

active cells over the total number of cells counted: score 0: carcinoma cells were stained less intensely than normal smooth muscle; score 1: <30% of carcinoma cells were stained, or carcinoma cells staining intensity was similar to normal smooth muscle, and score 2: >30% of carcinoma cells were stained more intensely than normal smooth muscle. Sections with scores 1 and 2 were considered positive.[16,24] The degree of expression of Ang-2 was graded as score 0 (no immunostaining in tumor cells or less intense to that seen in control), score 1 (staining equivalent), score 2 (more stained than control), or score 3 (intense staining easily seen under low power on a microscope), regardless of the number of cells stained.[18,25] In statistical analysis, Ang-2 scores were handled in two groups (negative: 0–1; positive: 2–3). Based on a preliminary study on 15 cases where we assessed the staining pattern of COX-2, uPA, and PAI-1 in the normal gastric epithelium and tumor areas, normal and benign gastric epithelia adjacent to the tumor were considered positive control for these factors. Immunostaining with all three antibodies was assessed in the cytoplasm of tumor cells. The degree of expression for C0X-2, uPA, and PAI-1 was graded as negative (no immunostaining in tumor cells or staining equivalent or less intense to that seen in nonmalignant epithelium) or positive (more stained than control), regardless of the number of cells stained.[19,26] The degree of expression of MMP-1 and MMP-9 was estimated, as described by other authors,[27] by semiquantitative evaluation into three groups according to the percentage of immunoreactive cells over the total number cells counted: score 0, if <10% of cells stained; score 1, if 10–25% were immunoreactive; score 2, if 26–50% were immunoreactive, and score 3 if >51% were immunoreactive. Sections with score ≥2 were considered positive.

Microvessel Density

For microvessel density (MVD) evaluation, quantitative vessel counts were performed by the method described by Weidner and assessed by international consensus.[28] The entire tumor sections were systematically scanned at ×40 magnification to find the areas of most intense neovascularization or hot spots. These were identified as having the highest density of brown staining, CD34-positive cells, or cell clusters. For each slide, the most vascular areas within the tumor mass were chosen. A ×250 field in these areas

was counted, and the average counts of the fields were recorded. If multiple vascular hot spots were present, counts were performed in each hot spot. Microvessels were defined as a discrete CD34-positive endothelial cell aggregate, with or without definable lumina.

The specimens were evaluated independently by two experienced investigators (AV and J.P M), and staining degree was assessed without knowledge of the clinical data of the individual patient at the time of the review. Conflicts in scores were resolved by consensus.

Statistical Analysis

Disease-specific survival and tumor recurrence were the main end points for the single bivariate and multivariate analysis of prognostic factors. Disease-specific survival was calculated from the date of surgery until death due to the cancer, whereas time to recurrence was established from the date of surgery to the date of recurrence (including either locoregional relapse or distant metastases).

For single bivariate analyses of disease-specific survival and tumor recurrence, Kaplan–Meier curves were plotted and then compared using log-rank statistics. For continuous variables (i.e., age and MVD), the cut-off level chosen was their median value. Multivariate analyses were performed in a forward stepwise fashion by the Cox proportional hazards model, including those variables with a p value$\leq$ 0.1 in the single bivariate analysis and adjusting by clinical variables with prognostic significance.

Differences were considered significant when p values were less than 0.05. All the calculations were performed by using the statistical SPSS package for Windows (version 11.05; SPSS Inc., Chicago, IL, USA).

Results

A total of 148 patients were observed prospectively for an average of 63±4 months. Patient characteristics and treatment parameters are described in Table 2. Five patients were lost to follow-up. A total of 93 patients died: 81 due to malignant disease and 12 without evidence of tumor. Eighty-one recurrences were seen, 36 of which presented as peritoneal or distant metastases, and 45 as local and regional recurrences.

The immunohistochemical detection levels of the angiogenic markers evaluated in the primary tumor is listed in Table 3.

Prognostic Factors of Tumor Recurrence

At the end of follow-up, the estimated mean time to recurrence was 52±4 months (range, 9–252 months), the probability of being free of recurrence was 62, 48, and 42% at 2, 5, and 10 years, respectively (Fig. 2a). There were significant associations between tumor recurrence and tumor VEGF, Ang-2, COX-2, PAI-1, and MMP-9 expression in the single bivariate analysis (Table 4). Other significant variables affecting tumor recurrence in the bivariate analysis were grade of curability (p=0.001), degree of differentiation (p=0.026), ratio of lymph nodes (p=0.001), pT stage (p=0.001), pN stage (p=0.001), and pTNM stage (p=0.001).

Multivariate analysis of tumor recurrence showed VEGF expression (p=0.001), grade of curability (p=0.004), ratio of lymph nodes (p=0.041), and extent of lymphadenectomy (p=0.002) to have significant prognostic value. The Cox

Table 2 Characteristics of the 148 Patients Included in the Study

Factor		Value
Age (year)[a]		68±12 (69)
Sex (n, %)	Male	99 (67)
	Female	49 (33)
Extent of gastrectomy (n, %)	Total	72 (49)
	Subtotal	76 (51)
Extent of lymphadenectomy (n, %)	D1	48 (32)
	D2	100 (68)
Signet-ring cell type (n, %)		36 (24)
Lauren's classification (n, %)	Intestinal	92 (62)
	Diffuse	56 (38)
Degree of differentiation (n, %)	Poor	70 (47)
	Moderate	73 (49)
	Well	5 (4)
Lymphatic invasion (n, %)		41 (28)
Microvascular invasion (n, %)		17 (11)
Neural invasion (n, %)		20 (13)
Ratio of involved-to-resected lymph nodes[a]		22±28 (9)
Grade of curability (n, %)[b]	A	75 (51)
	B	73 (49)
pT stage (n, %)[c]	T in situ	1 (1)
	T1	26 (17)
	T2	69 (47)
	T3	50 (34)
	T4	2 (1)
pN stage (n, %)[c]	N0	62 (42)
	N1	50 (34)
	N2	33 (22)
	N3	3 (2)
pTNM stage (n, %)[c]	I	56 (38)
	II	39 (26)
	III	42 (28)
	IV	11 (8)
Adjuvant therapy (n, %)		75 (51)

[a] Continuous variables were expressed as mean ± SD (median).
[b] According to the Japanese Gastric Cancer Association [22]
[c] According to the TNM classification [21]

Table 3 Prevalence of Expression of Molecular Factors Assessed in the Primary Tumor (n=148)

Molecular factors	Positive N (%)
VEGF	113 (76)
Ang-2	19 (13)
COX-2	51 (34)
uPA	13 (9)
PAI-1	22 (15)
MMP-1	54 (36)
MMP-9	43 (29)
MVD[a]	107 (72)

[a] The median value (≥101 vessels) of microvessel density (MVD) was considered as cut-off level

regression model, adjusted to the clinical variables, identified VEGF expression (p=0.002; HR, 2.81; 95% CI, 1.48 to 5.35) as the primary prognostic factor, and no other tumor marker variable could add any significant improvement for the prediction.

Kaplan–Meier estimates of the probability of being free of recurrence after stratifying the patients according to VEGF expression in the primary tumor is represented in Fig. 2c.

Prognostic Factors of Disease-Specific Survival

After a mean follow-up of 63±4 months (range, 9–252 months), 81 (55%) patients had died as a consequence of cancer progression, the probability of disease-specific survival being 66, 51, and 39%, at 2-, 5-, and 10 years, respectively (Fig. 2b). Single bivariate analysis revealed VEGF (p=0.003), Ang-2 (p=0.001), COX-2 (p=0.014), PAI-1 (p=0.024), and MMP-9 (p=0.006) expression, along with extent of lymphadenectomy (p=0.001), Lauren's classification (p=0.006), lymphatic invasion (p=0.001), ratio of involved-to-resected lymph nodes (p=0.001), grade of curability (p=0.001), pT stage (p=0.001), pN stage (p=0.001), pTNM stage (p=0.001), and adjuvant therapy (p=0.006), as significant factors influencing disease-specific survival.

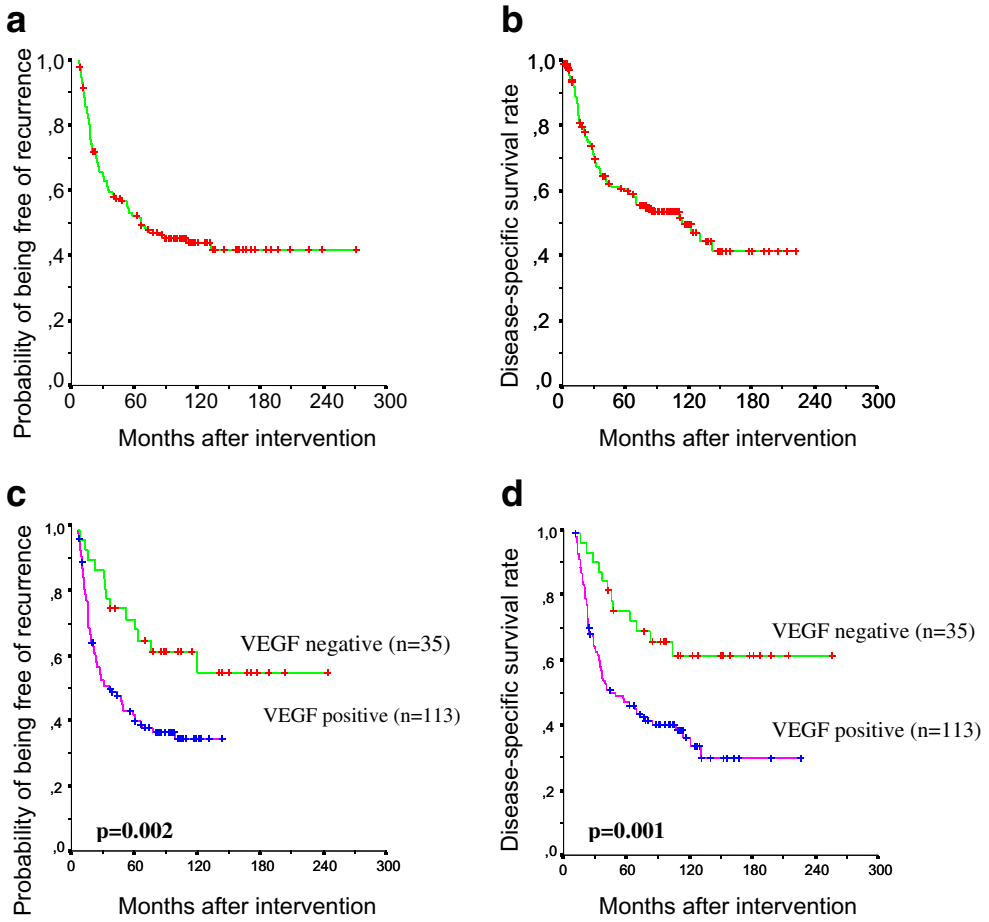

Figure 2 Kaplan-Meier estimates probability of being free of recurrence (**a**) and disease-specific survival (**b**) in the whole series (n=148) and after stratifying patients according to VEGF expression in the primary tumor (**c** and **d**, respectively).

Table 4 Cox Univariate Regression Analysis of Tumor Recurrence in all Patients

Parameter		Univariate analysis		
		p Value	HR	CI 95%
Grade of curability	A B	$p=0.001$	7.23	1.07–8.23
Degree of differentiation	Well Moderate Poor	$p=0.028$	1.85	1.40–2.36
Ratio of lymph nodes	<25% >25%	$p=0.001$	3.31	1.19–5.36
pTNM Stage	I–II III–IV	$p=0.001$	5.46	3.42–8.71
VEGF	Negative Positive	$p=0.040$	2.04	1.03–4.03
Ang-2	Negative Positive	$p=0.001$	3.10	1.60–5.99
COX-2	Negative Positive	$p=0.007$	1.85	1.18–2.89
MMP-9	Negative Positive	$p=0.013$	1.59	1.12–2.82
PAI-1	Negative Positive	$p=0.008$	2.45	1.24–4.85

HR Hazard ratio, *95% CI* confidence interval

Multivariate analysis for disease-specific survival showed VEGF expression ($p=0.016$), Ang-2 ($p=0.026$), and PAI-1 expression ($p=0.020$), grade of curability ($p=0.020$), ratio of lymph nodes ($p=0.028$), and extent of lymphadenectomy ($p=0.025$) to have significant prognostic value. The Cox regression model, adjusted to the clinical variables, identified VEGF expression ($p=0.001$; HR, 3.27; 95% CI, 1.76 to 6.10) as the primary prognostic factor, and no other tumor marker variable could add any significant improvement for the prediction. Kaplan–Meier analysis of disease-specific survival after stratifying patients according to VEGF expression in the primary tumor is depicted in Fig. 2d.

Discussion

The current TNM staging system of GC based on conventional pathologic features is still inadequate for the prognostic characterization because patients with identical clinical or pathological stages may differ widely in their clinical evolution. The assessment of tumor angiogenesis could provide supplementary prognostic information in patients with GC, identifying a subgroup with highly aggressive tumors and high likelihood of disease recurrence and death. An indirect way to measure angiogenic activity in cancers is to evaluate the expression of angiogenic factors in tumor tissue. We undertook the present immunohistochemical study, one of the largest to date, to simultaneously assess the expression of VEGF, Ang-2, COX-2, uPA, PAI-1, MMP-1, and MMP-9, and to determine which of these angiogenic factors was most closely correlated to GC recurrence and survival. This investigation demonstrated the prognostic value of VEGF, Ang-2, COX-2, PAI-1, and MMP-9 expression in GC patients undergoing a curative resection. All these factors were associated with decreased time to recurrence and disease-specific survival in Kaplan–Meier analysis. However, the Cox regression model, adjusted to the clinical variables, demonstrated that positive VEGF immunostaining was the only angiogenic marker with independent prognostic significance for poor clinical outcome.

Our report has potential limitations, namely, that the immunohistochemical study was conducted retrospectively and that 75 out of 148 patients (51%) received adjuvant chemotherapy. Clinical data, however, were collected prospectively, and immunohistochemical assessments were carried out in a blinded fashion using a methodology previously reported by others.

In many cancers, tumor VEGF expression was found to be a significant marker for tumor recurrence or reduced survival independent of conventional clinicopathological variables.[29] Four studies from Japan and our previous study identified VEGF as the strongest predictor of survival in GC by multivariate analysis.[14,16,30–32] However, it was still controversial which factor among those related to the process of angiogenesis was most important in the progression of GC. In the present study, we directly compared more angiogenic factors than had been previously evaluated in a large group of patients, and found, by multivariate analysis, that only VEGF was the primary prognostic factor. We had a large number of patients, most with earlier stages (64% stages I–II) and a longer follow-up (>5 years) than previous reports. Interestingly, 64% of our patients had stages I–II, so positive VEGF immunostaining was able to discriminate, even in these stages, patients with potential unfavourable outcomes who may benefit from a closer follow-up or their inclusion in protocols of adjuvant chemotherapy. VEGF immunostaining was present in a significantly greater percentage of gastric cancer patients than any other individual marker. This observation suggests that VEGF might be a final common pathway for other angiogenesis factors, but our data do not allow us to confirm or reject this hypothesis.

Preclinical studies of agents that selectively target VEGF and its receptors in GC have shown significant antitumor effects, confirming that this ligand/receptor system is a valid target for gastric cancer therapy.[33] Future areas of development may include the addition of newer chemotherapeutic agents combined with targeted therapies such as the anti-

VEGF agents (bevacizumab) in patients with predicted poor outcome based on tumor VEGF assessment.[34]

The mechanism of Ang-2 expression and its regulation in GC are mostly unknown. Increased Ang-2 mRNA levels have been detected in GC compared with normal tissue, and patients with increased levels of Ang-2 mRNA showed more frequent vascular involvement and more advanced stages of disease than those with low Ang-2-expression.[17,18,35] Recently, Etoh et al.,[17] using a coculture assay of endothelial cells (ECs) and Ang-2- transfected MKN-7 GC cells, demonstrated enhanced expression of uPA, PAI-1 and metalloproteinases (MMP-1, MMP-9) in ECs by Ang-2 derived from transfectants in the presence of exogenous VEGF. They concluded that overexpressed Ang-2, together with VEGF, might promote angiogenesis in GC. With regard to prognosis and in agreement with the results of Etoh et al.,[17] our study shows that the prognosis of patients with Ang-2 expression is shorter, but in multivariate analysis, Ang-2 expression was not an independent prognostic factor.

Over the past two decades, numerous studies have confirmed an association between COX-2 overexpression and tumor progression and increased angiogenesis in several solid malignancies.[8] Significant associations between COX-2 immunoreactivity and gastric cancer with respect to depth of tumor invasion, tumor grade, and lymph node involvement have been described.[36–38] An impact of COX-2 expression on survival has been found in some, but not all studies.[26,36] In our single bivariate analysis, COX-2 immunoreactivity was associated with decreased cancer-specific survival. However, contrary to the findings of Mrena et al.,[38] we failed to demonstrate high COX-2 as an independent prognostic factor in GC, either in early (stages I–II) and in advanced stages (III–IV).

It was originally believed that uPA promoted cancer dissemination simply by degrading the ECM, thus allowing invasion and metastasis. It is now clear that uPA has additional activities stimulating angiogenesis, mitogenesis, cell migration, and cell adhesion involved in cancer spreading.[39] Because uPA is directly involved in metastasis, it is an ideal candidate for investigation as a prognostic factor. In fact, high uPA concentrations have been shown to correlate with aggressive disease in patients with breast, esophageal, gastric, colorectal, and endometrial cancers.[40]

Heiss et al.[19] demonstrated the prognostic impact of uPA, uPA-R, and PAI-1 expression, determined by immunohistochemistry, in 139 patients with curatively resected GC. uPA and especially PAI-1 were inversely correlated with recurrence-free survival. In multivariate analysis, PAI-1 was a strong independent prognostic factor. Similarly, in a series of 76 GC patients[41] in whom uPA and PAI-1 tumor concentrations were measured by ELISA, these markers were inversely correlated with recurrence-free and overall survival, but only PAI-1 was an independent prognostic factor in multivariate analysis. Kaneko et al.[20] evaluated immuhistochemically the expression of uPA and PAI-1 in 101 GC patients. The rates of positive expression in cancer cells of uPA and PAI-1 were 22.8 and 36.6%, respectively. Expression of uPA and PAI-1 in tumor cells was significantly associated with poor differentiation and vascular invasion. Furthermore, multivariate analysis identified uPA expression as an independent prognostic factor. Our survival analysis demonstrated that patients with PAI-1 expression had a significantly lower survival rate than those without it. However, in our study, the expression rates of uPA and PAI-1 by immunohistochemistry, 9 and 15%, respectively, were lower than those observed in the studies by Heiss et al. and Kaneko et al.[19,20]. It should be emphasized that assessment of tumor expression of uPA and PAI-1 by immunohistochemistry (IHC) can be misleading because these proteins are synthesized and expressed in varying proportions by both tumor and stromal cells. Such heterogeneity is difficult to quantify using IHC. It is also unclear whether it is their (relative) levels in the stroma or in the tumor cells themselves that is the most relevant to patient outcome[42,43]

In summary, we found that VEGF expression in primary tumor tissue is significantly associated with a worse prognosis in GC patients after curative surgical resection. Prognostic information based on VEGF expression, unlike multiple other tumor markers that we have studied, was independent of classic clinico-pathological parameters such as primary tumor extent and degree of lymph node involvement. Our results may suggest the potential value of VEGF assessment to identify patients at high risk for tumor recurrence and for whom adjuvant systemic therapy might be recommended. Future studies, particularly clinical trials involving anti-angiogenic agents and standard chemotherapeutic regimens, will be required to demonstrate the ultimate clinical relevance of VEGF expression in the management of patients with GC.

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Is Totally Laparoscopic Gastrectomy Less Invasive Than Laparoscopy-assisted Gastrectomy?: Prospective, Multicenter Study

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Abstract
Background Laparoscopic surgery has been adopted for the treatment of gastric cancer, and many reports have confirmed its favorable outcomes. Most surgeons prefer to laparoscopy-assisted gastrectomy using minilaparotomy rather than totally laparoscopic procedures because of technical difficulties of intracorporeal anastomosis. We conducted this study to compare laparoscopy-assisted distal gastrectomy with totally laparoscopic distal gastrectomy. In addition, laparoscopic procedures were compared with open distal gastrectomy.
Material and methods This prospective, nonrandomized, multicenter study enrolled 60 patients with early gastric cancer at three branch hospitals of our institutes. Twenty-five- to 30-cm-long mid-line incision, 5-cm midline or transverse incision, and 3-cm U-shaped incision were used in open distal gastrectomy, laparoscopy-assisted distal gastrectomy, and totally laparoscopic distal gastrectomy, respectively. Postoperative outcomes, immunologic changes, and operation-related costs were compared between the three groups.
Results There was no difference in gender, mean age, body mass index, and tumor characteristics between the three groups. No operation-related death occurred. Estimated blood loss, number of additional analgesics use, first flatus, and soft meal diet time were significantly different between the three groups ($P<0.05$). In totally laparoscopic distal gastrectomy, the time to first flatus was significantly shorter than laparoscopy-assisted distal gastrectomy (3.7 vs. 2.8 days, in laparoscopy-assisted distal gastrectomy and totally laparoscopic distal gastrectomy, respectively, $P<0.05$). White blood cell count and C-reactive protein level at postoperative day 1 were significantly higher in open distal gastrectomy than the other groups; however, there was no difference between laparoscopy-assisted distal gastrectomy and totally laparoscopic distal gastrectomy. The operation-related costs were significantly greater in totally laparoscopic distal gastrectomy ($P<0.05$).
Conclusion Although totally laparoscopic distal gastrectomy needs more cost, totally laparoscopic distal gastrectomy provides shorter bowel recovery time than laparoscopy-assisted distal gastrectomy.

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Keywords Gastrectomy · LADG · TLDG · Prospective · Less invasive · Multicenter

Introduction

In Korea, the incidence of early gastric cancer (EGC) has increased by more than 40%[1,2] because of rapid advance of mass screening tests and diagnostic instrumentation. The prognosis of patients with EGC after curative surgery is highly favorable with the reported 5-year survival rates in the excess of 90%[3]; therefore, the quality of life of these patients has greatly been emphasized.[4] Considering the

quality of life, laparoscopic surgery has emerged as an alternative therapy for EGC. In Korea, 1,089 patients underwent laparoscopic gastric surgery in 2004, and the number of laparoscopic radical procedures has rapidly increased since 2001 (55 cases in 2001, 150 cases in 2002, 364 cases in 2003, and 738 cases in 2004).[5] Furthermore, in Japan, a total 5,271 laparoscopic gastrectomies have been performed between 1991 and 2003, and more than 1,500 gastrectomies were performed laparoscopically in 2003.[6]

Kitano et al.[7] first reported laparoscopic gastrectomy with Billorth I anastomosis for EGC in 1994. They used the term "laparoscopy-assisted distal gastrectomy" (LADG) because the minilaparotomy was needed for gastric transection and anastomosis. Most of the Korean and Japanese surgeons have preferred the "laparoscopy-assisted"-type gastrectomy because of the difficulties of intracorporeal anastomosis. Recently, several surgeons including the authors have reported the safety and feasibility of the "totally laparoscopic gastrectomy".[8–10] Compared with the laparoscopy-assisted procedure, the totally laparoscopic procedure appeared to be less invasive because it does not require minilaparotomy. Nevertheless, to the best of our knowledge, there has been no prospective study with regard to the difference in surgical results between totally laparoscopic gastrectomy and laparoscopy-assisted gastrectomy. Therefore, to clarify the differences between LADG and totally laparoscopic distal gastrectomy (TLDG), we compared clinical outcomes and immune response in patients who were enrolled prospectively at our institute. As the control, conventional open gastrectomy was added to this study to exam the differences.

Material and Methods

Study Design

Between September 2005 and October 2006, three branch hospitals of The Catholic University of Korea (Department of Surgery from Kangnam St. Mary's Hospital, Our Lady of Mercy Hospital, and St. Vincent's Hospital) participated in this study (CMCGS 0501 Trial). After obtaining the informed consents, 60 patients were assigned to three types of surgery. The 20 TLGDs were performed at Our Lady of Mercy Hospital, and the remaining 20 ODGs or LADGs were performed at Kangnam St. Mary's Hospital and St. Vincent's Hospital. Data on the patients enrolled was obtained from the CMCGS 0501 study protocol. This protocol contains the standardized surgical procedures, postoperative management, patient-controlled anesthesia, and critical pathway program to avoid possible bias. In addition, all surgical fields after surgery were photographed or recorded and discussed by all authors.

Inclusion and Exclusion Criteria

Inclusion criteria were patients under 70 years old who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, histologically proven gastric adenocarcinoma located at the lower or middle third of the stomach, and clinically T1N0 or T1N1 diagnosed by endoscopy, endoscopic ultrasound (EUS), and computed tomography scan. The exclusion criteria were (1) other primary malignancy, (2) operative cardiovascular or pulmonary risk and hepatic or renal dysfunction, (3) immunocompromised patients, (4) patients with a history of previous upper abdominal surgery, and (5) patients who were suitable for endoscopic mucosal resection. The operations were performed by three surgeons (Drs. Kim, Song, and Chin) who had 30 or more experiences of laparoscopic gastrectomy.

Surgery

According to the preoperative gastroscope and EUS findings, patients with cT1b(sm) N1 received D2 (D1+β+nos. 11p, 12a, and 14v) lymph node dissection and patients with cT1a(m) or T1b(sm) N0 received D1+β (D1+nos. 7, 8a, and 9). The distal half to two thirds of the stomach was resected.

Laparoscopic-assisted Distal Gastrectomy

As described previously,[11] LADG consisted of the following two steps: (1) laparoscopic procedure and (2) minilaparotomy procedure. During the laparoscopic procedure, the greater and lesser omentum were divided using laparoscopic ultrasound shears (Harmonic Scalpel; Ethicon Endo-Surgery, Cincinnati, OH, USA). The D1+β or D2 lymph node dissection was performed according to the preoperative study findings. After full mobilization of the stomach, a 3–5-cm right upper transverse skin incision was made for the Billroth I reconstruction or midline incision for the Billroth II reconstruction. The mobilized stomach was then pulled out through this minilaparotomy. After removing the specimens, Billroth I gastroduodenostomy using a circular stapler (Proximate CDH 25; Ethicon Endo-Surgery) or Billroth II gastrojejunostomy by hand sewing was performed.

Totally Laparoscopic Distal Gastrectomy

To obtain a safe proximal resection margin, intraoperative endoscopy was performed, and the expected resection line was marked with dye just above 2 to 3 cm proximal from the upper boarder of the tumor during operation. The laparoscopic procedure, such as omenta division, lymph

node dissection, and gastric mobilization, was identical to the LADG procedure. The stomach was fully mobilized and resected by using three or four linear staplers (ETS flex 45 endoscopic articulating linear cutter, Ethicon Endo-Surgery), and the specimen resected was placed in a laparoscopic bag. After U-shaped extension of the skin incision at the infraumbilical trocar site, the specimen was extracted from the abdominal cavity. Intracorporeal Billroth-I or Roux-en-Y reconstruction was performed as mentioned in a previous report.[9]

Conventional Open Distal Gastrectomy

For open distal gastrectomy (ODG), a 25- to 30-cm-long upper median skin incision was made, and D1+β or D2 lymph node dissection was performed; after removing the specimens, Billroth I gastroduodenostomy using a circular stapler (Proximate CDH 29 to 31; Ethicon Endo-Surgery) or Billroth II gastrojejunostomy was performed in the same manner as for the LADG.

Measurement of Clinical and Immunologic Differences

Clinicopathologic characteristics of patients including age, gender, body mass index (BMI), tumor size, histology, depth, number of retrieved lymph nodes, and status of resection margin were assessed. To compare postoperative outcomes, operation time, estimated blood loss, first flatus, soft meal diet start, complications, and postoperative hospital stay were examined. Furthermore, to measure postoperative systemic immune response, white blood cell counts (WBC) and plasma concentrations of C-reactive protein (CRP) and cortisol were measured preoperatively and on postoperative days 1 and 3. To exclude the influence of circadian rhythm on cortisol excretion, venous blood samples were obtained always at 7 A.M.

Perioperative Management

Patients who were enrolled in this study were treated routinely according to our perioperative management protocol. The nasogastric tube was not inserted, and one closed suction drain was used. The sips of water were started just after first flatus, and the standardized pain control protocol was used. All patients received continuous intravenous injection of mixed analgesics (150 mg of ketorolac and 250 mg of pethidine HCl in 100 ml of saline) via patient-controlled anesthesia at 2 ml/h for 3–4 days after surgery. If patients complained of pain, 50 mg of pethidine HCl was injected intramuscularly.

Cost

Costs in Korean Won were reported as mean±standard deviation. The total costs comprised operation-related costs, hospital costs, and other costs. The operation-related costs were divided into operative procedure, materials, and anesthesia fees. The hospital costs included prescription, injection, laboratory, radiology, and nursing services. Other costs were overhead costs such as administrative, housekeeping, and employee benefits. In this study, the operation-related costs, hospital costs, and total costs were compared between the three groups.

Statistical Analysis

For categorical data, the difference among three groups was determined by Pearson chi-square test. Meanwhile, all continuous data were expressed as mean±standard deviation and the difference in respective results among these three groups was investigated by one-way analyses of variance (ANOVA). The difference between the LADG group and TLDG group in particular was evaluated by one-way ANOVA

Table 1 Clinical Characteristics of Patients

Factors	ODG (n=20)	LADG (n=20)	TLDG (n=20)	P value
Gender				
Male/Female	13/7	12/8	13/7	NS
Age (year)	56.7±13.5	58.5±10.1	58.7±7.1	NS
BMI (kg/m^2)	23.4±2.5	22.8±2.8	23.0±3.1	NS
ECOG performance				
0/1	13/7	12/8	13/7	NS
Lymph node dissection				
D1+β/D2	5/15	4/16	7/13	NS

Values are mean±standard deviations

ODG Open distal gastrectomy, *LADG* laparoscopic-assisted distal gastrectomy, *TLDG* totally laparoscopic distal gastrectomy, *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group performance status, *NS* not significant, *D1+β* D1+nos. 7, 8a, 9, *D2* D1+β+nos. 11p, 12a, 14v

Table 2 Pathologic Findings of Patients

Factors	ODG (n=20)	LADG (n=20)	TLDG (n=20)	P value
Tumor				
Size (cm)	2.2±1.3	2.1±1.4	2.3±1.4	NS
Histology				NS
Differentiated	7	11	13	
Undifferentiated	13	9	7	
Depth of invasion				NS
Mucosa	13	16	12	
Submucosa	7	4	8	
Lymph node metastasis	0	1	2	NS
Number of retrieved lymph nodes	31.9±16.4	34.3±14.6	37.5±15.2	NS
Resection margin (cm)				NS
Proximal	4.0±1.7	3.8±2.2	4.8±1.8	
Distal	5.3±3.4	3.8±1.9	5.4±2.6	

Values are mean±standard deviations
ODG Open distal gastrectomy, *LADG* laparoscopic-assisted distal gastrectomy, *TLDG* totally laparoscopic distal gastrectomy, *NS* not significant, *SD* standard deviation, *N0* no lymph node metastasis, *N+* present lymph node metastasis

followed by post-hoc Turkey's Honestly Significantly Different (HSD) test. A P value less than 0.05 was regarded as significant.

Results

Clinicopathologic Characteristics

No patient in the LADG and TLDG groups was converted to open surgery. There was no significant difference in age, gender, BMI, and preoperative performance status between the three groups (Table 1). Furthermore, no statistical difference was seen in tumor size, histology, and depth of tumor invasion between the groups (Table 2). The mean number of lymph nodes retrieved was slightly larger in the TLDG group; however, it was not statistically significant (P>0.05).

Postoperative Outcomes

The operation time was slightly longer in laparoscopic groups than ODG but was statistically not significant (P>0.05). Intraoperative estimated blood loss, mean number of additional analgesics use, time of first flatus, and postoperative hospital stay were significantly different between the three groups (P<0.05). Between the ODG and two types of laparoscopic technique, a significant difference of outcomes, such as blood loss, additional analgesic use, and postoperative hospital stay was noted (P<0.05). The timing of first flatus was shorter in the TLDG group than in the LADG group and, consequently, soft meal diet was started earlier (4.8 vs. 3.4 days in LADG and TLDG, respectively, P< 0.05; Table 3).

The overall operation-related complications occurred in five (8.3%) patients and were not significantly different between the three groups: pancreatitis in ODG, wound infection, ileus, and intraabdominal abscess in LADG, and intraabdominal bleeding in TLDG. All patients with morbidities were well recovered with conservative management, and no mortality occurred.

Postoperative Inflammatory and Immune Function

WBC (Fig. 1) and CRP (Fig. 2) increased 1 day after surgery in all types of operation, and the increases of WBC were significantly higher in the ODG group than in other groups (WBC in 10^9/l: ODG 12.4±3.0, LADG 10.0±1.4,

Table 3 Surgical Outcomes and Postoperative Course

Factors	ODG (n=20)	LADG (n=20)	TLDG (n=20)	P^a	P^b
Operation time (min)	221.8±63.5	233.8±36.0	254.3±42.1	0.110	0.381
Blood loss (ml)	243.6±117.2	116.3±58.4	79.1±49.1	0.000	0.322
Additional analgesics	3.7±3.0	2.1±1.6	1.8±2.1	0.025	0.938
First flatus (day)	3.8±0.8	3.7±0.7	2.8±0.8	0.000	0.003
First soft meal diet (day)	5.6±2.1	4.8±1.0	3.4±0.6	0.000	0.009
Postoperative hospital stay	10.9±4.0	7.9±1.9	9.7±3.0	0.012	0.181

Values are mean±standard deviations
ODG Open distal gastrectomy, *LADG* laparoscopic assisted distal gastrectomy, *TLDG* totally laparoscopic distal gastrectomy, *SD* standard deviation
[a] P value was estimated by one-way ANOVA test
[b] P value was estimated by post-hoc (Turkey HSD) between LADG and TLDG

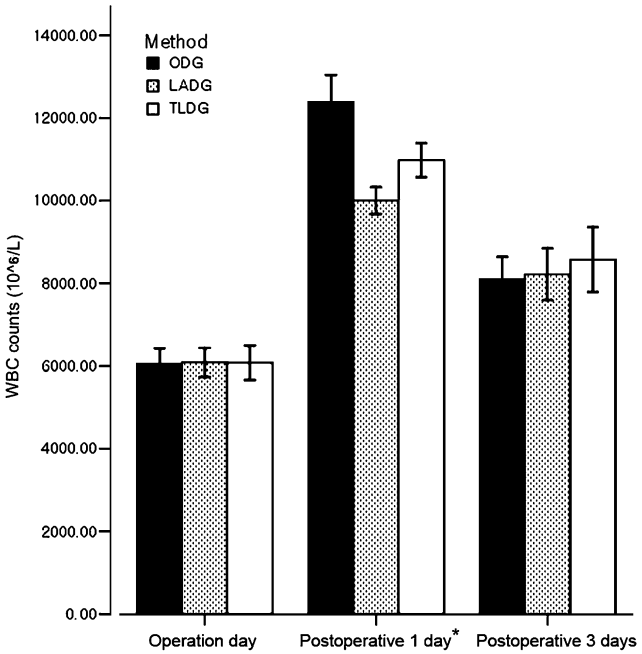

Figure 1 Changes in serum white blood cell (*WBC*) counts. Day after operation is on the *x*-axis and estimated level of WBC counts is on the *y*-axis. The WBC increased in all groups at postoperative day 1 and normalized at postoperative day 3. *Asterisk* indicates significant difference among three groups by one-way ANOVA ($P<0.05$). However, there was no difference of WBC counts at the first and third postoperative days between LADG and TLDG by post-hoc (Turkey HSD).

TLDG 10.9±1.8, $P<0.05$, CRP in mg/dl: ODG 7.55±4.7, LADG 5.61±2.8, TLDG 4.87±1.9). However, there was no difference in the increase in WBC and CRP on postoperative day 1 between the LADG and TLDG groups. Three days after operation, no significant differences in WBC and CRP were noted between all groups. Plasma cortisol concentrations (Fig. 3) increased significantly within 1 day after operation (cortisol in μg/dl: ODG 23.02±7.5, LADG 21.45±10.7, TLDG 19.72±8.6) and decreased on postoperative day 3. There were no significant differences between the LADG and TLDG groups on postoperative days 1 and 3.

Comparison of Costs

The operation-related costs and total costs were greater in TLDG group than other types of surgery. These differences resulted mainly from the costs of materials that were used in the operation room (Table 4). TLDG required more Endo GIA reloads than other types of surgery (2.2±0.6 for ODG, 3.0±0 for LADG, and 8.1±1.5 for TLDG, $P<0.05$).

Discussion

The term "LADG" was first used by Kitano et al.[7] in 1994 when the first LADG was reported in patient with EGC. LADG consists of laparoscopic ligation of gastric vessels and full mobilization of the stomach with or without duodenal resection plus resection of the stomach and anastomosis through minilaparotomy.[12] Theoretically, the favorable outcome of laparoscopic surgery is closely associated with minimal abdominal wall incision and least bowel contact during operation.[13] During LADG, surgeons usually pull out and resect the stomach and finally perform anastomosis by using a small abdominal wall incision. Minilaparotomy itself can cause operative trauma, although the degree of it is less than conventional open surgery that needs a large abdominal incision. On the other hand, a totally or completely laparoscopic procedure implies that the whole intra-abdominal procedure and reconstruction are performed only by laparoscopy without any minilaparotomy.[10] Our hypothesis was that the least incision would be least traumatic, and therefore TLDG would be less invasive.

Historically, the first laparoscopic gastrectomy was described by Goh et al.[14] in 1992, and their technique was totally laparoscopic gastrectomy with Billroth II anastomosis. Ohgami et al.[15] performed the first laparoscopic wedge resection for EGC. These totally laparoscopic techniques had frequently been used in the early 1990s; however, most surgeons have preferred the laparoscopy-assisted-type gastrectomy since the mid-1990s.[16–19] The

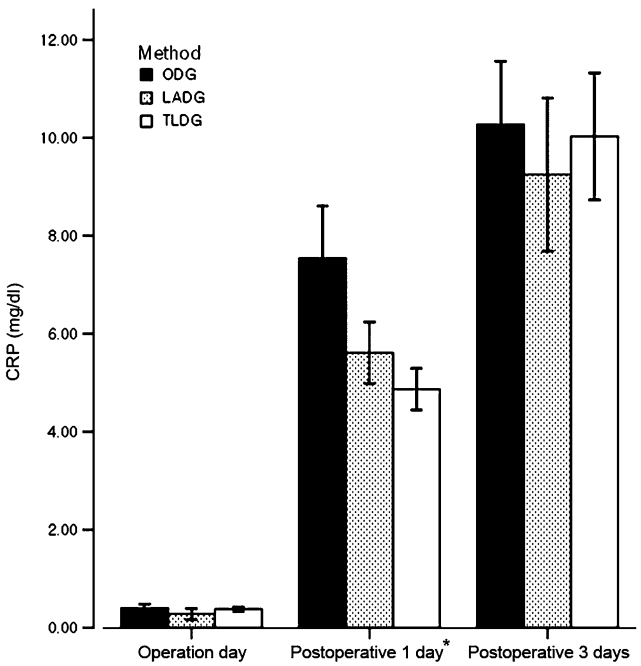

Figure 2 Changes of plasma concentrations of C-reactive protein (*CRP*). Day after operation is on the *x*-axis and estimated level of CRP is on the *y*-axis. The CRP increased in all groups at postoperative days 1 and 3. *Asterisk* indicates significant difference among three groups by one-way ANOVA ($P<0.05$). However, there was no difference of CRP at the first and third postoperative days between LADG and TLDG by post-hoc (Turkey HSD).

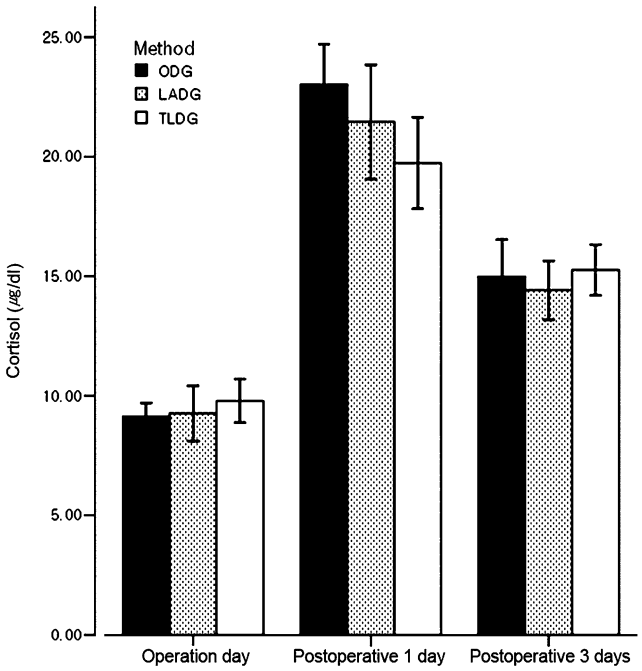

Figure 3 Changes of plasma cortisol concentrations. Day after operation is on the *x*-axis and estimated level of CRP is on the *y*-axis. The plasma cortisol increased in all groups at postoperative day 1 and normalized at postoperative day 3. Between LADG and TLDG, there was no difference of cortisol at the first and third postoperative days by post-hoc (Turkey HSD).

main reason for reluctance to use the totally laparoscopic technique is the difficulty of intracorporeal anastomosis. Recently, owing to the development of skill and instruments, several authors reported that laparoscopic intracorporeal anastomosis would be feasible and safe.[10,20] A Japanese surgeon reported a new method of intracorporeal gastroduodenostomy, so-called delta-shaped anastomosis, which could easily be performed using only laparoscopic linear staplers.[8] Based on this idea, we attempted to expand our application of the technique to other types of intracorporeal anastomosis after gastrectomy and recently reported the clinical outcomes of totally laparoscopic gastrectomy with intracorporeal anastomosis.[21]

In this study, we could not find any difference in operation time, estimated blood loss, and immunologic or inflammation changes between LADG and TLDG. Nevertheless, the time to first flatus and consequently the time to soft meal diet were significantly shorter in the TLDG group than in the LADG group. In LADG, extracorporeal anastomosis via minilaparotomy incision may cause forceful tension and injuries to the structures around the anastomosis because of limited vision, especially in an obese patient. However, because the whole anastomotic procedure can clearly be observed in TLDG, unnecessary manipulation can be avoided.

Besides of technical difficulty of intracorporeal anastomosis in TLDG, many surgeons are concerned about questionable intraoperative localization, longer operation time, and higher costs for using additional stapling devices.[21] In LADG, surgeons can easily localize the tumor via the minilaparotomy site; however, it is impossible in TLDG. To solve this problem, we performed intraoperative endoscopy in patients whose resection lines were difficult to determine. As well known, preoperative endoscopic clipping with intraoperative localization using laparoscopic ultrasonography[22] or endoscopic tattooing[23] may be useful to localize the exact site of tumor. In our series, the proximal cut margin from the tumor in TLDG was sufficient and not smaller than other types of surgery. For a more simple and time-saving reconstruction, we used endoscopic linear staplers in all TLDG patients, and this resulted in higher costs in the TLDG group than in the

Table 4 Costs for Each Type of Gastrectomy in Patients with Early Gastric Cancer

Components	ODG (*n*=20)	LADG (*n*=20)	TLDG (*n*=20)	P^a	P^b
Operation-related costs					
Operarive procedures	824±73	805±65	808±82	0.694	0.948
Materials	633±360	1,812±554	3,079±440	<0.001	<0.001
Anesthesia	308±59	322±52	366±38	0.002	0.021
Hospital costs					
Prescription	81±85	36±17	41±23	0.016	0.948
Injection	727±164	579±191	628±158	0.031	0.640
Laboratory	639±143	641±227	628±170	0.973	0.974
Radiology	63±49	63±51	60±42	0.972	0.974
Ward	498±139	420±132	479±141	0.194	0.379
Total costs	6,156±1,094	6,357±916	7,294±986	0.002	0.004

Values are mean±standard deviations. Data are presented as mean thousands of Korean Won±standard deviation

ODG Open distal gastrectomy, *LADG* laparoscopic-assisted distal gastrectomy, *TLDG* totally laparoscopic distal gastrectomy, *NS* not significant, *SD* standard deviation, *N0* no lymph node metastasis, *N+* present lymph node metastasis

[a] *P* value was estimated by one-way ANOVA test

[b] *P* value was estimated by post-Hoc (Turkey HSD) between LADG and TLDG

LADG or ODG group. This higher cost for the operation remains a big problem to be solved. We are currently trying to lower the cost by closing the entry hole of the stapler using an intracorporeal hand-sewn technique instead of stapling.

Although the current study is unique and designed as a prospective trial, there is a limitation: It is a nonrandomized study. Among the authors, only one surgeon (Dr. Kim) had enough experiences of TLDG; therefore, TLDG was performed only in Our Lady of Mercy Hospital, and the remaining 20 ODGs or LADGs were performed at Kangnam St. Mary's Hospital and St. Vincent's Hospital. However, all three surgeons had been trained at the same institute (The Catholic University of Korea), and clinical or pathological findings from all 60 patients who were enrolled in this study were not different between the three groups (Table 1). Therefore, we think that the comparison of different types of surgery could be quite legitimate.

In conclusion, TLDG is a less invasive procedure than LADG, especially in terms of bowel recovery, and it can safely be performed by experienced surgeons. However, to be popularized, the cost-effective methods of reconstruction should be developed.

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The Mirizzi Syndrome: Multidisciplinary Management Promotes Optimal Outcomes

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Abstract The Mirizzi syndrome (MS) is a rare cause of obstructive jaundice produced by the impaction of a gallstone either in the cystic duct or in the gallbladder, resulting in stenosis of the extrahepatic bile duct and, in severe cases, direct cholecystocholedochal fistula formation. Sixteen patients were treated for MS in our center over the 12-year period 1993–2005 for a prevalence of 0.35% of all cholecystectomies performed. One patient was diagnosed only at the time of cholecystectomy. The other 15 patients presented with laboratory and imaging findings consistent with choledocholithiasis and underwent preoperative endoscopic retrograde cholangiopancreatography, which established the diagnosis in all but one patient. All patients underwent cholecystectomy. An initial laparoscopic approach was attempted in 14 patients, of whom 11 were converted to open procedures. MS was recognized operatively in 15 patients with definitive stone extraction and relief of obstruction in 13 patients. T-tubes were placed in 10 patients and 1 patient required a choledochoduodenostomy. Two patients required postoperative laser lithotripsy via a T-tube tract to clear their stones; and in another patient, MS was detected and treated via postoperative endoscopic retrograde cholangiopancreatography (ERCP). MS remains a serious diagnostic and therapeutic challenge for endoscopists and biliary surgeons.

Keywords Cholelithiasis · Choledocholithiasis · Cholecystectomy · Endoscopic retrograde · Cholangiopancreatography · Mirizzi syndrome

Introduction

In 1948, an Argentinean surgeon Pablo Mirizzi first described an atypical presentation of gallstone disease in which the impaction of a gallstone in either the cystic duct or the gallbladder (GB) caused stenosis of the extrahepatic bile duct by extrinsic compression and/or fibrosis. In some cases, the associated inflammation was noted to progress to cholecystocholedochal fistula formation.[1] Now known as Mirizzi syndrome (MS), this rare cause of obstructive jaundice is reported to occur in 0.7–2.5% of all U.S. patients undergoing cholecystectomy.[2,3] It is of particular importance to surgeons because the diagnosis may not be appreciated preoperatively and because the surgical treatment of this condition is associated with a significantly increased risk of bile duct injury. Furthermore, intraoperative recognition of MS may be difficult, especially if a fistula is present or extensive adhesions complicate the dissection. Accurate definition of the biliary anatomy preoperatively, when possible, is thus critical for optimal surgical planning. To further characterize the contemporary management of this difficult problem, we reviewed our experience with MS over the last 12 years.

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Patients and Methods

We reviewed the medical records of 16 patients who were diagnosed with MS at our institution between August 1993

and July 2005. All patients were identified either from a surgical database maintained prospectively by the Department of Surgery or from an endoscopic retrograde cholangiopancreatography (ERCP) database maintained prospectively by one of the authors (GWWG). Records were reviewed for presenting clinical and laboratory findings, noninvasive imaging and ERCP findings, operative management, and patient outcome. This study was approved by the institutional IRB.

Patients were classified according to the system of Csendes et al.[4] Eight patients were type IA, two were type IB, four were type II, and two were type III. No patients were type IV. All 16 patients underwent cholecystectomy, representing 0.35% of the 4,589 patients who underwent cholecystectomy at our center during the study period. Fourteen patients underwent preoperative ERCP, which established the diagnosis of MS in 13 of the patients. Two additional patients underwent cholecystectomy without preoperative ERCP; the diagnosis of MS was established intraoperatively in one patient and postoperatively in the other.

Clinical Characteristics, Laboratory Findings, and Noninvasive Imaging

Table 1 illustrates the clinical characteristics at presentation. In 14 patients, the chief presenting complaint was acute upper abdominal pain. An additional patient presented with a chief complaint of constipation but upon questioning also admitted to 1 day of mild right upper quadrant pain. The last patient presented with painless jaundice. Table 2 summarizes pertinent laboratory findings upon admission. Of the 16 patients, 15 presented with abnormalities of liver-associated enzymes.

Table 1 Clinical Characteristics at Presentation

	N=16
Sex, M/F	7/9
Mean age, years (range)	48 (22–83)
Presenting symptoms (*n*)	
Acute abdominal pain	15
Location	
RUQ	9
MEP	2
RUQ+MEP	2
RUQ+MEP+LUQ	2
Mean duration, days (range)	2.7 (1–7)
Jaundice	12
Nausea and vomiting	7
Chronic abdominal pain	6
Mean duration, months (range)	83 (2–324)
Fever (>100.5°F)	4
Diarrhea	1
Constipation	1

RUQ: right upper quadrant, *MEP*: midepigastric, *LUQ*: left upper quadrant

Table 2 Laboratory Values at Presentation

Test	Mean (range)
WBC (1,000/μl)	8.9 (3.8–17.3)
Total bilirubin (mg/dl)	5.4 (0.5–12.6)
AST (IU/l)	549 (12–2,176)
ALT (IU/l)	602 (29–2,626)
Alkaline phosphatase (IU/l)	329 (100–692)
GGT (IU/l)	632 (37–1,707)
Amylase (IU/l)	175 (10–1,844)
Lipase (IU/l)	56 (18–131)

WBC: white blood cell, *AST*: aspartate aminotransferase, *ALT*: alanine aminotransferase, *GGT*: gamma-glutamyl transpeptidase

All 16 patients underwent abdominal ultrasonography (US) at presentation. All studies revealed gallbladder stones; and in one patient, a 9-mm cystic duct stone was also described. US showed dilation of the extrahepatic duct (caliber >6.0 mm) in 12 of 16 patients; the mean caliber in all patients was 8.1 mm (range 3.2–12.8). US detected dilation of the intrahepatic biliary tree in seven patients. Six patients additionally underwent computed tomography (CT) of the abdomen, revealing gallbladder stones in the five patients who were studied before cholecystectomy. CT revealed extrahepatic biliary dilation in five of six patients; and in one case, this dilation could be localized to the proximal extrahepatic duct. CT demonstrated intrahepatic biliary dilation in three of six patients. In all cases, the initial presumptive diagnosis after noninvasive evaluation was acute cholecystitis and/or choledocholithiasis. In no case was the diagnosis of MS established by noninvasive imaging.

ERCP Findings

Table 3 summarizes the ERCP findings in 15 patients. One patient underwent cholecystectomy without preoperative ERCP and the diagnosis of MS was not established until postoperative ERCP. Fourteen patients underwent preoperative ERCP with documentation of the diagnosis of MS in 13 cases. Of these patients, 4 had 2 preoperative ERCP procedures each, for a total of 16 preoperative ERCPs, and 1 other patient underwent both preoperative and postoperative ERCPs. All cases identified with MS during ERCP were characterized cholangiographically by the presence of stenosis in the extrahepatic bile duct corresponding to the site of the cystic duct insertion. In some cases, no stone could be visualized at the level of stenosis; in other cases, stones could be clearly demonstrated within the cystic duct

Table 3 ERCP Findings and Interventions in 15 Patients

Finding	Number
Stenosis of the extrahepatic bile duct	14
Cystic duct insertion identified at level of stenosis	14[a]
Intrahepatic biliary dilation	14
Pus present in bile duct	6
Stone(s) within cystic duct adjacent to bile duct	8
Actual or apparent bile duct stone(s)	6
Interventions	
Biliary sphincterotomy	14
Nasobiliary drain or stent placement	11[b]
Extraction of visualized or suspected BDS attempted	14
Successful extraction: complete/partial	2/2[c]
Extraction of cystic duct stone(s) attempted	5
Success	0

[a] In three cases, the cystic duct was shown to be nearly or completely obliterated with fusion of the gallbladder neck to the bile duct.
[b] Drain or stent placement was attempted in 14 patients but was unsuccessful in 3 because of lack of patient cooperation.
[c] See text.

or at the cystic duct–bile duct junction. Rarely, MS was recognized only after multiple attempts to extract stones that appeared to be within the bile duct were unsuccessful and it was realized that the stones were anatomically adjacent to but not within the bile duct (Figs. 1 and 2).

In the 14 patients in whom extraction of visualized or suspected bile duct stones was attempted, 1 to 6 passes were made using a 11.5-mm and/or a 15-mm stone extraction balloon. In several cases, both the passage of the guide wire and the balloon catheter beyond the point of obstruction were extremely difficult. Passage of stone extraction baskets above the level of stenosis was attempted in four patients but could be achieved in only three. These

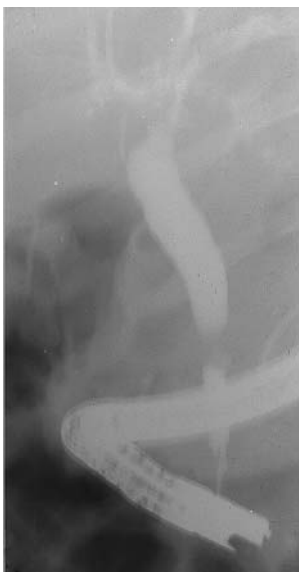

Figure 1 ERCP in Mirizzi syndrome. Stone in the cystic duct overlies the common bile duct and mimics the typical appearance of choledocholithiasis.

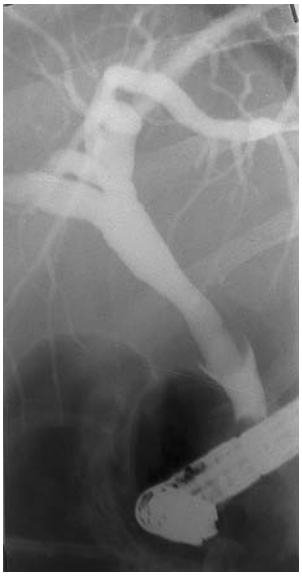

Figure 2 ERCP demonstrates the outline of the obstructing stone in the cystic duct. Contrast meniscus clearly extends outside the wall of the common bile duct.

interventions within the common bile duct yielded recovery of stone material in four patients. In two cases, small stone fragments were delivered to the duodenum but the majority of the stone burden remained in situ. In the third case, a discrete bile duct stone was crushed with a lithotripsy basket and delivered to the duodenum, however, several large stones remained within the adjacent cystic duct with associated compression of the common bile duct. In the fourth case, multiple stones were identified within the bile duct and successfully extracted. However, several stones were clustered adjacent to the bile duct within the gallbladder neck and could not be removed.

Endoscopic extraction of stones in the cystic duct was attempted in five cases. Passage of a guide wire through the cystic duct to the gallbladder past the obstructing cystic duct stones was attempted in four patients with technical success in two. In these two patients, stone balloons were advanced to the gallbladder neck, inflated, and pulled retrograde through the cystic duct to the duodenum, but no stone material could be dislodged. In the fifth patient, a basket was successfully passed deep within the cystic duct, but again, attempted removal of the stones was unsuccessful.

Operative Findings

Cholecystectomy was performed in all 16 patients; Table 4 summarizes the operative findings. The laparoscopic approach was attempted in 14 patients but converted to an open procedure in 11 patients (78.6%) because of indistinct anatomy (6), abnormal cholangiography (3), or technical problems (2). Of the patients, 15 were noted to have extensive adhesions and severe inflammation involving the gallbladder, liver bed, portal area, cystic duct, and/or

Table 4 Operative Characteristics in 16 Patients

	Number
Initial open cholecystectomy	2
Initial laparoscopic cholecystectomy	14
Conversion, laparoscopic to open with reason	11
Inflammation/adhesions/unclear anatomy	5
Abnormal IOC	3
Gallbladder perforation	1
Inadvertent choledochotomy	1
Failure to free cystic duct stone laparoscopically	1
Bile duct entered	11
Deliberate choledochotomy (for CBDE)	6
Defect created by removal of GB and/or stone	3
Inadvertent choledochotomy	1
Puncture for IOC	1
Closure: T-tube	10
Choledochoduodenostomy	1
Bile duct exploration	11
Direct	9
Transcystic	2
Location of stones identified/extracted	15
Cystic duct/bile duct junction	6
Cystic duct	4
Bile duct	3[a]
Gallbladder	2
Intraoperative imaging (IOC/laparoscopic US)	13/1
Stone at cyst duct/bile duct junction	4
Cystic duct stone	2
Inflammatory bile duct stenosis	2
Bile duct stone(s)	2
Normal	4

[a] In one patient, multiple BDS were removed at open CBDE but residual stones remained in the distal BD on the final cholangiogram. In another patient, a large stone adherent to the bile duct wall could not be removed and was left in situ.

common bile duct. Discrete inflammatory masses involving the cystic duct or bile duct were described in three patients.

The diagnosis of MS was established or confirmed intraoperatively in 15 of 16 patients, including the patient who was admitted with normal liver tests. In one patient, the presence of MS was not appreciated at the time of the initial operation. Because of nausea, vomiting, abdominal pain, and fever on the third postoperative day, an ERCP was attempted but failed to achieve biliary access despite needle–knife sphincterotomy. Subsequent percutaneous transhepatic cholangiography (PTC) revealed a high-grade distal bile duct stenosis without evidence of intraductal stones. A repeat ERCP on postoperative day 10 confirmed a tight stenosis in the distal bile duct, which was by-passed with extreme difficulty. No intraductal stone was noted, and multiple passes with a stone extraction balloon failed to yield stone material. The cystic duct stump was shown to insert low on the common bile duct, corresponding to the level of obstruction, suggesting distal bile duct compression from a stone in the adjacent cystic duct stump. A plastic endoprosthesis was placed and a repeat ERCP performed after a 3-month delay. After the extension of the biliary sphincterotomy, a large stone was successfully extracted from the junction of the cystic duct stump and the common bile duct with complete relief of biliary obstruction.

Postoperative Course and Management

The mean length of hospital stay in this series was 13.5 days (range 3–59). Initial postoperative recovery was uneventful in all patients except for a single case of *Clostridium difficile* diarrhea, which resolved with standard medical therapy. Postoperative T-tube cholangiography (TTC) was available in 11 patients and found to be normal in 5. In one patient, a 1.5-cm long inflammatory stricture was found in the middle aspect of the common bile duct. The patient required a brief interval of antibiotics but a repeat TTC 1 month later showed complete resolution of the stricture. Residual common bile duct stones were observed in another five patients. In three patients, stones passed spontaneously through a preexisting endoscopic biliary sphincterotomy and did not require further intervention. In the other two patients, ductal stones persisted and required endoscopic ablation and removal with the use of a Holmium laser using a previously described technique. Overall, MS was definitively treated during the index operation in 13 of 16 patients (81.3%).

Discussion

Born in Cordoba, Argentina, Dr. Pablo L Mirizzi (1893–1964) was recognized during his lifetime as a leading figure in surgery and is still recognized today for his enduring impact on current medical practice. Mirizzi's contributions to the surgical management of biliary tract disease occurred in the first half of the twentieth century at a time when the field was still in its infancy. Open cholecystectomy had only recently been introduced by Langenbuch in 1882 and surgeons were just beginning to confront the challenge of concomitant bile duct stones (BDS).[5] Courvoisier reported the first operative bile duct exploration in 1890,[6] but it was not until 1931 that Mirizzi first introduced intraoperative cholangiography (IOC).[7] This technique, in which a lipid contrast agent is injected into the cystic duct to achieve a radiographic image of the biliary tree, was initially termed *mirizzigrafia* and represented a major diagnostic advance. Such studies allowed for the intraoperative visualization of the biliary system and remain today as a vital element of the diagnostic algorithm used to identify biliary obstruction, BDS, biliary tract injuries, congenital ductal anomalies, and other biliary conditions.

In his original publication, Mirizzi described in detail several cases in which the intraoperative cholangiographic images were consistent with the syndrome that now bears his name. In each case, the common hepatic duct was obstructed by a gallstone located in the gallbladder. Subsequently, other investigators have demonstrated that MS commonly develops as a result of inflammatory changes involving the infundibulum of the gallbladder or the cystic duct in response to the impaction of a stone. The presence of a long intramural cystic duct or a low insertion of the cystic duct into the common bile duct appears to predispose to the syndrome, but these anatomic variants are not always present. With progressive inflammation, the gallbladder may contract and become fused to the common duct. This may produce secondary stenosis of the common duct and, in the severest cases, can promote fistula formation from direct pressure necrosis of the adjacent duct walls by the impacted stone.[2] These varying degrees of pathologic involvement are well-represented in our patients.

As also documented in the current series, Mirizzi's syndrome is not easily diagnosed in the preoperative period. In large part, this reflects the fact that the syndrome is not associated with a well-defined set of demographics or unique clinical features. The patients in our series ranged in age from 22 to 83 years. In addition, most presented with clinical and laboratory findings generally consistent with obstructive choledocholithiasis in which the degree of obstruction, as measured by serum enzyme and bilirubin levels, ranged from mild to severe. This absence of reliable clinical indicators presents a major challenge for primary care physicians and their consultants.

Because of these limitations, the preoperative diagnosis of Mirizzi's syndrome depends heavily on appropriate imaging studies. Plain abdominal films alone have not proven useful. Similarly, US or CT scans are not often definitive although both studies may demonstrate findings that strongly suggest the diagnosis, such as: (1) dilatation of the biliary tree above the level of the gallbladder neck, (2) impaction of a stone in the gallbladder neck, and (3) a normal caliber CBD below the level of impaction.[8] Recent case reports suggest that magnetic resonance cholangiography can also be an effective method of diagnosing MS using the same criteria.[9] In addition, Wehrmann, et al. reported using intraductal ultrasonography to achieve a diagnosis of MS in 30 patients with a sensitivity of 97% and a specificity of 100%.[10] Of note, the imaging findings associated with MS may be indistinguishable from those of a ductal malignancy. An appropriate clinical history and the presence of portal or hepatic mass lesions or adenopathy may help to differentiate these two different pathologies.

ERCP remains the most effective preoperative test for Mirizzi's syndrome and can provide a relatively precise localization and characterization of the source of the biliary obstruction. Typical findings of Mirizzi's syndrome at ERCP include (1) midbile duct obstruction with dilated proximal CHD and intrahepatic ducts combined with normal duct caliber distal to the obstruction, (2) insertion of the cystic duct at the point of obstruction and/or complete obliteration of the cystic duct, and (3) a stone visualized at the point of obstruction either within the cystic duct or the common duct. Nonetheless, even ERCP is not always successful; as evidenced by the one patient in our series in which the ERCP failed to establish the correct diagnosis.[11]

Therapy for Mirizzi's syndrome continues to be problematic and must be individualized depending on the stage of the disease and the expertise of the responsible consultants. The obstructing stone, whatever its precise anatomic location, is commonly refractory to endoscopic extraction; and thus in most reports, the definitive treatment of MS remains surgical. In our series, endoscopic stone extraction was attempted in 14 of 16 patients and resulted in the recovery of a single stone and additional stone fragments in only 4 patients. However, the biliary obstruction persisted in all cases. Cystic duct cannulation was performed in five patients without the successful removal of the stones. Nonetheless, temporary relief of biliary obstruction was provided in the majority of our patients by the endoscopic insertion of a plastic stent or drain. Biliary stents subsequently proved to be a valuable guide during operative dissections.

A greater role for endoscopic therapy has been recommended by several investigators. Seitz et al. achieved successful fragmentation and clearance of stones in 38 cases utilizing electrohydraulic lithotripsy delivered via cholangioscopy with a mother–daughter endoscope system.[12] Tsuyuguchi et al. used a similar approach in 25 patients diagnosed with Mirizzi syndrome.[13] They were able to clear the obstructing stone in all 23 type II patients. Nonetheless, four of the patients required rehospitalization for acute cholangitis when residual gallbladder stones migrated into the common bile duct. Cholangioscopy was unsuccessful in two type I patients. Whereas these advanced technologies are not typically available in most practice settings, they may represent the next logical step in the evolution of endoscopic methods available for the management of Mirizzi's syndrome.

Surgical intervention remains the definitive treatment for the majority of patients and should satisfy three goals: extraction of the obstructing stone, removal of the gallbladder, and restoration of normal biliary drainage. In general, the choice of the specific operative technique depends on a relatively precise definition of the biliary anatomy. With this in mind, McSherry et al. in 1982 classified MS into two anatomic groups, based on the results of ERCP and PTC: type I (external compression of

the CHD without fistula) and type II (erosion of the stone into the CHD with cholecystocholedochal fistula formation).[14] Csendes et al. further modified this classification to better guide surgical management and demonstrated in 219 patients that the more severe grades were associated with significantly higher rates of both postoperative morbidity and mortality.[4] In our series, there were no deaths, but 11 of 14 laparoscopic cases required conversion to an open procedure and 2 patients required additional postoperative procedures for the complete clearance of intraductal stones.

Like others, we found conventional retrograde dissection inadvisable in most cases because of the risk of injuring critical structures within the triangle of Calot. Our preferred surgical approach is now a fundus-down dissection with early incision of the gallbladder fundus or body to remove the impacted stone. The latter step can aid in the identification of the subtype of the disease as a sudden gush of bile into the open gallbladder strongly suggests the presence of a fistula. A cholangiogram should be obtained for clarification and confirmation.[2,15] Depending on the patient's age and the operative findings, frozen section pathologic analysis may also be indicated to assess the specimen for malignancy as the associated incidence of carcinoma with Mirizzi syndrome has been noted to be as high as 27.8%, presumably secondary to chronic inflammation.[16] Partial cholecystectomy is recommended in selected type I patients who have severe inflammation, as it minimizes the risk of CBD injury by limiting dissection in the inflamed tissues of the triangle of Calot. A subsequent CBDE is generally not necessary as the neck of the gallbladder and the cystic duct are left in situ.[15] This approach appears to be particularly useful when primary laparoscopic procedures are attempted as previously noted by Binnie et al.[17] and Rohatgi and Singh.[18] Similarly, Chowbey, et al. were able to complete a laparoscopic cholecystectomy in 78% of 27 patients with Mirizzi syndrome when they used an endoscopic stapler to divide the gallbladder infundibulum.[19] In 2003, Yeh et al. reviewed all available English language reports of laparoscopic treatment of MS and found a total of 82 cases, including 11 of their own.[20] An overall conversion rate of 31.7% was reported. In contrast, an audit of 39 patients with Mirizzi syndrome conducted by the Swiss Association of Laparoscopic and Thoracoscopic Surgery revealed a conversion rate of 74% for type 1 lesions and 100% for type 2 lesions; an experience similar to ours.[21] Our current approach is to begin with an exploratory laparoscopy but to convert to an open operation if inflammation is severe and anatomy is obscure.

Type II defects with small fistulae can be usually treated with either complete or partial cholecystectomy followed by closure of the fistula around a common bile duct T-tube.[2] A completion cholangiogram should be obtained to clear the duct. Direct suture of the ductal defect is generally inadvisable as such closure of the thickened and friable duct can be technically difficult and strictures or leaks may result.

For repair of larger defects (types III and IV), a longitudinal choledochotomy may be performed directly over the gallstone followed by a near-total cholecystectomy. A small pedicle of mobilized gallbladder wall can be sutured around a T-tube to assure patency of the common bile duct.[13,22,23] Larger fistulas may require a more generous choledochoplasty using a vascularized and bile-tolerant gallbladder flap.[4,24] However, in both cases, strictures can develop because of continued inflammation of the flap. For this reason, we and others generally prefer a biliary-enteric bypass with a Roux-en-Y choledochojejunostomy or a choledochoduodenostomy for large fistulas or badly damaged bile ducts.[2,15,25]

In summary, the Mirizzi syndrome remains a rare but important cause of obstructive jaundice and poses major challenges for both the endoscopist and the surgeon. Noninvasive laboratory investigations and specialized radiological imaging provide only supportive diagnostic information. A preoperative ERCP or PTC is usually necessary to establish the diagnosis and define the anatomy and can also be used to achieve preoperative decompression of the obstructed ductal system. Definitive therapy usually requires an operation that is tailored to the specific clinical and anatomic findings. Available surgical options range from simple cholecystectomy to more complex choledochoplasties and biliary-enteric anastomoses. Achieving optimal outcomes depends on a skilled, multidisciplinary team that is experienced with the management of advanced biliary disease.

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Voluntary and Involuntary Ligature of the Bile Duct in Iatrogenic Injuries: A Nonadvisable Approach

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Abstract
Background Bile duct injuries related to laparoscopic and/or open cholecystectomy are a frequent finding and require surgical treatment. Complete obstruction is due to either intentionally or unintentionally placed ligatures or clips. The intentional application is usually performed to "facilitate identification of the duct by bile duct dilation." Considering that we are a national referral center for such injuries, we decided to analyze our cases of voluntary and involuntary duct ligation after iatrogenic bile duct injury.
Methods We reviewed the files of patients with voluntary or involuntary bile duct ligation. Results of preoperative evaluation of the ducts, operative treatment, and postoperative results were analyzed.
Results A total of 413 patients were included. Forty-five patients presented with complete obstruction. In 15 cases, the ligature was intentional, and in 30 cases, occlusion was involuntary. Bile duct dilation (>10 mm) was demonstrated in one case of voluntary (6%) and three cases of involuntary ligations (10%). The remaining cases in both groups had no duct dilation and developed necrosis at the blinded duct and leakage proximal to the ligature, with different degrees of bilioperitoneum and/or biloma. In all cases, a Roux-en-Y hepatojejunostomy was performed.
Conclusion Bile duct ligature produces dilation in a very small number of patients (less than 10%) and usually produces necrosis of the blinded stump with subsequent bile leakage. Placement of a subhepatic drain and transference of the patient to a qualified center for reconstruction is the best approach if the primary surgeon is not able to do the repair.

Keywords Bile duct injury

Introduction

Bile duct injuries, including minor lesions that present as biliary leaks, are common: of every 1,000 cases of cholecistectomy, one to three have a major bile duct injury.[1] They are most frequently produced by the laparoscopic approach, although there is no significant difference compared to the open approach. They have been proven to lower life expectancy, have a very negative effect on the patients' quality of life, and have a high impact on cost.[2]

Bile duct injuries are multifactorial; however, misrecognition or "heuristic" mistakes are the most common cause.[3] Complete transection and/or obstruction of the main duct are some of the most difficult to repair (Fig. 1). These are classified as Strasberg E injuries,[4] Stewart-Way III,[5] or Bismuth I–V,[6] and often require a bilioenteric anastomosis. These lesions can be seen in cases of duct ablation and obstruction due to a clip or ligature, bile leakage from an external bile fistula, or duct obstruction without section or ablation. In some instances, the ligature of the duct is not recognized by the surgeon, and in others, it is deliberately performed to "facilitate duct identification by causing dilation" [sic].

Bile duct injury repairs are frequent in our practice because we are a national referral center for such lesions. With the purpose of evaluating the consequences of duct ligation done

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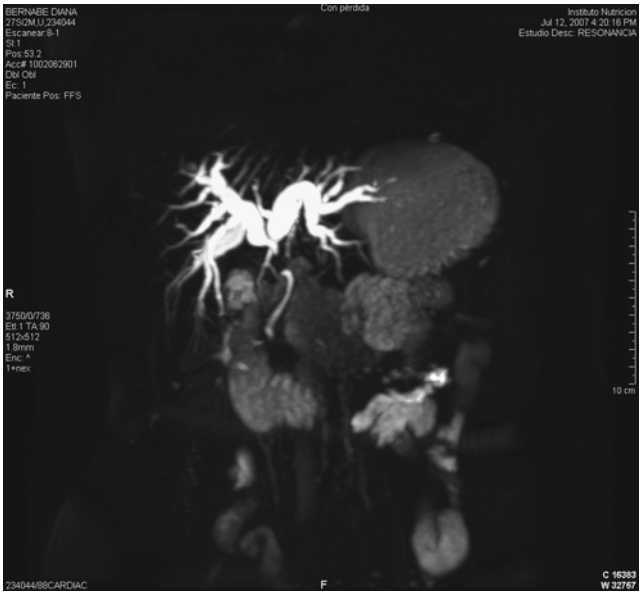

Figure 1 MRI showing obstruction of the duct with dilation of the intrahepatic biliary tree. This condition was observed in less than 10% of the cases.

at the index operation, the files of patients with bile duct injuries after voluntary and involuntary ligature, in the context of iatrogenic injuries, were reviewed.

Methods

We reviewed the files of those who had voluntary or involuntary bile duct ligation among patients referred to our hospital for surgical treatment of a bile duct injury between January 1990 and December 2006. Results of preoperative evaluation of the ducts, operative treatment, and postoperative results were analyzed. Bile duct dilation was defined as a duct diameter greater than 10 mm as measured by preoperative ultrasound and or cholangioresonance. Patients treated by means of endoscopy and/or radiology were excluded.

Results

A total of 413 patients with bile duct injuries were referred to our institute for surgical repair. Two hundred and sixty-seven were female and 146 were male, with a mean age of 37 (17–73 years). Of these, 128 were seen in the last 2 years.

A total of 33 patients were treated at the index operation. The remaining had different clinical conditions with or without attempt of repair. A subset of 45 patients arrived hours or days (8–144 h, mean $\bar{x}$ 74) after the index operation with only subhepatic drainage and no attempt at repair (Table 1). Of these, 15 were known to have voluntary placement of a ligature (referred in the transfer note), and in the rest (30), the binding was involuntary. In the 15 cases of voluntary ligature, the duct was obstructed with a heavy and large suture ("in order to be easily identified"). In those with involuntary ligature (30 cases), the obstruction was caused by clips (25) and/or sutures (5), some placed with the goal of achieving hemostasis and others because the duct was misidentified.

Bile dilation (>10 mm diameter) was present in one case of the voluntary ligation group (6%) and in three cases of the nonvoluntary group (10%) (Fig. 2). From these, we identified 27 cases of fistulization (internal 5 and external 22); 25 were secondary to clip ligature and 2 were as a result of suture ligature. In the voluntary group, 14 cases had a fistula (internal 4, external 10). Fistula developed secondary to necrosis of the binded duct and leakage proximal to the ligature, resulting in diverse degrees of bilioperitoneum and/or biloma.

In all cases, a Roux-en-Y hepatojejunostomy was performed. The mean follow up was 64 months for this group after repair. Two cases required reoperation because of stenosis of the anastomosis and recurrent cholangitis. Two cases had recurrent cholangitis without jaundice; these patients were treated conservatively with antibiotics. One of these patients developed secondary biliary cirrhosis after 8 years and is on the waiting list for a liver transplant.

Discussion

The results of our retrospective analysis of patients with duct ligature (voluntary and involuntary) show that most patients develop a biliary fistula rather than dilation. The acute ligated duct provokes pain and quick deterioration of the liver function as evidenced by abnormal levels of specific clotting factors (factor V), prealbumin, and prothrombin time (if the patient has not been managed with fresh plasma). We observed deterioration of liver function tests (elevated bilirrubin, aminotransferases, and a drop in seric albumin) in all cases. Ligature usually causes high intraductal pressure proximal to the ligature. The abrupt

Table 1 Voluntary vs. Involuntary Ligature

	Voluntary	Involuntary
Patients n=45	15	30
Suture	15	5
Fistula	14	2
Clip	0	25
Fistula	0	25
Dilation >10 mm	6%	10%

increase in pressure results in necrosis of the duct proximal to the ligature and subsequent fistulization rather than dilation. Bile extravasation produces bilioperitoneum and/or biloma with different degrees of systemic repercussion.

The protocol at our institution for the evaluation of these patients includes liver function tests and evaluation of concomitant hepatopathy (secondary to long-term obstruction or secondary biliary cirrhosis), definition of bile duct anatomy, and status of the previous repair attempt. A general evaluation including liver function and cardiorespiratory tests and an ultrasound are the initial studies. Reconstruction can be planned if extra- and intrahepatic dilation of the ducts is observed in a stable patient. Fistulography is performed in those patients with a "T" tube or a drain to evaluate possible fistulae to adjacent viscus[7] and to determine if the biliary tree can be filled with contrast for the evaluation of its anatomy.

Patients with a bile duct injury can present several scenarios, ranging from very stable patients with mild jaundice and/or controllable cholangitis to critically ill patients with ventilatory and systemic requirements. Some cases require drainage of the bile ducts because of obstructive jaundice and cholangitis. In these patients, percutaneous drainage is done, as well as a cholangiography to outline the anatomy. We usually keep the drains in situ until the repair is done.

Endoscopic retrograde cholangiography is done in most patients in whom a biliary leak is suspected and in those in whom duct continuity is demonstrated. Small lateral leaks, cystic stump insufficiency, and small leaks in the gallbladder bed can be treated by means of sphincterotomy and/or endoprothesis placement.[8]

When the patient is stable and the endoscopic and/or radiological treatment is not viable (loss of continuity of the ducts or the radiologist is unable to dilate the former anastomosis) the patient is scheduled for an elective repair.

Cases of ducts with loss of continuity require repair by a bilioenteric anastomosis. For most of the surgical-interested groups, including us, the Roux-en-Y hepatojejunostomy is the procedure of choice.[9] Some are repaired during the index operation (34 cases, 9 from our hospital).[10] Others arrive hours or days after the injury with biliary fistula, with bilioperitoneum and/or biloma, and with/without multiple organ failure.[11] Other subsets of patients arrive with obstructive jaundice weeks or months after the cholecystectomy, and a large number of patients arrive with a previous repair attempt with jaundice and/or a history of cholangitis.

The Roux-en-Y hepatojejunostomy is performed after complete dissection of the right upper quadrant. Specific care is taken to identify the route left by the scars from the drains, to rule out fistulization to the colon, small intestine (uncommon) or duodenum. In our experience, this is the most common site of fistulization if a drain (T tube or other) has been maintained for a long period of time.

The hilus is carefully dissected, trying to keep the arterial supply intact, and the hepatic artery is identified (in one case, the main artery and portal vein were transected at the index operation and an end-to-end anastomosis and portal vein reconstruction were performed). After identification of the transected and/or ligated duct, an anterior opening is done directing it to the left duct. To avoid damage of the arterial supply of the duct, the opening is made in the anterior aspect. A Roux-en-Y hepatojejunostomy is done with everted 5–0 absorbable monofilament sutures. If the patient already has a Roux-en-Y hepatojejunostomy, complete dissection of the limb is done so as to rule out wrong construction and inadequate position with obstruction. We have identified several cases with this condition.

The condition and diameter of the duct has to be individualized to any given patient. In some instances the duct is found with an inflammatory reaction due to bile leakage, with or without ischemic damage and variable diameter. The duct can present a large inflammatory and/or ischemic reaction and variable anatomical conditions, and surgical strategy is designed accordingly. We have found that, in our series, patients treated by means of an anastomosis done at the level of the confluence with extension to the left duct achieve the best results.

A frequent question from surgeons in surgical meetings is if the duct should be previously bound for days or weeks until dilation occurs, thus offering the opportunity of a technically easier anastomosis. Evidently, every surgeon wants to find a healthy dilated duct that makes the anastomosis easier; if this were the case, then bilioentric anastomosis could be performed by a general surgeon

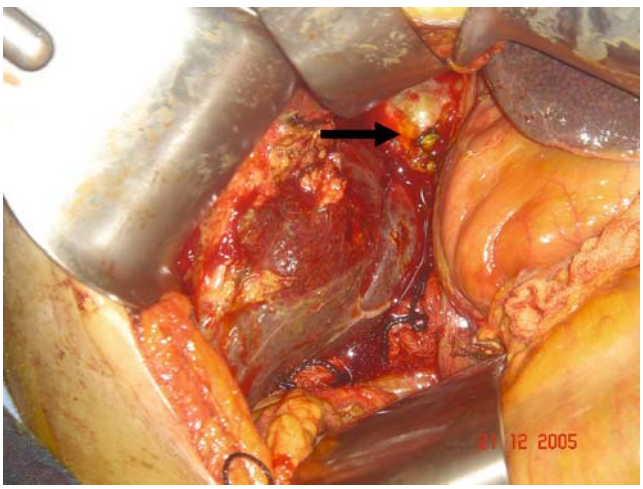

Figure 2 Intraoperative view of the hepatic hilus; the *arrow* points to the dilated ligated bile duct. A heavy ligature can be seen placed in the duct.

without specific experience in bile duct repair. The surgeon that identifies a bile duct transaction he/she cannot repair should not intentionally clip or ligate the proximal biliary tree because the probability of dilation is less than 10%; we believe early referral of the patient is mandatory.

This probability has also been suggested by experts in the field. Bismuth and Majno discuss delaying the primary repair considering the spectrum and classification of the injuries.[6] After treating the complications of the injury (bile peritonitis, biliary fistula), the repair is postponed until the biliary tree has dilated, followed by sequential ultrasound and finally operating when the confluence has reached a 10-mm width. According to their experience, the duct takes 2 to 3 months to dilate. They state that, occasionally, a shorter interval is enough if the duct has been occluded by a clip.

Unlike acute obstruction, the gradual pressure increase due to an extrahepatic carcinoma of the distal bile duct, pancreas, or ampule allows gradual dilation. Thus, the bilioenteric anastomosis in these patients plus the integrity of the duct results in a technically easier procedure. Even those performed as part of a Whipple surgery with or without dilated ducts are easier to construct, compared to those of an iatrogenic bile duct injury.

We are unable to conclude in this study if fistulization is more common with clip ligature or suture because of sample size. Most of the involuntary cases had a clip in the ductal stump and five cases had a suture, and in the voluntary cases, only sutures were placed. The clipped group was larger than the suture group. In spite of sample size limitations, it appears that there is no difference between ligature and clip ligation.

According to our observations, bile duct ligature produces dilation in a very small number of patients (less than 10% of the cases). Ligature of the duct usually produces necrosis of the ligated stump, with subsequent bile leakage with bilioperitoneum or biloma that usually deteriorates the condition of the patient. Concluding, we consider that placement of a subhepatic drain, and transfer of the patient is the best approach if the primary surgeon is technically unable to perform the repair.

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Outcome of Surgical Treatment of Hilar Cholangiocarcinoma

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Abstract To evaluate surgical results and the effect of adjuvant chemotherapy in cases of hilar cholangiocarcinoma, we retrospectively analyzed 27 consecutive patients who underwent surgical resection (eight bile duct resections, 18 bile duct resections plus hepatectomy, one hepatopancreaticoduodenectomy). There was no operative mortality, and the morbidity was 37%. Curative resection (R0 resection) was achieved in 20 (74%) patients. Overall survival at 3 and 5 years was 44% and 27%, significantly higher than that of 47 patients who did not undergo resection (3.5% and 0% at 3 and 5 years, $p<0.0001$). Survival of patients with positive margins (R1/2 resection) was poor; there were no 5-year survivors. However, survival was better than that of patients who did not undergo resection (median survival: 22 vs 9 months, $p=0.0007$). Univariate analysis identified lymph node metastasis as a negative prognostic factor ($p=0.043$). Median survival of patients who underwent adjuvant chemotherapy was significantly longer than that of patients who did not (42 vs. 22 months, $p=0.0428$). Resection should be considered as the first option for hilar cholangiocarcinoma. There appears to be a survival advantage even in patients with cancer-positive margins. Adjuvant chemotherapy may increase long-term survival.

Keywords Hilar cholangiocarcinoma · Surgery · Survival · Bile duct cancer · Chemotherapy

Introduction

Hilar cholangiocarcinoma (Klatskin-type tumor[1]) is a rare neoplasm arising from the epithelium of the common hepatic duct or its first or second bifurcation. Although this neoplasm has been characterized as a slow-growing and late metastasizing tumor, it develops adjacent to the portal vein, hepatic artery, or liver parenchyma, and it readily invades these regions. In addition, liver dysfunction secondary to obstructive jaundice develops in most patients. These factors result in treatment difficulty and a poor prognosis.[1,2]

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Surgical resection with complete removal of all cancer tissues offers patients the only chance for a cure and long-term survival.[3–6] If hilar cholangiocarcinoma is not resected, the median survival of patients is less than 1 year.[7,8] Recent developments in perioperative management and surgical procedures including biliary drainage,[9] portal vein embolization,[10] major hepatectomy,[7,11,12] and even hepatopancreaticoduodenectomy,[13] have reduced operative morbidity and mortality and increased resectability; however, results of surgical treatment of hilar cholangiocarcinoma remain unsatisfactory. Moreover, because of the low incidence and complexity of the tumor, prognostic factors after treatment have not been fully evaluated and the optimum treatment strategy is still debated.[7,8,14,15] Issues include whether patients should be treated palliatively or by tumor resection with or without concomitant liver resection. Also, the effect of adjuvant therapy is open to discussion.

We conducted a retrospective study of patients with hilar cholangiocarcinoma to determine the short- and long-term results of surgical resection and factors that might influence survival. The effect of postoperative chemotherapy was also analyzed.

Patients and Methods

Patients

Between 1990 to 2005, 74 patients (52 men and 22 women) with hilar cholangiocarcinoma were treated at the First Department of Surgery, Miyazaki University Hospital. The median age of these patients was 68 years (range 47–90 years). Hilar cholangiocarcinoma was defined as a tumor in the upper common, right, or left hepatic duct.

The diagnostic evaluation for hilar cholangiocarcinoma was based on the results of ultrasonography, computed tomography, magnetic resonance cholangiography, endoscopic retrograde cholangiography, percutaneous transhepatic cholangiography, and/or abdominal angiography. The final diagnosis was based on surgical specimens, endoscopic transpapillary forceps biopsy/brush cytology, percutaneous transhepatic cholangioscopy-guided biopsy, and clinical course. The lesions were classified by site and extent according to the Bismuth-Corlette classification system[16]: type I (n=7, 9.5%), type II (n=4, 5.4%), type IIIa (n=14, 18.9%), type IIIb (n=10, 13.5%), and type IV (n=39, 52.7%).

The choice of therapeutic procedures depended on the extent of the tumor and the patient's clinical condition. If the tumor was considered resectable, surgery was the first choice for patients in good clinical condition. Contraindications to resection included medical comorbidities, distant metastatic disease, extensive bilateral intrahepatic extension, and extensive intrahepatic extension combined with contralateral vascular involvement or atrophy. Surgery was considered suitable for 27 patients (36%) and tumor resection was performed with or without liver resection. In 47 patients (64%) with an unresectable tumor or a poor clinical condition, palliative endoscopic transpapillary and/or percutaneous transhepatic biliary drainage was performed.

Surgical Procedures

Bismuth–Corlette classifications of the 27 patients who underwent tumor resection were as follows: type I (n=2, 7.4%), type II (n=2, 7.4%), type IIIa (n=6, 22.2%), and type IIIb (n=6, 22.2%), and type IV (n=11, 40.7%). In patients with jaundice, endoscopic biliary drainage or percutaneous transhepatic biliary drainage was performed before surgical resection. Biliary drainage was performed until the bilirubin level was reduced, ideally to <2 mg/dl. In patients with cholangitis, resection was performed after alleviation of inflammation. To avoid postoperative liver failure, portal embolization[10] with gelatin sponge particles was carried out, depending on liver function and the volume of liver parenchyma to be resected, which was calculated by means of computed tomography.[10,17] All surgical resections were carried out with the intent of achieving histologically clear margins. At laparotomy, complete exploration of the abdominal cavity was carried out to exclude peritoneal and omental carcinomatosis and occult metastatic disease. Bile duct resection proceeded from the level of pancreas upward and lymphatic tissue was taken from around the hepatoduodenal ligament to the celiac trunk. In cases of bile duct resection without hepatectomy, exploration was continued as far as the intrahepatic bile ducts to provide access to the distended ducts above the tumor. The distended ducts were transected at levels macroscopically free of the tumor. Proximal and distal bile duct margins were assessed on frozen sections during surgery. If surgical margins were shown to be positive, additional resection was performed as far as was technically feasible until clear margins were obtained. In patients with a Bismuth type IIIa, IIIb, or IV lesion, whenever it was feasible, in-continuity hepatic resection was also carried out with bile duct resection. Some patients were judged not to tolerate hepatic resection because the estimated volume of remnant liver was too small or their medical condition was poor. Bile duct resection was applied to such patients if the tumor was assessed to be resectable and invasion to hepatic parenchyma was absent. All extended right hepatectomies and left hepatectomies included caudate lobectomy. Biliary continuity was restored by Roux-en-Y biliary-enteric anastomosis.

Eight of our patients underwent bile duct resection only (two type I lesions, one type II lesion, three type IIIb lesions, and two type IV lesions), and all eight patients underwent Roux-en-Y cholangiojejunostomy with two or more divided segmental hepatic ducts. Nineteen patients underwent bile duct resection plus hepatectomy (one type II lesion, six type IIIa lesions, three type IIIb lesions, and nine type IV lesions). The following procedures were performed: right hepatectomy (five patients), extended right hepatectomy (five patients), left hepatectomy (three patients), and extended left hepatectomy (six patients). The biliary system was reconstructed by Roux-en-Y cholangiojejunostomy. The Whipple procedure was necessary in one patient because of extension of the tumor into the distal part of the common bile duct.

Tumors were classified according to the TNM staging system of the International Union Against Cancer (UICC).[18] Residual tumors were also classified according to the UICC system, with histologically confirmed tumor-free margins classified as R0 (no residual tumor, 20 patients), microscopically tumor-positive resection margins classified as R1 (microscopic residual tumor, five patients), and macroscopically tumor-positive margins classified as R2 (macroscopic residual tumor, two patients).

Nonsurgical Palliative Procedures

Forty-seven patients were given palliative care only. Bismuth–Corlette classifications were as follows: type I (n=5, 10.6%), type II (n=2, 4.3%), type IIIa (n=8, 17.0%), type IIIb (n=4, 8.5%), and type IV (n=28, 60.0%). Initially, a plastic biliary endoprosthesis was inserted by therapeutic duodenoscopy or by percutaneous transhepatic approach. When the tumor was confirmed to be unresectable, the patient was assigned to insertion of an expandable metallic stent if he or she agreed.

Chemotherapy

Cisplatin (CDDP) combined with 5-fluorouracil (5-FU) was primarily used for chemotherapy against hilar cholangiocarcinoma. In 2005, gemcitabine (GEM) combined with S-1 was introduced as a primary regimen. We offered these regimens to all patients; however, some did not agree. In such patients, fluoropyrimidines were orally given and the others did not receive chemotherapy.

Of the 27 patients who underwent resection, 12 received chemotherapy postoperatively (eight underwent R0 resection and four underwent R2 resection). Five patients received CDDP (6 mg m^{-2} day^{-1}) from day 1 to day 4 in combination with 5-FU (500 mg m^{-2} day^{-1}), which was administered on day 5; these patients underwent two to five treatment cycles. GEM (500 mg m^{-2} day^{-1} given on days 1, 8, 15) combined with S-1 (40 mg/day from day 1 to day 14) was administered to two patients; one underwent one cycle and the other two cycles. Oral fluoropyrimidines were given daily to five patients for 2–36 months: tegafur/uracil 300–400 mg/day to four patients and carmofur 300 mg/day to one patient. Extracorporeal radiotherapy to 40 Gy was used in one patient who was given CDDP/5-FU.

Sixteen of the 47 patients who did not undergo surgical resection received chemotherapy with or without radiotherapy. CDDP/5-FU (four to five cycles) was administered to six patients, four of whom also received extracorporeal radiotherapy (30–60Gy). GEM/S-1 (one to six cycles) was given to five patients, one of whom received 50 Gy of extracorporeal irradiation. Three patients were given oral fluoropyrimidines for 8–24 weeks without radiotherapy. Of the remaining two patients, one received GEM (1,000 mg m^{-2} day^{-1})/5-FU (250 mg per body per day) twice at 7-day intervals without radiation, and the other was treated by arterial infusion of 5-FU/doxorubicin/mitomycin C via the common hepatic artery plus intraluminal (30 Gy) and extracorporeal (30 Gy) radiotherapy.

Patient Follow-Up

Patients were followed up at our outpatient clinic every 1–3 months, and median follow-up time was 22.7 months. Operative mortality was defined as death within 30 days after surgery.

Statistical Analysis

Patient survival was calculated according to the Kaplan–Meier method, and univariate analysis was performed with the log rank test. A multivariate Cox model was used to analyze for which univariate analysis yielded a p value of $\leq$0.15. Variables were tested until a final model with a p value <0.05 for each factor was obtained.[19] All statistical analyses were performed with JMP 6.03 (SAS Institute Inc).

Results

Mortality and Morbidity

There was no operative mortality (0%). Fourteen postoperative complications occurred in 10 of the 27 patients who underwent surgical resection; thus, the complication rate was 37%. Of the 19 patients who underwent concomitant hepatic resection, nine (47%) had 13 complications, with anastomotic leakage being the most common (n=6), followed by hepatic failure (n=2), bile leakage from the cut surface of the liver (n=2), intraabdominal bleeding (n=1), liver abscess (n=1), and jejunal perforation (n=1). Of the eight patients who underwent bile duct resection alone, one (13%) suffered postoperative hepatic failure. The morbidity rate did not differ between patients treated by bile duct resection combined with hepatic resection and those treated by bile duct resection alone (p=0.0702).

Resectability and Curability

Tumor resection was performed in 27 of the 74 patients; thus, the resectability rate was 36%. R0 resection was considered curative resection. Of the 27 tumor resections, 20 (74.1%) were determined histologically to be curative resections. Curative resection was performed in 14 (73.7%) of the 19 patients who underwent both bile duct and liver resection and in six (75.0%) of the eight patients who underwent bile duct resection alone. There was no significant difference in curability between these two groups (p=0.9431).

Survival

Overall survival at 1, 3, and 5 years after tumor resection was 84.9%, 44.4%, and 26.7%, respectively. Overall survival at 1, 3, and 5 years after nonsurgical treatment was 34.0%, 3.5%, and 0%, respectively. Median survival after resection was significantly longer than survival after

nonsurgical treatment (23 vs. 9 months; $p<0.0001$). Survival was markedly decreased in patients with a positive margin (R1/2 resection, none survived 5 years) in comparison to that in patients with a negative margin, but the difference was not significant. Survival was significantly shorter for patients who did not undergo resection than for patients who underwent R1/2 resection (22 vs. 9 months, $p=0.0007$, Fig. 1).

Prognostic Factors for Survival after Surgical Resection

Univariate analysis revealed that lymph node metastasis ($p=0.0430$) and lack of adjuvant chemotherapy ($p=0.0428$) were significant predictors of poor overall survival after surgical resection (Table 1). Median survival of patients with lymph node metastasis was 22 months; that of node-negative patients was 42 months. No node-positive patient survived 2 years after surgery (Fig. 2). Age, sex, Bismuth–Corlette classification, UICC stage, histopathologic grade, pathologic vascular or neural invasion, residual tumor status, and operative procedures (concomitant hepatic resection or concomitant vascular resection) did not affect overall survival after surgical resection (Table 1).

Multivariate analysis using Cox's proportional hazard model identified lack of adjuvant chemotherapy as a negative prognostic factor for survival (relative risk 1.708, 95% confidence interval 1.019–3.075, $p< 0.0422$).

Effect of Chemotherapy

Twelve of the 27 patients who underwent surgical resection received adjuvant chemotherapy. Overall median survival was significantly longer for patients given chemotherapy than for those not given chemotherapy (42 vs 22 months, $p=0.0428$, Fig. 3a). Median survival was longest in patients who underwent R0 resection and chemotherapy (101 months), followed in order by those who underwent R1/2 resection and chemotherapy (41 months), R0 resection without chemotherapy (23 months), and R1/2 resection without chemotherapy (22 months). Concerning lymph node status, four of five patients with positive nodes received adjuvant chemotherapy, and there was no difference in median survivals between patients with chemotherapy and those without chemotherapy (23 vs. 22 months, $p=0.7543$). Of the 22 patients without lymph node metastases, 11 received adjuvant chemotherapy. Median survival of patients with chemotherapy seemed to be longer than those without chemotherapy, although statistical significant was not obtained (101 vs. 23 months, $p=0.1016$). Of the 47 patients who did not undergo surgical resection, 16 underwent chemotherapy with a therapeutic intent. Median survival of patients who received chemotherapy tended to be longer than that of patients who did not (11 vs. 6 months), but statistical significance was not obtained ($p=0.0745$, Fig. 3b).

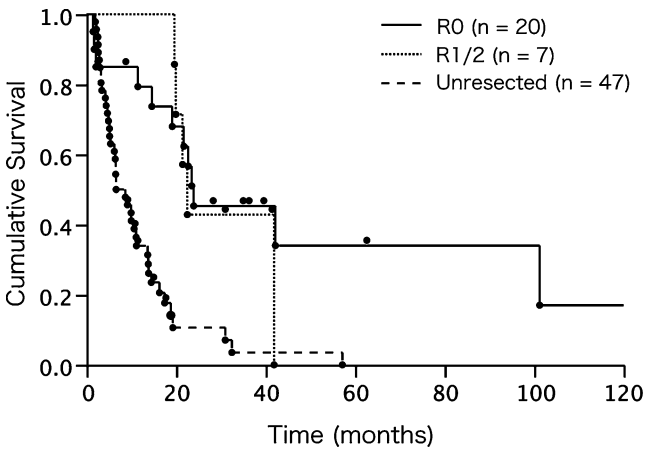

Figure 1 Overall survival curves in patients with no tumor residue (*R0*), macro- or microscopic tumor residue (*R1/2*), and nonsurgical resection (*Unresected*). Survival was counted from the day of admission for nonsurgical resection and from day of surgery in others. Significant differences were found between the R0 group and the unresected group ($p<0.0001$) and between the R1/2 group and the unresected group ($p=0.0007$).

Discussion

The present retrospective study was conducted to evaluate results of surgical treatment of hilar cholangiocarcinoma. Surgical resection of the tumor significantly improved survival, even if the resection was not considered curable. Survival of patients who underwent postoperative chemotherapy was significantly longer than that of those who did not. These results indicate that surgical resection followed by adjuvant chemotherapy should be the preferred treatment strategy for hilar cholangiocarcinoma.

Recent developments in surgical procedures and perioperative management have increased the safety of resection of hilar cholangiocarcinoma. Postoperative mortality, once reported to be as high as 18%,[20] has been reduced to less than 10%.[7,11,12] Operative mortality in our series was 0%, probably because of suitable biliary decompression[9] to reduce jaundice and restore liver function as well as to preoperative portal embolization[10] to provide adequate functional volume of the remnant liver. The safety of the procedure provides a rationale for an aggressive surgical approach to hilar cholangiocarcinoma.

The reported resectability of hilar cholangiocarcinoma varies greatly from 25%[14] to 95%.[12] This variation is caused by the fact that some studies included only patients referred for possible surgical resection and did not include patients that presented with unresectable disease. Resectability in our series was 36%; that of Jarnagin et al.[5,7] and

Table 1 Univariate Analysis of Factors Potentially Influencing Postoperative Survival of Patients with Hilar Cholangiocarcinama

Factor	Number (*n*)	Survival (%)		Median survival	
		3 years	5 years	Month	*p* value
Age					
Less than 70 years	17	53.3	35.6	42	0.1586
70 years or older	10	30.0	15	23	
Sex					
Male	19	44.7	29.8	23	0.9181
Female	8	43.8	21.9	24	
Bismuth classification					
I or II	4	50.0	50.0	125	0.4501
III or IV	23	43.3	21.6	23	
T category					
pT1 or 2	8	50	50	125	0.2324
pT3 or 4	12	33.3	0	22	
N category					
pN0	22	55.3	33.2	42	0.0430
pN1	5	0	0	22	
UICC stage					
I	12	41.7	27.8	23	0.7778
II, III, or IV	15	46.7	23.3	24	
Histopathologic grade					
G1 or 2	22	41.8	31.4	24	0.7887
G3	4	50.0	0	42	
Hepatic invasion					
Positive	10	40.0	0	24	0.2623
Negative	11	56.8	37.9	42	
Perineural invasion					
Positive	1	0	0	11	0.1022
Negative	18	47.6	31.8	24	
Portal vein invasion					
Positive	3	0	0	23	0.9883
Negative	19	41.5	27.6	23	
Hepatic artery invasion					
Positive	2	0	0	N.A.	0.8552
Negative	19	41.5	27.6	23	
Residual tumor status					
R0	20	45.3	34	23	0.6513
R1 or 2	7	42.9	0	22	
Hepatic resection					
Yes	19	44.7	29.8	24	0.8834
No	8	43.8	21.9	23	
Vascular resection					
Yes	3	66.7	66.7	24	0.2555
No	24	41.3	20.6	125	
Adjuvant chemotherapy					
Yes	12	63.6	47.7	42	0.0428
No	15	29.1	0	22	

Wizigmann et al.[8] was 36% and 33%, respectively, both of which included surgically and palliatively treated patients.

Introduction of concomitant liver resection has contributed an increased resection rate in surgical treatment of hilar cholangiocarcinoma.[11,12,21] However, whether hepatic resection should be performed in all patients with hilar cholangiocarcinoma is controversial. According to Launois et al.,[22] the indication for associated hepatectomy depends

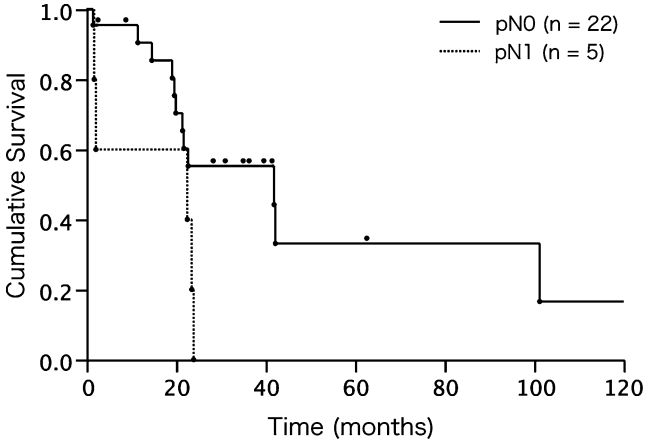

Figure 2 Overall survival curves after resection according to lymph node involvement. Significant difference was found between patients with lymph nodes negative for tumor cells (*pN0*) and those with positive nodes (*pN1*). p=0430.

on tumor location and TNM classification. To the contrary, Jarnagin et al.[7] claimed that hepatic resection should be considered for all patients because bile duct resection combined with hepatic resection yield more R0 resections and longer survival than did bile duct resection alone. In the present study, R0 resection rates and overall survival did not differ between patients who underwent concomitant liver resection and those who underwent bile duct resection alone, although clinical backgrounds including Bismuth types were different between the groups. We performed bile duct resection without hepatectomy for three Bismuth I or II tumors and five Bismuth III or IV tumors, whereas hepatic resection was carried out for one Bismuth II tumor and 18 Bismuth III or IV tumors. These results suggest that concomitant hepatic resection is necessary to clear most Bismuth III or IV tumors; however, extended resection is not always necessary, particularly for Bismuth I or II tumors. This is supported by the results of other studies in which long-term survival was obtained even with bile duct resection alone.[23–25] Combined hepatic resection is the principal choice of treatment for Bismuth III and IV tumors whenever it is feasible; however, bile duct resection without hepatectomy may be the alternative to highly selected patients, especially those whose medical condition is poor and tumor invasion to hepatic parenchyma is absent.

The prognosis of hilar cholangiocarcinoma is highly dependent on whether the patient is treated by surgical resection or palliation.[3–6] In our series, median survival of patients who did not undergo resection was 9 months, and no patient survived 5 years, whereas 5-year survival of patients who underwent resection was 26.7%, and median survival was 23 months. These results are comparable to previously reported 5-year survival rates of 12–35% with 14–35 months of median survival[3,7,22–27] and no 5-year survival without resection (4–10 months median survival).[3,5,6] Thus, surgical resection appears to be the only potentially curative therapeutic modality. Many authors have also reported a negative surgical margin (R0 resection) to be an important prognostic factor.[6–8,21,26–28] In the present series also, survival of patients with a positive margin (R1/2 resection) was poorer than that of patients who underwent R0 resection, although statistical significance was not observed. None of our patients who underwent R1/2 resection survived 5 years, but one of our patients who underwent R0 resection survived 10 years. These results indicate that, alone, resection with a negative surgical margin offers the chance of cure in patients with hilar cholangiocarcinoma. We found that resection, even R1/2 resection, conferred a survival benefit over palliative treatment; however, this result is controversial. Several authors[7,8] reported that survival after resection with a positive margin was not better than that after palliative treatment. Others,[3,6,29] however, observed better survival among patients who underwent resection even with positive margins than

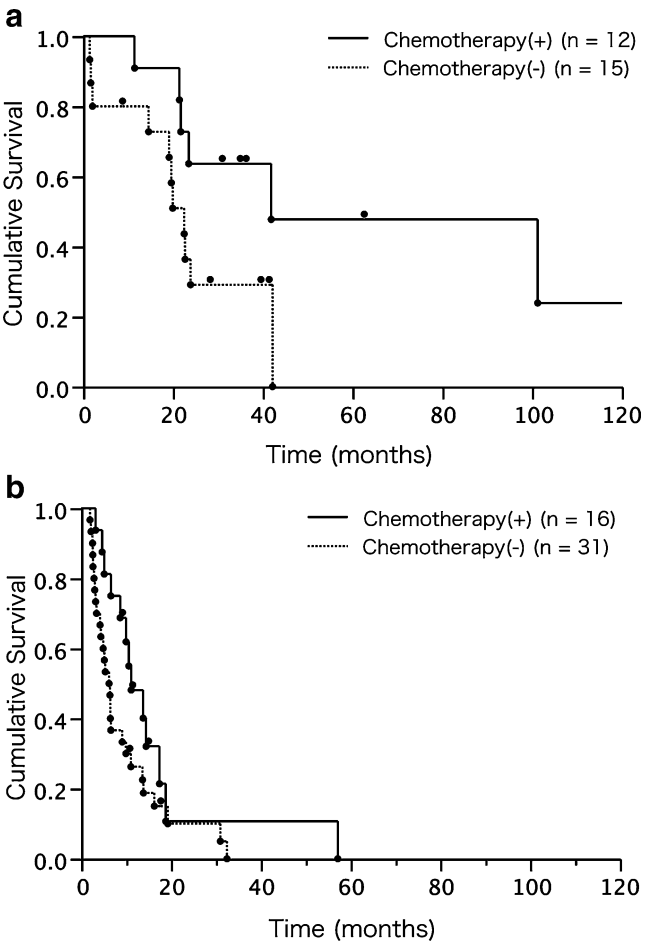

Figure 3 (**a**) Overall survival curves after resection in patients with or without adjuvant chemotherapy. Significant difference was found between two groups (p=0.0428). (**b**) Overall survival curves in unresected patients with or without chemotherapy. There was no significant difference (p=0.0745).

among patients who did not undergo resection. The discrepancy may be caused by differences in patient selection, surgical approach, and type of palliative treatment between studies. In light of the poor prognosis of unresected tumors and difficulty in predicting exact margin status preoperatively, surgery should be considered for all patients with hilar cholangiocarcinoma, except those with distant metastasis, a poor general condition, or a locally advanced tumor.

Lymph node metastasis is the most commonly reported risk factor for poor survival after surgical resection.[6,27,28] We too identified lymph node metastasis as a negative prognostic factor. No patients with positive lymph nodes survived 5 years, as reported elsewhere.[30,31] However, whether to consider lymph node metastasis as a contraindication for surgery is controversial. Kitagawa et al.[32] reported a 15% 5-year survival rate among patients with regional lymph node metastasis treated by extended lymphadenectomy including paraaortic nodes. Five-year survival of node-positive patients has been reported by others.[11,33] In addition, Kosuge et al.[21] and Silva et al.[34] reported that survival of patients with metastasis was similar to that of patients without nodal involvement if the metastasis was limited to regional nodes. These conflicting results may be because of differences in the extent of lymph node dissection and the accuracy of pathologic diagnosis of metastatic nodes between studies. Further studies are needed to identify the effect of lymph node metastasis on survival and the efficacy of extended lymph node dissection.

The efficacy of adjuvant therapy for hilar cholangiocarcinoma remains controversial. Although adjuvant radiotherapy does not usually confer a survival benefit,[15] some have reported that postoperative radiotherapy might provide some benefit,[35,36] especially in the management of patients with a microscopically positive margin.[37,38] However, there is no reported evidence that adjuvant chemotherapy is effective for hilar cholangiocarcinoma.[39] Patients in the present study who received chemotherapy after surgical resection survived significantly longer than those who did not receive chemotherapy, and multivariate analysis identified adjuvant chemotherapy as an independent prognostic factor for survival. Serafini et al.[40] and Hughes et al.[41] reported improved outcomes with surgical resection followed by 5-FU-based chemotherapy and radiation in patients with distal bile duct cancer. These results, together with ours, suggest a possible benefit of adjuvant chemotherapy for hilar bile duct cancer. The present study was retrospective; thus, patients were not randomized to chemotherapy vs. no chemotherapy, the agents used and treatment schedules were not identical, and there may have been a selection bias for patients who recovered satisfactorily from surgery. An appropriate randomized controlled study is needed to clarify the effect of adjuvant chemotherapy on prognosis of hilar cholangiocarcinoma.

Conclusion

Only R0 resection offers a chance of long-term survival to patients with hilar cholangiocarcinoma. Resection should be considered the first option because resection seems to confer a survival advantage even in patients with positive margins. Lymph node metastasis is an important negative predictor of survival, and the prognosis for patients with positive nodes is poor even when R0 resection was performed. Adjuvant chemotherapy may be beneficial for improving survival; however, further prospective randomized studies are needed.

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Usefulness of Absorbable Sutures in Preventing Surgical Site Infection in Hepatectomy

Shinji Togo · Toru Kubota · Takuji Takahashi · Kenichi Yoshida · Kenichi Matsuo · Daisuke Morioka · Kuniya Tanaka · Hiroshi Shimada

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Abstract We evaluated the usefulness of synthetic absorbable sutures (Vicryl) in preventing surgical site infection (SSI) after hepatectomy. A rat model of 60% partial hepatectomy was used. Bleeding from the cut surface of the liver was controlled by using two suture types: silk and Vicryl. In the Vicryl group, the lesser omentum was slightly adherent to the cut surface of the liver, while in the silk group, the suture remained, and severe adhesions were found. The number of *Staphylococcus aureus* was significantly larger in the silk group. We compared a group of patients (n=125) who underwent hepatectomy using silk with one (n=188) using Vicryl. The respective incidences of SSI and infection on the cut surface of the liver in the Vicryl group (3.2, 1.6%) were significantly lower than in the silk group (11.2, 8.8%). In accordance with the results of multivariate analysis, duration of operation, use of silk sutures and the complication of bile leakage were selected as independent factors. The risk of SSI in the silk group was 3.4 times that in the Vicryl group. The use of synthetic absorbable sutures, instead of silk sutures, in all the procedures of hepatectomy contributed significantly to the prevention of SSI.

Keywords Silk suture · Absorbable suture · Surgical site infection · Hepatectomy

Introduction

Silk sutures are still used in abdominal surgery in many facilities in Japan. However, an infection may develop around a silk suture in a superficial or an internal surgical wound, resulting in continuous pus discharge. In such cases, the suture is removed, and healing is achieved.[1] Approximately 30 years ago, a clinical randomized controlled study was conducted to compare absorbable with nonabsorbable sutures and found that silk sutures promoted granulation and caused infection.[2] Consequently, absorbable sutures are used in most facilities in the United States and Europe. Researchers have compared synthetic absorbable sutures with silk sutures and have reported the usefulness of the former. In the field of digestive surgery, however, such studies have generally been limited to clinical studies focusing on the use of various sutures at the time of skin closure.[2] No researchers have reported on the usefulness of absorbable sutures in treating the cut surface of the liver in intraperitoneal procedures, especially hepatectomy. In the present study, we evaluated the usefulness of absorbable sutures in the process of hepatectomy, from basic and clinical viewpoints.

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Material and Methods

Animal Experiment

Animals, Operations, and Experimental Design

Eight-week-old Wistar male rats maintained on a standard diet were used for this study. The rats were maintained on a daily 12-h light/12-h dark cycle. After they were anesthetized with diethylether, partial hepatectomy (60%) was performed in each using a technique described by Higgins and Anderson.[3] Briefly, using a long laparotomy incision, the Glisson's

sheaths were ligated separately, and the left lobe was resected. Next, the median liver lobe was sutured separately five times using silk sutures and braided polyglycolide lactide (Vicryl, Johnson & Johnson Corp., Tokyo, Japan) approximately at the edge of its proximal one-third, and then about two-thirds was resected (Fig. 1). Three ligations were performed, and the suture was cut to the proper length to leave 5 mm of extra suture material at the end. Then, 2 ml of physiological saline containing *S. aureus* was sprayed on the cut surface of the liver, and the abdominal wall wound was closed. In this experiment, we diluted 1 ml of *S. aureus* (Sigma, Missouri, USA) with physiological saline and increased the volume to 20 ml. Rats were killed at two time points: 1 and 4 weeks after partial hepatectomy. At each time point, the remnant liver tissue was collected after all the blood had been drained out of it. NIH guidelines were followed for all animal experimentation.

Grouping

The rats were divided into four groups of ten each in the following manner: first, they were divided into two groups, one whose cut liver surfaces were sutured with Vicryl (Vicryl group), and the other, with cut surfaces sutured with silk sutures. Each group was then divided further into two subgroups: one, of rats whose sutured sites were exposed to *S. aureus* in physiological saline, and one, whose rats had sutured sites exposed to physiological saline alone. Five rats were selected from each group for examination 1 and 4 weeks after surgery.

Evaluation Items

Observation of Adhesion to Adjacent Organs in the Abdominal Cavity and to the Cut Surface of the Liver

After the abdomen was re-opened, the condition of adhesions to the adjacent organs was observed. Then, the stump of the liver was removed along with the ligatures to allow counting and histopathological examination of the resulting cultured bacterial colonies.

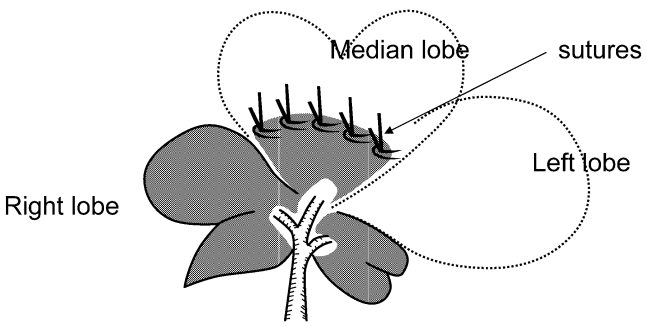

Figure 1 Schema of 60% hepatectomy in rat. We modified the 70% partial hepatectomy model developed by Higgins and Anderson by resecting the left lobe and leaving a part of the medial lobe. In this manner, we prepared a 60% partial hepatectomy model.

The pour-plate method was selected for the bacterial cultures, and yolk-added mannitol agar medium was used as the selection medium. We prepared six dilution series ranging from 10^1 to 10^6. The bacterial liquid of each dilution series was inoculated into the selected media for 48-h incubation at 37°C. The number of colonies was calculated to obtain the bacterial count, and the result was expressed as the number of bacteria present in 1 g of liver tissue segment.

Histological Examination

The liver tissues fixed in 10% formalin were processed for routine histological examination with hematoxylin and eosin staining.

Clinical Investigation

We selected 313 patients who underwent hepatectomy without reconstruction of the intestine or the bile duct during the period from April 2000 to March 2006. In principle, silk suture material was used before April 2003, while synthetic absorbable suture was used after April 2003. We divided the patients into the following two groups for comparison: a group of 125 patients who underwent ligation at the cut surface of the liver with silk suture during the period from April 2000 to March 2003 and another of 188 patients who underwent the same procedure with synthetic absorbable suture between April 2003 and March 2006.

The routine technique for hepatectomy adopted in this department is the anatomical resection of the liver.[4] The Cavitron Ultrasonic Surgical Aspirator (CUSA) and the irrigation bipolar electric cautery are used for resection. All drains are placed to form a closed suction system. For routine antimicrobial prophylaxis (AMP), administration of first- and second-generation cephem antibiotics was initiated 30 min before surgery. During surgery, additional AMP was administered every 3 h, and after surgery, for 1 or 4 days.

Bile Leakage

Diagnosis[5] of biliary complications was based on one or more of the following postoperative findings: (1) drainage of bile from the abdominal wound and indwelling drain, showing a total bilirubin level of more than 5 mg/ml or three times the serum level in the discharge fluid; (2) an intra-abdominal accumulation of bile confirmed by percutaneous drainage; and (3) cholangiographic evidence of bile leakage.

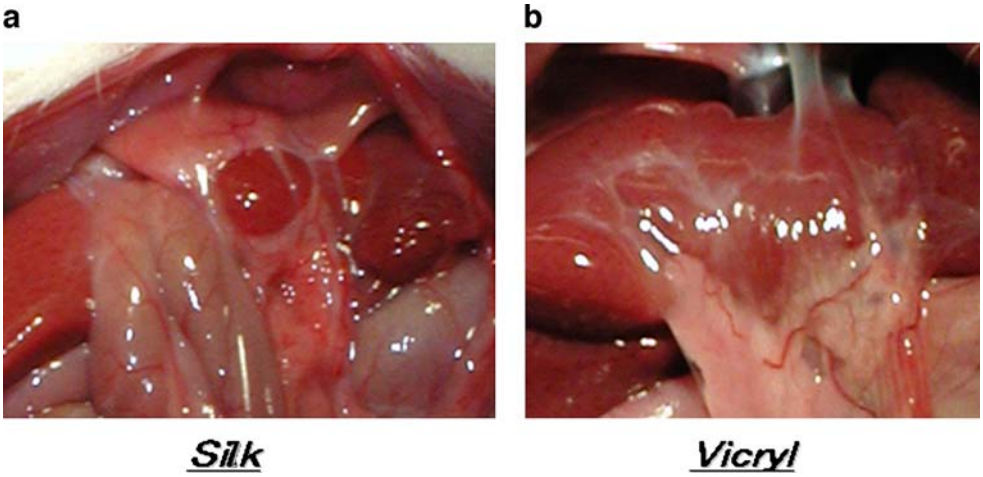

Figure 2 Gross findings at cut surface of liver. The rats were sacrificed 4 weeks later. In the silk suture group (**a**), the sutures remained on the cut surface and the small intestine, diaphragm and greater omentum were firmly attached to it. In the Vicryl suture group (**b**), however, only a few sutures remained, and slight adhesion of the greater omentum was recognized.

Postoperative Infection

Remote infection (RI) was defined as a condition in which bacteria are detected in the sputum or the urine, and signs of inflammation such as leukocytosis and fever are also present.

The definition of SSI followed that in the guidelines [6] for prevention of surgical site infection, issued by Centers for Disease Control and Prevention. Organ/Space SSI occurring within 30 days after the operation and infection appearing to be related to the operation involved any part of the anatomy (e.g., any organ, organs or space(s)). other than the primary incision, which was opened or manipulated during the operation, and at least one of the following: (1) purulent drainage from a drain introduced through a wound or incision into the organ/space, (2) isolation of organisms from a culture of fluid or tissue aseptically obtained from the organ/space, (3) an abscess or other evidence of infection involving the organ/space, that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

Infection of the cut surface of the liver was defined as follows. In the case of drain insertion into the cut surface, infection was indicated by pus discharge from the drain insertion site and by the presence of bacteria confirmed by bacterial culture. After the drain was removed, procedures such as CT scanning demonstrated collection of fluid on the cut surface of the liver, and objective findings such as tenderness or an elevated white blood cell count suggestive of infection were found. When we suspected an infection of the cut surface, we usually carry out percutaneous drainage, and if bacteria are found by culture of the extracted fluid, we diagnosed SSI. However, in the present study, if drainage could not be performed, we regarded even cases in which bacteria had been suppressed by antibiotic treatment as infection-positive.

Statistics

Results are expressed as the mean±SD. Continuous variables were evaluated using the unpaired Student's *t* test and the Mann–Whitney test. Categorical data were com-

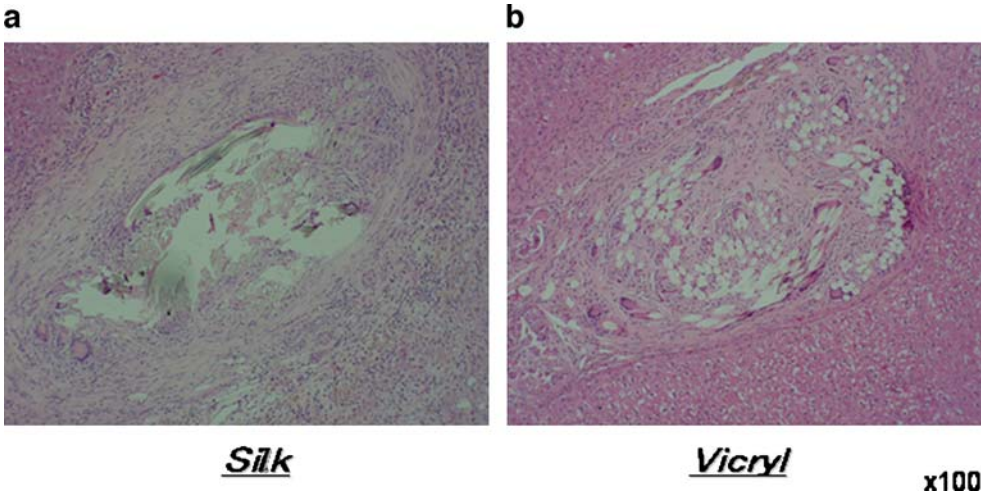

Figure 3 Amount of *S. aureus* in liver tissue after surgery. The number of *Staphylococcus aureus* present in 1 g of liver tissue segment was evaluated. The bacterial numbers obtained 1 and 4 weeks after surgery were significantly larger in the silk suture group (**a**) than in the Vicryl suture group (**b**). Within the 4 weeks, the number had increased by 1,000 times.

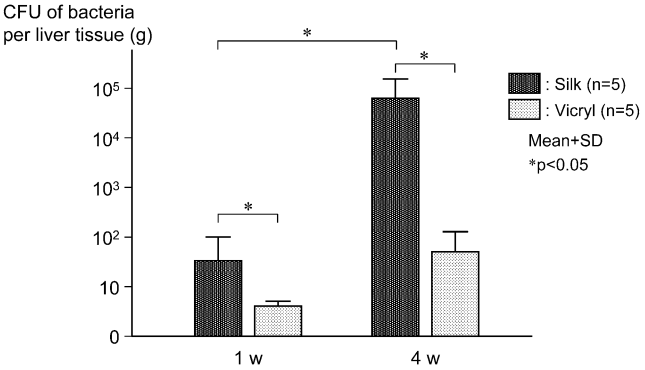

Figure 4 Histological findings of suture-granulomas at cut surface of liver. In the silk suture group, the silk sutures clearly remained, and marked peripheral fibrosis and tissue reactions were observed. In the Vicryl suture group, however, only a few sutures remained, and mild peripheral fibrosis and tissue reactions were recognized.

pared using the χ^2 test and Fisher's exact test, where appropriate. Multivariate analysis was performed with logistic regression analysis performed with the STAT-view version 5.0 software (SAS Institute Inc., USA). A level of $P<0.05$ was considered statistically significant.

Results

Basic Experiment

Condition of Adhesions to Adjacent Abdominal Organs and on Cut Surface of Liver

As shown in Fig. 2, in the Vicryl group, the lesser omentum was slightly adherent to the cut surface of the liver 4 weeks after surgery. By contrast, in the silk suture group, the suture remained on the cut surface of the liver, and moreover, the diaphragm and the duodenum adhered firmly to the liver cut surface and were extremely difficult to separate from it.

Number of S. aureus on Cut Surface of the liver

S. aureus was not detected in the groups of rats that underwent treatment with Vicryl or silk suture and were exposed to physiological saline alone. The number of *S. aureus* colonies counted after culture was significantly larger ($p<0.05$) in the group of rats that underwent treatment with silk suture and was exposed to physiological saline containing *S. aureus*. This difference was recognized 1 and 4 weeks after surgery (Fig. 3).

Histological Assessment

The remaining silk sutures were clearly observed, and marked fibrosis and tissue reactions were recognized around the sutured sites in the silk suture group. On the other hand, only parts or traces of the Vicryl sutures remained, and mild fibrosis and tissue reactions were recognized around the sutured sites in the Vicryl suture group (Fig. 4).

Clinical Results

A total of 125 patients underwent ligation of the cut surface of the liver with silk suture (silk suture group), while a total of 188 patients underwent the same procedure with Vicryl suture (Vicryl suture group). In the evaluation of background factors, no significant differences in preoperative factors were recognized between the two groups (Table 1). Regarding the perioperative factors, the operation time was significantly longer in the silk suture group, although no significant differences in the remaining factors were recognized between the two groups (Table 2).

Incidence of Postoperative Infection

The incidences of postoperative infections, SSI and RI, were significantly lower in the Vicryl suture group than in the silk suture group. Although there was no significant difference in the incidence of superficial SSI between the two groups, the incidence of organ/space SSI was significantly lower in the Vicryl suture group. There was no difference in the incidence of bile leakage between the two groups (Table 3).

Risk Factors for Surgical Site Infection

Twenty of the 313 patients had surgical site infections. A total of 14 independent clinical variables, including 8 preoperative and 6 surgical variables, were analyzed

Table 1 Patient Profiles (1)

	Silk group (N=125)	Vicryl group (n=188)	p-value
Age	62.8±10.7	62.5±10.8	0.8311
Sex (M/F)	83/42	133/65	0.9545
Disease (HCC/LM/OT)	61/57/7	79/92/17	0.3487
Underlying disease (NL/CH/LC)	62/32/31	106/45/37	0.4418
DM (0/1/2)	91/12/22	151/8/29	0.1782
ICG-R15	13.4±6.4	12.3±6.6	0.1359
ALB	4.01±0.74	4.12±0.65	0.2164
T-Bil	0.76±0.36	0.74±0.37	0.5514
Plt	18.2±9.7	19.5±6.4	0.2889
PT	1.05±0.16	1.03±0.15	0.1246

HCC Hepatocellular carcinoma, *LM* liver metastasis., *OT* other liver disease, *NL* normal lever, *CH* chronic hepatitis, *LC* liver cirrhosis, *DM* diabetes mellitus, *ICG-R15* indocyanine green retention test, *ALB* albumin, *T-Bil* total bilirubin, *Plt* prothrombin time

Table 2 Patient Profiles (2)

	Silk group (N=125)	Vicryl group (n=188)	p-value
Duration of Op.	394±126	362±106	0.0156
Blood loss	1171±1073	986±1075	0.1361
Transfusion	282±563	180±540	0.1014
Resected vol. (%)	28.7±22.0	29.4±16.8	0.7458
Extent of liver resection			
≥1 segment	50	62	
2 segments	27	42	0.2960
3 segments	14	41	
4 segments	23	35	
4< segments	11	8	

Op Operation, *Segment* Couinaud's classification

univariately as possible risk factors for postoperative infection. Six of these differed significantly between the silk and Vicryl suture groups, namely: value of serum albumin, duration of operation, blood loss, blood transfusion, use of absorbable sutures, and bile leakage (Table 4).

Multivariate analysis using a logistic regression model involving the six significant factors determined by univariate analysis identified three significant independent variables: duration of operation, use of absorbable sutures, and bile leakage (Table 5). According to logistic analysis, if absorbable suture had not been used, the risk of postoperative infection would have increased by 3.427 times.

Discussion

Hepatectomy, which involves division of the bile duct, is classified as semi-aseptic surgery, often called clean-contaminated surgery. Hepatectomy has various disadvantages, such as glucose intolerance associated with loss of hepatic function, lowered immunity, a relatively long duration of operation and a relatively large blood loss. Accordingly, hepatectomy entails a high risk of SSI.[7] Some patients undergo extended hepatectomy and suffer hepatic failure associated with postoperative infection. Furthermore, the complication of bile leakage prolongs the hospital stay. Accordingly, it is imperative to introduce sufficient measures to prevent SSI.

Table 3 Incidence of Postoperative Infections

	Silk group (N=125)	Vicryl group (n=188)	p-value
Postoperative			
Infections	17(13.6%)	12(6.4%)	0.0310
SSI	14(11.2%)	6(3.2%)	0.0045
Superficial	3(2.4%)	3(1.6%)	
Organ/Space	11(8.8%)	3(1.6%)	
RI	12(9.6%)	6(3.2%)	0.0171
Bile fistula	9(7.2%)	6(3.2%)	0.1039

SSI Surgical site infection, *RI* remote infection

Table 4 Risk Factors for Surgical Site Infections

	SSI(+) (n=20)	SSI(−) (n=293)	P-value
Age	65.4±9.2	62.4±10.8	0.2379
Sex (M/F)	16/4	187/103	0.3299
Serum albumin	3.87±0.46	4.09±0.41	0.0189
Serum T-Bil.	0.70±0.37	0.75±0.37	0.5509
ICG-R15	13.2±6.8	12.7±6.5	0.7268
Disease (HCC/ LM/OT)	10/10/0	127/139/27	0.3573
Underlying disease			
(NL, CH, LC)	13/3/4	155/74/64	0.5116
DM(+/±/−)	4/2/14	47/18/228	0.8330
Op. length (min)	484±109	367±112	<0.0001
Blood loss (ml)	2350±1888	972±941	<0.0001
Transfusion (ml)	1046±1151	165±434	<0.0001
Proportion resected (%)	32.1±21.0	29.0±18.9	0.4724
Suture (silk/non-silk)	14/6	111/182	0.0045
Bile fistula (Y/N)	8/12	7/286	<0.0001

HCC: hepatocellular carcinoma, LM; liver metastasis, OT: other liver disease, NL: normal liver, CH: chronic hepatitis, LC: liver cirrhosis, DM: diabetes mellitus

Silk suture is made from the protein fibers that silkworms produce in the process of cocooning. The fibers are twisted to increase tension and ease of use. Unlike the knot of a single-fiber suture, which unravels easily, the knot of the silk suture remains firmly in place and rarely comes off. Because a foreign substance delays the phagocytic process of normal phagocytes, the silk suture, which is used for wound closure, remains in place for tens of years after surgery.

In the 1950s, Elek and Conen[8] demonstrated that silk suture had an adjuvant effect of accelerating clinical infection in the surgical wound. In human volunteers, they noted that an injection of 10^6 *Staphylococcus pyogenes* was required to elicit a pus-forming clinical infection. Under identical conditions, except for the inclusion of a braided silk suture, the concentration of the pus-forming dose was drastically reduced to 100 cocci. The results of

Table 5 Multivariate Analysis of Factors Contributing to Surgical Site Infections, by Logistic Regression Analysis

Variable	ARR	P value
Op. length (375 min)	7.311 (1.293–41.351)	0.0244
Use of silk +	3.427 (1.046–11.231)	0.0419
Bile fistula +	17.532(4.004–76.002)	0.0001

Values in parenthesis are 95% confidence intervals. ARR: adjusted relative risk

this study indicate that the introduction of staphylococci on a silk suture can increase the development of infection by as much as 10,000-fold. Consequently, the presence of a non-absorbable foreign substance in the surgical wound increases the probability of infection.

A large variety of tissue reactions to silk suture have been observed, and the clinical problems associated with such reactions have been frequently pointed out. In 1901, Braun[9] reported that after ligation of the greater omentum of abdominal adipose tissues with silk suture, tumors developed in the greater omentum as a result of inflammation due to the silk. In a case where silk suture was used to repair a fistula formed by tracheal fenestration, a granuloma developed around the suture.[10] In another case, the silk suture used in treating the bladder wall and the tissues around the uterine cervix formed a large granuloma that was easily mistakable for a tumor.[11]

Like silk suture, the twisted absorbable suture is easy to use. The surface of the absorbable suture is gradually hydrolyzed, and the microorganisms on its surface are exposed to the biological phagocytic process. Even if they manage to hide within the absorbable suture, this suture can be only a transient shelter. Therefore, a synthetic absorbable suture appears to be markedly resistant to infection.

The chemical composition of the suture appears to be the most important determinant of early infection. The incidence of infection in contaminated tissue containing nylon and polypropylene sutures was lower than the infection rate of tissues containing any other nonabsorbable suture. Among the absorbable sutures, polyglycolic acid (PGA) sutures appeared to elicit the least inflammatory response in contaminated tissues. An experiment was conducted to evaluate bacterial adhesion to various synthetic sutures. Among PGA suture materials, Vicryl was regarded as highly resistant to infection because the number of bacteria adherent to it was the smallest.[12]

In the field of digestive surgery, randomized control trials (RCTs) were conducted in the 1970s and 1980s, and some researchers reported the superiority of PGA sutures to silk suture with respect to resistance to SSI. Adams[13] conducted an RCT to compare the treatment of accidental wounds with PGA sutures with that with silk sutures. The results obtained showed that the incidence of inflammatory reactions, especially of purulent infections, was lower in the PGA suture group than in the silk suture group. In the field of neurosurgery, a similar RCT was performed,[14] and the incidence of suture fistulas was higher in the silk suture group. Accordingly, the use of PGA suture was recommended for a buried suture.

In the process of resection of the liver, silk suture is generally used for ligation of the vessels in Glisson's capsule in Japan. The use of silk suture results in infectious granulation on the cut surface of the liver, leading to infection of the cut surface. In our animal experiment, the number of bacteria increased by approximately 1,000 times in the presence of silk suture. In this environment, adhesion to adjacent organs was accelerated, and abscess formation was occasionally observed.

We conducted a retrospective analysis of clinical cases and recognized that the incidence of organ/space SSI, especially infection of the cut surface of the liver, was significantly reduced after April 2003, when a switch was made to the absorbable type for all ligatures used on the cut surface of the liver. This finding was good evidence of the superiority of absorbable sutures.

Conclusion

We concluded that the use of synthetic absorbable sutures, instead of silk sutures, in all the procedures of hepatectomy contributed significantly to the prevention of development of SSI.

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ORIGINAL ARTICLE

Surgical Anatomy of Hepatic Hilum with Special Reference of the Plate System and Extrahepatic Duct

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Abstract
Background When resecting hilar cholangiocarcinoma, the surgeon cannot visualize the hilar vessels through thick connective tissue known as the plate system. Little has been reported regarding the anatomical relationship between the plate system and the extrahepatic bile duct.
Methods Twenty-five formalin-fixed cadaveric livers were dissected carefully and 7 were sectioned sagittally. The extent, composition, and distribution of the extrahepatic bile ducts within the system were investigated. The length between the confluence of the hepatic duct and the branch point of the segmental duct (level I) and the length between the branch point of the segmental duct and the segmental Glisson's pedicle (level II) were measured.
Results The plate system—composed of the hilar, cystic, Arantian, and umbilical regions—was easily separated from the hepatic parenchyma. Histologically, dense connective tissue with abundant capillaries, lymphatic vessels, and neural fibers were noted. Level I of B1pcp and B4a measured 13.0 and 14.7 mm, respectively. Level II measured 8.6 and 17.3 mm, respectively.
Conclusions The bile ducts in the plate system correspond to the extrahepatic bile ducts and their lengths are variable for every segment. Knowing the lengths of the resectable extrahepatic bile ducts is useful for deciding which segment should be resected according to the cancerous invasion.

Keywords Surgical anatomy · Plate system · Extrahepatic bile duct · Hilar cholangiocarcinoma

Abbreviations

CL	caudate lobe
H.E.	hematoxylin eosin
SP	Spiegel lobe
PCP	paracaval portion
IVC	inferior vena cava
CP	caudate process
PP	posterior portion of the right portal vein
UP	umbilical portion of the left portal vein
LHD	left hepatic duct
RHV	right hepatic vein
MHV	middle hepatic vein
LHV	left hepatic vein
FV	fissure vein
GB	gallbladder
CBD	common bile duct
PV	portal vein
GX	Glisson's of segment X
BX	bile duct of segment X
AX	artery of segment X
pcp	paracaval portion
PHA	proper hepatic artery
cp	caudate process
sp	Spiegel lobe
RPV	right portal vein
CA	cystic artery
CD	cystic duct
AD	Arantian duct

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ne	neural fibers
ly	lymphatic vessels
c	small capillaries
b	small bile ducts

There is agreement in the literature for the hilar and upper bile duct carcinoma that whenever feasible, resection is the most appropriate treatment to allow for prolonged survival and a potential cure.[1–5] Right and left hepatectomies were previously applied;[6] however, postoperative hepatic failure caused by excessive liver resection is sometimes accompanied by poor hepatic function. One solution to this problem is to reduce the hepatic volume to be resected as much as possible. Complete resection of the caudate lobe is thought to be essential for a successful surgical strategy for treating hilar cholangiocarcinoma,[1,7] and recent improvements in surgical techniques and discoveries in surgical anatomy of the hepatic hilum made it possible to perform a limited hepatectomy such as an isolated caudate lobectomy.[8] On the other hand, the tumor-free margin is a common predictor of postoperative survival in multivariate analysis.[2–5] Therefore, how to balance both the operative safety and the necessarily radical nature of the surgery is one of the most serious problems in patients with hilar cholangiocarcinoma and poor hepatic function. In such cases, knowledge of the delineation between resectable extrahepatic bile ducts and hepatic segments that need to be preserved is required. However, the surgeon cannot peer into the bile duct through the plate system, which is a fibrous connective tissue enveloping the hilar vessels. This article focuses on the surgical anatomy of the hepatic hilum with special attention to the relationship between the plate system and the extrahepatic bile duct.

Material and Methods

Thirty-two livers from adult cadavers were obtained from the Department of Anatomy, Yokohama City University School of Medicine. The agreements for the study had been obtained from all of the bereaved family members. These 25 livers were dissected carefully to visualize the plate system enveloping the hilar bile ducts and vessels, and 7 livers were sectioned sagittally. Fine dissection was performed using forceps by removing the hepatic parenchyma anteriorly. The hepatic veins, Glisson's pedicles, the plate system, and all of Glisson's pedicles of the caudate lobe (CL) were completely exposed. Seven livers were sectioned sagitally parallel to the inferior vena cava at serial 1 cm intervals. The hepatic hilum area of the three sectioned specimens was embedded in a paraffin block for H.E staining for histological examination. In addition, on the dissection samples, the branch point of each segmental (or subsegmental) bile duct was evaluated after opening them to periphery. The portal vein was also incised on its dorsal side to identify all of the portal branches of the caudate lobe from the inside. As indicated by Kumon et al.,[9] the portal branches of the CL are defined as those originating from the main portal trunk, the right and left portal veins in this study. The caudate lobe was subdivided into the Spiegel lobe (SP) (occupying the left side of the ligamentum venosum), the paracaval portion (PCP) (surrounding the IVC), and the caudate process (CP) (the right inferior side of the right portal vein). The distance between the confluence of the hepatic duct and the branch-point of each segmental (subsegmental) bile duct was measured as level I, and the distance between the branch-point of each bile duct and that of each Glisson's pedicle was measured as level II. The results were shown according to branching patterns of the posterior bile ducts, which were of the supraportal and infraportal types.

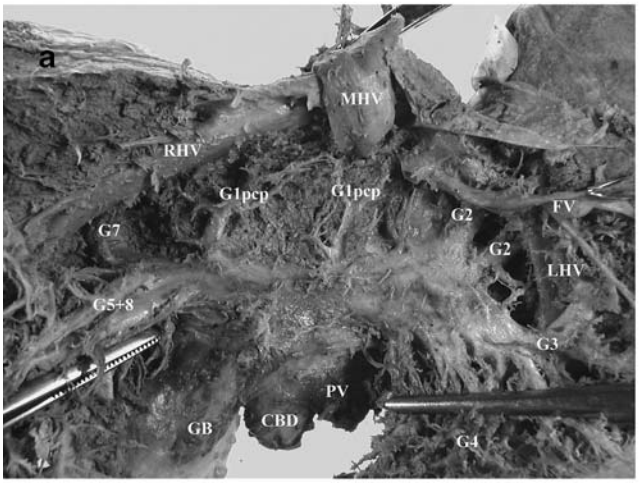
Result

Extent and Composition of the Plate System

The plate system is a fibrous connective tissue comprised of the hilar plate in the hepatic hilum, the umbilical plate enveloping the umbilical portion of the portal vein, the cystic plate in the gallbladder bed, and the Arantian plate covering the ligamentum venosum (Fig. 1). The hilar and the umbilical plate measured 30.8±9.7 mm (mean±SD) on the right side and 41.8±10.0 mm on the left side from the confluence of the hepatic duct (Fig. 2).

Glisson's pedicle was continuous from the plate system, but the hilar plate was easily dissected from the hepatic parenchyma because of the absence of small branches arising from the hilar plate, whereas Glisson's pedicle was difficult to remove from the hepatic parenchyma because of the presence of such small branches. Moreover, the portal vein, the hepatic arteries, and the bile ducts ran separately from each other in the plate system whereas they were gathered and bundled in Glisson's pedicle.

The hilar plate was connected with the cystic plate at the right ventral edge, Glisson's pedicles of the right lobe on the right side, Glisson's pedicle of the CP at the right dorsal edge, and Glisson's pedicle of the PCP on the cranial side. The umbilical plate was connected to the ligamentum teres hepatis on the ventral side and the Arantian plate on the dorsal side. Glisson's pedicles of the medial and lateral segments branched from the umbilical plate, and in addition, Glisson's pedicle of the SP, which had a very thin Glisson's sheath compared to the others, just posterior to the point where the Arantian ligament was attached to the umbilical plate.



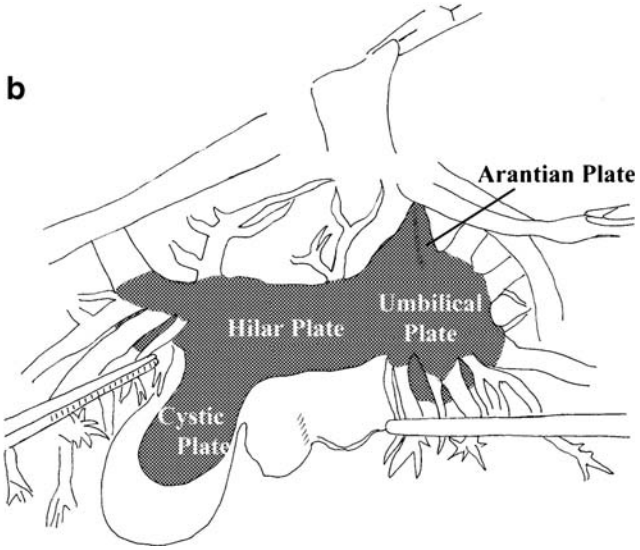


Figure 1 Anterior view of post dissection specimen. **a** The plate system was covering the hepatic hilum. The hilar plate was easily dissected from the hepatic parenchyma as a result of the absence of small branches arising from it, whereas Glisson's pedicle was difficult to remove from the hepatic parenchyma as a result of the presence of small branches. *RHV* right hepatic vein, *MHV* middle hepatic vein, *LHV* left hepatic vein, *FV* fissure vein, *GB* gallbladder, *CBD* common bile duct, *PV* portal vein, *GX* Glisson's of segment X, *pcp* paracaval portion. **b** Schema of the plate system. The plate system was composed of the hilar plate, the umbilical plate, the Arantian plate, and the cystic plate.

On the sagittal section of the posterior portion of the right portal vein (PP), the hilar and the cystic plates were enveloping the three vessels subtotally (Fig. 3). We identified three vessels running apart from each other in the hilar plate. At the confluence of the hepatic duct, the hilar plate formed a semicircular shape (Fig. 4). The anterior and posterior margins consisted the fusion line of the hepatic capsule and the hepatoduodenal ligament. The fusion line was thick in the ventral portion and thin in the dorsal portion. On the dorsal side of the hilar plate, there were small bile ducts of the CP and the SP. On the umbilical portion (UP), the umbilical plate was enveloping the portal vein and connected to the Arantian duct at the posterior aspect (Fig. 5). The presented case of the sagittal section had a variation of the infraportal bile duct of segment 3.

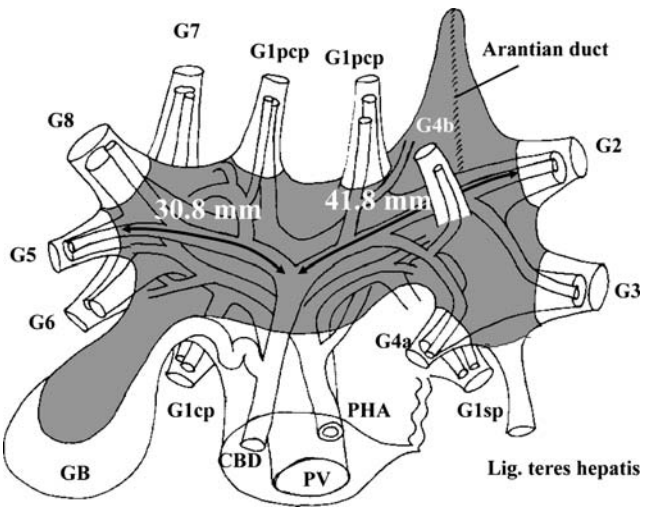


Figure 2 Diagram of the hepatic hilum. The bile ducts were running in the hilar and umbilical plates. They measured 30.8±9.7 mm (mean±SD) on the right side and 41.8±10.0 mm on the left side from the confluence of the hepatic duct. *GB* gallbladder, *CBD* common bile duct, *PV* portal vein, *PHA* proper hepatic artery, *GX* Glisson's of segment X, *pcp* paracaval portion, *cp* caudate process, *sp* Spiegel lobe.

Histological examination of the sagittal section of the porta hepatis revealed abundant connective tissue—including neural fibers, lymphatic vessels, small capillaries, and small bile ducts (Fig. 6). These structures were surrounding the portal triad and were clearly defined from the liver parenchyma by the fibrous tissue derived from the hepatic capsule. The connective tissue was dense in the hilar plate and gradually lessened toward the hepatoduodenal ligament.

Distribution of the Extrahepatic Bile Ducts in the Plate System

Among all of Glisson's pedicles of the caudate lobe, segments 2 and 3 were examined, whereas only the major branches of the other segments were studied. Most of the second-order bile ducts and some of the third-order bile ducts were included in the plate system. Twenty cases of the posterior bile duct (Bp) were running on the cranial side of PP (=supraportal branch), whereas three cases of Bp and two cases of B6 were running on the caudal side of PP (=infraportal branch). The B4 drainage pattern was shown according to the Kawarada's classification:[10] type I (B4 joined the left hepatic duct [LHD] close to the hilar confluence), 5/25; type II (B4 joined the

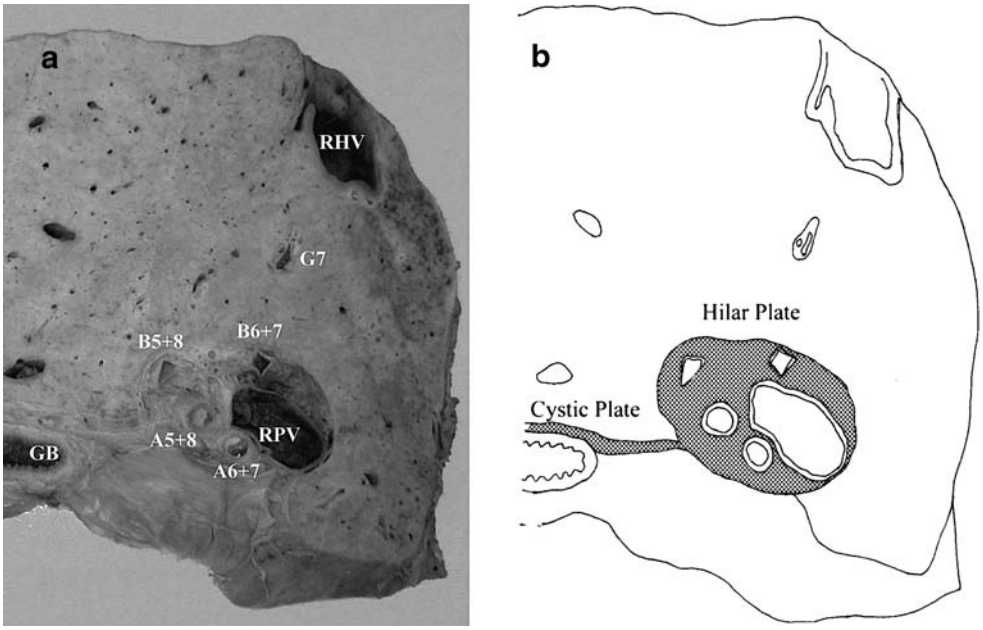


Figure 3 **a** Sagittal section of the posterior portion of the right portal vein. **b** The hilar and cystic plates were enveloping three vessels subtotally. *RHV* right hepatic vein, *G7* Glisson's of segment 7, *BX* bile duct of segment X, *AX* artery of segment X, *RPV* right portal vein.

LHD far from the hilar confluence), 13/25; and type III (combined type), 7/25.

In the cases of supraportal posterior bile ducts, the distance between the confluence of the hepatic duct and each branch-point of the bile duct (level I) revealed bile ducts of the paracaval portion (B1pcp) as 13.0 mm, those of the posterior segment (Bp) as 13.2 mm, and those of segment 4a (B4a) as 14.7 mm (Fig. 7, Table 1). The distance between each branch-point of the bile duct and that of Glisson's pedicle (level II) revealed B1pcp as 8.6 mm, which was the shortest, and B4a as 17.3 mm, which was the longest. The sum of level I and level II, which corresponds to the length between the confluence of the hepatic duct and the branch-point of the each Glisson's pedicle revealed B1pcp as 21.6 mm, Bp as 29.6 mm, and B4b as 30.7 mm.

In cases of infraportal posterior bile ducts, level II was longer than those of the supraportal cases, excluding B5a and B5b, and were statistically significant ($p<0.05$) in the B1pcp, B4a and Bp (Table 2).

The length from the confluence of the hepatic duct to the right side of PP and the right side of UP, both of which

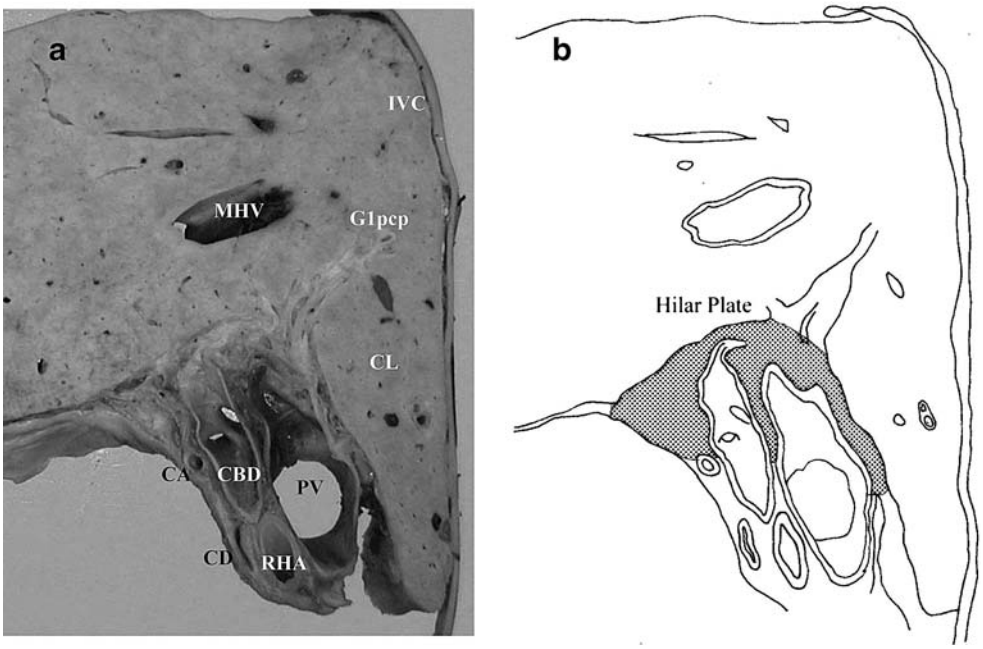


Figure 4 **a** Sagittal section of the confluence of the hepatic duct. **b** The hilar plate formed a semicircular shape. The anterior and posterior margins consisted of a fusion line of the hepaic capsule and the hepatoduodenal ligament. *White* and *black stars* indicate orifices of the bile ducts of the posterior and anterior segments, respectively. *IVC* inferior vena cava, *MHV* middle hepatic vein, *G1pcp* Glisson's of the paracaval portion, *CL* caudate lobe, *CA* cystic artery, *CBD* common bile duct, *PV* portal vein, *CD* cystic duct, *RHA* right hepatic artery.

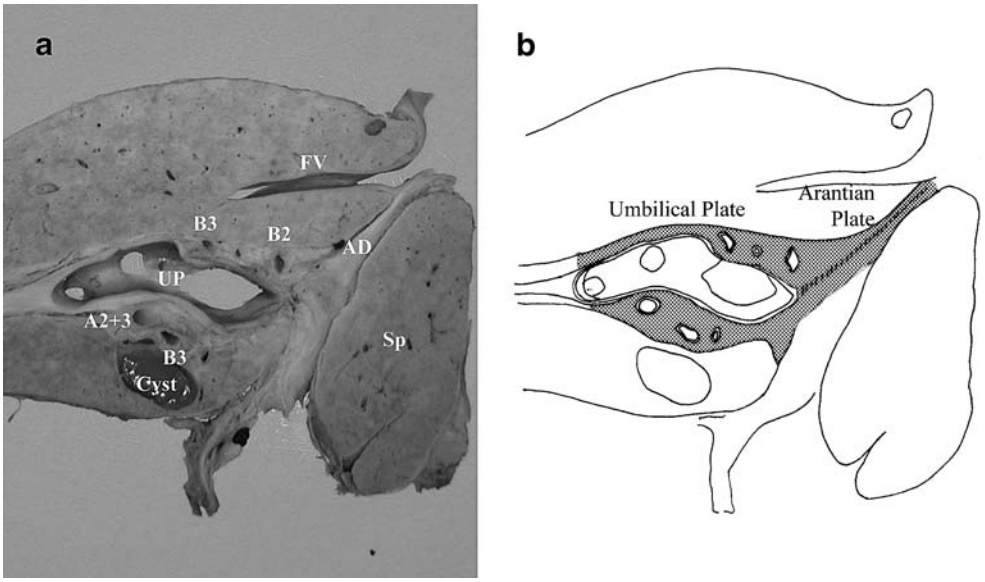


Figure 5 **a** Sagittal section of the umbilical portion of the portal vein. **b** The umbilical plate was enveloping the portal vein connected to the Arantian duct in the posterior portion. The presented case had a variation of the infraportal bile duct of segment 3. *White stars* indicate orifices of the portal vein of segment 4. *FV* fissure vein, *AD* Arantian duct, *Sp* Spiegel lobe, *UP* umbilical portion, *BX* bile duct of segment X, *AX* artery of segment X.

were considered to be anatomical landmarks intraoperatively, measured about 25 and 30 mm, respectively.

Discussion

The plate system was originally mentioned by Walaneus et al. in 1620, but in relation to surgical anatomy, Couinaud et al. reported it precisely in 1957 and 1989.[11,12] However, recent progress in surgical procedures for hilar cholangiocarcinoma requires more detailed anatomical knowledge of the plate system. Currently, there are many surgical procedures for hilar cholangiocarcinomas varying from local excisions to major hepatectomies, and the selection or indications of these procedures are difficult to determine, especially for patients with poor hepatic function. Therefore, we have to estimate the hepatic segments to be resected according to the cancerous invasion present in each case. In this paper, we focused on the relationship between the plate system and the bile duct, which is important for the selection of an appropriate operative procedure of hilar cholangiocarcinoma.

Numerous anatomical investigations about hepatic vessels using cast and radiological studies made remarkable progress in liver surgery and, in this decade, the surgical anatomy of the hepatic hilum (including the caudate lobe) was also clarified.[12–17] However, the plate system's contri-

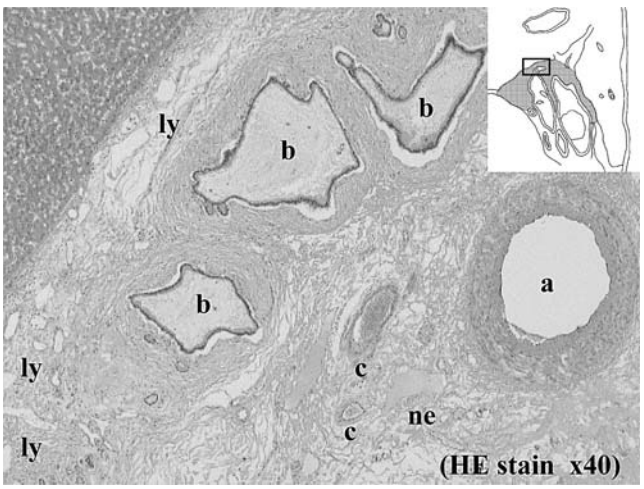


Figure 6 Histological findings of sagittal section of the hilar plate (H.E. stain, original magnification ×40). There was abundant connective tissue including neural fibers (*ne*), lymphatic vessels (*ly*), small capillaries (*c*) and small bile ducts (*b*). The examined site is shown on the right upper schema.

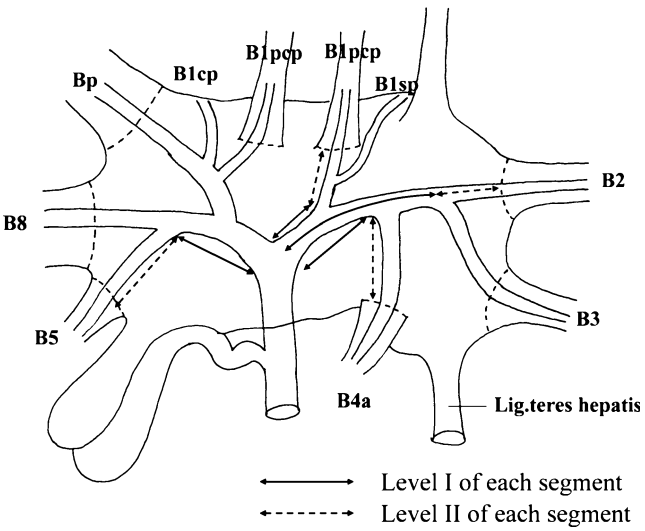


Figure 7 The length of the bile ducts in the plate system. Distance between the confluence of the hepatic duct and the branching point of each segmental (subsegmental) bile duct was measured as level I and distance between branching point of each bile duct and that of each Glisson's pedicle was measured as level II.

Table 1 Results of the Bile Duct Lengths in the Plate System in the Supraportal Posterior Bile Duct Type

	Number of examined bile duct	Level I, mean±SD (mm)	Level II, mean±SD (mm)	Level I+II, mean±SD (mm)
B1pcp	65	13.0±7.2	8.6±4.7	21.6±6.6
B2	20	28.1±13.7[a]	13.7±9.3[a]	41.8±10.0[a]
B3	20	28.1±6.9[a]	16.5±8.9[a]	44.6±9.5[a]
B4a	38	14.7±6.9[b]	17.3±6.3[a]	32.0±11.0[a]
B4b	31	18.7±10.3[a]	12.0±7.2[a]	30.7±10.6[a]
B5a	34	22.3±9.8[a]	10.8±8.3[b]	33.1±10.0[a]
B5b	24	20.5±9.6[a]	10.3±7.3[b]	30.8±9.7[a]
Bp	20	13.2±10.6[b]	16.5±5.8[a]	29.6±9.3[a]

Level I is the distance between the confluence of the hepatic duct and the branching point of the segmental bile duct.
Level I is the distance between the branching point of the segmental bile duct and that of Glisson's pedicle.
B1pcp: bile duct of the paracaval portion, *BX*: bile duct of segment X, *Bp*: bile duct of the posterior segment.
[a] Statistically significant ($p<0.05$) compared with B1pcp.
[b] Not significant compared with B1pcp.

bution to the complexity of the hepatic hilum was difficult to investigate by such indirect methods. The dissection method used in this study was useful to identify the plate system as it would have been seen during actual operative procedures. Moreover, by adding the incision of bile ducts and portal vein, even small branches of the CL could be identified. The bile ducts of the CP and the SP are very small in diameter and run on the dorsal side of the hilar plate. Sagittal section examinations provided the three-dimensional information about the relationship between the plate system and the hilar vessels.

The edge of the plate system consists of the fusion line of the hepatoduodenal ligament and the hepatic capsule, based upon the findings of sagittal section examinations. Although there was not much connective tissue behind the portal vein compared to in front of it, it is reasonable to believe that it is part of the plate system because of the continuity from the anterior plate and the existence of small bile ducts draining from CP and SP. The plate system was continuous to Glisson's pedicle intrahepatically, and Couinaud represented, in the schema of his literature, that the branch point of Glisson's pedicles is the boundary of the plate system. We also defined the boundary of the plate system the same way, for the following two reasons.

First, the hepatic parenchyma was stuck to Glisson's pedicle, but not to the plate system. Second, the arteries, the portal veins, and the bile ducts ran separately within the plate system, although close together in Glisson's pedicle. Although cancer cells affect the bile duct in the plate system, the invaded bile duct can be resected without hepatic parenchymal resection for oncological reasons;[18] however, if the cells involve Glisson's pedicle, it is very difficult to resect the invaded bile duct alone. For resecting hilar cholangiocarcinoma, it is important to estimate whether cancerous invasion along the bile duct is within the plate system or not. Consequently, the bile ducts in the plate system corre-

Table 2 Results of the Bile Duct Lengths in the Plate System in the Infraportal Posterior Bile Duct Type

	Number of examined bile duct	Level I, mean±SD (mm)	Level II, mean±SD (mm)	Level I+II, mean±SD (mm)
B1pcp	10	10.7±5.4	15.6±8.6	26.3±8.8
B2	5	31.4±12.2[a]	17.8±6.3[b]	49.2±7.5[a]
B3	5	31.4±12.2[a]	22.6±5.7[b]	54.0±11.2[a]
B4a	9	16.8±2.3[a]	23.9±3.8[a]	40.7±4.8[a]
B4b	6	16.5±2.8[a]	16.5±8.2[b]	33.0±7.7[b]
B5a	5	19.0±9.6[b]	8.0±7.2[b]	27.0±8.2[b]
B5b	5	17.6±3.2[a]	6.8±3.6[b]	24.4±5.5[b]
Bp or B6[c]	5	10.4±6.5[b]	24.8±10.6[b]	35.2±6.8[b]

B1pcp: bile duct of the paracaval portion, *BX*: bile duct of segment X, *Bp*: bile duct of the posterior segment.
Level I is the distance between the confluence of the hepatic duct and the branching point of the segmental bile duct.
Level II is the distance between the branching point of the segmental bile duct and that of Glisson's pedicle.
[a] Statistically significant ($p<0.05$) compared with B1pcp.
[b] Not significant compared with B1pcp.
[c] Including two cases with infraportal bile duct of only B6.

spond to the actual extrahepatic bile ducts. If cancerous invasion is beyond the plate system at a certain segment, the segment has to be removed with radical surgery.

In terms of the surgical aspects, the limits of the resectable extrahepatic bile ducts are considered to be approximately at the right edge of PP and right edge of UP, and the length from the confluence of the hepatic duct measured 25 and 30 mm, respectively. Most of the second-order bile duct branches and some of third-order branches are all included in the plate system.

In the operation of hilar cholangiocarcinoma, the plate system is the key anatomical structure in the hepatic hilum because extrahepatic bile ducts cannot be dissected from the plate system and the decision as to whether a certain hepatic segment should be removed or not depends on the relationship between cancerous invasion and the extension of the plate system. How much plate system we are able to preserve depends in part upon the selected surgical procedure. For example, in cases of supraportal posterior bile ducts, if cancer cells invade into the root of B1pcp and 10 mm of cancer-free length are necessary for surgical margin, the liver parenchyma of B1pcp has to be resected because its level II length is less than 10 mm. However, for segment B4a, the liver parenchyma of segment 4a possibly can be preserved because its level II length is over 15 mm. Between the supraportal and infraportal type level II lengths, the infraportal type were longer (excluding B5a and B5b). Therefore, in the infraportal type left lobe, the paracaval portions and posterior segments were relatively preservable segments. Thus, understanding the relationship between the plate system and the bile duct is useful for determining the degree of possible hepatic parenchymal preservation. The result of level I+II of B1pcp shows a length of 21.6 mm, which is remarkably short compared to other bile ducts. It is consistent with the fact that the CL is the most frequently involved segment in the liver, and it is also proof of the necessity of caudate lobe resection for hilar cholangiocarcinomas.

Our results provide new information about the surgical anatomy of the hepatic hilum with special attention to the plate system. Furthermore, this information is useful for appropriate selection of an operative procedure in patients with hilar cholangiocarcinoma and poor hepatic function.

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Perioperative Morbidity Affects Long-Term Survival in Patients Following Liver Resection for Colorectal Metastases

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Abstract
Background Hepatic resection is the treatment of choice in patients with colorectal liver metastases. Perioperative morbidity is associated with decreased long-term survival in several cancers. The aim of this study was to assess the impact of perioperative morbidity and other prognostic factors on the outcome of patients undergoing liver resection for colorectal metastases.
Methods One hundred ninety seven patients undergoing liver resection with curative intent were investigated. The influence of prognostic factors, such as complications, tumor stage, margins, age, sex, number of lesions, transfusion, portal inflow obstruction, and era and type of resection, was assessed using univariate and multivariate analysis. Complications were graded using an objective surgical complication classification.
Results The 5-year survival rate was 38%, with a median follow up of 4.5 years. The disease-free survival rate at 5 years was 23%. The perioperative morbidity and mortality rates were 30 and 2.5%, respectively. The median survival of patients with perioperative complications was 3.2 years, compared to 4.4 years in those patients without complications ($p<0.01$). For patients with positive resection margins, the median survival was 2.1 years, compared 4.4 years in patients with a margin ($p=0.019$).
Conclusion Perioperative morbidity and a positive resection margin had a negative impact on long-term survival in patients following liver resection for colorectal metastases.

This paper has been presented at the annual meeting of the Royal Australian College of Surgeons 2006 and was accepted for oral presentation at the IHPBA 2006 meeting in Edinburgh.

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Keywords Perioperative complications · Colorectal metastases · Liver resection · Prognostic factors · Hepatectomy

Introduction

Hepatic resection with curative intent is considered the treatment of choice in patients with colorectal metastases confined to the liver. Advances in surgical techniques, staging, and perioperative care have contributed to improved results. Major centers have reported perioperative mortality rates of less than 5% in series including major resections.[1–4] Numerous uncontrolled studies have assessed long-term survival and disease-free survival and reported 5-year survival following hepatic resection with curative intent ranging from 25 to 37%.[1,2,4,5] In the more recent series, improved 5-year actuarial survival rates up to 58% are reported.[6,7]

There are well known risk factors for survival in patients undergoing liver resection for colorectal metastasis. More advanced stage of the primary and positive resection margins of the liver resection are consistently associated with a reduced overall survival,[1,2,8] whereas synchronous metastases and number of lesions have been reported as both significant and nonsignificant for the long-term prognosis.[9–12]

However, very little information exists about the impact of perioperative morbidity on the outcome in patients following liver resection for colorectal metastases. A single study has reported reduced long-term survival in patients with perioperative morbidity.[13] The concept of perioperative morbidity as a risk factor for survival is well known in other cancer surgery, such as esophageal, pancreas, and colorectal cancer.[14–16]

The lack of standardized definitions for perioperative complications is one confounding factor contributing to the limited evidence in this field. To address this issue, we used an objective surgical complication classification, which has been developed recently and has been proven to be very reliable.[17]

The aim of this study was to assess the impact of prognostic factors, in particular perioperative morbidity, ranked by a quantitative surgical complication classification, on the long-term survival in patients undergoing liver resection for colorectal metastases.

Methods

Patients and Data Collection

Patients who underwent liver resection for colorectal metastases from February 1992 until June 2005 at Flinders Medical Centre, Ashford Community Hospital, and Queen Elizabeth Hospital in Adelaide were included in a prospective database. Data about the operation, transfusion, tumor characteristics, and postoperative complications were recorded prospectively by the responsible surgeons. Data about resection margins, tumor number and size, staging of the primary, chemotherapy, recurrence, and follow-up period were obtained from patients' charts and direct follow-up with the respective general practitioners, referring physicians, oncologists and surgeons. Mortality was cross-checked with the state (South Australian) cancer registry.

Preoperative tumor staging was performed using contrast-enhanced computer tomography or magnetic resonance imaging. In addition, chest x-ray or computer tomography of the chest and colonoscopy were performed. Positron emission tomography was used selectively, in the latter part of the series, to rule out extrahepatic disease.

Surgical Therapy

Laparotomy and abdominal exploration including intraoperative ultrasound was performed routinely in each case to confirm and assess the intrahepatic tumors. Only patients undergoing single-stage surgery with curative intent were included. Resections were classified as nonanatomical wedge resections, segmentectomy, sectionectomy, hepatectomy, or extended hepatectomy according to the classification of the International Hepato-Pancreatico-Biliary Association.[18] All resections were performed or supervised by three hepatobiliary surgeons (GM, JC, and RP). The parenchymal dissection was achieved using a combination of clip dissection, cavitron ultrasonic aspirator, waterjet dissector, argon beam, and ultrasonic shears. Portal inflow occlusion was applied at the discretion of the operating surgeon. Hepatic resection was not combined with colorectal resection in this study.

Prognostic Factors

Potential prognostic factors were identified from previous reports[6,19] and were used for univariate and multivariate analysis: sex, age (under or over 70 years[20]), tumor stage (Dukes classification), tumor number (single or multiple), resection margin, perioperative complications, blood transfusions, period of operation (before and after 2001), portal inflow occlusion (applied or not applied), extent of resection (hemihepatectomy and extended hemihepatectomy were considered extensive resections, other resections were considered as less extensive resections), and type of resection (anatomic and nonanatomic). The resection margins were defined as involved if the margin was microscopically less than 1 mm. The period of operation was chosen such as to achieve a balance of sufficient patient number and adequate follow-up in both groups. Data about carcinoembryonic antigen levels were incomplete and not included in the analysis.

Assessment of Complications

Complications that occurred within 28 days of the operation were defined as "perioperative." A recently published standardized complication classification system was used to grade postoperative complications.[17] The grading of the severity of a complication is based on the therapy used to correct it. This grading eliminates the inconsistencies of different complication definitions. Briefly, grade 1 complication includes minor deviation from the normal postoperative course without the need for any specific treatment. Grade 2 complications can be treated solely by drugs, blood transfusion, physiotherapy, and nutritional support. Grade 3 complications require interventional or surgical treatment. Grade 4 complications are life-threatening complications

requiring ICU management. Grade 5 is defined as death of the patient. If a patient had more than one complication, only the highest-ranked complication was used for the analysis. In-hospital mortality was defined as a perioperative complication.

Statistics

All statistical analysis was performed using SPSS® (version 12.0.1). Overall survival rates and disease-free survival were analyzed using Kaplan–Meier survival statistics. Univariate analysis was performed to calculate the impact of different prognostic determinants. Differences in survival rates were computed using the log rank test. Differences were considered significant if p was less than 0.05. Multivariate analysis of all prognostic factors was performed using Cox regression analysis to adjust for confounding factors.

Results

Demographics

We investigated a total of 197 consecutive patients with metastatic colorectal cancer who underwent liver resection with curative intent at Flinders Medical Centre, Ashford Community Hospital, and Queen Elizabeth Hospital. The median follow-up was 4.5 years, and there were 124 men (63%) and 73 women (37%). The median age was 64 years (range 22 to 92 years). Sixty-seven patients (34%) were older than 70 years, 106 (54%) were between 50 and 70 years, and 24 (12%) were younger than 50 years.

Tumor Characteristics

The primary tumor was in the colon in 127 cases (65%) and in the rectum in 70 cases (35%). One hundred twenty five (63%) of the colorectal tumors had involved regional lymph nodes and were classified as Dukes C. Thirty-five (18%) patients presented with synchronous liver metastasis at the diagnosis of the primary. One hundred twenty three (62%) patients underwent resection for a single metastasis, whereas the remaining 74 (38%) had two or more lesions. Sixty-seven (34%) patients had preoperative chemotherapy. Different chemotherapy regimens were used, and the number of administered cycles was variable. Therefore, we did not include the use of chemotherapy in the analysis.

Surgical Therapy

An anatomical resection was performed in 108 patients (55%); the remaining 89 underwent a nonanatomical resection. Ninety-two operations were performed before 2001. In 63 patients (32%), the interval between the resection of the primary and the liver resection was less than 6 months. In 79 patients (40%), the interval was 6 to 24 months, and in 54 patients (28%), it was more than 24 months. The resection margin was clear in 173 patients (88%). In 24 patients, the resection margin was involved. A Pringle maneuver was applied in 76 patients. In 27 patients, information about the Pringle maneuver was not available. One hundred three out of 197 patients did not receive any blood transfusion during or after the procedure. In 12 patients, no information about the use of blood transfusions was recorded.

Complications

Fifty-nine patients (30%) experienced perioperative complications. Complications were graded into five categories according to their severity.[17] Details are given in Table 1. Fourteen patients suffered from biloma or biliary leakage. Five patients experienced cardiac complications. Three patients developed postoperative liver failure with encephalopathy and increased international normalized ratio and decreased factor V, which required prolonged ICU stay. Twenty-six patients had pulmonary complications, including pneumonia, atelectasis, pleural effusion, and pneumothorax. Eleven patients had other complications including urinary infection, wound infection, hematoma, unexplained fever, deep venous thrombosis, and delirium. Five patients died during the hospitalization within 5 to 48 days after the operation. The overall in hospital mortality was, therefore, 2.5%. Two patients died as a result of postoperative sepsis and multiorgan failure. Two died from a myocardial infarction and one patient due to postoperative liver failure. Two of these five patients died within 28 days after the operation. The complication rate in patients over 70 years of age was 34% (23 out of 67), compared to 28% (36 out of

Table 1 Incidence and Severity of Postoperative Complications

Complication Grade	Patients (n)	Percent
1	4	2.0
2	28	14.2
3	12	6.1
4	10	5.1
5	5	2.5

Incidence and severity of complications according to a standardized complication classification.[17] Grade 1: Minor deviation from the normal postoperative course without the need for any specific treatment. Grade 2: Complications that can be treated solely by drugs, blood transfusion, physiotherapy, or nutritional support. Grade 3: Complications that require interventional or surgical treatment. Grade 4: Complications that are life-threatening and require ICU management. Grade 5 is defined as death of the patient

130) in patients under 70 years. This observation was statistically not significant (chi square test). The extent of the hepatic resection on the other hand was associated with a higher perioperative complication rate. Thirty five percent (44 out of 126) of patients with a hemihepatectomy or an extended hemihepatectomy experienced a complication, vs. 21% (15 out of 71) of patients undergoing less extensive hepatic resection ($p=0.042$). The prevalence of complications in the 82 patients who received blood transfusions was significantly higher than in patients not receiving blood transfusions ($p<0.01$).

Long-Term Outcomes

The actuarial survival at 5 years was 38%, with a median survival of 4.1 years. The 1- and 3-year survival rates were 88 and 62%, respectively. Using univariate analysis, survival was not influenced by tumor number, stage of the primary, transfusion requirement, resection type (anatomical vs. nonanatomical), extent of resection, period of operation, and occlusion of hepatic inflow. In contrast, positive resection margins, perioperative complications, female sex, and age over 70 years were significant predictors of overall survival (Table 2). Even when we excluded the patients that died in the perioperative period, we found the same results. To analyze the impact of the severity of the complications on survival, we compared severity grades 3, 4, and 5 vs. grade 1 and 2 complications. There was a significantly reduced median survival in patients with more severe complications of 2.1 years, compared to 4.1 years in patients with no or minor complications ($p<0.012$). Complications were more likely to occur in the extensive resections, but the effect of morbidity on outcome was independent of this.

In the multivariate analysis, age and sex were no longer predictive factors for reduced survival. However, the presence of complications or positive resection margins were still significant predictors of reduced survival (Table 3). The Kaplan–Meier curves for survival stratified by resection margins and complications are given in Figs. 1 and 2.

Disease-Free Survival

A total of 103 patients developed a recurrence during the follow-up period. Seventy had a local recurrence in the liver, whereas the others developed recurrence in the lung, bone, or elsewhere. Twenty-one patients with recurrence confined to the liver underwent repeat hepatectomy; the remaining patients received palliative chemotherapy or supportive care. The overall disease-free survival at 5 years was 23%, with a median disease-free survival of 1.7 years. Patients with a positive resection margin had a significantly lower disease-free survival of 0.7 vs. 1.8 years, as expected ($p<0.01$) (Table 4). Twenty-one patients out of 24 with involved margins developed a local recurrence or died within the follow-up period. Twenty-eight out of 59 patients who suffered from a perioperative complication developed recurrent disease. The disease-free survival in patients with perioperative complications was significantly shorter ($p=0.04$) (Table 4). These results were confirmed in the multivariate analysis. All other prognostic factors did not reach statistical significance in the multivariate analysis (Table 5).

Discussion

The major finding of this study is that patients suffering from postoperative complications after liver resec-

Table 2 Predictors of Overall Survival: Univariate Analysis

	Patients (*n*)	Median Survival	CI 95%	*p* Value
Resection margins				
Clear	173	4.4	3.6–5.2	0.019
Involved	24	2.1	1.8–2.5	
Tumor number				
Solitary	123	3.6	3.0–4.3	0.272
Multiple	74	4.7	3.4–6.0	
Complications				
Absent	138	4.4	3.2–5.7	<0.01
Present	59	3.2	2.1–4.4	
Transfusion				
Yes	82	4.4	2.8–6.0	0.934
No	103	4.1	3.2–5.0	
Extent of resection				
Extensive	126	4.3	3.5–5.1	0.928
Less extensive	71	3.6	2.7–4.5	
Resection type				
Anatomic	108	3.9	2.9–4.8	0.490
Nonanatomic	89	4.1	2.8–5.4	
Period of operation				
Before 2001	92	4.1	3.2–5.0	0.670
After 2001	105	3.6	3.1–4.8	
Sex				
Female	73	2.5	1.1–3.8	0.015
Male	124	4.5	3.9–5.2	
Age				
<70 years	130	4.7	3.5–5.9	0.012
≥70 years	67	3.0	2.0–4.1	
Nodal status				
Positive	125	3.4	2.5–4.3	0.062
Negative	71	4.9	3.6–6.2	
Pringle				
Applied	76	4.3	2.9–5.7	0.629
Not applied	94	3.6	2.4–4.8	

Median survival in years. Differences in survival rates were computed using log rank test
CI 95% = 95% confidence interval

Table 3 Predictors of Survival: Multivariate Analysis

Risk Factor	HR (95% CI)	*p* Value
Margin involved	2.1 (1.1–4.1)	0.028
Complications present	2.2 (1.3–3.7)	0.003
Age (>70 years)	1.3 (0.7–2.2)	0.376
Female	1.5 (0.9–2.5)	0.142
Multiple lesions	0.9 (0.5–1.5)	0.670
Extensive resection	0.8 (0.5–1.3)	0.325
Nonanatomical	1.1 (0.6–1.8)	0.816
Nodal positive	1.5 (0.9–2.6)	0.153
Era before 2001	1.4 (0.8–2.4)	0.198
Pringle applied	0.9 (0.5–1.5)	0.652

Cox regression analysis of patient survival
HR = hazard ratio, 95% CI = 95% confidence interval

tion for colorectal metastases had a reduced survival rate. This study clearly showed that the incidence and the severity of complications were a prognostic factor for survival. Furthermore, advanced age was not a risk factor for reduced survival or development of complications. It should also be emphasized that, although the extent of resection influenced morbidity, the impact of morbidity on long-term survival was independent of the extent of resection.

The correlation of perioperative morbidity and long-term survival is a well recognized concept in cancer surgery. Infections, anastomotic leakage, and multiorgan failure have been shown to be associated with decreased survival after tumor resection in previous studies.[14–16,21] In patients undergoing liver resection for colorectal metastasis, there has been only one other group that investigated the impact of perioperative morbidity on long-term survival.[13] Their survival rates were almost identical compared to the outcomes in the current study, but the follow-up period was considerably shorter.

While mortality is an objective parameter, morbidity is only poorly defined, and this shortcoming has severely hampered conclusive analysis of its impact on outcome.[22–24] Therefore, we used an objective surgical complication classification, which grades the complications according to their therapeutic relevance.[17] For the first time, we correlated the findings of this classification to the outcome in patients undergoing liver resection for colorectal metastasis.

The rationale behind the observation that complications affect the long-term outcome is unclear. It has been postulated that severe complications like septicemia lead to an extended period of immunosuppression, which allows residual tumor cells to further proliferate and survive in the host.[25] This could explain the reduced disease-free survival rate in some patients with complications.

Positive resection margins were identified as an independent risk factor for survival. The influence of positive resection margins on disease-free survival and overall

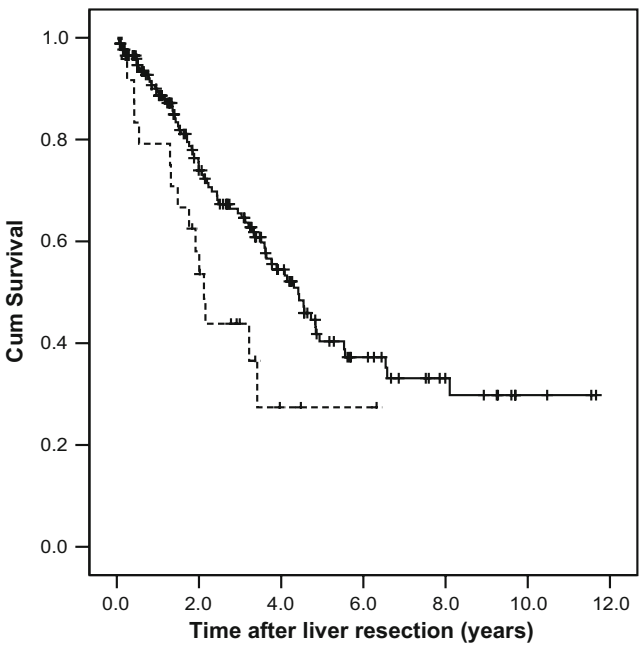

Figure 1 Overall survival according to resection margins. Kaplan–Meier curve of patients undergoing hepatectomy for colorectal metastasis. *Dotted line*: For patients with positive resection margins (n=24), the median survival was 2.1 years. *Continuous line*: Patients with clear resection margins (n=173) had a median survival of 4.4 years. Differences of survival were assessed using log rank test (p=0.019).

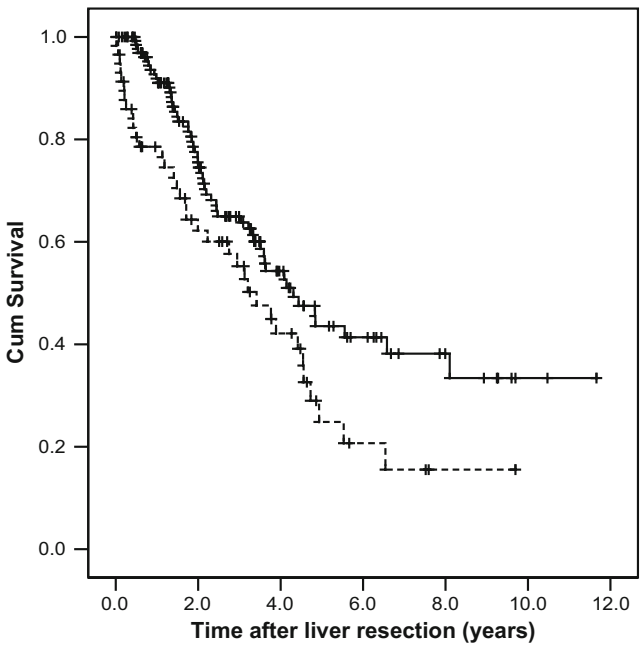

Figure 2 Overall survival according to perioperative complications. Kaplan–Meier curve of patients undergoing hepatectomy for colorectal metastasis. *Dotted line*: Patients with complications (n=59) had a median survival of 3.2 years. *Continuous line*: Patients without perioperative complications (n=138) had a median survival of 4.4 years. Differences of survival were assessed using log rank test (p<0.01).

Table 4 Predictors of Disease Free Survival: Univariate Analysis

	Patients (*n*)	Median Survival	CI 95%	*p* Value
Resection margins				
Clear	173	1.8	1.4–2.3	<0.01
Involved	24	0.7	0.3–1.0	
Tumor number				
Solitary	123	1.8	1.4–2.3	0.718
Multiple	74	1.4	0.8–2.1	
Complications				
Absent	138	1.8	1.3–2.3	0.041
Present	59	1.4	0.8–2.1	
Transfusion				
Yes	82	2.0	1.2–2.8	0.542
No	103	1.5	1.3–1.8	
Extent of resection				
Extensive	126	1.6	1.2–2.0	0.975
Less extensive	71	1.8	1.2–1.4	
Resection type				
Anatomic	108	1.7	1.3–2.2	0.703
Nonanatomic	89	1.7	1.1–2.3	
Period of operation				
Before 2001	92	1.8	1.2–2.3	0.599
After 2001	105	1.5	1.1–2.0	
Sex				
Female	73	1.6	1.0–2.2	0.626
Male	124	1.7	1.2–2.2	
Age				
<70 years	130	1.5	1.2–2.9	0.411
≥70 years	67	1.9	1.3–2.5	
Nodal status				
Positive	125	1.5	1.0–2.0	0.084
Negative	72	2.4	1.5–3.2	
Pringle				
Applied	76	1.4	1.0–1.9	0.919
Not applied	94	1.8	1.3–2.4	

Median survival in years. Differences in survival rates were computed using log rank test
CI 95% = 95% confidence interval

survival has been confirmed by other groups in many reports.[8,10] Remaining tumor cells predispose to a local recurrence, and early recurrence translates to a decreased overall survival. In patients with positive margins, the reduced overall survival and disease-free survival rates in our study are in accordance with other reports.[2,5,6,11] Therefore, clear resection margins should be achieved whenever they are possible, although repeated resections are feasible and show favorable results in selected patients.[26,27]

In contrast to the study of Choti et al.,[6] we could not confirm any difference of survival according to the era of resection. Most studies report survival rates between 25 and 37%. Two recent publications achieved remarkable 5-year survival rates over 50%.[6,7] However, the median follow-up periods of these cohorts were only 22 and 31 months. Reasons for the better results are thought to be improved staging, patient selection, and increased use of new chemotherapy regimens. Whether survival following resection in more recent times is really associated with an improved survival will need to be confirmed with longer follow up of the reported cohorts.

Advanced age has been a risk factor for long-term survival in our univariate analysis in accordance to the recently published results of Nagano et al.[28] However, we could not confirm these findings in the multivariate analysis. The study of Nagano showed no difference in perioperative morbidity and mortality in aged and young patients, and the aged group still achieved a remarkable long-term outcome of 34%. These findings are in accordance with our results. Therefore, advanced age cannot be regarded as a contraindication to hepatic resection for colorectal liver metastasis.

Although we collected data about chemotherapy, the chemotherapy regimens and the administered cycles of chemotherapy pre- and post-liver surgery were very heterogeneous. Therefore, we were not able to make any meaningful analysis regarding the influence of chemotherapy on mortality or complications.

In conclusion, postoperative morbidity and positive resection margins have an impact on long-term survival and disease-free survival in patients following resection for colorectal metastases. Advanced age is not an independent risk factor for either survival or perioperative morbidity. The results of this study are consistent with many others on the decreased survival associated with positive resection margins. Of greater interest is the finding of decreased survival associated with the incidence and severity of perioperative complications. This does indicate that there are potential benefits in performing the surgery with meticulous technique to minimize complications such as subphrenic abscess, perioperative bleeding, and biliary

Table 5 Predictors of Disease Free Survival: Multivariate Analysis

Risk Factor	HR (95% CI)	*p* Value
Involved margins	2.2 (1.3–3.8)	0.005
Complications present	1.8 (1.2–2.8)	0.006
Age (>70 years)	0.9 (0.6–1.3)	0.502
Female	1.1 (0.7–1.7)	0.669
Multiple lesions	1.0 (0.7–1.6)	0.864
Extensive Resection	0.8 (0.4–1.6)	0.471
Nonanatomical	0.9 (0.6–1.4)	0.673
Nodal positive	1.3 (0.9–2.1)	0.214
Era before 2001	1.1 (0.7–1.6)	0.750
Pringle applied	0.9 (0.6–1.3)	0.494

Cox regression analysis of disease free survival
HR = hazard ratio, 95% CI = 95% confidence interval

leakage. Careful postoperative care to avoid pulmonary and other complications could be beneficial.

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Acinar Cell Carcinoma of the Pancreas: An Institutional Series of Resected Patients and Review of the Current Literature

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Abstract
Introduction Acinar cell carcinoma (ACC) is a rare, malignant neoplasm with a generally poor prognosis. We report our institutional series of 14 patients with ACC to determine current guidelines for their evaluation and treatment.
Materials and Methods The Johns Hopkins pathology prospective database was reviewed from 1988 to 2006 to identify patients with pancreatic neoplasms possessing features of acinar cell differentiation. Retrospective review and follow-up was performed for each patient.
Results Fourteen patients with ACC were identified with a median age of 57 years. All patients presented with abdominal pain or discomfort with none showing evidence of lipase hypersecretion syndrome. Each patient underwent surgical resection, including nine pancreaticoduodenectomies and five distal pancreatectomies. Median tumor size was 3.9 cm with 12 patients found to have stage IIB disease or worse. Four patients underwent neoadjuvant chemoradiation. Eight of the fourteen patients developed recurrent disease. Overall median survival and disease-free survival were 33 and 25 months, respectively, as compared to a median survival of 18 months for pancreatic adenocarcinoma.
Conclusion Acinar cell carcinomas are rare, aggressive neoplasms that are difficult to diagnose and treat. Operative resection represents the best first-line treatment. These lesions have a better prognosis than the more common pancreatic adenocarcinomas.

Keywords Acinar cell · Resection · Carcinoma · Pancreas

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Introduction

Acinar cell carcinomas (ACCs) are rare, malignant neoplasms of the exocrine pancreas accounting for approximately 1% of primary pancreatic neoplasms. [1–3] First described in 1908 by Berner, [4] they recapitulate the growth pattern and secretory products of normal pancreatic acini, often producing digestive enzymes such as trypsin, chymotrypsin, lipase, and amylase. [5–7] ACC can present with a variety of nonspecific symptoms including weight loss and abdominal pain, and less commonly with the jaundice that is classically seen in pancreatic adenocarcinoma. [3] A paraneoplastic syndrome of subcutaneous fat necrosis, polyarthralgia, and eosinophilia due to increased serum lipase has also been reported in some patients, now known as the lipase hypersecretion sydrome. [5,8–11] In general, the preoperative diagnosis of ACC is difficult, with computed tomography

Table 1 Current Acinar Cell Carcinoma Literature

Reference	No. of Pts	M/F	Pts with HOP tumor (%)	Median Survival (m)
[17]	12	6:6	50	5.0
[5]	28	24:4	56	18.0
[20]	4	2:2	50	21.5
[8]	39	31:8	53	19.0
[12]	10	7:3	60	18.8

HOP, head of pancreas; *M/F*, male/female; *Pts*, patients

(CT) only infrequently providing diagnostic clues. [12] Tissue diagnosis, given the similarity of ACC to endocrine tumors cytologically and histologically, often requires additional immunohistochemical assays or, rarely, electron microscopy for definitive confirmation. [5,13,14] Prognosis is generally poor, with patients frequently presenting with metastatic disease and having a high incidence of recurrence.[5,8]

Given its low incidence, characterizing the natural history of ACC and the appropriate therapeutic approach remains difficult with current guidelines based only on a limited number of small case series and anecdotal experiences.[5,8,11,17–20] Review of the literature (Table 1) demonstrates estimates of survival, ranging from 4 months to 7.5 years,[16] with the largest series to date reporting a median survival of 19 months.[8] In addition, the clinical course of ACC remains in question, with some series demonstrating it to be as aggressive as pancreatic adenocarcinoma[21,22] while others describe a more indolent pattern similar to lower-grade endocrine lesions.[5,23] Numerous reports have differentiated ACC from other more common pancreatic malignancies at a molecular and histologic level.[24–26] Nonetheless, a thorough description of its clinical manifestations and behavior as a distinct neoplasm remains incomplete.

In this study, we present our institutional experience of 14 patients with ACC, all of whom underwent surgical resection of their disease at the Johns Hopkins Hospital. We evaluate demographic factors, clinical and pathologic features, and outcomes in these patients, combining our results with a thorough literature review to both verify and expand upon current guidelines for the evaluation and treatment of these malignancies.

Materials and Methods

This study was approved by the Institutional Review Board of the Johns Hopkins Hospital. A retrospective review of prospectively collected data between 1988 and 2006 at the Johns Hopkins Hospital was performed for all patients having pancreatic neoplasms with features of acinar cell differentiation. The patients were identified using the Johns Hopkins Pathology database, and tumor types included acinar cell carcinomas and mixed acinar-endocrine carcinomas. Only the patients with tissue specimens obtained during surgical resection or biopsy at our institution were included as part of the study. Surgical resectability was determined using preoperative abdominal CT scans. Resection of disease involved either a pancreaticoduodenectomy or distal pancreatectomy with splenectomy. For each patient, we recorded demographic information, existing comorbidities, preoperative symptoms and imaging results, operative and pathological findings, tumor staging, postoperative complications, and mortality. Follow-up was conducted using postoperative clinic notes to monitor recurrent disease and survival. Survival and disease-free probabilities were estimated using Kaplan-Meier methods.

Results

Retrospective review of the Johns Hopkins Pathology database revealed 14 patients with ACC from 1988–2006. Patients at our institution (Table 2) had a median age of 57 years (range 33–77) with 64% being female. Common preoperative comorbidities included hypertension (57%), diabetes (29%), and smoking (29%). Abdominal pain or discomfort was the most prevalent presenting symptom (100%), followed by weight loss (36%), nausea/vomiting (29%), and jaundice (21%). No patients presented with symptoms indicative of lipase hypersecretion syndrome. Four of fourteen (29%) patients (patients 2, 3, 5, 14) were initially considered to have unresectable disease due to

Table 2 Patient Characteristics and Symptoms

Characteristic	Value (%), n=14
Female gender	9 (64)
Age (years)	
Median	57
Range	33–77
Alcohol	1 (7)
Coronary artery disease	2 (14)
Diabetes	4 (29)
Hypertension	8 (57)
Obesity	0 (0)
Smoking	4 (29)
Abdominal pain/discomfort	14 (100)
Jaundice	3 (21)
Lipase hypersecretion syndrome (subcutaneous fat necrosis, polyarthralgia, eosinophilia)	0 (0)
Nausea/vomiting	4 (29)
Pancreatitis	2 (14)
Weight loss	5 (36)
Neoadjuvant chemoradiation	4 (29)

Table 3 Tumor Resection Characteristics

Pt	Rx	Size (cm)	+ LN (%)	TNM	Stage	Other features	F/U
1	P	3.5	2/18 (11)	T2N1Mx	IIB		DOD, 32 mo
2	P	2.5	2/12 (16)	T3N1Mx	IIB	Invasion of peripancreatic soft tissue	DOD, 33 mo
3	P	3.5	0/12 (0)	T2N0Mx	IB		A&W, 79 mo
4	P	0.7	6/19 (32)	T1N1Mx	IIB		DOD, 63 mo
5	D	2.5	0/5 (0)	T2N0M1	IV	Multiple liver lesions positive for tumor	DOD, 95 mo
6	D	3.4	0/14 (0)	T2N0M1	IV	Positive peritoneal nodule excised	A&W, 47 mo
7	P	3.0	8/16 (50)	T3N1Mx	IIB	Extension to distal CBD	A&W, 27 mo
8	D	8.0	5/13 (39)	T3N1Mx	IIB	Large vein invasion	DOD, 9 mo
9	P	5.0	0/29 (0)	T3N0Mx	IIA	Extension to distal CBD, wall of duodenum	DOD, 4 mo
10	P	4.2	10/12 (83)	T3N1Mx	IIB	Extension to distal CBD, positive hepatic artery LN	A&W, 17 mo
11	D	23.5	5/8 (63)	T3N1Mx	IIB	Extensive angiolymphatic and large vein invasion	A&W, 12 mo
12	P	6.5	4/20 (20)	T3N1Mx	IIB	Extension to wall of duodenum	DOD, 6 mo
13	D	12.5	1/11 (9)	T3N1Mx	IIB	MAEC, invasion of peripancreatic soft tissue	A&W, 5 mo
14	P	4.5	2/6 (33)	T3N1Mx	IIB	MAEC, extension to duodenal wall	A&W, 1 mo

A&W, alive and well; *CBD*, common bile duct; *DOD*, dead of disease; *D*, distal pancreatectomy; *F/U*, follow-up; *LN*, lymph node; *MAEC*, mixed acinar-endocrine carcinoma; *P*, pancreaticoduodenectomy; *Pt*, patient; *Rx*, resection

extensive tumor invasion of surrounding structures (e.g., transverse mesocolon, superior mesenteric vein encasement) or the presence of metastatic disease (e.g. multiple liver lesions, extensive regional lymphadenopathy). These patients underwent neoadjuvant chemoradiation in an effort to downstage previously unresectable disease, each utilizing gemcitabine, 5-fluorouracil, or adriamycin as part of their chemotherapy regimens. The patients were then reevaluated by CT scan for surgical resection. Each patient demonstrated an improvement in overall tumor burden enough to warrant surgical resection. Common features seen on preoperative CT scan include a hypodense-appearing neoplasm (six patients), a necrotic tumor core (five patients), a partially cystic structure (five patients), and ill-defined, thickened borders (three patients).

Table 3 describes the operative and pathological characteristics of each patient's tumor resection. All 14 patients had their disease surgically resected, with 9 patients undergoing a pancreaticoduodenectomy and 5 patients having a distal pancreatectomy with a concurrent splenectomy. Median tumor size was 3.9 cm (0.7 cm–23.5 cm). Patient 5 initially presented with multiple metastases to the liver that responded well to neoadjuvant chemoradiation, which allowed the patient to undergo operative resection of the lesion including a concurrent partial right hepatectomy. Patients 13 and 14 possessed features of ACC as part of a mixed acinar-endocrine carcinoma MAEC and were considered part of the group analysis given their similarity to pure ACC histologically and clinically.[25] Diagnostic immunohistochemistry was done in all 14 patients, revealing positive staining of tumor cells for trypsin and lipase in 9 and 5 patients, respectively. Further diagnostic confirmation through electron microscopy was done in three patients and demonstrated large, but varying, amounts of zymogen granules and rough endoplasmic reticulum within tumor cells. Using 2006 AJCC criteria, pathological staging of the resected specimens revealed only one patient to have a T1 lesion, while T2 and T3 lesions were present in four and nine patients, respectively. The majority of patients (n=10) had positive regional lymph node metastases. Meanwhile, only patients number 5 and 6, both of whom had negative regional lymph nodes, also had distant metastases. Overall TNM staging demonstrated 12 of 14 patients with stage I or II disease, while patients 5 and 6 possessed stage IV lesions given their M1 status.

Postoperative patient characteristics and survival data are displayed in Table 4. Median duration of hospital stay was 8 days (range 5–14 days) with delayed gastric emptying representing the only immediate postoperative complication (15%). Postoperative follow-up was available for all 14 patients with a median follow-up time of 15 months. Eight of fourteen patients (57%) developed recurrence of their disease, demonstrated on postoperative follow-up CT scans. Five patients recurred locally within the surgical bed, while seven patients had distant metastases to the lungs, liver, or other intraabdominal structures. Median disease-free survival for all patients was 25 months, with estimated disease-free survival at 1 year and 2 years being 64 and 55%, respectively. In addition, median survival for all patients was 33 months with actuarial survival at 1 year and 2 years estimated to be 75% each. When patients with MAECs were excluded, median survival and disease-free survival remained 33 and 25 months, respectively.

Discussion

Acinar cell carcinoma is a rare, malignant tumor of the exocrine pancreas that has only been studied in the

Table 4 Postoperative Characteristics and Survival

Characteristic	Value (%), n=14
Duration of stay (days)	
Median	8
Range	5–14
Delayed gastric emptying	2 (14)
Pancreatic leak	0 (0)
30-day mortality	0 (0)
Disease-free Survival	
Median (months)	25
1-year	64
2-year	55
5-year	34
Survival	
Median (months)	33
6-month	84
1-year	75
5-year	37
Recurrence	8 (57)

scientific literature through small retrospective case series and reports.[5,8,11,17–20] This study, involving a total of 14 patients with ACC within our institution, contributes to the limited amount of data currently available discussing these lesions. Further characterizing these neoplasms in terms of their potential etiology, clinical and histopathological manifestations, therapeutic approach, and prognosis will help distinguish these tumors from more commonly seen malignancies of the pancreas, such as adenocarcinoma and endocrine tumors.

Although 82% of the pancreas is occupied by acinar cells, ACC accounts for less than 1% of all pancreatic malignancies, as compared to pancreatic adenocarcinoma which represents 75%.[27] Despite the large volume of pancreatic operations performed at our institution, approximately 400 cases per year, the presence of only 14 patients with resected ACC over 18 years reinforces their low incidence. Consequently, only a small number of retrospective series have been able to characterize its demographics and clinical presentation. Holen et al. reported a median age of 60 (range: 15–87),[8] similar to that found by Klimstra et al. (mean: 62, range: 40 to 81),[5] and also in this study (median: 57, range: 33–77). These data suggest an overall younger age of presentation for ACC than pancreatic adenocarcinoma; however, very rarely have these lesions been recognized in children.[3,24] Meanwhile, the overwhelming dominance of ACC in males seen by Holen et al. (31:8 M:F ratio)[8] and Klimstra et al. (24:4 M:F ratio)[5] is in contrast to 64.3% of our patients being female. Whether or not sex is significant as an epidemiological factor for this tumor remains unknown.

Commonly reported presenting symptoms included abdominal pain, weight loss, and nausea/vomiting, similar to the distribution seen in our patients.[5,8] Jaundice is less frequently associated with ACC, seen in 21% of our patients and in only 12% of patients by Klimstra et al.[5] However, ACC tends to occur slightly less frequently in the head portion of the pancreas (64.3% in our study, 56% reported by Klimstra et al.,[5] 53% reported by Holen et al.[8], and 50% reported by Webb[17]) than the typical pancreatic neoplasm (70%).[28] Therefore, the lower incidence of jaundice in ACC patients might be explained by its increased frequency as a body and tail lesion, representing a possible distinguishing factor from pancreatic adenocarcinoma. Recognition of symptoms associated with lipase hypersecretion syndrome, including subcutaneous fat necrosis, polyarthralgia, and eosinophilia, may also help solidify a preoperative diagnosis given their specificity for ACC. Several of the first described cases of ACC were discovered through this unusual constellation of symptoms.[18] However, none of our patients presented with this syndrome, corresponding with the current literature that suggests that lipase hypersecretion syndrome is a distinctive but rare finding in these patients.[5,8,12]

Consistent with current practice guidelines for suspected pancreatic malignancy,[29] diagnostic tests such as carbohydrate associated antigen (CA 19-9) levels[30] and abdominal ultrasonography, CT, MRI, and endoscopic ultrasonography are useful in establishing both a preliminary diagnosis and treatment options. Although all of our patients underwent abdominal CT as part of their preoperative evaluation, establishing a diagnosis of ACC from this modality is difficult. Tatli et al. describe pure ACC as an exophytic, well-marginated, hypovascular mass on both CT and MRI, often either oval or round with cystic, necrotic areas when large.[31] Meanwhile, Chiou et al. concluded that ACCs are generally heterogeneous, hypodense masses on CT, notable for well-defined enhancing capsules, occasional internal calcification, and rare intratumoral hemorrhage. In addition, it is suggested that these tumors enhance at a level between pancreatic adenocarcinoma and endocrine tumors of the pancreas.[12] Reinforcing these findings, preoperative CT scans of our patients showed a number of hypodense lesions with or without a cystic structure, central necrosis, and ill-defined borders. In retrospect, none of our patients were definitively diagnosed preoperatively through CT, emphasizing that these descriptions are somewhat nonspecific and based on a limited number of cases. However, they may aid the experienced radiologist in suggesting ACC as part of a differential when a pancreatic neoplasm with these features is seen.

Currently, definitive diagnosis of ACC requires a thorough histopathological examination of tissue obtained through either biopsy or operative resection. Macroscopically, ACCs are generally large, well-circumscribed lesions, reportedly ranging in size from 2 to 30 cm. On gross

examination, they often appear yellowish or tan in color with a soft, lobulated consistency,[3] and tend to occur most frequently within the head of the pancreas.[5,8] Sporadic cases of ACC have also been found growing within pancreatic ducts,[32] arising in heteropic pancreatic tissue within stomach,[33] and as cystic masses.[34] Consistent with previously reported data, our cases demonstrated a wide range of tumor sizes (0.7–23.5 cm), with several of our patients (62%) presenting with a mass in the pancreatic head or uncinate process, requiring a pancreaticoduodenctomy. At a cellular level, ACC exhibits acini with peripherally placed nuclei and small apical lumens (recapitulating the normal growth pattern of nonneoplastic pancreatic acini), trabeculae, glands, or diffuse sheets of cells separated by minimal fibrovascular stroma (Figure 1).[3] Cells generally display uniform nuclei with rare pleomorphism and prominent nucleoli.[5] Immunohistochemical markers for ACC include well-known digestive enzymes normally produced by the pancreas. Trypsin was found to be the most commonly expressed enzyme within the literature (97% of cases), followed by lipase (84.5%), chymotrypsin (66.1%), and amylase (14.3%), which is consistent with the trypsin- and lipase-rich staining pattern seen in our study group. The high frequency of trypsin reactivity in ACC, as opposed to its absence among endocrine tumors, makes it an attractive specific marker for distinguishing these otherwise similar appearing lesions.[3,7] Other smaller series have reported the production of alpha-fetoprotein (AFP) by ACC cells, proposing it as a possible marker of acinar differentiation within these tumors.[19,27,35] Similar to our results, electron microscopy (EM) reveals zymogen granules in varying numbers among tumor cells, in contrast to relatively uniform amounts in nonneoplastic pancreatic acini.[36]

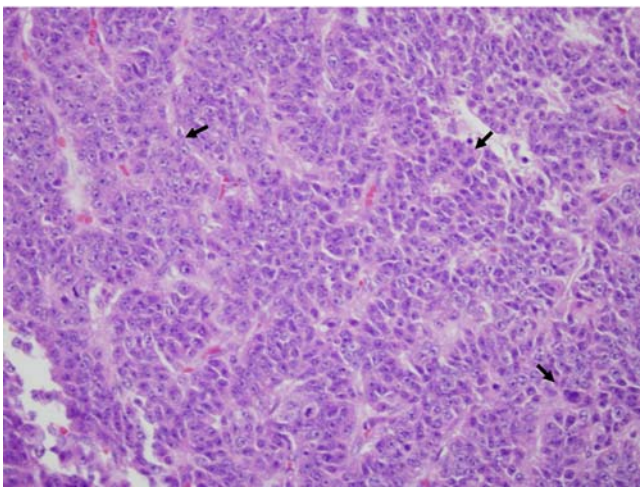

Figure 1 Acinar cell carcinoma, intermediate power view Intermediate power (400×) view of hematoxylin–eosin stained acinar cell carcinoma. The tumor grows in a trabecular pattern, and features uniform cells with amphophilic cytoplasm, round nuclei with vesicular chromatin and prominent nucleoli.

Another diagnostic consideration is the distinction between ACCs, mixed acinar-endocrine carcinomas (MAECs), and pure endocrine tumors. Ohike et al. compared patients with ACC and mixed acinar-endocrine carcinoma, demonstrating that they shared most clinicopathological features including histological differentiation, tumor size and location, and nuclear p53 expression, concluding that both may originate from a common precursor. In addition, even with large numbers of endocrine cells, MAECs rarely expressed one of the known pancreatic or gastrointestinal hormones.[25] These results justify the inclusion of the two mixed acinar-endocrine carcinoma patients within this study. However, our own comparison study of these two neoplasm types would be less informative given the disproportionate number of patients in the two groups. In addition, given the potentially better prognosis for pure endocrine tumors, it is important to distinguish these neoplasms from ACC so that the appropriate level of aggression is used in their oncologic management. Endocrine tumors have been reported to mimic ACCs due to cytologic and histologic subtleties seen in fine needle aspiration or resected specimens.[14] This diagnostic pitfall indicates why accurate diagnosis of ACC typically cannot be done by histology alone, instead requiring immunohistochemical staining or EM.[13] Given the nonspecific symptoms and imaging findings that are often seen with pancreatic neoplasms, this potential confusion between ACC and more common endocrine tumors provokes the question of whether the incidence of ACC is being underestimated. If the diagnosis of ACC is not considered, these lesions will likely be misdiagnosed as pancreatic endocrine neoplasms.

Operative resection remains the optimum therapy for patients presenting with ACC. Holen et al. reported a median disease-free survival of 14 months and a median actuarial survival of 36 months for those patients treated initially by operative resection (18 of 39 patients), as opposed to only 14 months overall survival for those who did not undergo resection.[8] In contrast, earlier work by Klimstra et al. demonstrated a more dismal survival of only 22.6 months in 18 resected patients.[5] All 14 patients in our study underwent surgical resection of their disease, demonstrating a median disease-free survival of 25 months and a median actuarial survival of 33 months, similar to that seen in surgically resected patients by Holen et al.[8] One of these patients (patient 5) required a concurrent right partial hepatectomy for distant metastases as well, after which the patient survived for 95 months, the longest among our patients. Furthermore, our estimated 5-year survival of 37% in resected patients is encouraging in comparison to values

of less than 10% seen in populations of surgical and nonsurgical ACC patients from other series.[5,8] Meanwhile, no large series exist describing the neoadjuvant or adjuvant treatment of ACC with radiation or chemotherapy, limiting our knowledge of their effectiveness. Anecdotal reports have discussed the use of drugs such as 5-fluorouracil, streptozotocin, cisplatin, and doxorubicin as part of their treatment regimens with variable success.[5,8,37,38] Riechelmann et al. report the treatment of recurrent ACC in the form of pulmonary and abdominal metastases with weekly paclitaxel, demonstrating an unusual 4-year survival.[16] Contributing to these limited data, four of our patients underwent successful neoadjuvant chemoradiation treatment using either gemcitabine, 5-fluorouracil, or adriamycin, ultimately allowing for the resection of their tumors. However, the effectiveness of adjuvant chemoradiation is questionable given our recurrence rate of 57%, with six of the eight recurrences occurring within the first two disease-free years. In total, these data support the conclusion that surgical resection is the best first-line treatment for ACC if lesion resectability can be achieved.

The overall reported prognosis and survival of patients with ACC remains variable, with conflicting data on the indolence of ACC in comparison to pancreatic adenocarcinoma.[5,21–23] Holen et al. results showed an overall median survival of 19 months, including patients undergoing either surgical resection or adjuvant chemoradiation as their first-line treatment.[8] A similar median survival of 18.1 months was also reported by Klimstra et al.[5] These values both fall between the reported median survival of ductal adenocarcinoma (6 months)[39] and endocrine neoplasms of the pancreas (40–60 months).[40] When looking at surgically resected pancreatic adenocarcinoma with completely negative margins, our institution reports a median survival of only 18 months,[41] considerably less than the 33 months seen in this series of ACC patients. Although these data suggest ACC to be more indolent than pancreatic adenocarcinoma, it is important to recognize that patients still often present with disease metastatic to lymph nodes or other distant tissue such as the liver.[3] The large majority (12 of 14) of our patients presented preoperatively with disease stage IIB or higher, while four of our patients were deemed unresectable due to the size and extent of their disease on initial diagnosis. In addition, we observed a high recurrence rate of 57%, representing both local and distant metastases, similar to the 72% reported by Holen et al. in their resected patients. These high recurrence rates are suggestive that ACC is somewhat aggressive in nature, creating distant micrometastases not seen on presentation despite otherwise well-circumscribed local disease.[8] The role of neoadjuvant and adjuvant chemotherapy must be further studied in this setting to determine if they can improve on both the recurrence rate and survival of these patients.

As a rare neoplasm, acinar cell carcinoma remains a difficult malignancy to both study and treat. Unfortunately, this low incidence makes it difficult to perform larger, randomized trials looking at the clinical behavior of ACC. With only a limited amount of literature available, institutional series such as ours are useful in helping to characterize the origin, natural history, and appropriate treatment modalities for ACC. The data we have presented and reviewed suggest that definitive diagnosis and evaluation of ACC can be challenging. When possible, operative resection represents the best first-line treatment for resectable ACC due to its more favorable survival, which may be enhanced when combined with a planned neoadjuvant and/or adjuvant chemoradiation regimen. The clinician must however be wary of the aggressive nature of this disease, demonstrated through frequent and significant metastatic spread and recurrence. This series of patients contributes useful clinical, pathological, and prognostic data that can be used by physicians to guide their decision-making when faced with a potential acinar cell carcinoma.

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Surrogate Markers of Resectability in Patients Undergoing Exploration of Potentially Resectable Pancreatic Adenocarcinoma

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Abstract Despite extensive preoperative staging, a significant number of pancreatic cancers are unresectable at surgical exploration. Patients undergoing pancreatic exploration with a view to resection were studied and comparisons are then made between those undergoing resection and a bypass procedure to identify surrogate markers of unresectability. One hundred thirteen consecutive patients underwent pancreatic exploration for head-of-pancreas (HOP) adenocarcinoma with curative intent. Fifty-five underwent pancreaticoduodenectomy and 58 underwent a bypass procedure. Student's *t* test, receiver operator characteristics (ROC) and logistic regression were used to compare the predictive value of preoperative patient variables collected retrospectively. The bypass group had a significantly higher median CA19.9 than the resection group ($P=0.003$). Platelet count and neutrophil–lymphocyte ratio (NLR) were also significantly different ($P=0.013$ and $P=0.026$, respectively). ROC analysis indicated that age ≤65, platelet count $>297\times10^9$/l, CA19.9 ≤473 Ku/l, and CA19.9–bilirubin ratio were predictive variables for resectable disease. NLR and CA19.9–bilirubin ratio had specificity values of 92.9 and 97.0%, respectively. From logistic regression, a raised CA19.9 was found to be an independent risk factor for unresectable disease ($P=0.031$). A significant proportion of patients with HOP adenocarcinoma are understaged preoperatively. Preoperative serology including platelet count, NLR, CA19.9, and CA19.9–bilirubin ratio may be used as additional discriminators of resectability particularly for high-risk patients.

Keywords Pancreatic cancer · Resectability · Inflammatory markers · Neutrophil · Lymphocyte · CA19.9 · Platelet · Bilirubin

Introduction

Adenocarcinoma of the head of the pancreas has a poor prognosis. Surgery remains the only curative treatment for this devastating disease. Unfortunately, the majority of patients will have metastatic or locally advanced disease at presentation, with only 20% of cases eligible for resection at the time of diagnosis.[1] Furthermore, pancreaticoduodenectomy is associated with 3–5% perioperative mortality and significant morbidity.[2] The overall 5-year survival after resection is 15–20%, although this may approach 40–50% in patients with favorable prognostic factors, e.g., small tumor, negative resection margin, low tumor marker level, and no evidence of lymph node metastasis.[2–4]

CT imaging, laparoscopy with or without the use of intraoperative ultrasonography, and endoscopic ultrasonography are all established investigations that improve the accuracy of preoperative staging.[5–7] Despite this, a significant number of pancreatic cancers are found to be unresectable at surgical exploration. A thorough selection process is, therefore, critical in ensuring that only patients with potentially curable disease proceed to resection.

This study compared preoperative factors that may influence resectability in patients with head-of-pancreas cancer that were deemed to have operable disease preoperatively. We aimed to identify surrogate markers of

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resectability in this group of patients, which could be used in the selection process for pancreaticoduodenectomy.

Methods

Patients

This study examined retrospectively the cohort of patients with adenocarcinoma of the head of the pancreas who were selected for pancreaticoduodenectomy from 1999 to 2006 at the Department of Hepatobiliary and Pancreatic Surgery, Leicester General Hospital. Within this population of patients, the study compared the resectable group of patients (who were selected for curative surgery and underwent a pancreaticoduodenectomy) with the bypass group of patients (who were selected for curative surgery but were found to have extrapancreatic tumor spread intraoperatively). The latter group of patients proceeded to have a double bypass in the form of hepaticojejunostomy-en-y and gastrojejunostomy. All data were collected retrospectively from medical records; hence, there was no requirement for ethics approval.

Each patient underwent a rigorous staging process to determine tumor resectability prior to being selected for potentially curative surgery. Patients with resectable disease on contrast-enhanced helical CT imaging underwent staging laparoscopy and intraoperative ultrasound scan (IOUS) to identify extrapancreatic disease below the resolution level of conventional CT imaging. All suspicious peritoneal or hepatic deposits were biopsied. Endoscopic ultrasonography (EUS) was not routinely available to this group of patients; therefore, it did not form part of the staging process. Patients with tumor size favorable for resection (diameter <4.0 cm) and no evidence of extrapancreatic spread of disease were subsequently consented for pancreatic exploration with a view to proceed to pancreaticoduodenectomy. The tumor is deemed unresectable in the presence of extrapancreatic spread of disease confirmed on frozen section. Peripancreatic nodal involvement did not exclude patients from resection with curative intent. However, involvement of lymph nodes outside the resection site implied unresectability. The operating surgeon ultimately made the decision on the resectability of a tumor based upon all available evidence. All patients in the bypass group had intraoperative biopsy to confirm primary pancreatic malignancy.

Comparison Factors

Comparisons between the two groups were made in relation to the patients' demographics, socioeconomic status, radiological staging, and serology results. Tumor size and suggestion of lymph node involvement on preoperative CT imaging were recorded. Serological data included full blood count, urea and electrolytes, liver function tests, and CA19.9 level. Time from diagnosis to surgery was also noted.

Statistical Analysis

Student's *t* test, Fisher's exact test, and Chi-squared test were applied to compare the groups on all factors. Receiver operator characteristics (ROC) curve and univariate logistical regression were utilized for further analysis of factors that showed a significant difference between the groups on Student's *t* test analyses. The chief outcome variable was tumor resectability. All statistical analyses were carried out using statistical software MedCalc™ version 9.3.0.0. A value of $P<0.05$ was considered statistically significant.

Results

Between 1999 and 2006, Leicester General Hospital received 1,202 new pancreatic cancer referrals. One hundred thirteen of these patients underwent pancreatic exploration with curative intent, comprising only 9% of the referrals. Of this number, only 5% proceeded to a resection with curative intent.

The resectable group included the 55 patients who underwent a pancreaticoduodenectomy and the bypass group included the remaining 58 patients who underwent a double bypass. There was no significant difference in the time from diagnosis to laparotomy between the two groups. There were also no significant differences noted between patient demographics, including gender, body mass index, and socioeconomic status (Table 1). The bypass group was found to be significantly older than the resection group ($P=0.049$). The median tumor size was significantly larger in the bypass group when measured with IOUS ($P=0.047$), but such difference was not demonstrated by preoperative CT scan ($P=0.086$).

On comparison of preoperative serological results between the two groups, the bypass group had a significantly higher CA19.9 level, lower platelet count, higher neutrophil–lymphocyte ratio (NLR), and higher CA19.9–bilirubin ratio with *P* values of 0.003, 0.013, 0.026, and 0.022, respectively. Other serological studies, including full blood count and liver and renal function tests, were not notably different between the two groups. There was no difference in the proportion of patients requiring biliary stenting to relieve jaundice preoperatively ($P=0.221$).

Tumor characteristics between the two groups were compared. The bypass group was noted to have a significantly larger tumor size than the resection group

Table 1 Comparison Between the Resection Group and the Bypass Group (variables that are significantly different between the groups are in bold)

Variables	Resection Group		Bypass Group		*P* value
	Number/Median	Range/Percentage	Number/Median	Range/Percentage	
Gender					
Male	31	58.5%	33	56.90%	1.000
Female	22	41.5%	25	43.90%	
BMI	24	17 to 35	25	18 to 33	0.962
Age	**63**	**30 to 80**	**66.5**	**30 to 80**	**0.049**
Occupation					
Professional/managerial	8	19%	7	20%	0.897
Skilled nonmanual	14	23.70%	9	32.10%	
Skilled, manual	13	17.30%	13	68.40%	
Not working	7	9.90%	6	17.10%	
Radiological staging					
Tumor size on CT (mm)	25	15 to 60	34	20 to 80	0.086
Tumor size on IOUS (mm)	**30**	**20 to 60**	**40**	**20 to 80**	**0.047**
Lymphandenopathy	9	17%	9	15.50%	1.000
Stented	20	37.7%	15	25.90%	0.221
Diagnosis to surgery (days)	11	3 to 43	14	17 to 21	0.052
Serology					
CA19.9 (ku/l)	**183**	**5 to 3,581**	**573**	**3 to 12,000**	**0.003**
White cell count ($\times 10^9$/l)	7.65	1 to 20.6	7.5	4 to 15.5	0.820
Neutrophil ($\times 10^9$/l)	4.9	2 to 16.2	5.2	2.25 to 13	0.913
Lymphocytes ($\times 10^9$/l)	1.57	0.52 to 8.1	1.3	0.3 to 7.2	0.088
NLR	**3.53**	**2.57 to 4.85**	**3.9**	**0.9 to 30.3**	**0.026**
Hemoglobin (g/dl)	12.35	8.9 to 16.2	12.4	8 to 16.3	0.885
Platelet count ($\times 10^9$/l)	**311.5**	**165 to 778**	**264.5**	**31 to 473**	**0.013**
Sodium (mmol/l)	136	127 to 143	135	123 to 143	0.140
Potassium (mmol/l)	3.8	3.1 to 5.0	3.8	2.5 to 4.8	0.326
Urea (mmol/l)	4.5	1.7 to 11.5	4	1.7 to 13.5	0.805
Creatinine (μmol/l)	78	49 to 139	76.5	40 to 140	0.685
Albumin (g/l)	36	25 to 47	34.5	18 to 148	0.231
Alkaline phosphatase (iu/l)	258.5	61 to 6,681	288	64 to 2,492	0.967
Alanine transaminase (iu/l)	65.5	5 to 381	64	9 to 187	0.345
Bilirubin (μmol/l)	70	5 to 363	162	2 to 481	0.207
CA19.9–bilirubin ratio	**1.8**	**0.1 to 86.2**	**7.8**	**0.009 to 1,222.2**	**0.022**

when assessed intraoperatively by ultrasonography during staging laparoscopy (median diameter of 40 vs. 30 mm, $P=0.047$). However, there was no significant difference between the groups in the tumor size recorded on staging CT scan.

The ROC curve was utilized to analyze the value of NLR (>1.93), CA19.9–bilirubin ratio (>71.18), age (>65), platelet count ($\leq 297\times 10^9$/l), and CA19.9 (>473 Ku/l) in predicting which patients were not suitable for curative resection. The areas under the ROC curves plotted were 0.60, 0.60, 0.62, 0.62, and 0.67, respectively (Table 2). Figure 1 presents the ROC curve for CA19.9 as a predictor of unresectability. Pancreatic exploration was the gold standard test, which all the patients in this study underwent. This was used to determine tumor resectability and, hence, true and false-positive values. NLR and CA19.9–bilirubin

Table 2 ROC Curve Analysis for Preoperative Markers

Factors	Cutoff Value	Area Under the ROC Curve	Sensitivity (95% CI)	Specificity (95% CI)
CA19.9	>473 Ku/l	0.67	81.8 (64.5–93.0)	55.6 (35.3–74.5)
Platelet count	≤297×109/l	0.62	57.7 (43.2–71.3)	70.7 (57.3–81.9)
Age	>65	0.62	75.5 (61.7–86.2)	53.5 (39.9–66.7)
CA19.9–bilirubin ratio	>71.18	0.60	29.6 (13.8–50.2)	97.0 (84.2–99.5)
NLR	>1.93	0.60	26.5 (15.0–41.1)	92.9 (92.7–98.0)

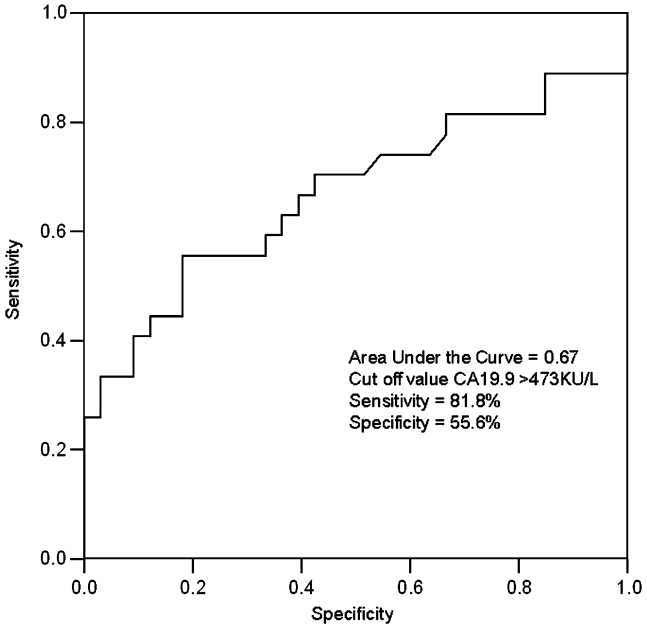

Figure 1 ROC curve for CA19.9 as predictor of unresectability.

ratio had high specificity for unresectability (92.9 and 97.0%, respectively), whereas CA19.9 on its own was the most sensitive predictor of unresectability (81.8%). When the above factors were analyzed with logistic regression, a raised CA19.9 was identified as an independent factor for predicting unresectable disease (P=0.031).

Discussion

Overall 5-year survival for patients with adenocarcinoma of the head of the pancreas is only 5%. Following curative pancreaticoduodenectomy, this rises to 20–40%. Pancreatic exploration may be associated with serious risks and an argument could be made that, for high-risk cases, such operations should be avoided if a curative resection is not achievable. This approach needs to be balanced against the merits of bypass surgery as palliation in patients who have unresectable disease at open exploration. This study found that more than half of the patients selected for curative surgery for adenocarcinoma of the head of pancreas, despite undergoing a rigorous staging process, did not have resectable disease. The low resectability rate in this study is a reflection of the highly selective approach on tumor suitability for resection, based predominantly on tumor size and the absence of extrapancreatic disease, adopted by our unit. In comparing a number of preoperative factors between the resectable group and the bypass group of patients, the study has identified five factors that could be used to further identify suitability for curative surgery. The strongest of these factors was CA19.9, followed by platelet count, age, CA19.9–bilirubin ratio, and NLR.

The function of the tumor marker, CA19.9, as a predictive factor for resectability is consistent with other studies[8–10] and is perhaps unsurprising given its noted proportional relationship with tumor size and burden.[11] This study tentatively explored whether taking serum bilirubin level into account when interpreting the CA19.9 would provide a more sensitive and specific predictor of resectability. This was postulated because of the known spurious elevation of CA19.9 in patients who are jaundiced with cholangitis.[12,13] Hence, by adjusting CA19.9 level according to bilirubin level, it was hoped that jaundice could be removed as an obfuscating factor. The CA19.9–bilirubin ratio was identified as a predictive factor for resectability, showing very good specificity (97.0%) but by sacrificing sensitivity (29.6%). Therefore, overall, the CA19.9 on its own was found to be a stronger prognostic factor with a greater balance in sensitivity and specificity (81.8 and 55.6%, respectively).

It was found that the ROC curve, plotted for NLR, was a weak overall predictor for resectability but, like the CA19.9–bilirubin ratio, was highly specific (92.9%). There is evidence that NLR is a good prognostic factor in other cancers, such as colorectal cancer,[14] and it has also been identified as a predictor for postoperative complications following colorectal surgery.[15] In this study, both NLR and CA19.9–bilirubin ratio were found to have high positive predictive values for unresectability (88.9 and 76.5%, respectively). Therefore, both results could have an integral role in the staging process for pancreaticoduodenectomy. After extensive literature searches, this would appear to be the first time these factors have been explored with regards to resectability of head-of-pancreas adenocarcinoma.

The bypass group was statistically older and had a larger median tumor size on IOUS as compared to the resection group. However, no difference in the tumor size was demonstrated between the groups using contrast-enhanced helical CT scan, suggesting that IOUS may be a superior method to CT scan in assessing tumor size. This is an area that should be further explored prospectively, as this may be a good indicator for tumor resectability.

A number of the predictive factors for resectability, identified in this study, function as markers of inflammation. The role of the host inflammatory response in determining tumor spread has been increasingly recognized.[16,17] Cytokines and growth factors released from an inflammatory response have a function in regulating the growth of tumors.[18] Inflammatory mediators released as part of the systemic inflammatory response to a tumor also produce an intense catabolic response,[19] posing a great demand on host metabolism that will inevitably lead to progressive nutritional deprivation, ultimately contributing to complication and the reduction in survival in patients with pancreatic cancer. Given the findings within this study and the relationship

between host inflammatory response and tumor growth, it is postulated that C-reactive protein (CRP), a marker of host inflammatory response not routinely measured for these patients, could also be used as a predictor of resectability and should be explored in future studies.

Previous studies have suggested that an elevated platelet count preoperatively is associated with poor survival following resection for pancreatic cancer,[20] suggesting that antiplatelet agents have a role in inhibiting tumor metastasis.[21] However, this study found that the median platelet count in the resection group was higher than that of the bypass group and that a platelet count of $\leq 297 \times 10^9$/l is a predictor of unresectability. This is consistent with the evidence provided by Schwarz and colleague indicating that low preoperative platelet count correlates with poorer overall and disease-free survival following surgical resection.[22] Such variable findings may be a reflection that thrombocytopenia and thrombocytosis are both likely to contribute to poor outcome. It may therefore be problematic to rely on platelet count as a predictor of resectability.

The focus of this paper is to identify preoperative factors that predict resectability and result in improved selection of patients for resection. The ROC analysis for these factors showed that they have a moderate value as a test for resectability, and only CA19.9 was identified as a possible independent predictor by logistic regression. Also, due to the rigorous process in selecting individuals for pancreaticoduodenectomy, this study was based on a small number of patients. This in turn affects the validity of the predictive value of the factors.

These preoperative parameters on their own could not be used to exclude patients from pancreatic exploration. However, they may have a key role in deciding where a more targeted approach to preoperative staging is required. It has previously been suggested that patients with a low CA19.9 level could bypass staging laparoscopy and proceed directly to formal exploration.[10] Findings from this study suggest that CA19.9–bilirubin ratio and NLR, with their high specificity, would be better suited than CA19.9 at indicating when to "fast-track" patients for laparotomy. Nevertheless, utilizing the preoperative factors in this way would carry a risk of understaging tumors and subjecting more patients to unnecessary laparotomy than at present. Further work is required to validate the findings of this study. With supporting evidence from further studies conducted in other centers, it may be feasible that these factors could be used as an adjunct to the selection process for surgery. In this respect, the CA19.9–bilirubin ratio, with its very high specificity in determining unresectability, could be used as a marker to decline surgery in high-risk patients. If a decision is made not to proceed to open exploration, then it would be reasonable to not perform a staging laparoscopy.

The predictive factors identified in this study may be better used to indicate when additional preoperative staging is needed. Both 3D-CT imaging and combined CT with positron emission tomography (CT-PET) have been reported as having some value in identifying local invasion and the presence of small metastases.[23,24] Patients with high markers of unresectability, such as an elevated CA19.9, could be selected for such further staging. Because CT-PET is a modality with comparatively little data in staging of pancreatic cancer, open exploration may still be indicated despite positive findings on CT-PET if all other staging assessments deemed the tumor resectable. Its role in determining unresectability must be validated by open operative assessment. EUS is also recommended in some centers as a routine preoperative staging tool[25] but was unavailable to this patient group. EUS may have a role in further discriminating tumor operability. However, laparoscopy and/or open exploration are still required to exclude the presence of radiologically occult liver or peritoneal metastases. In addition, open exploration would still be required to assess other features of unresectability, such as tumor size and lymph node metastases outside the resection site, even if EUS indicated the possibility of inoperable disease on these specific criteria. Our institution is in the process of incorporating EUS as part of the staging process in our institution. Further study similar to this should be conducted once this is established. In patients who are deemed to have operable disease following all their preoperative staging investigations but have very elevated markers of unresectability, a high index of suspicion for unresectable disease must be maintained and careful assessment at open exploration must be undertaken.

In this study, various preoperative variables that may predict tumor resectability were identified. These variables are predominantly markers of the host inflammatory response with an underlying pancreatic cancer. It is worth noting that the patients who proceeded to a curative resection in this series have concomitantly low surrogate inflammatory markers preoperatively and have been found to have an excellent median survival of 54 months.[3] These same markers have not been found to correlate with long-term survival in our patients, presumably due to the relatively small numbers of patients actually undergoing resection. However, this finding does lend support to the notion that the host response can be used as a marker of tumor resectability and possibly long-term survival by acting as an index of tumor burden. It may be possible to develop this further by using inflammatory markers alongside radiological and laparoscopic staging to determine suitability for resection in addition to long-term survival following resection. Further studies to demonstrate the correlation between such a scoring system with tumor resectability and outcome following curative resection are warranted.

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Synthetic Extracellular Matrix Enhances Tumor Growth and Metastasis in an Orthotopic Mouse Model of Pancreatic Adenocarcinoma

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Abstract Individuals with pancreatic cancer have one of the poorest survival rates among the major cancers, suggesting the need to develop new therapeutic approaches. An effective animal model that mimics the progression and metastases of human pancreatic adenocarcinoma does not exist. The goal of this investigation was to develop a model that would compare the growth and metastasis of orthotopically injected pancreatic cancer cells to cells encapsulated within a synthetic extracellular matrix (sECM). The hypotheses tested were that the cells within the sECM would grow more quickly and more frequently develop metastasis to distant organs. MiaPaCa-2 cells expressing red fluorescent protein, either in serum-free media or within a hyaluronan-based hydrogel, were injected into the pancreas of nude mice. Tumors were monitored for 8 weeks via intravital red fluorescent protein imaging. Cells encapsulated within the sECM grew more quickly and produced larger tumors compared with the cells alone. In addition, the cells within the sECM developed metastasis more frequently. Therefore, the encapsulation of human pancreatic cancer cells within an injectable sECM improved the rate of tumor growth and metastasis in an orthotopic mouse model. The advantages of this new approach can be utilized to investigate the mechanisms of tumor progression and test novel therapeutic agents in vivo.

Keywords Orthotopic model · Pancreatic adenocarcinoma · Extracellular matrix · Hydrogel

Introduction

Pancreatic adenocarcinoma (PA) is an aggressive malignancy for which the most effective treatment is complete surgical resection, often including removal of the head of the pancreas, the duodenum, and the common bile duct. Unfortunately, only about 10% of patients present with localized disease amendable to surgery, and despite this aggressive operative approach, greater than 80% of patients resected develop progressive disease and expire within 5 years.[1, 2] There are currently no proven means to treat patients after complete resection of disease to prevent such recurrence.

Metastatic spread of cancer requires multiple cellular reprogramming events that result in escape from apoptosis, promotion of angiogenesis, and replication and growth independent of a basement membrane. The complex cellular mechanisms, which allow an independent rogue cell to establish a secondary site of tumor growth, involve cell/extracellular matrix and cell/cell interactions, receptor-mediated signaling, cytoskeletal rearrangements, and altered transcriptional programs.[3–5] Characterizations of these mechanisms in PA are necessary to identify intervention strategies that will prevent progression of the disease after a complete surgical resection of a primary pancreatic adenocarcinoma.

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Models designed to investigate metastatic tumor growth, such as those involving direct injection of tumor cells into systemic circulation, injection of tumor cells into distant organs, or implantation of tumor fragments into distant organs, fail to mimic the clinical spread of pancreatic cancer. Orthotopic implantation of subcutaneously grown tumors is a well-characterized model, but does not allow investigation of the early stages of PA development, including the initiation of tumor neovascularization. In the clinical setting, subjects with best prognostic factors, including complete resection of the tumor, absence of lymph node involvement and absence of vascular invasion, often succumb to metastatic disease, suggesting that metastasis occurs early in the course of the disease. Therefore, animal models that allow examination of cellular mechanisms in the early stages of PA progression are urgently needed.

Current animal models of PA have low rates of tumor progression and metastases.[6] Orthotopic delivery of tumor cells in a three-dimensional (3D) matrix may overcome these shortcomings by providing a contained, growth-enhancing environment in which tumor cells could propagate.[7] By allowing the tumor cells to proliferate within the matrix, the cells would more likely progress to metastatic disease, and, in contrast to implanted tumor sections, this procedure would allow the cells to express the appropriate orthotopic signals for tumor establishment. The current investigation utilizes a sECM composed principally of hyaluronan (HA). This sECM has been shown to improve vocal cord healing,[8] stimulate angiogenesis,[9] accelerate bone repair,[10] and enhances tumor growth in breast, colon, and ovarian orthotopic animal models.[11] The use of a 3D matrix for orthotopic implantation of various tumor cell types has precedent using a reconstituted basement membrane preparation, Matrigel, where enhanced tumor growth and increased metastasis are observed relative to implantation of cells alone.[12, 13–15] Matrigel has severe technical limitations, including its lot-to-lot variability and difficulty in handling during injection of cell suspensions. An injectable, in situ gelling matrix that can be easily manipulated in the laboratory would be desirable for pancreas implantation of PA tumor cells. The sECM matrix tested in this study has several advantages including: controlled, reproducible composition, allows formation of a uniform cell suspension, and gels within 10 min of the addition of a cytocompatible crosslinker at body temperature or room temperature.[7, 16] Previous trials by our collaborators have shown improved tumor growth in this cECM-utilizing ovarian cancer, breast cancer, and colon cancer cell lines.[11]

We evaluated the growth and metastasis of orthotopically injected human PA cells, MiaPaCa-2, coalesced in sECMs of two different compositions—a crosslinked hyaluronan derivative alone and a crosslinked HA-gelatin mixture. We hypothesized that the encapsulation of the PA cells within the sECM would enhance tumor growth and metastasis compared with PA cells within media. To allow real-time intravital imaging of tumor progression and metastasis, we employed MiaPaCa-2 cells stably transfected to express high levels of red fluorescent protein.[17, 18–20] This model provides a more biologically relevant context to study the mechanisms of PA development and metastases in vivo.

Materials and Methods

Laboratory Animals

Male nude mice (NCr-nu/nu) between 4 and 6 weeks of age were maintained in a barrier facility equipped with HEPA-filtered racks. All the procedures and observations were performed in a biological laminar-flow hood. All studies were conducted with the approval and guidance of the University of Utah Institutional Animal Care and Use Committee.

Cell Culture

The human pancreatic cancer cell line MiaPaCa-2 was obtained from the American Type Culture Collection (Rockville, MD). Cells were maintained in DMEM supplemented with 10% heat-inactivated fetal bovine serum (Gibco, Grand Island, NY). Cells were cultured at 37°C in a 5% CO_2 incubator.

Red Fluorescent Protein Transfection

The pDsRed2-C1 vector (Clontech, Palo Alto, CA) was used to engineer MiaPaCa-2 clones stably expressing red fluorescent protein (RFP). This vector expresses RFP and neomycin-resistance gene on the same bicistronic message, and has been demonstrated to exhibit low toxicity in mammalian cell lines. RFP plasmid transduction was initiated by Lipofectamine 2000 transfection reagent (Invitrogen, Carlsbad, CA). The transfection efficiency was determined by fluorescence microscopy at 24 h post transfection. Cells were then harvested by trypsin/EDTA and subcultured into selective medium that contained 200 μg/ml G418 (Gibco, Grand Island, NY). Clones expressing high levels of RFP were isolated, expanded, and transferred using conventional culture methods. The RFP-expression clones were isolated in the absence of G418 for 10 passages to verify stable expression of RFP in vitro.

Synthetic Extracellular Matrix

The crosslinkable hydrogels CMHA-S, crosslinked hyaluronan derivative alone, and Extracel™, a crosslinked HA-

gelatin mixture, were prepared with modifications of previous methods for HA-DTPH (Glycosan BioSystems, Salt Lake City, UT),[21, 22] Gelatin-DTPH was prepared as described.[22] Solutions of 2.5% (*w*/*v*) CMHA-S and 3% (*w*/*v*) gelatin-DTPH were prepared by dissolving CMHA-S and gelatin-DTPH in RPMI medium 1640 (Gibco, Rockville, MD) and adjusting the pH of the solution to 7.4 with 1.0 N NaOH. A solution of 4% (*w*/*v*) poly(ethyleneglycol) diacrylate (PEGDA; 3,400 kDa, Nektar Therapeutics, Huntsville, AL) was prepared by dissolving PEGDA in Dulbecco's phosphate-buffered saline (DPBS, Gibco, Rockville, MD). All solutions were sterilized by filtration (pore size 0.45 μm), aliquoted, and stored in a −80°C freezer.

Orthotopic Injection Technique

The mice were initially weighed and randomly assigned to an experimental group. The groups consisted of three different matrices (serum-free media, CMHA-SX, or Extracel™), presence or absence of tumor cells, and two time points (4 and 8 weeks) for a total of 12 groups. For the tumor induction surgery, mice were anesthetized in a sealed isoflurane-infused chamber and surgery was preformed under anesthesia provided by isoflurane nose-cone inhalation. All procedures were done under aseptic conditions. The tail of the pancreas was exposed through a left subcostal 4-mm incision into the peritoneal cavity. Mice in the three tumor groups received a single subcapsular injection of 10^6 red fluorescent protein-labeled MiaPaCa-2 cells suspended in either 0.125 mL serum-free media (DMEM; Cells Alone), in CMHA-SX matrix (HA + Cells), or in Extracel™ (HA-G + Cells). Control mice were injected with 0.125 mL of either serum-free (Serum Alone), in CMHA-SX matrix (HA Alone), or in Extracel™ (HA-G Alone). The abdomen was closed using two interrupted 6-0 silk sutures closing both skin and muscle simultaneously. All procedures were done utilizing a 12× Universal S3B microscope (Carl Zeiss, Thornwood, NY).

Observation Period and Assessment of Tumor Progression

After the primary surgery, high-resolution (3,456 pixels × 2,304 pixels) whole-body digital images (EOS Digital Rebel, Canon USA, Lake Success, NY) of each mouse were obtained once a week to monitor primary tumor growth and presence of metastasis.[20] The red fluorescent protein was visualized with an Illumatool Bright Light System that consisted of a 540-nm excitation filter and a 540-nm viewing filter (Model LT-9900, LightTools Research, Encinitas, CA). Animals were imaged under nose-cone induced isoflurane general anesthesia. Primary tumor area was quantified using public domain software (National Institutes of Health ImageJ; http://rsb.info.nih.gov/ij/).

At necropsy, a whole-body in vivo image and an image with the abdominal cavity open was taken of each animal. The whole-body image was utilized for primary tumor area measurement as described above. The open cavity image was utilized to identify the location of metastases, by the visibility of the RFP. After imaging, the primary tumor was removed and weighed. A portion of the primary tumor and representative metastasis were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin for histological analysis.

Statistical Analysis

The relationship between final tumor area measured from intravital imaging and final tumor mass was determined utilizing least squares linear regression followed by a Pearson's test of significance. Differences in final primary tumor mass between the six tumor groups were determined utilizing an analysis of variance (ANOVA) followed by a Tukey's honestly significantly different (HSD) post hoc test. Finally, intravital imaging weekly tumor size was compared between the groups with a repeated measures ANOVA followed by a post hoc test. A p value <0.05 was considered significant.

Results

In-Vivo Imaging of Tumor Growth

After implantation, the red fluorescent protein expressing primary tumors were visible by intravital imaging at 4 weeks post implantation (Fig. 1). Therefore, tumor progression was measured over time from week 4 through week 8. There were no statistical differences between HA + Cells and HA-G + Cells over the 4-week time course. However, by week 5, both the HA + Cells and HA-G +

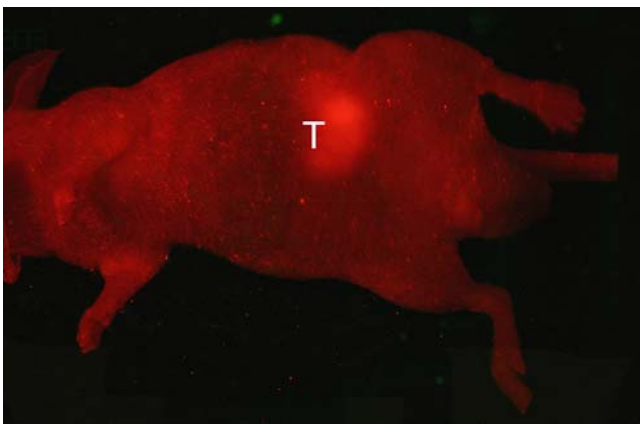

Figure 1 Photographic image demonstrating the primary pancreatic tumor (*T*) is visible via intravital imaging at 4 weeks post implantation of RFP-transfected MiaPaCa-2 cells.

Cells groups had statistically larger tumors compared with the Cell Alone group (Fig. 2). There was also a statistically significant linear correlation between final tumor area, as measured by intravital imaging, and final tumor mass (y= 43.6 mm^2/g(x) + 26.1 mm^2; R^2=0.8118; p<0.05), suggesting that intravital imaging was a valid method of monitoring tumor growth over time (data not shown). In addition, we found red fluorescent imaging improved our identification of micrometastases at necropsy as small tumors were clearly identified by the presence of RFP.

Tumor Morphology and Metastases

At 4 weeks post implantation there were no differences among the three groups in terms of tumor mass (Fig. 3). However, by 8 weeks the HA + Cells and HA-G + Cells groups had significantly larger tumors compared with all three groups at 4 weeks. The 8-week Cell Alone group was not statistically different from the 4-week groups or HA + Cells and HA-G + Cells at 8 weeks. This supports the intravital imaging data that the Cell Alone tumors were smaller than the HA + Cells and HA-G + Cells tumors. However, the HA-G + Cells group appeared to have more consistent tumor growth compared with the HA + Cells at 4 and 8 weeks, with most tumors being above 500 and 2,000 mg, respectively (Table 1).

In terms of metastases, one animal in the HA + Cells 4-week group exhibited tumor spread to the small bowel mesentery (Table 1), whereas none of the HA-G + Cells and Cells Alone animals had any visible metastatic tumors at 4 weeks. By 8 weeks, two of the HA + Cells and three of the HA-G + Cells animals had metastatic spread of the tumors to sites distant from the pancreas including the diaphragm, spleen, liver, and mesentery (Table 1). The Cell

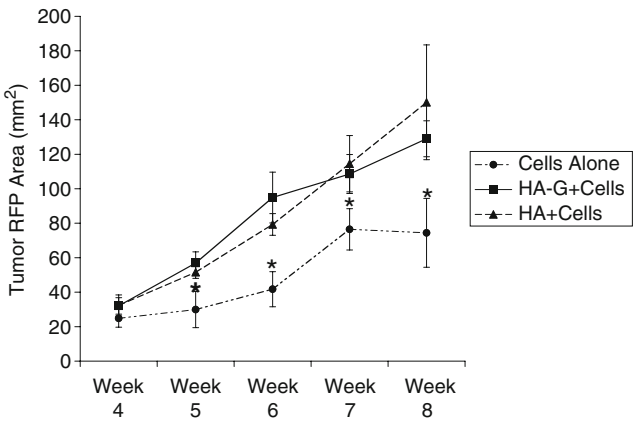

Figure 2 Tumor size by intravital imaging. The area of the primary tumor was monitored weekly with intravital imaging from week 4 through week 8. By week 5 both the HA and HA-G cell groups has larger primary tumors compared with the cells only group. *Statistically different from HA and HA-G, p<0.05.

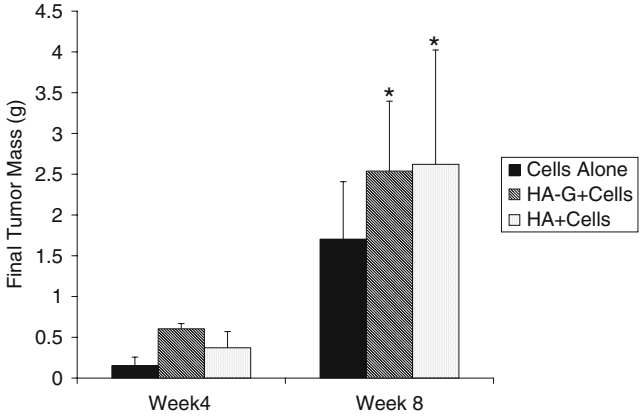

Figure 3 Tumor weights at necropsy. HA and HA-G cells, at 8 weeks, had statistically larger tumors (*) at necropsy compared with the cells only, HA cells, and HA-G cells at 4 weeks. p<0.05.

Alone group did not exhibit any visible metastasis by 8 weeks. One difference noted between the groups was that three of the 4-week HA-G + Cells and three of the 8-week HA-G + Cells had sidewall implants, as viewed by RFP imaging. These implants were located at the site of injection and were not counted as metastases. None of the HA + Cells and Cell Alone groups had sidewall implants. As a control, four additional animals were given intraperitoneal (IP) injections of MiaPaCa-2 cell (10^6) to determine if the metastasis was seeding or true metastasis. The IP-injected cells resulted in tumors attached to the abdominal wall at various locations within the abdomen. However, none of the free peritoneal injections resulted in tumors in similar sites to the metastases from the orthotopically injected cells, such as the mesentery, spleen, and liver.

Histological characteristics of the primary tumors between the three groups exhibited similar morphology at 4 and 8 weeks. At 4 weeks, tumors consisted mainly of viable tumor cells with minor inflammation in the surrounding tissue and within the tumor. One difference that was noted at 4 weeks was the presence of residual synthetic extracellular matrix within the tumors of all five HA + Cells animals and one HA-G + Cells animals. The tumor cells grew in clusters within the HA matrix and, as these clusters grew, appeared to merge into one large tumor mass (Fig. 4). There were some necrotic tumor cells within the synthetic extracellular matrix, and inflammatory cells near the sites of necrotic cells. The HA Alone group also had synthetic extracellular matrix present, with mild inflammation around the outside boundary. At 8 weeks, the tumors in all three groups had regions of central necrosis and an accompanying inflammatory response (Fig. 5). The metastatic tumors were composed of viable tumor cells with limited necrotic tissue within the tumor. Morphologically, the distant tumors and primary tumors looked similar in terms of cell morphology, cell density, and vascularity.

Table 1 Pathological characteristics of tumor progression

Group	Week	Tumor Present	Tumor Mass >500 mg*	Tumor Mass >2000 mg†	Metastases Present	Ascites Present
Cells Alone	4	4	1	N.A.	0	0
	8	5	N.A.	2	0	1
HA	4	5	3	N.A.	1	0
	8	5	N.A.	3	2	2
HA-G	4	5	5	N.A.	0	0
	8	5	N.A.	4	3	0

Data indicate the number of mice in each group that exhibited the characteristic listed. *N*=5 mice per group.
*Tumor mass at 4 weeks only
†Tumor mass at 8 weeks only

Discussion

We have demonstrated, in this initial evaluation of a nude mouse model of pancreatic adenocarcinoma, the ability to produce primary tumors, metastatic disease, and monitor tumor growth in vivo. We found that the use of two formulations of an in situ crosslinkable, injectable 3-D sECM improved tumor growth and metastatic frequency compared with direct injection of the cell within the pancreas. The use of red fluorescent protein imaging enabled the visualization of tumor in vivo and more accurate identification of micrometastasis at necropsy.

Currently available models of metastatic PA typically utilize direct implantation of cells into the nude mouse peritoneal cavity, spleen, pancreas, or portal vein, as well as orthotopic implants of subcutaneous tumors.[6] The utility of these models to investigate the mechanisms of PA are limited as the primary tumor either does not develop orthotopically or there is limited metastatic potential. Specifically, models using direct cell implantation into the peritoneal cavity, the portal vein, or the spleen have the highest rate of distant tumor spread, but these models do not replicate the cell signaling and biologic changes necessary for a primary tumor to develop viable secondary metastatic cell implantation and growth.[6, 23] The implantation of pancreatic tumor tissue grown subcutaneously in a primary animal and implanted directly into the pancreas body of a secondary animal has more predictable rates of tumor growth and liver and regional node metastases (rates of 50–80%).[23–25] Yet, this technique is labor and resource intensive. In addition, as the tumor was formed before implantation into the pancreas, it may not be possible to investigate the early molecular changes and vascularization that precede distant organ metastasis, as they may occur very early in tumor progression.

The model described herein involves orthotopic implantation of tumor cells encapsulated in an injectable sECM. The use of the sECM enhances tumor growth and metastasis, as demonstrated in this work by the larger tumors and more frequent metastasis in the HA an HA-G Cells groups compared with the Cells Alone group. The rates of metastases in the HA + Cells and HA-G + Cells groups were 40% and 60%, respectively, at only 8 weeks of tumor growth, whereas the Cell Alone group had smaller tumors and no visible metastatic spread by 8 weeks. Progression of the local primary tumor in this model requires tumor implantation and vascularization. In addition, extrapancreatic spread of disease in this model requires the mechanisms necessary for a rogue cell to escape from the primary tumor, migrate through the circulatory or lymphatic system, extravasate into a new tissue location, invade and attach to the new ECM, and stimulate neovascularization. Our model more accurately mimics the mechanisms necessary for natural tumor progression and metastases to the small bowel mesentery and liver.

Finally, some previous studies have utilized implantation of harvested human primary pancreatic tumor tissue

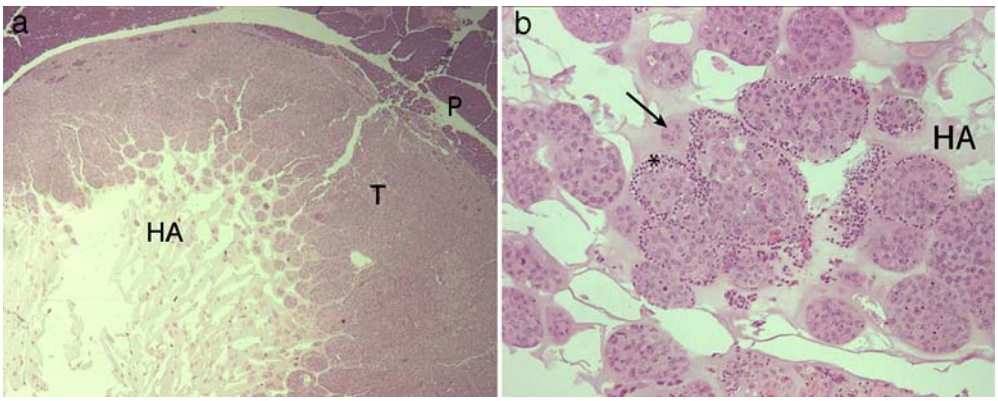

Figure 4 Histological assessment of implanted tumors. **a**) At 4 weeks hydrogel was present within the primary tumor (*T*) in the *HA* + cell group. The tumor cells appeared to grow in isolated clusters that merged into a large tumor mass. 4×. **b**) Encapsulated within the synthetic extracellular matrix were viable and necrotic tumor cells (arrow), with inflammatory cells (*) present in the surrounding area. 20×.

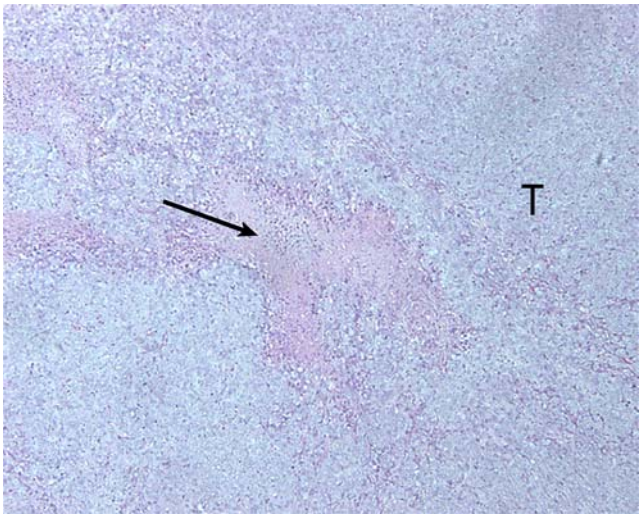

Figure 5 The primary tumor (*T*) had regions of necrosis (arrow) at 8 weeks, and an accompanying inflammatory response near the sites of necrosis. 10×.

directly into the pancreas body. These models have more predictable rates of tumor growth and liver and regional node metastases, yet the genetic characteristics and protein expression profiles of these human tumors require additional investigation, as opposed to the well-defined tumor cell lines of known genetic mutation and tumor marker expression status.[6, 26, 27]. The use of well-characterized cell lines also allows for manipulation in tissue culture before implantation, for example through transfection with RNA interference molecules or expression vectors.

The current investigations confirm the benefits of implanting cells within an sECM, improved tumor growth, and metastasis that have been demonstrated in other orthotopic cancer models including breast, colon, and ovarian.[11] In addition, a subsequent study within our lab has demonstrated similar tumor growth and metastasis utilizing a second pancreatic cancer cell line, ASPC-1.[28]

In this model, HA + Cells and HA-G + Cells were cross-linked before pancreatic implantation, with the transition time between liquid and a more viscous, but still injectable state taking about 2 min. Therefore, the tumor cells could be homogeneously distributed throughout the matrices and then implanted in the viscous state. The implantation of the tumor cells in a more viscous state may prevent extrapancreatic cellular contamination at the time of pancreatic implantation, by the formation of a semisolid form. We feel this sECM has significant advantage over the more universally utilized extracellular matrix, Matrigel™, as temperature control of the gel is not necessary, making the gel more versatile and easier to use. Our tumor growth rates are comparable to those widely published with Matrigel™.[6, 12] In this model development study, we found the HA + Cells group did not have any sidewall tumor implants. However, as noted previously some of the HA-G animals exhibited sidewall implants. Therefore, we compared intrapancreatic injections to free intraperitoneal injections to determine if the visible extrapancreatic tumors were from seeding or metastasis. The injection methods demonstrated different patterns of growth. Specifically, tumor progression after intrapancreatic injection of HA-G with tumor cells resulted in mesenteric nodules consistent with lymphatic spread. In contrast, the free peritoneal injection of HA-G with tumor cells resulted in peritoneal surface implants only, confirming that mesenteric spread in our model is likely not associated with peritoneal contamination at the time of cell implantation. The HA+Cells had the advantages of enhanced tumor growth compared with the Cells Alone and no sidewall implants. Whereas the HA-G+Cells had the advantages of enhanced cell growth compared with the Cells Alone and a faster degradation rate compared with the HA+Cells group. Therefore, future research should examine formulation of HA-G with less gelatin to combine the beneficial aspects of both the HA and HA+G groups. Indeed, a hydrogel prepared with a 95:5 (*w*/*w*) ratio of CMHA-S to gelatin-DTPH was optimal for repair of damaged rabbit vocal folds7 and exhibited excellent cell attachment, spreading, and proliferation with human dermal fibroblasts.[29]

The addition of red fluorescence transfected cells in this model allowed accurate intravital monitoring of tumor growth and improving evaluation of extent of disease at necropsy. Our data confirm that intravital imaging accurately reflects tumor growth, demonstrated by the correlation between RFP intensity and tumor mass. The ability to monitor tumor progression intravitally will facilitate the evaluation of therapeutic interventions, as it makes it possible to monitor chemotherapeutic or genetic intervention effects on tumor progression, in real-time, without necessitating animal necropsy. This, again, allows real-time study and limits the animal resources necessary for complete therapeutic response analysis.

In summary, we have demonstrated a model in which cancer cells may be injected directly into the body of the nude mouse pancreas. The use of a synthetic extracellular matrix improved tumor growth and metastasis compared with implantation of cells within media. By enabling the cells to express red fluorescence protein, it is possible to monitor therapeutic interventions intravitally. As such, this novel orthotopic mouse model of human pancreatic adenocarcinoma will increase our ability to investigate the mechanisms of tumor progression, metastasis, and therapeutic treatments.

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An Antecolic Roux-en Y type Reconstruction Decreased Delayed Gastric Emptying after Pylorus-Preserving Pancreatoduodenectomy

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Abstract The aim of this study was to identify a preferable procedure reducing the incidence of delayed gastric emptying (DGE) after pylorus-preserving pancreatoduodenectomy (PPPD). Data on 132 consecutive patients with pancreatobiliary disease, who underwent PPPD, were collected retrospectively. A retrocolic Billroth I type reconstruction (B-I group) and an antecolic Roux-en Y type reconstruction (R-Y group) were performed for 54 and 78 patients after PPPD, respectively. Clinical measures of DGE were compared between the two groups. The incidence of DGE was 81% in B-I group and 10% in R-Y group ($P<0.001$). The type of reconstruction ($P<0.001$), operative time ($P=0.016$), and postoperative complications ($P=0.001$) were significantly associated with DGE by univariate analysis. Only the type of reconstruction ($P<0.001$) was identified as an independent factor, which was associated with DGE by multivariate analysis. An antecolic Roux-en Y type duodenojejunostomy could be a useful reconstruction method after PPPD to prevent the occurrence of DGE.

Keywords Pylorus-preserving pancreatoduodenectomy · Billroth I type reconstruction · Roux-en Y type reconstruction · Antecolic fashion · Retrocolic fashion · Delayed gastric emptying

Introduction

Pancreatoduodenectomy has become accepted as a safe and appropriate surgical treatment providing the possibility of cure for patients with periampullary malignant tumors, including pancreatic carcinoma, ampullary carcinoma, and distal cholangiocarcinoma. Conventional pancreatoduodenectomy (with gastrectomy) was first performed successfully by Whipple et al.[1] in 1935, and a few years later, Watson described a pylorus-preserving pancreatoduodenectomy (PPPD), which preserved the whole stomach and 1 in. of duodenum.[2] The advantages of the PPPD are a lower frequency of dumping and a better postoperative gastrointestinal quality of life than the pancreatoduodenectomy with equal morbidity, mortality, and long-term survival.[3–6] However, the PPPD has been associated with a higher incidence of delayed gastric emptying (DGE) than the pancreatoduodenectomy,[6–10] although different opinions existed.[3–5] The incidence of DGE was reported to range from 22% to 52% of patients undergoing PPPD.[9–17] DGE is transient and not life threatening, but it results in a significant prolongation of hospital stay and contributes to increased hospital costs. Therefore, there have been many attempts to reduce the incidence of DGE after PPPD by modification of the reconstruction method[12,14,18–20] and administration of erythromycin[15,21] or cisapride.[22]

In this study, we compared clinical measures of DGE between patients undergoing a retrocolic Billroth I type reconstruction and patients undergoing an antecolic Roux-en Y type reconstruction after PPPD. The aim of this study was to identify a useful reconstruction method to minimize the incidence of DGE after PPPD.

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Materials and Methods

Data Collection

Data on 132 consecutive patients with pancreatobiliary disease, who underwent PPPD at Hiroshima University Hospital, were collected retrospectively between January 1994 and December 2006. Pancreatoduodenectomy with antrectomy or distal hemigastrectomy was excluded in this study. A Billroth I type reconstruction with retrocolic fashion (B-I group) was performed until December 2000, and a Roux-en Y type reconstruction with antecolic fashion (R-Y group) was performed after January 2001 (Fig. 1). All operations were performed by the same team of hepatobiliary-pancreatic surgeons throughout the study. A single chief surgeon (Y. M.), who had performed more than 100 pancreatoduodenectomies, led all operations.

Data concerning patient demographics (age, gender, and pathological diagnosis) and perioperative factors (partial resection of the portal vein, operating time, blood loss, blood transfusion, and postoperative complications) were recorded. To evaluate the incidence of DGE, daily output from the gastrostomy tube, the day of closure of the gastrostomy tube, the starting day of liquid or solid foods, and percentage of oral intake of solid foods on the 10th and 14th postoperative days were also recorded. These data were compared between the B-I group and R-Y group.

Gastric emptying was considered delayed when postoperative gastric suction was required for more than 10 days or when there was an inability to tolerate a solid diet on or before the 14th postoperative day.[11,13,23] Percentage of oral intake of solid foods was defined as the ratio of actual intake to the total provided diet. A pancreatic fistula was defined according to the criteria of the International Study Group on Pancreatic Fistula.[24] A biliary fistula was defined as persistence of biliary drainage for more than 5 days with confirmation by fistulography.[23] Operative mortality was any death occurring within 30 days of the procedure.

Surgical Procedures

At the time of pancreatoduodenal resection, the right gastric artery and left gastric vein were divided at their origins. The duodenum was transected 2 to 4 cm distal to the pylorus. A duct-to-mucosa pancreaticogastrostomy was performed to provide enteric drainage of the pancreatic remnant. After pancreatoduodenal resection, the pancreatic stump was dissected from the superior mesenteric and splenic vein for a distance of 2 cm. A 3-cm incision in the seromuscular layer of the posterior gastric wall was made. A row of interrupted 4-0 nonabsorbable monofilament sutures was placed between the seromuscular layer of the posterior gastric wall and the anterior wall of the pancreas (approximately 0.5 cm from the cut edge of the pancreas). A 0.5-cm incision of the exposed gastric submucosa/mucosa was made at the opposite side of the main pancreatic duct. A row of interrupted 5-0 absorbable monofilament sutures was then placed between the gastric submucosa/mucosa and the main pancreatic duct, which was completed by a total of eight 5-0 absorbable monofilament sutures including the posterior and anterior sutures. The duct-to-mucosa method was completed by applying a row of interrupted 4-0 nonabsorbable monofilament sutures between the seromuscular layer of the posterior gastric wall and the posterior wall of the pancreas. When external drainage of pancreatic juice was performed, the pancreatic tube was inserted into the main pancreatic duct, and exteriorized through the anterior gastric wall and the anterior abdominal wall. When external drainage of the pancreatic juice was omitted, a pancreaticogastric stent was placed as an internal drain of the pancreatic juice to the stomach. This stent was typically removed spontaneously within 1 or 2 months after surgery. After pancreatic reconstruction, an end-to-side choledochojejunostomy and end-to-end duodenojejunostomy in a retrocolic position was performed for the B-I group, whereas an end-to-side choledochojejunostomy and end-to-side duodenojejunostomy in an antecolic position was

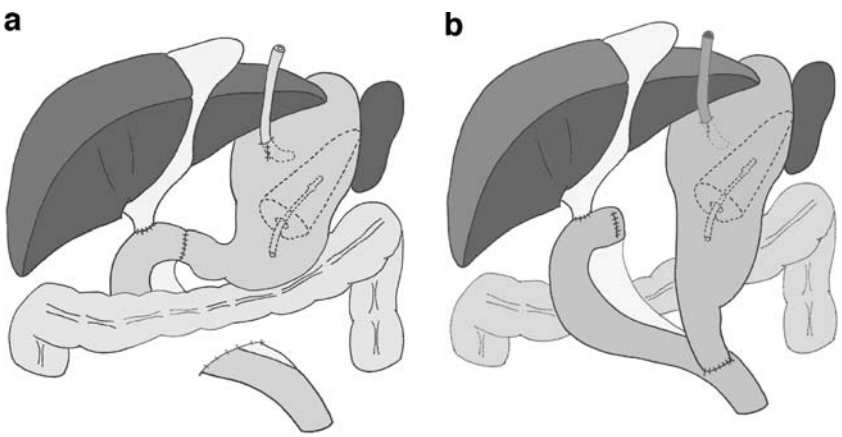

Figure 1 Schematic illustration of a Billroth I type reconstruction in a retrocolic fashion (**a**) and a Roux-en Y type reconstruction in an antecolic fashion (**b**) after pylorus-preserving pancreatoduodenectomy.

performed for R-Y group (Fig. 1). A tube gastrostomy was performed in all patients to remove the gastric and pancreatic juice and to decompress the gastric lumen. The gastrostomy tube was closed when drainage volume was <500 ml/day. The pancreatic tube and gastrostomy tube were usually removed on the 14th–21st postoperative day. All patients had two drains placed at the time of surgery, one each near the choledochojejunostomy and the pancreaticogastrostomy. These drains were removed on the fifth postoperative day if there was no pancreatic or biliary fistula. All patients received a histamine H_2-receptor antagonist during the postoperative period as prophylaxis for marginal ulceration. No patient received somatostatin analogues during the perioperative period.

Statistical Analysis

Data were presented as mean±SD. Statistical comparison was carried out between the B-I group and R-Y group. The χ^2 test and Student's t test were used for comparison. A multivariate analysis was performed using a multiple logistic regression model to identify the perioperative factors, which were considered to have influence on DGE. A $P<0.05$ was considered statistically significant. Statistical analysis was carried out using the Macintosh version of StatView (version 5.0; SAS Institute, Cary, NC, USA).

Results

Patient Demographics and Perioperative Factors

No operative mortality occurred in the 132 patients. There was no significant difference in age, gender, and pathological diagnosis between B-I and R-Y groups. Partial resection of the portal vein was more frequently performed for R-Y group as compared with B-I group ($P=0.049$). Although operative time did not differ between two groups ($P=0.178$), blood loss of B-I group was higher than that of R-Y group ($P=0.001$), and blood transfusion was more frequently required in the B-I group than in R-Y group ($P=0.002$). There was no significant difference in occurrence of pancreatic fistula between two groups ($P=0.495$), although postoperative complications more frequently occurred in B-I group as compared with R-Y group ($P<0.001$, Table 1).

Table 1 Perioperative Characteristics of Patients Undergoing Billroth I Type and Roux-en Y Type Reconstruction after Pancreatoduodenectomy

	Type of Reconstruction		*P* Value
	B-I Type ($n=54$)	R-Y Type ($n=78$)	
Age (years)	64±12	67±11	0.082
Gender			
Male	36	46	0.370
Female	18	32	
Pathological diagnosis			
Pancreatic carcinoma	14	25	NS
Ampullary carcinoma	17	15	
IPMN	13	21	
Distal cholangiocarcinoma	8	9	
Chronic pancreatitis	1	1	
Miscellaneous	1	7	
Portal vein resection			
Yes	2	11	0.049
No	52	67	
Operative time (min)	356±90	369±78	0.178
Blood loss (ml)	1,820±1,470	1,230±850	0.002
Blood transfusion			
Yes	26	17	0.001
No	28	61	
Pancreatic fistula			
Yes	2	5	0.495
No	52	73	
Postoperative complications			
Yes	25	15	<0.001
No	29	63	

B-I Billroth I, *R-Y* Roux-en Y, *NS* not significant; *IPMN* intraductal papillary-mucinous neoplasm

Clinical Measures of DGE

Clinical measurements of DGE are listed in Table 2. The incidence of DGE was 81% (44 of 54 patients) in B-I group, compared with 10% (8 of 78 patients) in R-Y group ($P<0.001$). There were significant differences ($P<0.001$) in postoperative maximum output volume from the gastrostomy, the number of days with high-volume (>500 ml) gastrostomy tube drainage, the number of days with gastrostomy tube drainage, the numbers of days until liquid and solid foods began, percentages of solid foods intake on the 10th and 14th postoperative days, and length of postoperative hospital stay (Table 2).

Perioperative Factors Influencing DGE

Perioperative factors, which have influence on DGE, were sought by univariate and multivariate analysis. The type of reconstruction ($P<0.001$), operative time ($P=0.016$), and postoperative complications ($P=0.001$) were significantly associated with DGE by univariate analysis (Table 3). These three factors were entered into multivariate analysis using a multiple logistic regression model. Only type of reconstruction ($P<0.001$) was identified as an independent factor, which was associated with DGE (Table 4).

Discussion

Delayed gastric emptying (DGE) is the most frequent postoperative complication after PPPD. However, the reported incidence of DGE varies between 22% and 52%[9–17] because of a lack of a uniform definition of this complication. Various definitions of DGE include gastric decompression for more than 7[25] or 10 days[11,15] and inability to tolerate a solid diet after the 10th[26] or the 14th postoperative day.[11,12,18] The most recent DGE definition requires either gastric suction for more than 10 days or the inability to tolerate a solid diet on or before the 14th postoperative day.[11,13,23] We chose this definition for our present study. As a result, the incidences of DGE in the B-I group and in the R-Y group were 81% and 10%, respectively, and a Roux-en Y type reconstruction was identified as the only independent factor, which reduced the occurrence of DGE.

According to the previous literature, the incidence of DGE in a Billroth I type reconstruction has been reported to range from 32% to 72%.[9,12,27] It was reported that the reason for the higher rate of DGE in a Billroth I type reconstruction was that the stomach was anastomosed closely to the pancreato- and hepaticojejunostomy in the limited room of the upper quadrant of the abdomen and that this procedure caused torsion or angulation of the reconstructed alimentary tracts.[12] We believe that an important practice for preventing DGE after PPPD is to put the stomach at as straight and vertical a position as possible.[14,20] With this arrangement, the food is emptied smoothly from the stomach to the jejunum by gravity, although the stomach is atonic and without peristalsis. However, if a Billroth I type reconstruction is performed after PPPD, it is difficult to put the stomach at a vertical position because of the performance of a choledochojejunostomy. In fact, the stomach, when a Roux-en Y reconstruction was selected after PPPD, was commonly observed with postoperative upper gastrointestinal X-rays in a vertical position in our series (Fig. 2). The lower incidence of DGE in a Roux-en Y type reconstruction is mainly caused by a vertical stomach position, we believe.

Recently, Tani et al.[18] reported a result of a randomized controlled trial that an antecolic reconstruction for duodenojejunostomy during PPPD decreases the rate of DGE compared with a retrocolic reconstruction. Similar results

Table 2 Comparison of Clinical Measures of Delayed Gastric Emptying Between Billroth I Type and Roux-en Y Type Reconstruction

	Type of Reconstruction		*P* Value
	Billroth I Type ($n=54$)	Roux-en Y Type ($n=78$)	
Delayed gastric emptying			
Yes	44	8	<0.001
No	10	70	
Maximum gastrostomy tube output (ml/day)	1,290±898	394±346	<0.001
Gastrostomy tube output < 500 ml/day (days)	12.1±9.0	1.7±4.4	<0.001
Closure of gastrostomy tube (days)	16.1±7.5	4.8±3.5	<0.001
Liquid foods begun (days)	16.8±7.1	5.9±1.4	<0.001
Solid foods begun (days)	21.7±8.2	8.6±3.5	<0.001
Solid foods intake at the 10th POD (%)	1.1±7.3	38.0±29.0	<0.001
Solid foods intake at the 14th POD (%)	14.6±27.0	59.6±27.5	<0.001
Length of postoperative hospital stay (days)	47.3±27.9	34.0±16.5	<0.001

POD Postoperative day

Table 3 Univariate Analysis of Perioperative Factors Influencing Delayed Gastric Emptying

Factors	Delayed Gastric Empting		*P* Value
	Yes (n=52)	No (n=80)	
Gender			
Male	34	48	0.533
Female	18	32	
Age (years)			
<70	32	40	0.193
≧70	20	40	
Type of reconstruction			
Billroth I type	44	10	< 0.001
Roux-en Y type	8	70	
Portal vein resection			
Yes	2	11	0.062
No	50	69	
Operative time (min)			
<350	32	32	0.016
≧350	20	48	
Blood loss (ml)			
<1,200	20	43	0.086
≧1,200	32	37	
Blood transfusion			
Yes	22	21	0.054
No	30	59	
Pancreatic fistula			
Yes	3	4	0.847
No	49	76	
Postoperative complications			
Yes	24	16	0.001
No	28	64	

were reported by other authors in retrospective studies.[16,28] They speculated that retromesenteric passage of afferent jejunum can cause venous congestion and bowel edema, which can in turn retard the recovery of jejunal peristalsis at the site of duodenojejunostomy and result in DGE. In this study, an antecolic reconstruction was utilized for the R-Y group but not for B-I group. This practice might have contributed to the lower incidence of DGE in the R-Y group.

It has been reported that sparing the right gastric artery[29] or the left gastric vein [17] decreases the incidence of DGE after PPPD because these procedures prevent ischemia or

Table 4 Multivariate Analysis of Perioperative Factors Influencing Delayed Gastric Emptying

Factors	Relative Risk	95%CI	*P* Value
Type of reconstruction			
Billroth I type	31.6	11.4–88.2	<0.001
Roux-en Y type	1.0		

CI Confidence interval

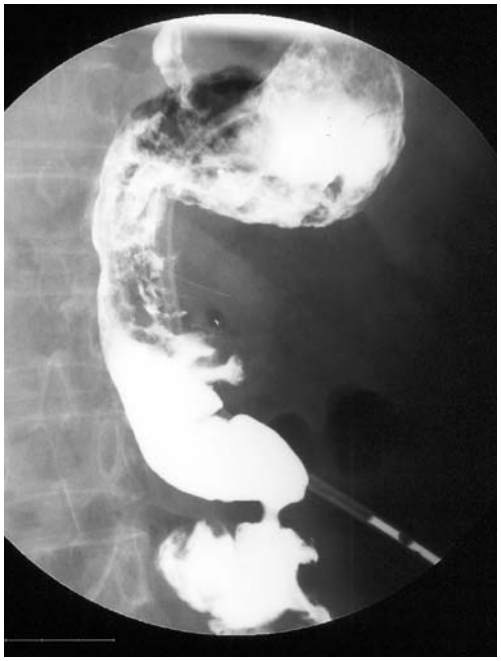

Figure 2 Upper gastrointestinal x-ray image of a patient undergoing a Roux-en Y duodenojejunostomy in an antecolic fashion after pylorus-preserving pancreatoduodenectomy on the 14th postoperative day. The contrast medium flowed smoothly through the stomach to the jejunum.

congestion of the preserved duodenum and antrum. In the present study, both the right gastric artery and the left gastric vein were divided at their origin in both B-I and R-Y groups. However, the incidence of DGE extremely decreased in R-Y group. We believe that dividing the right gastric artery and the left gastric vein were not associated with a higher incidence of DGE.[14]

We used tube gastrostomy for all patients to decompress the gastric lumen and remove the pancreatic and gastric juice because tube gastrostomy provided more complete decompression of the gastric lumen and was more comfortable for patients than nasogastric suction. However, gastrostomy itself may promote DGE because it can disturb gastric motility. In our series, however, the frequency of DGE was low in the R-Y group despite the performance of gastrostomy. We assume that gastrostomy does not correlate with DGE.

Other postoperative complications including pancreatic fistula, biliary fistula, and intra-abdominal abscess are thought to be the most important factors associated with DGE.[11,16,27,28,30] The reasons why other postoperative complications may lead to DGE are not fully understood. It has been suggested that gastroparesis, as a consequence of local inflammation, may cause DGE in these cases.[11] In our series, postoperative complications were associated significantly with the frequency of DGE by univariate analysis. However, they were not found to be an independent factor associated with DGE by multivariate analysis.

Conclusions

In conclusion, this retrospective study showed that an antecolic Roux-en Y type duodenojejunostomy reduced the incidence of DGE after PPPD. As compared with a retrocolic Billroth I type reconstruction, the antecolic Roux-en Y reconstruction was the only independent factor, which reduced the incidence of DGE. This procedure could be a useful reconstruction method after PPPD to prevent the occurrence of DGE. Unfortunately, the nonconcurrent, retrospective, and non-randomized nature of our study weakens the overall conclusion.

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Role of Selective α and β Adrenergic Receptor Mechanisms in Rat Jejunal Longitudinal Muscle Contractility

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Abstract
Gut motility is modulated by adrenergic mechanisms. The aim of our study was to examine mechanisms of selective adrenergic receptors in rat jejunum. Spontaneous contractile activity of longitudinal muscle strips from rat jejunum was measured in 5-ml tissue chambers. Dose–responses (six doses, 10^{-7}–3×10^{-5}M) to norepinephrine (NE, nonspecific), phenylephrine (PH, α_1), clonidine (C, α_2), prenalterol (PR, β_1), ritodrine (RI, β_2), and ZD7714 (ZD, β_3) were evaluated with and without tetrodotoxin (TTX, nerve blocker). NE(3×10^{-5}M) inhibited 74 ± 5% (mean ± SEM) of spontaneous activity. This was the maximum effect. The same dose of RI(β_2), PH(α_1), or ZD(β_3) resulted in an inhibition of only 56 ± 5, 43 ± 4, 33 ± 6, respectively. The calculated concentration to induce 50% inhibition (EC50) of ZD(β_3) was similar to NE, whereas higher concentrations of PH(α_1) or RI(β_2) were required. C(α_2) and PR(β_1) had no effect. TTX changed exclusively the EC50 of RI from 4.4 ± 0.2 to 2.7 ± 0.8% ($p < 0.04$). Contractility was inhibited by NE (nonspecific). PH (α_1), RI(β_2), and ZD(β_3) mimic the effect of NE. TTX reduced the inhibition by RI. Our results suggest that muscular α_1, β_2, and β_3 receptor mechanisms mediate adrenergic inhibition of contractility in rat jejunum. β_2 mechanisms seem to involve also neural pathways.

Keywords Contractility · Motility · Jejunum · Rat · In vitro · Adrenergic · Adrenergic receptor · α-Adrenergic receptors · β-Adrenergic receptors

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Introduction

The modulation of gastrointestinal muscular activity is dependent on the interaction of two complex neural networks, the central nervous system with the extrinsic nerves (vagal, sympathetic) that connect with the enteric nervous system, which is completely intrinsic within the bowel wall.[1] In the gastrointestinal tract, interaction between the central nervous system and the enteric nervous system is important for the response to stress, for eating, and for behavior.[2]

The upper gastrointestinal tract and the distal colon and rectum are mainly modulated by vagal motor pathways. In the small bowel, vagal input is supplied to myenteric neurons,[3] which influence the generation of motor patterns.

The nerve cell bodies of the intestinal sympathetic nervous system are located in the prevertebral ganglia, and enter the gut with their postganglionic fibers. In the gut wall, no adrenergic nerve cell bodies are present.[1] Most if not all sympathetic postganglionic fibers affecting motility are thought to synapse in the enteric nervous system and

not directly on smooth muscle cells. Indeed, no synapses exist between adrenergic nerves and the nonsphincter muscle cells in the gut.[4] In earlier research, despite the predominant, direct adrenergic input to the enteric nervous system, we found strong, adrenergic inhibitory motor mechanisms in rat jejunum and ileum occurring preferentially at the level of these smooth muscle cells rather than in the enteric nervous system;[5,6] these effects appeared to be independent of input from the enteric nervous system.

Directing pharmacologic therapy at the receptors occurring on smooth muscle cells in the gut could therefore be one approach to target gastrointestinal motility disorders through adrenergic pathways. Up to now, treatments targeting adrenergic pathways in the gastrointestinal tract have not been successful. One reason is that the agents used produce substantial cardiovascular side effects.[7] Therefore, mechanisms and pathways of specific subtypes of adrenergic receptors involved in modulating contractile activity of the gut are of considerable interest.

The effect of selective stimulation of β-adrenergic receptors, especially the effect of β_3 receptor agonists on contractile activity in rat jejunal longitudinal muscle, has not yet been examined. In the rat ileum, we previously showed the importance of β_3 receptor mechanisms for contractile activity.[8]

In the current study, our first aim was to identify the effect of the stimulation of all subtypes of adrenergic receptors on jejunum longitudinal smooth muscle of the rat. Our second aim was to determine if these receptor-specific mechanisms were mediated at the level of the smooth muscle and/or via the enteric nervous system. Our hypothesis, based also on our findings in the rat ileum,[8] was that α_1, β_2, and β_3 receptor mechanisms all mediate inhibitory responses and that these mechanisms are active directly at the level of the smooth muscle and not indirectly via effects mediated through the enteric nervous system.

Materials and Methods

Preparation of Tissue

Procedures and animal care were performed according to the guidelines of the Department of Agriculture of the Canton of Bern, Switzerland. Male Wistar rats were used in all experiments. Anesthesia was achieved by intraperitoneal sodium pentobarbital (5mg/100g; Abbott Laboratories, North Chicago, IL). A 5-cm segment of the jejunum was removed, beginning 2cm anal to the ligament of Treitz, and stored in cold Krebs-Ringer's buffer (concentration in mM: NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0 calcium disodium edetate 0.26, and glucose 11.1). The proximal end of the specimen was marked.

Recording of Contractile Activity

The segment of the proximal jejunum was immersed in chilled, modified Krebs–Ringer's bicarbonate solution and opened along the mesenteric border. The tissue was pinned flat in a Petri dish, and eight full-thickness muscle strips per rat were prepared in the direction of the longitudinal muscle layer. Silk loops were tied at both ends of the strips. The muscles were suspended vertically in 5-ml organ chambers (Radnoti Glass Technology, Monrovia, CA) filled with modified Krebs–Ringer's bicarbonate solution maintained at 37.5°C. The solution was bubbled with 95% O_2 and 5% CO_2 (Carbagas, Bern, Switzerland). The lower end of the muscle strip was connected to a fixed glass hook in the chamber, while the upper end was attached to a noncompliant force transducer (Radnoti Glass Technology), thereby allowing measurement of isometric force.

Experimental Design

After an equilibration period of 80–90min, with buffer solution changed every 20–25min, each strip was stretched incrementally at 10–15-min intervals to its optimal length (L_o). L_o is defined as the length beyond which further stretching did not increase the amplitude of spontaneous contractions. The entire experiment was then performed at this L_o; strips without spontaneous activity were not used (2% of all muscle strips).

After baseline spontaneous activity was recorded, one substance per chamber was administered in a cumulative manner. Norepinephrine (NE) was chosen as the nonselective adrenergic agonist, phenylephrine and clonidine as α_1- and α_2-selective agonists, and prenalterol, ritodrine, and ZD7114 as β_1-, β_2-, β_3-selective agonists, respectively. Drugs were added in six cumulative doses (range 1×10^{-7}–3×10^{-5}M) every 10min. The highest dose used was 3×10^{-5}M, according to our previous work using only NE.[5,6] One chamber contained a control strip to confirm stable activity for the duration of the experiment, and the last chamber contained a spare strip.

After the dose–response experiment, the chambers were washed four times with modified Krebs–Ringer's buffer. When spontaneous contractions returned to baseline activity, tetrodotoxin (TTX; 1×10^{-6}M) was added to every chamber. TTX is thought to abolish almost all enteric neural input by blocking neuronal sodium channels. After a 15–20-min equilibration period, the same dose–response experiment was repeated in each chamber with the same agonist.

At the conclusion of the experiment, the length of each strip between the two ties of silk loops and wet weight were measured.

Data Analysis

Total spontaneous contractile activity was quantified as the integral of the generated force ($g \times$ time as total area under the contractile curve) measured for 5min at L_o, while responses to adrenergic agonists were quantified by measuring the integral of force for 5min immediately after drug administration. The integral of force was calculated by computerized methodology using a special software (AcqKnowledge, Biopac Systems, Goleta, CA), normalized per millimeter squared of cross-sectional area (CSA) for each muscle strip.

The CSA was calculated using the following equation:

$$\mathrm{CSA}\left(\mathrm{mm}^2\right) = \text{tissue wet weight}(\mathrm{mg})/\text{tissue length}(\mathrm{mm}) \times \text{tissue density}\left(\mathrm{mg}/\mathrm{mm}^3\right)$$

Tissue length and weight were measured at the end of the experiment, and smooth muscle tissue density was assumed to be 1.05mg/mm^3.[9]

The dose–response curve for each agonist was obtained by defining spontaneous contractile activity as 100%. To quantify these dose–response curves, the negative of the natural log (ln) of the equipotent concentration that caused a 50% response (EC_{50}) was estimated for each agonist based on the dose–response curve. A greater EC_{50} represents a smaller concentration of an agonist needed to induce 50% inhibition of spontaneous activity.

Values are presented as mean ± standard error of the mean (SEM). Student's *t* tests with a Bonferroni correction were used to compare the effects of each specific agonist with spontaneous activity at all doses and the respective effect of NE. The effect of TTX on spontaneous activity, on EC_{50}, and on each dose of the respective agonist was evaluated in the same way.

Changes of the amplitude were analyzed as follows. The amplitude after the highest dose of each agonist without TTX was calculated as a percentage of the amplitude at L_o. After the second dose–response with a neural blockade, the amplitude after the highest dose was calculated as a percentage of the amplitude after the equilibration with TTX (L_{oTTX}).

Drugs

L-Phenylephrine hydrochloride, clonidine hydrochloride, ritodrine hydrochloride, and NE bitartarate salt were purchased from Sigma (St. Louis, MO). Prenalterol and ZD7114 hydrochloride were purchased from Astra Zeneca (Södertälje, Sweden). TTX was purchased from Juro (Luzern, Switzerland).

Results

Spontaneous Contractile Activity

Spontaneous phasic contractile activity was recorded shortly after suspending the muscle strips in the organ chambers. After the addition of TTX (after the first adrenergic dose–response experiments, washout, and restoration of spontaneous activity), contractile activity remained the same (92.7 ± 4 to 88.1 ± 4g/5min/mm^2; $p > 0.05$).

Effect of Nonselective Adrenergic Stimulation

In all strips treated with NE, the amplitude and the baseline tone were reduced in a dose-dependent manner, while the frequency of contractions remained unchanged. At the higher doses, an initial increase in basal tone was observed (Fig. 1a). Inhibition of spontaneous contractile activity induced by the highest dose of NE (3×10^{-5}M) was 73.7 ± 5%. Blocking all neural activity within the bowel wall with TTX (1×10^{-6}M) changed neither the dose response to NE (Table 1) nor the effect of the highest dose of NE on the reduction in the amplitude (Table 2).

Effect of α-Agonists

Phenylephrine (α_1-agonist) inhibited contractile activity by reducing the area under the curve but not the basal tone in a dose-dependent fashion (Fig. 1). However, the EC_{50} was less than for NE, and the inhibition (at 3×10^{-5} M) was less compared to an equimolar dose of NE (Table 1; Figs. 1 and 2a). TTX had no effect on α_1 receptor-mediated inhibition induced by phenylephrine. Neither the reduction in the area under the curve nor the change of basal tone was dependent

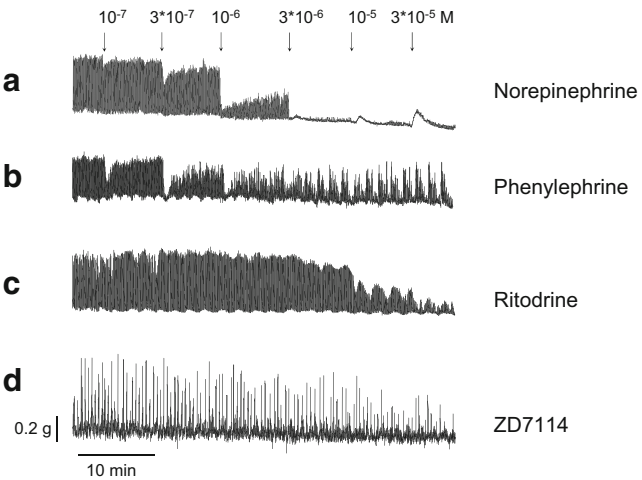

Figure 1 Effect of **a** norepinephrine, **b** phenylephrine (α_2), **c** ritodrine (β_2), and **d** ZD7114 (β_3) on spontaneous activity. Cumulatively administered molar doses of agents caused a dose-dependent decrease in contractile activity.

Table 1 Inhibitory Effect of Selective Adrenergic Agonists on Rat Jejunal Longitudinal Muscle without and with Tetrodotoxin (TTX; 10^{-6}M)

	Response to 3×10^{-5}M dose[a]		EC_{50}	
	without TTX	with TTX	without TTX	with TTX
Norepinephrine	74 ± 5*	81 ± 4*	5.6 ± 0.2	5.8 ± 0.1
Phenylephrine, α_1 α_1	43 ± 4*, **	42 ± 5*, **	1.9 ± 0.8**	2.2 ± 0.9**
Clonidine, α_2	1 ± 9**	16 ± 5*, **	NA	NA
Prenalterol, β_1	5 ± 6**	19 ± 4*, **	NA	NA
Ritodrine, β_2	56 ± 5*	44 ± 10*, **	4.4 ± 0.2**	2.7 ± 0.8**, ***
ZD7114, β_3	33 ± 6*, **	37 ± 7*, **	5.8 ± 2	3.5 ± 0.4**

NA Not applicable, as no inhibition was seen
*$p < 0.006$ compared to spontaneous activity before adding respective drug
**$p < 0.05$ to NE
***$p < 0.05$ to EC_{50} without TTX
[a] Values: percent inhibition, mean ± SEM; n = 10 rats; EC_{50} represents calculated negative log of molar value resulting in 50% inhibition of spontaneous activity.

on presynaptic mechanisms (Tables 2 and 3). Clonidine (α_2-agonist) with and without TTX had no demonstrable effect on contractile activity.

Effect of β-Agonists

Differing effects of the three β-adrenergic agonists were noted. Prenalterol (β_1-agonist) with or without TTX had no effect. In contrast, ritodrine (β_2-agonist) and ZD7114 (β_3-agonist) both induced a marked dose-dependent inhibition of 56 ± 5 and 44 ± 10% at the highest dose (3×10^{-5}M), respectively (Table 1, Fig. 2b). At smaller concentrations, the inhibition induced by ZD7114 was even stronger compared to NE (Fig. 2b). TTX did not influence the dose–response of ZD7114 (β_3-agonist), but it decreased the inhibition of ritodrine (β_2-agonist). This effect seems to be due primarily to a smaller reduction in the amplitude. (Tables 2 and 3, Fig. 3). Ritodrine without TTX (3×10^{-5}M; β_2-agonist) reduced the amplitude by 60 ± 6% compared to the amplitude at L_o.

Table 2 Reduction in Amplitude Induced by Adrenergic Agonist without or with Tetrodotoxin (TTX; 10^{-6} M)

	Response to 3×10^{-5}M dose[a]	
	Without TTX	With TTX
Norepinephrine	33±8	15±2**
Phenylephrine, α_1	79±4	85±5
Clonidine, α_2	91±6	99±4
Prenalterol, β_1	100±10	97±12
Ritodrine, β_2	**40±6**	**57±5***
ZD7114, β_3	80±6	66±6

*$p<0.05$ vs without TTX
**$p=0.055$ vs without TTX
[a] Values represent percent (mean±SEM; $n=10$ rats) of amplitude after the highest dose of agonist (3×10^{-5} M) compared to the amplitude before dose response experiment (100%).

In the presence of TTX, the reduction in the amplitude was smaller (43 ± 5%, $p < 0.05$).

The EC_{50} for ZD7114 did not differ from the EC_{50} for NE (5.8 ± 2 vs 5.6 ± 0.2, $p > 0.05$), suggesting a similar molar inhibitory effect of ZD7114. However, the EC_{50} of ritodrine and NE (4.4 ± 0.2 vs 5.0 ± 0.3, $p < 0.05$) differed,

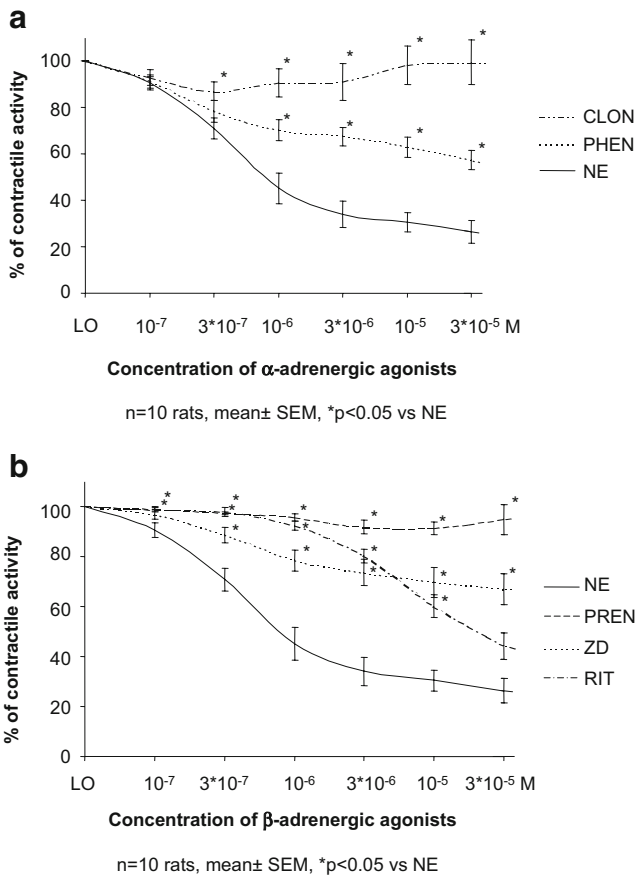

Figure 2 Dose–responses of **a** clonidine (α_1) and phenylephrine (α_2) and **b** prenalterol (β_1), ritodrine (β_2), and ZD7114 (β_3) compared with norepinephrine. Values represent percent mean±SEM (n=10 rats).

Table 3 Reduction in Basal Tone Induced by Adrenergic Agonist without or with Tetrodotoxin (TTX; 10^{-6} M)

	Response to 3×10^{-5} M dose[a]	
	Without TTX	With TTX
Norepinephrine	76±9	84±8
Phenylephrine, α_1	51±7	49±11
Clonidine, α_2	15±3	18±11
Prenalterol, β_1	18±9	29±9
Ritodrine, β_2	73±9	63±12
ZD7114, β_3	64±7	63±12

[a] Values represent percent (mean±SEM; $n=10$ rats) reduction in the baseline tone after the highest dose of agonist (3×10^{-5} M) compared to the baseline tone before the dose–response experiment (100%).

suggesting that β_2 receptors have a smaller influence. This influence seems to decrease even more after TTX. The dose–response curve of ritodrine under neural blockade with TTX was shifted more to the right, and the EC_{50} was 2.7 ± 0.8, compared to 4.4 ± 0.2 for NE ($p < 0.05$; Fig. 2b). These findings suggest that there is a neural β_2 receptor-dependent inhibitory pathway in rat longitudinal jejunum smooth muscle.

Discussion

We designed our study to characterize the involvement of specific adrenergic α_1, α_2, β_1, β_2, or β_3 receptor mechanisms in the inhibition of contractile activity of longitudinal smooth muscle in the rat jejunum. As a potential novel therapeutic target for motility disorders, adrenergic pathways modulating gut motility are of particular interest. The identification of specific receptor subtype mechanisms is required to target effects on intestinal contractile function, possibly minimizing or even avoiding cardiovascular side effects.

Our main findings were that α_2 and β_1 receptor mechanisms do not appear to be involved in the adrenergic modulation of gut contractile activity in the rat jejunum, either directly on the smooth muscle cells or indirectly via the enteric nervous system. In contrast, α_1, β_2, and β_3 pathways reproduced, in part, the inhibition induced by NE, a nonselective, global adrenergic agonist. Blocking enteric neural activity within the muscle strip (with TTX, 10^{-6}M) reduced only the response of β_2 receptor stimulation, suggesting involvement of enteric neural mechanisms.

Because generally not much is known about the role of α receptors in intestinal contractility, our results with the involvement of α_1 but not α_2 receptors in inhibitory modulation of motor activity in the rat jejunum are of special interest. Similar to our findings, Fox et al.[10] detected an inhibitory effect on contractile activity of α_1 receptors in rat jejunum. In contrast to our results, Fox et al.[10] found an α_2 receptor-mediated inhibition as well. Another group documented the induction of neuronal nitric oxide synthase expression after stimulation of α_2 receptors in rat jejunum, suggesting a potential inhibitory effect by α_2 receptors, however, without physiologically measuring the effect on contractile activity.[11] Sagrada et al., [12] however, measured an inhibitory influence on contractile activity of α_2 receptors as well as α_1 receptors in rat jejunum. This difference can be explained by the fact that they performed an in vivo study where conditions and confounding effects such as circulation are not controlled as well as in vitro in tissue chambers.

Of greatest interest is a comparison of our results with data from human studies. A case report of a patient with pheochromocytoma, in whom paralytic ileus was treated successfully with the α receptor antagonist phentolamine and later with prazosin (a selective α_1 receptor antagonist),[13,14] suggests that α mechanisms may be involved in human small bowel contractile activity. It is interesting to note that α_2 pathways did not seem to play a role in an in vitro study in human tissue.[14] Therefore, it seems likely that the α-adrenergic influence in control of human small bowel contractility is dependent on α_1 receptors. This is in accordance with our present results in the rat jejunum, where α_1 mechanisms but not α_2 pathways appear to influence contractile properties in vitro.

Generally, the role of α receptors seems to differ between species and anatomical regions of the gut. In

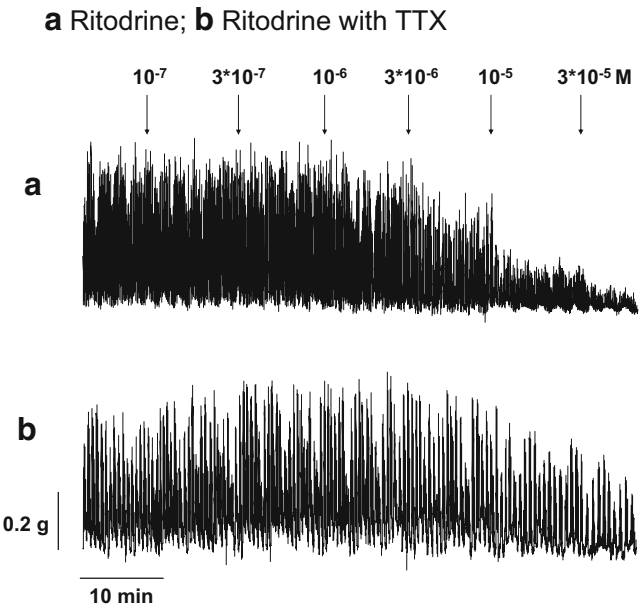

Figure 3 **a** Effect of ritodrine (*Rt*; β_2) on spontaneous activity. Ritodrine was administered cumulatively and caused a dose-dependent decrease in contractile activity. **b** In the presence of TTX, the dose-dependent reduction in amplitude was smaller, thus reducing the overall inhibitory effect induced by ritodrine.

rabbit jejunum, only α_1 but not α_2 receptors mediate inhibition,[15,16] and in canine jejunum, equine jejunum, and rat colon, only α_2 but not α_1 inhibitory mechanisms have been described.[17–21] We have previously shown inhibitory α_1 mechanisms in the rat ileum.[8] In rabbits, α_1 mechanisms can be part of inhibitory pathways not only in jejunum but in other anatomic regions of the gut as well.[22]

In our study, inhibitory mechanisms mediated by β_2 adrenergic receptors were identified. These results are in accordance with our findings in rat ileum, where β_2 adrenergic receptors are an important part of inhibitory mechanisms of adrenergic influence.[8] The finding in the rat jejunum is also consistent with results in rabbit jejunum,[23] whereas in canine jejunum, β_2 pathways had no influence on contractile activity.[17] Fox et al.[10] found an inhibitory effect of β adrenergic receptors in rat jejunum without conclusively assigning these mechanisms to specific subtypes of β adrenergic receptors.

Because β_3 receptors seem to be abundantly present in gastrointestinal tissue, they have been of particular interest.[24,25] Our results are in accordance with our previous study in rat ileum [8] and with the data of Brown and Summers,[26] where β_3 pathways are shown to play a major role in the inhibition of rat ileum. In the study of Fox et al.,[10] β_3 pathways could not be selectively examined. Our results suggesting a major inhibitory role of β_3 mechanisms in rat jejunal smooth muscle add important knowledge to rat gut contractile physiology.

In addition, we tried to distinguish between muscle-related mechanisms and pathways involving the enteric nervous system, as under pathologic conditions, adrenergic mechanisms might be compromised at either level of control.[5,27,28] The pathways of the specific adrenergic α_1, α_2, β_1, or β_3 receptor seem to be independent of the enteric nervous system because none of these mechanisms were sensitive to TTX. It is interesting to note that part of the β_2 inhibition in our experiments appears to be modulated by presynaptic mechanisms. Blockade of neural β_2 mechanisms by TTX resulted in less inhibition of contractile activity. The neurally mediated effect appears to occur by a decreased reduction in amplitude rather than a reduction in baseline tone (Fig. 3). This finding is interesting, as it differs from our results in the rat ileum, where the neural part of β_2 inhibitory mechanisms affected basal tone and not amplitude. This might reflect a different β_2-adrenergic influence in the jejunum compared to the ileum, which is conceivable because global motor patterns (i.e., myoelectric motor complex) change their characteristics from oral to aboral along the small bowel.[29,30]

Our results are in contrast to the findings of Fox et al.,[10] where presynaptic mechanisms are not involved in β-adrenergic pathways. This difference could be explained by a different approach of excluding neural input. While they eliminated only the myenteric neurons with an application of benzalkonium chloride to the bowel in an operation 15days before the in vitro experiment, we treated the muscle strips during the experiment with TTX, which represents an acute near-complete abolishment of neural activity.

Whereas in other groups and study designs, no distinction between muscle or neutrally mediated inhibition was made,[31] we think that such findings are important. Considering gastrointestinal motility disorders in neurological diseases such as diabetic neuropathy or other postneurotomy syndromes (e.g., postvagotomy gastro paresis), it is possible that a lack of neural input could result in impaired modulation of contractile activity by β_2 mechanisms. Thus, further studies are required.

Conclusion

We conclude that adrenergic inhibition in the rat jejunum may be an additive effect of the three specific adrenergic mechanisms noted to inhibit contractile activity (α_1, β_2, and β_3). None of the specific pathways alone reached the degree of inhibition achieved by NE. Our previous data in the rat ileum,[8] other previous results in rabbit ileum,[31] and studies in human colon by Manara et al.[32] support this concept of the involvement of several receptors in inhibitory mechanisms.

When we compare our results with the literature, not only the high degree of regional variability (anatomic region and muscle layer) but also differences between species is striking. Regarding differences between anatomic regions, we have now shown that receptor-specific adrenergic inhibitory mechanisms seem to be similar in rat jejunum and rat ileum. In comparison to the human gut, it is of interest that α_1 receptor mechanisms (but not α_2 pathways) played a role in our present rat jejunum and previous rat ileum study.[8] The scarce data from the literature suggest a similar constellation of contractile α-adrenergic mechanisms in human small bowel. If this similarity is confirmed in the future, the rat small bowel might be attractive to further model α_1 pathways in pathologic states.

For β_2 and β_3 receptors, differences between species are evident as well, but we do not have comparable data for human jejunum. Species differences, especially for β_3 pathways, would be of interest, as these receptors are abundantly present in gastrointestinal tissue and are therefore of interest for gastrointestinal motility.[33,34] Our findings of an important role of inhibitory β_3 mechanisms in rat jejunal contractile activity are novel and add to the understanding of rat small bowel contractile properties. Because we have shown that α-adrenergic mechanisms seem to have a similar effect in the rat jejunum and in human jejunum, in future studies, it will be of special interest to address the similarities between rat and human β_3 pathways in jejunal smooth muscle.

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Laparoscopic Versus Open Ileo-Colonic Resection in Crohn's Disease: Short- and Long-Term Results from a Prospective Longitudinal Study

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Abstract Possible relations between surgical approaches, frequency, and severity of Crohn's disease recurrence after ileo-colonic resection is unknown. We aimed to assess perioperative outcomes and postsurgical complications of laparoscopic versus standard open surgery and to detect differences between the two groups in endoscopical recurrence and patients' satisfaction. Twenty-eight consecutive patients undergoing elective ileo-colonic resection by either laparoscopic approach (n=15) or conventional open surgery (n=13) were prospectively enrolled. No mortality or major intraoperative complications were observed in both groups. Significant differences between groups were the median operating time found shorter in the open group than in the laparoscopic group (p=0.003), the higher dosage of pain killers needed in the open group (p=0.05), the passage of flatus and\or stool after surgery found faster in group A (p=0.004) and the shorter recovery period in the laparoscopic group (p=0.007). Colonoscopy was performed in 27 patients. The frequency and pattern of recurrence did not differ between the two groups (p=0.63). Patients' satisfaction was significantly in favor of laparoscopy. Present findings support the feasibility and advantages in the short-term of laparoscopic ileo-colonic resection in patients with Crohn's disease. No differences were observed in terms of frequency, time of onset, and severity of recurrence in a 1-year follow-up.

Keywords Crohn's disease surgery · Laparoscopic surgery · Recurrence · Quality of life

Introduction

Laparoscopic (lap) ileo-cecal resection has been proposed with increasing interest in surgical treatment of Crohn's disease (CD).[1] As CD is a benign disease, laparoscopic treatment is not ethically questionable. However, long-standing inflammation and physiopathologic characteristics of the disease may determine the procedure long, tricky, or even hazardous.[2–4]

It is clear that laparoscopic approach to surgery in CD can be proposed only after its feasibility and effectiveness is demonstrated. Furthermore, prospective and randomized trials, analyzing significant short- or long-term clinical benefits, may indicate laparoscopy as the procedure of choice for ileo-colonic resection in CD.

A correlation between clinical outcome of CD patients after laparoscopy[5–10] and host immune response[11–15] has been postulated, although statements at this regard are not conclusive. Although recurrence of the lesions is an almost ineluctable event in CD,[16,17] possible relations between surgical approaches, frequency, and severity of recurrence after ileo-colonic resection is unknown.

On the basis of these observations and as the role of laparoscopy in CD is still undefined, in a prospective nonrandomized longitudinal study, we compared the short- and long-term outcome of CD patients undergoing ileo-colonic resection by using a laparoscopic or laparotomic approach and followed up for 1 year.

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The primary end point of the study was to assess the perioperative outcomes and postsurgical complications of laparoscopic surgery versus standard open surgery in a consecutive nonselected series of patients in regular follow-up in a referral Inflammatory Bowel Disease (IBD) center undergoing ileo-colonic resection in a single surgical unit. Differences between the two groups in terms of time free from clinical and endoscopical relapse, including frequency severity and prevalent pattern of postoperative recurrence were investigated. At this purpose, clinical activity was assessed every 3 months for 1 year and finding compatible with endoscopical recurrence searched at 1 year. Patients' satisfaction regarding the surgical procedure was also recorded and a specific questionnaire fulfilled.

Materials and Methods

Patients

In a prospective nonrandomized longitudinal study, 28 consecutive patients undergoing elective resection for ileo-colonic CD from October 2004 to June 2005 at the gastrointestinal (GI) surgical unit of the University "Tor Vergata" of Rome were prospectively enrolled. All patients were in regular follow-up at the referral IBD center of the same university hospital. In all patients, the diagnosis of CD was assessed according to conventional clinical, endoscopical, histological and radiological criteria. No absolute specific contra-indications to laparoscopic ileo-colonic resection are indeed reported in CD patients. Inclusion criteria were: (1) regular follow-up at the GI unit of the University "Tor Vergata" of Rome, Italy; (2) indication for elective ileo-colonic resection for CD related to complications, refractory or steroid-dependent disease; (4) resection performed at the GI surgical unit of the University "Tor Vergata" of Rome, Italy; (5) agreement to follow the study protocol; (6) written informed consent. Exclusion criteria included (1) age<15 or >65, (2) BMI>30; (3) emergency surgery.

Demographic and clinical characteristics of the 28 patients are summarized in Table 1. As shown, there were 14 men and 14 women, with a median age of 33 years (range, 16–64) and a median disease duration of 4 years (range, 0–38). Indication for surgery was symptomatic ileal stenosis in most of the patients (79%), followed by abdominal abscess (25%), entero-enteric or entero-cutaneous fistula (14%) and medical therapy failure (steroid-dependence) in one patient (4%; Table 2). Most of the 28 patients had more than one single complication. Treatment at time of surgical indication included oral corticosteroids (68%), mesalazine (43%), antibiotics (43%), and azathioprine (21%; concomitant drug treatments in most of the patients).

Surgical Treatment

Enrolled patients underwent elective ileo-colonic resection by either laparoscopic approach (group A, LAP; $n=15$) or conventional open surgery (group B, OPEN; $n=13$; Table 1). Both surgical approaches were performed by experienced GI surgeons. This is a nonrandomized study, however, surgical approach was not selected on the basis of clinical and anatomopathological characteristics of the disease (as demonstrated by homogeneous incidence of fistula and abscess in the two groups; Table 1), but the only bias was the availability of a surgeon with advanced

Table 1 Demographics and Clinical Characteristics of CD Patients Undergoing Laparoscopic (Group A) or Laparotomic (Group B) Ileo-Colonic Resection

	Group A Laparoscopy ($n=15$)	Group B Laparotomy ($n=13$)	p Value (>0.05 ns)
Age median (range), years	32 (16–45)	36 (24–64)	0.06
Gender (M/F)	7/8	7/6	
BMI median (range), kg/m	22 (19.7–29.4)	23 (18–28.4)	0.65
CD duration median (range), years	3 (0–16)	4 (0–38)	0.18
CD site	12 I; 3 I–C	12 I; 1 I–C	
Pre-operative treatment n patients (%) [a]			
Azathioprine (2–2.5 mg/kg)	2 (13%)	4 (30%)	0.37
Corticosteroids (from 1 mg/kg)	12 (80%)	7 (54%)	0.22
Mesalazine (2.4 g/day)	5 (33%)	7 (54%)	0.44
Antibiotics (ciprofloxacin, metronidazole)	5 (33%)	7 (54%)	0.44
Disease complications(%)[b]			
Stenosis	14 (93%)	9 (69%)	0.15
Entero-enteric fistulae	8 (53%)	8 (62%)	0.71
Intra-abdominal abscess	3 (20%)	4 (31%)	0.67
Entero-cutaneous fistula	0	1 (8%)	0.46
Extraintestinal involvement (uveitis)	1 (7%)	0	Ns

I Ileum, *I–C* ileum-colon

[a] Sixty percent of the patients in group A and 62% in group B received ≥2 concomitant treatments for CD.

[b] Seventy-three percent of the patients in group A and 62% in group B showed ≥1 complication.

Table 2 Perioperative Outcome

	Group A Laparoscopy (n=15)	Group B Laparotomy (n=13)	*p* Value (>0.05 ns)
Indication for surgery, *n* patients (%)[a]			
Medical therapy failure	0	1 (8%)	0.46
Stricture with partial obstruction	14 (93%)	8 (62%)	0.06
Enteroenteric/enterocutaneous fistula	1 (7%)	2/1 (23%)	0.31
Intra-abdominal abscess	3 (20%)	4 (31%)	0.67
Length of resected bowel			
Median (range), cm	110 (70–130)	102.5 (45–160)	0.46
Anastomosis (side to side/end to side)	15/0	13/0	
Duration of surgical procedure			
Median (range), min	185 (120–240)	140 (100–220)	0.003
Intraoperative complications, *n* patients (%)			
Intraoperative bleeding	0	0	
Intraoperative blood transfusion	1	1	Ns
Postoperative blood transfusion	3 (20%)	2 (15%)	Ns
Conversion	2 (13%)		
Adjunctive procedures, *n* patients (%)			
Additional small bowel resection	4	1	
Rectal segmentary resection	1	1	
Colecistectomy	1	1	
Meckel diverticulectomy	2	0	
Fistula suture	1	4	
Fimbrioplasty	1	0	

[a] Some patients had more than one indication for surgery.

training in GI laparoscopic surgery. Laparoscopy was converted to laparotomy according to surgeon's judgment during surgical resection.

A three-port approach was used for the laparoscopic procedures. All three trocars were 10–12 mm and placed infra-umbilical, suprapubic, and in left iliac fossa; in case an intra-abdominal anastomosis was performed, an additional 5 mm trocar was placed in epigastrium. The mesenterium was divided using radiofrequency scalpel (Ligasure LS® 110, Valleylab) and eventually stapled or oversewn if particularly thick. The anastomosis was performed either mechanically or manually in a side-to-side fashion. The laparoscopic approach was considered successful whenever it was possible to complete the entire intestinal resection. One of the port incision was extended up to 4 cm to extract the resected intestine and eventually used to fashion the anastomosis. The procedure was to be converted to open surgery if the time of dissection was superior of 90 min. Converted laparoscopic cases were analyzed on an intention-to-treat basis.

The open ileo-colonic resection was formally the same as the laparoscopic technique, but it required a midline laparotomy (15 cm±3).

In both groups, the same postoperative protocol was used. Patients were allowed to oral intake when there was return of bowel function. All patients were discharged from the hospital when in general well-being and able to return to daily activity. Fast track protocol was not used in any patient.

Study Protocol

In a prospective longitudinal study, recurrence was assessed 1 year after ileo-colonic resection, using ileocolonoscopy as gold standard. The degree of recurrence and the prevalent pattern of the lesions was assessed by one single endoscopist, according to Rutgeerts et al.,[16] on a 0 to 4 score, as previously reported.[23]

To detect possible early asymptomatic postoperative recurrence requiring more aggressive treatment and to assess the possible role of noninvasive techniques for detecting CD recurrence, a subgroup of ten compliant patients were also studied at 3, 6, and 12 months by small intestine contrast ultrasonography (SICUS) and wireless capsule endoscopy (WCE). SICUS was performed after 375 ml (range, 250–500 ml) polyethilen glycole (PEG; Promefarm, Milano, Italy) ingestion. WCE was performed by using the given M2A capsule.[18–25] WCE was not performed in patients showing by SICUS or colonoscopy findings compatible with strictures, in relation to the impact risk. In all patients, clinical activity of CD was assessed at 12 months according to the Crohn's disease activity index (CDAI).[26] All patients were treated with mesalazine (2.4 g/day) within 1 month from surgery for 1 year.

At 12 months, patients were also asked to fill a specific treatment-satisfaction questionnaire modified from Dunker's et al. Hospital Experience Questionnaire[27] (Fig. 1).

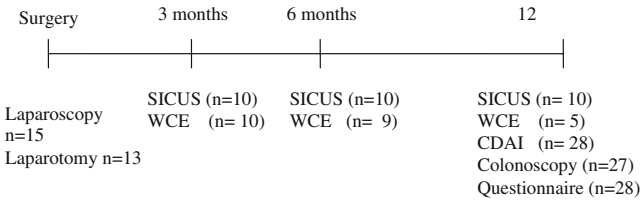

Figure 1 Follow-up schedule of enrolled patients. As shown, ileo-colonic resection was performed using a laparoscopic approach in 15 patients and a laparotomic approach in 13 patients.

Statistical Analysis

Parameters analyzed as confounding criteria are indicated in Table 1. Tables 2 and 3 show the confounding criteria considered for the assessment of the peri- and postoperative period. All data were collected on a Microsoft® Excel spreadsheet. Results were expressed as median and range of observed values. Qualitative data were statistically compared using Fisher's exact test; quantitative data showing normal distribution were compared using a paired *t* test. Regardless of the statistical analysis used, a $p<0.05$ value was considered statistically significant.

Results

Patients

Among the whole group of 28 patients, 15 underwent laparoscopic (LAP; group A) and 13 had an open (OPEN; group B) ileo-colonic resection. Two laparoscopic procedures were converted to laparotomy after a trial dissection (conversion rate, 13.3%) because of an extremely friable mesenter related to the presence of enteric fistulas and abscesses in one patient and of a large inflammatory mass occupying most of the pelvis in the second patient. In these two cases, data were collected and analyzed on an intention-to-treat basis.

In all patients, histologic analysis of the resected bowel tissue confirmed the diagnosis of CD involving the distal ileum, including also the cecum or the right colon in four patients.

Table 1 shows demographics and clinical characteristics of CD patients undergoing LAP (group A) or OPEN (group B) ileo-colonic resection. As shown, there are no significant differences between the two groups.

Table 3 Clinical Outcome After Surgery

	Group A Laparoscopy (n=15)	Group B Laparotomy (n=13)	p Value (>0.05 ns)
Length of hospital stay median (range), days	7 (5–10)	7 (6–28)	0.14 ns
Passage of flatus median (range), days	3 (2–4)	4 (3–8)	0.004
Analgesic requirement median (range), days	5 (3–8)	5 (3–8)	0.35 ns
Analgesic requirement median (range), doses	7 (3–17)	11 (4–21)	0.05
Opioid (100 mg tramadolo or 10 mg morphine)	2 (1–4)	2 (1–8)	0.09 ns
Non-opioid (30 mg ketorolac)	5 (0–16)	6 (0–16)	0.35 ns
Tolerance to solid diet median (range),days	6 (4–7)	6 (4–26)	0.17 ns
Return to normal activity (sport/work) median (range), days	40 (30–90)	70 (35–150)	0.007
Complications within 30 days			
n patients (days to recover)	2	2	Ns
Abdominal abscess		1 (20)	0.46
Surgical wound infection	2 (10/14)	1 (20)	Ns
Complications in the long term (1 year)			
Adhesions/ileus	0	0	
Incisional hernia	0	0	
Clinical and endoscopical follow-up (1 year)			
Symptomatic recurrence (CDAI>150)	0/15 (0%)	0/13 (0%)	Ns
Endoscopic recurrence	13/14 (93%)	13/13 (100%)	
Rutgeert's score, median (range)	3 (0–4)	3 (1–4)	0.63 ns

Perioperative Clinical Outcomes

There were no major intraoperative complications in both groups. Perioperative results are summarized in Table 2. Surgical resection was successfully completed laparoscopically in all but two patients in group A (87%). The only significant difference between groups was the median operating time found shorter in the OPEN group (140 min; range, 100–220) than in the LAP group (185 min; range, 120–240; $p=0.003$).

Short- and Long-Term Outcome

Significant differences between groups A and B were found analyzing the short-term outcome as outlined in Table 3. Pain after surgery was evaluated on analgesic requirement basis, and the dosage of pain killers administered per patient was significantly higher in the OPEN group (median and range in LAP versus OPEN: 7 doses (range 3–17) versus 11 doses (range 4–21); $p = 0.05$). Passage of flatus and\or stool after surgery was faster in group A than in group B (LAP versus OPEN: median 3 days (range 2–4) versus median 4 days (range 3–8); $p = 0.004$). Similarly, there was a statistically significant shorter recovery period (time between hospital discharge and return to normal activities and work) in the laparoscopic group: LAP median 40 days (range 30–90) versus OPEN median 70 days (range 35–150; $p=0.007$).

Frequency of postoperative complications at 30 days was comparable between the two groups. Two patients from the LAP group showed superficial infection of the surgical incision that required, respectively, 10 and 14 days of outpatient medications. One patient in the OPEN series had an abdominal abscess possibly caused by a small anastomotic leakage that completely healed after a CT-guided drainage of the abscess cavity and 20 days of total parenteral nutrition. The second patient in the open group had an abscess at the site of surgical incision that required a 6-day admission at the GI unit, surgical drainage, and wound toilette, followed by complete healing within 20 days of outpatient medications.

No long-term (1 year) surgery-related complications, including death, strictures, adhesions ileus/symptoms, or incisional hernias were observed in the two groups, and no patients required any additional surgical treatment related to CD at 1 year. Among the 14 females enrolled, 3 from the LAP group became pregnant after surgery (Fig. 1).

Clinical and Endoscopical Recurrence

The frequency and severity of recurrence in patients resected using a laparoscopic or laparotomic approach was investigated in a 1-year follow-up. All 28 patients completed the clinical follow-up at 1 year and maintained the clinical remission (CDAI<150) while on mesalazine (2.4 gr/day). Among the 10 compliant patients also studied by non-invasive techniques, SICUS showed lesions compatible with recurrence in four out of ten patients at 3 months, in eight out of ten patients at 6 months, and in all the ten patients at 12 months. WCE detected findings compatible with CD recurrence in nine out of ten patients at 3 months, in eight out of nine patients at 6 months (one patient did not perform WCE because of a high-impact risk related to lumen narrowing detected by SICUS), and in four out of five patients at 12 months (five patients did not perform WCE because of lumen narrowing detected by SICUS or colonoscopy).

Ileocolonoscopy represented the gold standard for assessing CD recurrence at 1 year. Among the 28 patients completing the clinical follow-up, ileocolonoscopy was performed in 27, as 1 asymptomatic patient was already clearly pregnant at the time. Endoscopic recurrence was, therefore, assessed in 14 patients from the LAP and in 13 patients from the OPEN group. Results are shown in Table 3. Among the whole group of 27 patients assessed by ileocolonoscopy, recurrence was detected in 26 (96.2%). The frequency of recurrence was, therefore, comparable between the two groups (LAP, 13 out of 14, 92.8%, versus OPEN, 13 out of 13, 100%). The median endoscopic score of recurrence in the whole group of 27 patients was 3 (range, 0–4) and did not significantly differ between the two groups (LAP versus OPEN: median 3, range 0–4, versus median 3, range 1–4; $p=0.63$). The prevalent pattern of CD lesions (fistulizing, fibrostricturing, or inflammatory) assessed by endoscopy at 1 year was also comparable in the two groups (LAP group: 2 fibrostricturing, 12 inflammatory; OPEN group: 1 fibrostricturing, 12 inflammatory). The presence of fibrostricturing recurrence not allowing passage of the endoscope (grade 4 recurrence with stenosis) was observed in two patients from the LAP group and in one patient from the OPEN group. The recurrence involved the perianastomotic area (including the neoterminal ileum only and/or the anastomosis) in all patients from both the LAP and OPEN group, as it is in most cases. In particular, among the 13 CD patients from the LAP group showing recurrence, recurrent lesions involved both the anastomosis and the neoterminal ileum in six patients, only the neoterminal ileum in three patients, and only the anastomosis in four patients. Among the 13 patients with endoscopic recurrence at 1 year from the OPEN group, lesions involved both the neoterminal ileum and the anastomosis in the 12 and only the neoterminal ileum in the remaining patient, whereas no patient showed lesions involving the anastomosis only.

Treatment Satisfaction Questionnaire

Patients also filled out the specific treatment satisfaction questionnaire (TSQ)[27] to evaluate differences between the two surgical techniques in subjective outcomes and in "treatment's compliance according to patient expectation."

Figure 2a–c shows the results from the TSQ (patients with converted LAP procedure were considered part of group B–OPEN). As shown, patients' satisfaction regarding the surgical scar, the body damage after surgery, delay of work activity, delay of normal diet, postoperative pain, and length of hospitalization was significantly in favor of laparoscopy than laparotomy (Fig. 2).

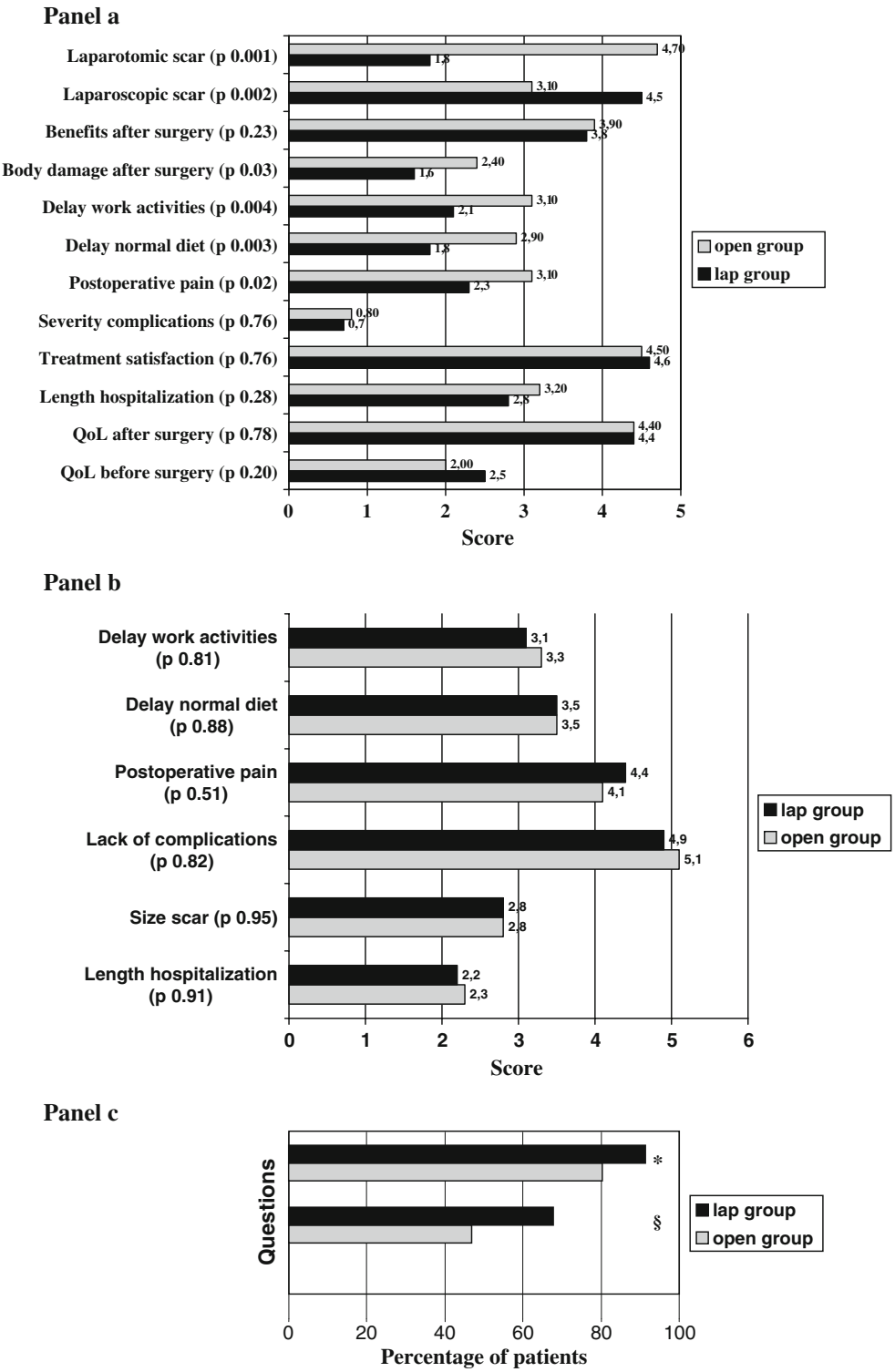

Figure 2 **a–c** Histograms showing results from the treatment satisfaction questionnaire (TSQ) in patients with ileocolonic resection performed using a laparoscopic or laparotomic approach. ***a*** Results from TSQ. ***b*** Patient's perception of the most relevant aspect of the treatment. ***c*** *Asterisk* Percentage of patients in both groups that ideally would prefer the laparoscopic approach in case of a second operation and *section sign* are willing to pay for having a laparoscopic operation

The other parameters considered did not significantly differ between patients resected using the laparoscopic versus the laparotomic approach (Fig. 2a–c).

Discussion

Laparoscopic surgery in CD patients is attractive and promising (minimal scars, less adhesions, faster recovery) but also challenging and controversial.

To assess feasibility and efficacy of laparoscopic ileo-colonic resection, we designed a prospective nonrandomized longitudinal study that assigned a patient to laparoscopic or laparotomic surgical resection on the basis of the casual availability the day of surgery of an expert GI laparoscopic surgeon. All the enrolled patients were in regular follow-up at the same referral IBD unit. In our CD population, the two comparative groups were comparable in terms of demographics and clinical characteristics at baseline. Apart from age and emergency surgery, morbid obesity was the only exclusion criteria used, and these patients were not included in the study protocol. However, a BMI>30 is observed in a small subgroup of patients in our IBD referral center.

Therefore, present findings allow an appropriate comparison in terms of short- and long-term postsurgical outcome between patients with ileo-colonic resection performed by using two different surgical approaches.

By our knowledge, only two randomized studies compared the outcome of laparoscopic and laparotomic ileo-cecal resection for CD. The study from the Cleveland Clinic randomized preselected CD patients after a diagnostic laparoscopy that basically allowed surgeons to select a subgroup of patients with more favorable disease.[28] Differently, in the Dutch study, the procedure was only laparoscopic assisted, as the major part of the operation was a standard open procedure. In fact, both the intestine and the mesentery with its vessels were divided through the mini-laparotomy, and all the anastomoses were manually fashioned after the open resection was completed.[29]

The main purpose of the present study was to demonstrate the feasibility of the minimally invasive approach in the majority of patients undergoing elective ileo-colonic resection for CD. Although present findings are preliminary and the number of patients is small to draw conclusive statements at this regard, the conversion rate was very low (13%), being comparable to other studies.[30] This finding was observed in spite of the high frequency of fistulizing disease and presence of abscesses at time of surgery. No mortality or morbidity was observed in our study population, thus being comparable between the 2 groups.

Present findings from a prospective longitudinal study, using as only criterion the availability of an expert laparoscopic surgeon for choosing the surgical approach, strongly suggest that it is feasible, safe, and ethically acceptable to blindly randomize CD patients undergoing elective ileo-colonic resection to a laparoscopic or laparotomic surgery. Present findings suggest a better postsurgical outcome in patients resected according to a laparoscopic approach when considering recovery of bowel functions, doses of analgesics required, and recovery to normal activities (p=0.004, 0.05, and 0.007, respectively). Moreover, as the outcome of surgery in CD patients appear not to be worsened after laparoscopic surgery, our findings confirm that laparoscopic ileo-colonic resection is equivalent to the standard procedure in terms of "curative" resection of all the affected bowel, and of treatment of complications (i.e., abscesses, fistulae).

Beside the already known advantages of laparoscopy,[30–33] its use in CD may play a major role in this particular population of patients, often requiring surgery at young age. The psychological impact of a less invasive surgical approach, associated with a smaller scar, earlier recovery, and return to daily activities, may represent a relevant issue in CD population. On the basis of the results from the present study, enrollment of new patients and longer follow-up studies are ongoing in our IBD unit to assess the potential long-term benefits of laparoscopic surgery (e.g., adhesions, recurrence, hernias) in CD.[33,34] The specific IBD QoL questionnaire SF-36 and GIQLI are not appropriate to evaluate the differences between the two surgical techniques. We, therefore, used a modified version of the TSQ questionnaire previously proposed by Dunker et al.,[27] useful to focus on body-image satisfaction and hospital-staying experience, also considering possible reinterventions. In our study, treatment's satisfaction assessment showed a high acceptance of surgical treatment in both groups, being considered useful and beneficial. Laparoscopy showed advantages in terms of cosmesis and postoperative subjective experience during hospitalization and recovery. In addition, 92% of patients from the laparoscopic group and 80% of patients from the laparotomic group referred to hypothetically prefer the mini-invasive laparoscopic approach in the eventuality of a subsequent surgical treatment.

Additional aim of the present study was to address whether a laparoscopic versus a laparotomic surgical approach may influence the clinical outcome and the frequency and prevalent pattern of the lesions assessed by colonoscopy 1 year after surgery. As a matter of fact, although the etiology of CD remains unknown, current evidences indicate that a genetically inappropriate host immune response toward luminal antigens, particularly the common bacterial flora, plays a major role in the pathogenesis of the disease.[35–41] Whether a laparoscopic versus a laparotomic approach may influence the host immune response has been investigated in both benign and malignant diseases.[35,36] Despite the large number of

studies, little is still known about possible clinical implications of these immunologic aspects in CD, and no studies investigated the possible influence of laparoscopy on the frequency and severity of CD recurrence.[42] Results from our prospective longitudinal study assessing the clinical and endoscopical outcome in an homogeneous cohort of CD patients undergoing elective laparoscopic or open ileo-colonic resection failed to support differences in terms of both clinical relapse and of frequency and severity of endoscopical recurrence at 1 year in the two groups. In our series, all patients resected by using either a laparoscopic or laparotomic approach indeed maintained clinical remission 1 year after surgery. The frequency of recurrence was also observed in a comparable proportion of patients from both groups. In fact, all enrolled patients but one developed asymptomatic endoscopic recurrence at 1 year. The prevalent pattern of the lesions at 1 year was also comparable in the two groups.

Our occasional finding that three out of the eight females became pregnant after laparoscopic surgical resection further supports a favorable clinical outcome of laparoscopic surgery. Possible differences in terms of clinical outcome in relation to the surgical approach are under investigation in this cohort of patients, as a longer follow-up period may be required. At this purpose, new and promising noninvasive diagnostic techniques such as SICUS and WCE may be useful for future studies aimed to investigate the natural history of CD recurrence after ileo-colonic resection.

Conclusion

Present findings support the feasibility of laparoscopic ileocolonic resection in a nonselected consecutive series of CD patients. We confirmed the well-known advantages in the short-term (postoperative recovery) and safety of this technique. Results from the present study also indicate a significant preference of patients for the mini-invasive approach because of its cosmetic results, hospital experience, and surgical treatment acceptance.

On the other hand, in our CD population, no differences were observed in terms of frequency, time of onset, and severity of clinical and endoscopical recurrence in a 1-year follow-up. Long-term results, including frequency of adhesions, hernias, and reoperations, are under investigation in a larger population of patients and require a longer follow-up.

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Percutaneous Transhepatic Duodenal Diversion for the Management of Duodenal Fistulae

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Abstract
Purpose The aim of this study was to determine the success of the nonoperative management of persistent duodenal fistulae (DF) with percutaneous transhepatic duodenal diversion (PTDD).
Methods Retrospective chart review identified six patients with DF managed by PTDD from 2006 to 2007. Patient outcomes and complications were assessed.
Results The etiology of DF included pancreatic surgery (three patients), gastrectomy (two patients), and Crohn's disease (one patient). PTDD was performed by interventional radiology at a median time of 37 days after fistula recognition. After PTDD, fistula drainage decreased from 775 cc/day (range 200 to 2,525 cc/day) to <50 cc/day at a median of 8 days. Patients were discharged 32 days (median) after PTDD. One patient with Crohn's disease required definitive surgical treatment. Of the remaining five patients, the PTDD tube was capped at 27 days (median) after placement and was removed on an outpatient basis at 79 days (median) after placement. There was no mortality, no fistula recurrence, or complications associated with PTDD placement.
Conclusions We present an algorithm for the nonoperative management of persistent postoperative DF. In this limited series, PTDD was highly effective at definitively treating DF, especially in the acute setting. PTDD should be considered by surgeons facing the management of postoperative DF.

Keywords Percutaneous transhepatic duodenal diversion · Duodenal fistulae · Postoperative management

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Introduction

The development of a postoperative duodenal fistula (DF) is a difficult complication that can occur after complex upper gastrointestinal or pancreatic operations. Because of significant advances in the field of surgery, particularly the management of peptic ulcer disease, DF are a rare occurrence; however, they continue to be a challenging surgical problem. DF can result in increased patient morbidity and mortality, prolonged hospitalization, increased number of invasive procedures, difficultly maintaining nutrition, and prolongation of sepsis.[1,2]

The surgically placed duodenostomy tube has been the gold standard for the intraoperative management of the difficult duodenal closure and can be effective in preventing or controlling DF.[3] However, the management of postoperative DF poses a challenging problem for the surgeon. The patients are often septic, malnourished, and have a hostile abdomen. Traditionally, duodenal diversion and control of

the fistula has been achieved with high risk, complex operative drainage. We observed that percutaneous transhepatic biliary drainage was highly successful at completely controlling biliary drainage after bile duct injuries. We hypothesized that percutaneous transhepatic drainage of the duodenum would successfully control DF and be a definitive management strategy. We report the outcomes of six consecutive cases of postoperative DF that were managed with percutaneous transhepatic duodenal diversion (PTDD).

Case Reports

Patient #1

A 46-year-old male presented to an outside facility with severe acute necrotizing pancreatitis secondary to alcohol abuse. A computed tomography (CT) scan showed gas bubbles in the retroperitoneum, and he was then transferred to our institution with infected pancreatic and peripancreatic necrosis (Fig. 1). The patient was stabilized with intravenous fluids and antibiotics in preparation of operation.

The patient was taken to the operating room for open debridement and necrosectomy with external drainage (Fig. 2). On postoperative day 2, bile was noted in the right-sided drain that was placed near the hepatic flexure and duodenum. A DF was diagnosed with an upper gastrointestinal contrast study (Fig. 3). The patient was managed conservatively for several weeks with a transpyloric nasogastric tube for duodenal decompression, a nasojejunal feeding tube, and intravenous antibiotics. Despite conservative measures, the patient had persistent poor nutritional status (prealbumin of 4.6 mg/dl (nl 18–30 mg/dl), and the fistula failed to resolve with an output of over 2,000 cc/day.

Interventional radiology placed a percutaneous transhepatic duodenal tube 36 days after DF formation to divert

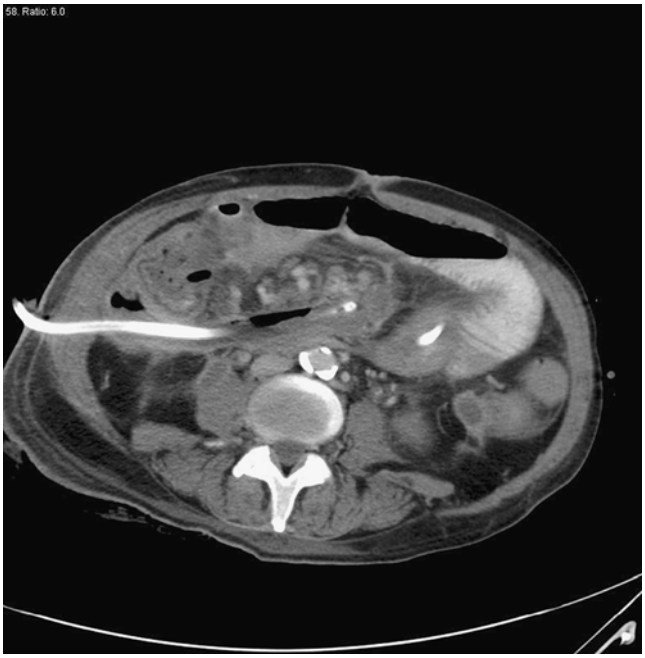

Fig. 2 CT, postoperative pancreatic debridement and necrosectomy with external drainage

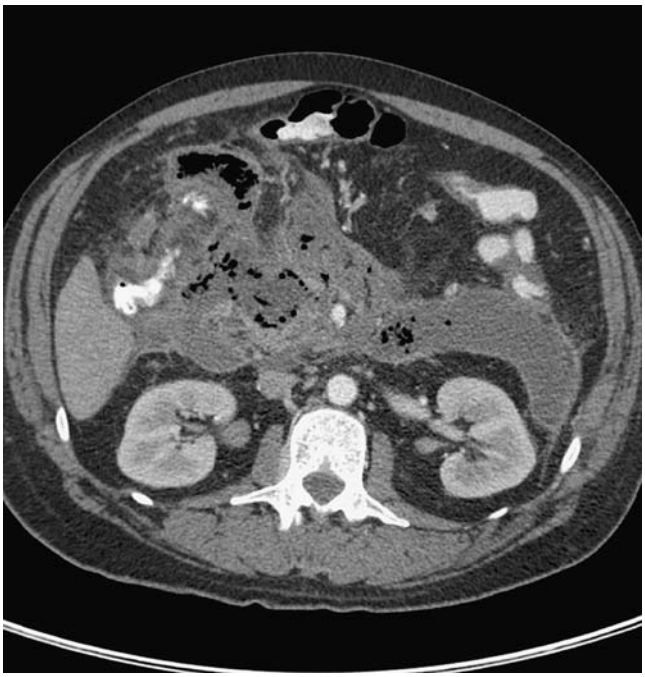

Fig. 1 CT, acute necrotizing pancreatitis on presentation

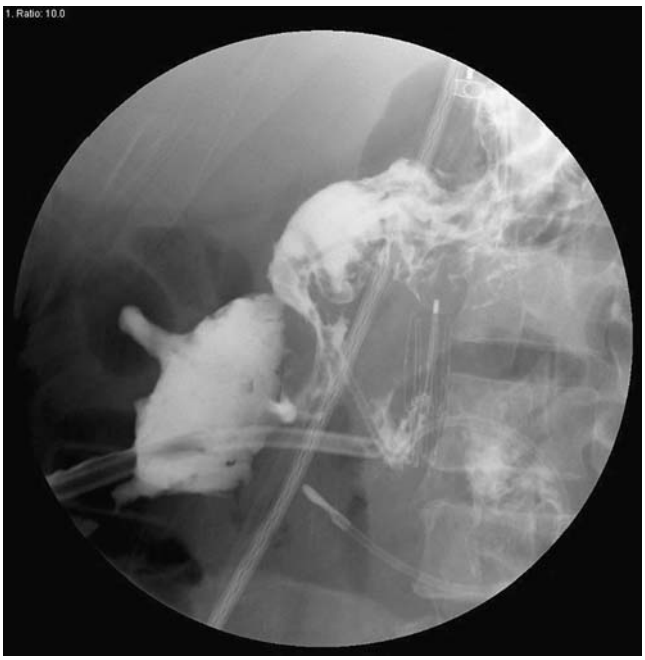

Fig. 3 Upper GI study demonstrating the DF controlled by an external drain

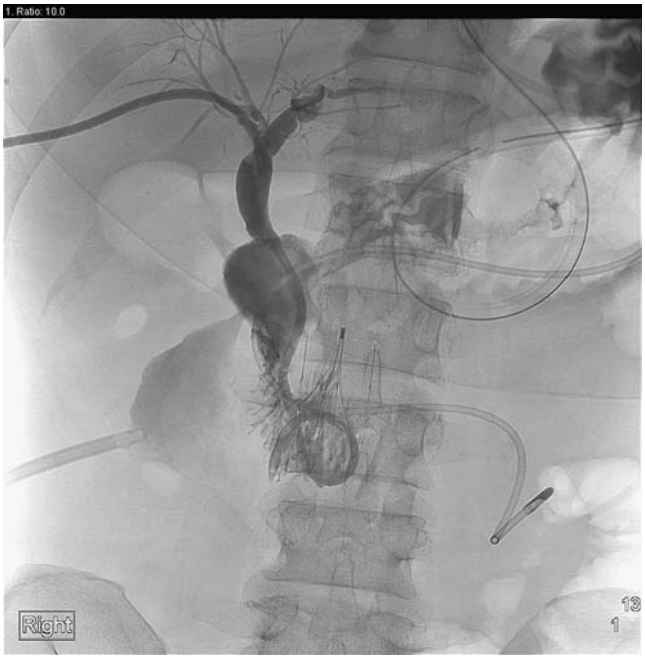

Fig. 4 Percutaneous transhepatic duodenostomy tube demonstrating duodenal leak

the bile and duodenal secretions from the fistula (Fig. 4). Output from the fistula significantly diminished (<50 cc/day) 12 days after PTDD and completely resolved 16 days after PTDD. Prealbumin increased to 18.6 mg/dl. All external pancreatic drains were removed. Oral intake was started and tolerated 7 days after PTDD. Subsequently, the PTDD tube was capped 33 days after its placement and the patient was discharged home. Seventeen days after discharge, a radiologic tube study showed complete resolution of the DF and the tube was removed in the clinic (Fig. 5).

Patient #2

A 69-year-old male presented to an outside institution with a perforated duodenal ulcer and subsequently underwent a subtotal gastrectomy with Billroth II reconstruction. On postoperative day 2, the patient developed a duodenal stump leak and was taken back to the operating room for an exploratory laparotomy with oversewing of the duodenal stump. The DF persisted with high output (mean 900 cc/day) and the patient had a complicated intensive care unit course for 45 days. The patient was then transferred to our institution for further management of the high-output DF.

The patient underwent fluid resuscitation, was continued on TPN, and broad spectrum antibiotics were started. Four days after admission and 39 days after the development of the DF, interventional radiology placed a PTDD tube. DF drainage decreased from 900 to 50 cc/day within 8 days as the output was shifted through the PTDD. The DF completely resolved at 10 days post PTDD. A nasojejunal feeding tube was placed 3 days after PTDD placement and enteric feeding was accomplished.

The PTDD tube was capped 27 days after its placement and the patient was discharged home. The patient was seen in the clinic 1 month after discharge, and the tube was removed after a radiologic study, which showed complete resolution of the DF.

Methods

Retrospective chart reviews of consecutive patients who developed a postoperative DF or were transferred to our facility with that complication were included in the study. The hospital and posthospital course was reviewed to determine the etiology and duration of the fistula, patient clinical and demographic factors, and outcome of the treatment. Complications related to the fistulae and placement of the PTDD tube were recorded. Because of the low number of patients, only a descriptive analysis was performed.

Percutaneous Transhepatic Duodenal Drainage Technique

All procedures were performed by the Interventional Radiology Section of the Department of Radiology at University of Alabama at Birmingham (UAB). The patients were placed in the supine position in one of our angiography suites (Phillips Allura Xper FD 20 or FD 10/20) with the right arm extended and supported by an arm board.

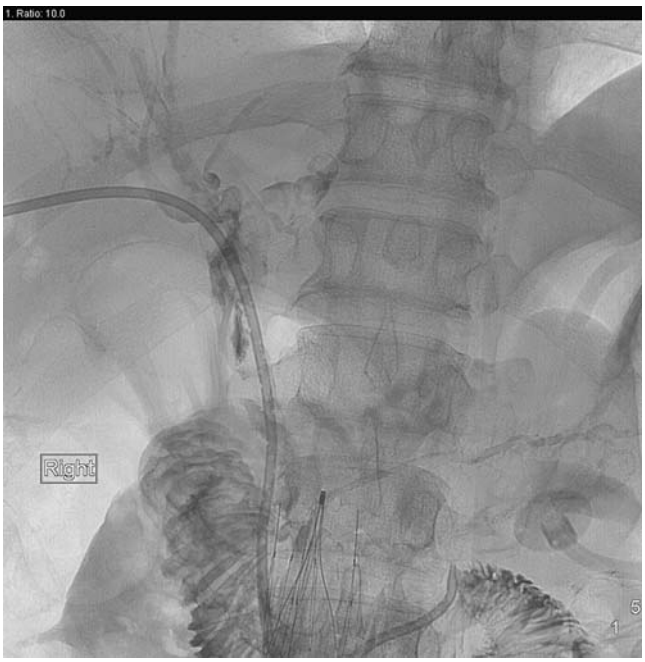

Fig. 5 PTDD tube and healed DF

Conscious sedation was provided, and monitoring of vital signs and level of sedation was performed continuously throughout the procedure by a registered nurse. The biliary tree was then approached from a right midaxillary approach using a NEFF set (Cook Medical, Bloomington, IN, USA). Cholangiography was performed after the initial access into the biliary tree with a 22-gauge, 15 cm needle. A .018 guide wire was then advance into the biliary tree under fluoroscopic guidance. The tract was dilated with the NEFF set and a .035 glide wire advanced into the duodenum, across the ampulla of Vater. An 8- or 10-French internal/external biliary drain (Angio Tech, Gainesville, FL, USA) was then advanced over the wire and sutured in place. The distal end of the catheter was placed with fenestrations in the intestinal lumen. The catheter was left to gravity drainage. All stents were flushed with 10 cc of sterile saline two times a day.

Results

Six consecutive patients were treated at the UAB, by the Section of Gastrointestinal Surgery and the Section of Vascular and Interventional Radiology, for DF from 2006 to 2007. Three patients underwent initial operation at UAB, and two patients were transferred after developing a postoperative DF at an outside institution. One patient developed a delayed fistula as a complication of surgical treatment of duodenal Crohn's disease. Five patients were male and the mean age was 50 years. Initial operations consisted of subtotal gastrectomy with Billroth II reconstruction (two patients), infected pancreatic necrosectomy (two patients), and a standard pancreaticoduodenectomy (high-output fistula to the surgical incision arising at the pancreaticojejunostomy; one patient).

The patient population and outcomes are shown in Table 1. A PTDD was placed in all patients after the development of a DF at 37 days (median) after conservative management failed. Before PTDD, fistula drainage was an average of 775 cc/day (range 200 to 2,525 cc/day). After PTDD, fistula output decreased to <50 cc/day at 8 days (median) after PTDD placement. The PTDD output averaged 641 cc/day (range 258 to 1,492 cc/day), resulting in fairly complete pancreaticobiliary diversion. One patient with Crohn's disease required fistula excision and strictureplasty for definitive treatment. Of the remaining five patients, PTDD tubes were capped at a median of 27 days (range 12 to 47 days) after placement. Patients were discharged at a median of 32 days (range 12 to 61 days) after PTDD placement with a total median time of hospital stay of 58.5 days. PTDD tubes were removed 79 days (median) after placement on an outpatient basis without difficulty after clinical and radiographic resolution of DF. Patients underwent a mean of 1.7 (range 0 to 5) additional interventional radiology procedures after the original placement of PTDD, including tube changes and fistulograms, before resolution and tube discontinuation. There was no complication associated with PTDD placement, no mortality, and no fistula recurrence. One patient had a concomitant biliary stricture that was managed successfully with the PTDD stents, accounting for the patient with five stent changes.

Table 1 Patient demographics and outcomes after percutaneous transhepatic duodenal diversion

Case	Age/sex	Presentation	Operation	Fistula output (cc/24 h)	Fistula to PTDD (days)	PTDD to output <50 cc/24 h (days)	PTDD to removal (days)	PTDD to discharge (days)
1	M/46	Necrotizing pancreatitis	Pancreatic debridement and necrosectomy	2525	36	12	50	37
2	M/69	Perforated duodenal ulcer	Billroth II gastrectomy	900	39	8	55	27
3[a]	M/30	Crohn's disease	Oversewing of perforated duodenal Crohn's disease	200	71	11	71	13
4	M/56	Ampullary carcinoma	Pylorus-preserving pancreaticoduodenectomy	200	28	4	88	61
5	M/50	Necrotizing pancreatitis	Pancreatic debridement and necrosectomy	430	38	8	87	12
6[b]	F/49	Bleeding duodenal ulcer	Billroth II gastrectomy	405	9	2	194	41

[a] Patient 3 had a chronic DF requiring fistula excision and strictureplasty for definitive treatment.
[b] Patient 6 had a concomitant inflammatory biliary stricture requiring prolonged PTDD catheter placement.

Discussion

We present the first report in the literature of using PTDD for the definitive management of DF. Our high rate of success in this diverse and complex patient population provides a promising nonsurgical option for the management of this difficult problem. Even in the patient with Crohn's disease that ultimately required surgical intervention, PTDD was critical in allowing the skin to heal in preparation for definitive surgical treatment.

Tsiotos et al.[4] reported that 31% of patients developed gastrointestinal fistulae after pancreatic necrosectomy; of these, 26% were duodenal in origin. The incidence of DF after surgery for peptic ulcer disease is only around 2–3% with an associated mortality rate of 50%.[5,6] The prevention of DF is the utmost important technical detail that often needs to be addressed when performing emergency surgery for peptic ulcer disease or necrotizing pancreatitis. Operative factors that may contribute to the prevention of intestinal fistula formation include the use of healthy bowel for anastomosis away from the inflamed or diseased tissue, tension-free anastomosis, meticulous hemostasis, secure abdominal wall closure, and maintenance of adequate oxygen-carrying capacity.[7] When dealing with a difficult duodenal stump or closure, the gold standard for DF prevention or control is the placement of a duodenostomy tube intraoperatively.[3,4] However, when presented with a postoperative DF or dislodgement of the duodenostomy tube, we have demonstrated that PTDD can definitively manage the fistula without the need for further surgical intervention.

We present an algorithm for the management of persistent postoperative DF (Fig. 6). Initially, the treatment for DF begins with a conservative approach. Conservative treatment of fistulae includes bowel rest, correction of fluid and electrolyte imbalances, parenteral nutrition, and control of sepsis.[1,4,8,9] Many studies suggest that a trial of somatostatin is worthwhile to decrease the time to closure, although conflicting results are reported in the literature.[10–13] The reported success rate of closure with conservative management ranges from 25% to 75%.[14] If the fistula has not closed after 6 weeks of optimal medical therapy, it is unlikely to do so without further intervention.[14]

A variety of nonsurgical procedures to treat DF have been described in the literature. Fistuloscopy and percutaneous injection of fibrin glue as an adjuvant technique for sealing gastrointestinal fistulae has been described with reported success.[1,15,16] Percutaneous gelfoam injection has also been successfully used to obliterate the fistula tract.[17] Success with wound vacuum-assisted closure system is anecdotal, but

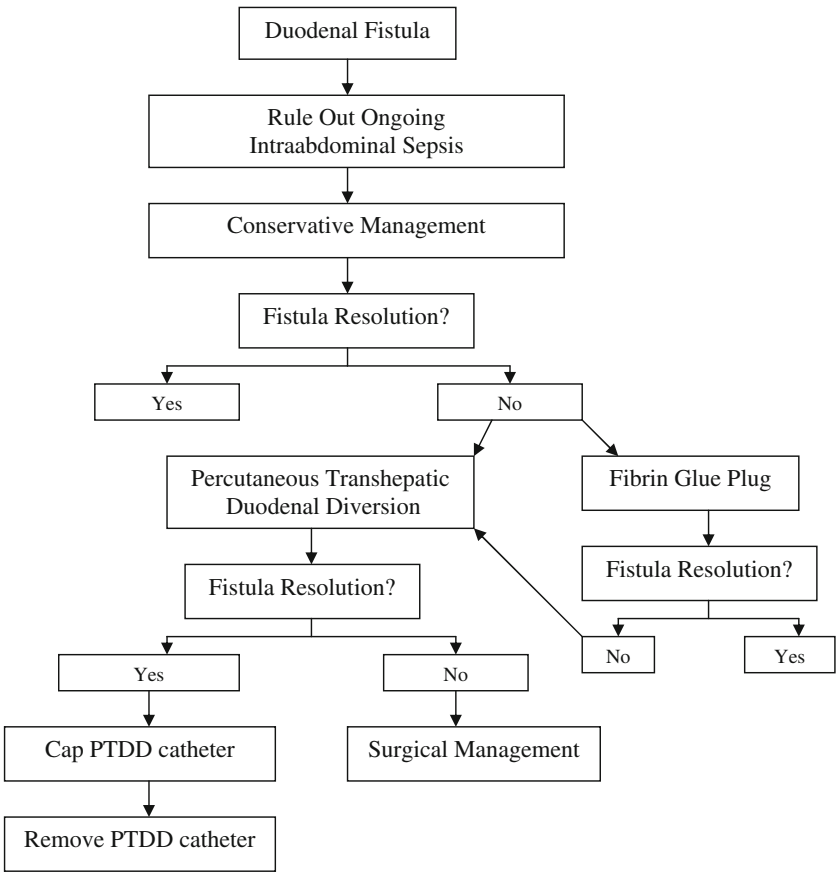

Fig. 6 Algorithm for management of persistent postoperative DF

may have some value in wound care and healing of the fistula.[10] When conservative and nonsurgical treatment fails, persistent fistulas require definitive intervention.[9,18]

We have shown that PTDD is a highly successful nonoperative intervention that not only controls the DF, but results in definitive treatment. The PTDD tube converts a short tract fistula to a long tract fistula, if you will, by diverting the drainage through the liver. This, in essence, converts the high-output duodenocutaneous fistula to a low-output fistula through the cutaneous tract allowing for the closure of that tract. The success of this approach for the management of DF hinges on an experienced and willing interventional radiologist to perform these procedures. The technical difficulty of placing catheters into a nondilated biliary system should not be underestimated. However, percutaneous transhepatic cholangioscopy, in the setting of nondilated intrahepatic bile ducts, has been described as safe and reliable.[19] Percutaneous biliary drainage in patients with nondilated intrahepatic ducts has been reported to have a technical success rate of 90% and complication rate of 9%.[20] A recent study assessed the complications associated with percutaneous transhepatic cholangioscopy.[21] Complications included cholangitis, bacteremia, bile duct injury, hemobilia, hemoperitoneum, and rupture of sinus tract. DF is a rare and complex surgical problem and will likely be managed at tertiary care centers. As such, most interventional radiologists at these centers have experience in performing percutaneous transhepatic catheters for iatrogenic biliary injuries where the biliary system is often nondilated. If PTDD is unsuccessful or cannot be technically performed, surgical management is the next option.

The surgical management of DF is difficult and remains one of the most challenging conditions managed by surgeons.[22,23] Some authors describe these fistulas as a "surgical disaster."[18] Processes that most often prevent closure by medical management include ongoing infection, inflammatory conditions, ischemia, radiation injury, malignancy, distal obstruction, and epithelialization of the fistula tract.[14] Factors such as inflammation and dense adhesions make dissection and mobilization difficult and hazardous.[23] Therefore, operative treatment if often delayed for 3 to 6 months to allow for a decrease in inflammation and adhesions, and improvement in the patient's overall medical condition, thus prolonging hospitalization and increasing costs.[10,24] Deciding when and how to surgically repair DF is a difficult decision given its high morbidity and mortality rates.[24]

Surgical approaches for the treatment of persistent fistulae are resection of the fistula and reclosure.[8,9,14] Often, it is not possible to resect the diseased duodenal segment without a major operation, so closure of the defect with a serosal patch or Roux-en-Y anastomosis has been performed.[11,14,23] More recently, a small series has shown success using a rectus abdominis flap to close refractory DF.[25]

The present study has several limitations. First, this is a retrospective study of a rare surgical problem presenting in various clinical scenarios. Although we do not have a control group, all patients failed the standard conservative management and further intervention was necessary. Second, the placement of the PTDD is technically difficult and requires access to an interventional radiologist with low complication rates. Whereas no patients in this study had complications associated with PTDD placement, it is a risk given that it is performed through an undilated biliary system. Finally, the number of patients in the study was relatively small and it involved a single institution, limiting the generalizability of this study.

Conclusions

DF after upper gastrointestinal surgery result in significant patient morbidity and prolonged treatment courses. PTDD is a successful tool in selected patients with DF and may reduce morbidity and the need for high-risk reoperation. Furthermore, once fistula control is obtained, hospital stay is shortened and the fistulae are able to be managed on an outpatient basis. In this limited series, PTDD was highly effective at definitively treating DF, especially in the acute setting. PTDD should be considered by surgeons facing the management of postoperative DF.

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Keyhole Deformity: A Case Series

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Abstract
Objective Keyhole deformity is frequently encountered after posterior internal sphincterotomy but may be observed after lateral internal sphincterotomy or in patients without any history of previous anal surgery. The aim of the present study is to emphasize the surgical significance of this entity and discuss the possible strategies in the treatment of the deformity.
Material and Methods Patients in whom keyhole deformity developed after surgical or conservative treatment applied for chronic anal fissure in our clinic and patients referred from other centers were recruited.
Results Nine-hundred twenty-six patients were treated for chronic anal fissure. A hundred of these patients directly underwent lateral internal sphincterotomy. The remaining 826 patients initially received conservative management, and 676 of them eventually underwent lateral internal sphincterotomy. In total, 15 patients were diagnosed to have significant keyhole deformity. Initially, all patients received conservative treatment for keyhole deformity, which was successful in two patients. Of the 13 patients in whom conservative management failed, nine underwent advancement flap reconstruction and the remaining four diamond flap reconstruction.
Conclusion Keyhole deformity is occasionally seen as a late complication of chronic anal fissure and may be well tolerated by the patients without any well-defined symptoms. The treatment strategy is directed toward the degree of functional alteration.

Keywords Keyhole deformity · Chronic anal fissure · Sphincterotomy · Conservative treatment · Surgical treatment

Introduction

Anal fissure is a linear, longitudinal split in the lining of the distal anal canal. It is commonly diagnosed in the third decade of life but may occur at any age. Men and women are affected equally. Anal fissure usually presents with severe, sharp anal pain during and several hours after defecation.[1] One of the most recent and interesting hypothesis has been the proposal that the underlying pathophysiology for fissure development is ischemia. Gibbons and Read[2] have suggested that the elevated resting pressure is a primary event rather than a consequence of the fissure. Anal fissure can be classified as either acute or chronic. Acute forms usually heal spontaneously or with conservative measures, but a proportion progresses to the chronic form, and these usually fail to heal without some form of pharmacological or surgical intervention.[3] However, nonsurgical methods rarely promote healing of a chronic anal fissure (CAF) characterized by a deep, intractable ulcer, the internal anal sphincter (IAS) being visible at its base.[4] Therefore, surgical treatment is almost uniformly recommended for such fissures in the chronic state, lateral internal sphincterotomy (LIS) being the time-honored treatment. LIS lowers the pressure exerted by the IAS, restores normal perfusion of the anoderm, and leads to relief of pain and healing of the fissure.[5]

This study was presented at the 11th Meeting of the Turkish Society of Colon and Rectal Surgery, Bodrum, August 26–30 2007.

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Internal anal sphincterotomy was introduced for treating anal fissures by Eisenhammer[6] in the 1950s. It was originally performed posteriorly in the midline, but this often led to the so-called keyhole deformity, and therefore, lateral subcutaneous sphincterotomy was popularized by Notaras[7] who first reported it in 1969. According to Notaras, after midline posterior internal sphincterotomy, scarring and epithelization of the gap created by the separation of the edges of the divided internal and subcutaneous external anal sphincter muscles will, in a certain number of cases, result in a characteristic posterior midline furrow deformity.[7] A posterior midline incision is associated with a keyhole deformity, which can cause significant problems including anal wetness and soiling. Up to 40% of patients develop some degree of incontinence. A lateral incision is associated with a much lower incidence of soilage and incontinence and is generally the preferred approach.[8] Retrospective reviews have provided data comparing posterior midline sphincterotomy with lateral sphincterotomy. Incidence rates for persistence varied from 2 to 25% in the posterior midline sphincterotomy group and from 0 to 10% in the LIS group.[9] Although Notaras has reported the development of keyhole deformity to be due to posterior internal sphincterotomy, there have been reports of keyhole deformity after LIS or in patients without any history of anal interventions.[7,10] Therefore, the aim of the present study is to share our experience of keyhole deformity, to emphasize the surgical significance of this entity, and to discuss the possible strategies in the treatment of the deformity.

Material and Methods

Patient Selection Patients who were diagnosed to have keyhole deformity were specified. Patients with keyhole deformity uniformly suffered from purulent discharge and anal pruritus. Symptoms were graded as severe, moderate (tolerable), or none. Only patients with severe symptoms were included and treated. Keyhole deformity was defined as the observation of the anal canal in the shape of a keyhole instead of a slit-like appearance upon gentle retraction of the buttocks.[11] Although keyhole deformity can be encountered after hemorrhoid surgery, all the cases with keyhole deformity defined in our series were observed to be related to anal fissure. The diagnosis of CAF was based on the observation of posterior ulcer, induration at the edges, and exposure of the horizontal fibers of the IAS and symptoms (postdefecatory or nocturnal pain, bleeding, or both) lasting for more than 2 months. A keyhole deformity was differentiated from a nonhealing fissure based on the altered symptoms of purulent discharge with no pain, normal or low anal pressures, and the epithelialized surface of the deformity (Fig. 1a). On the contrary, nonhealing fissures maintained their pretreatment features, such as pain at defecation and digital examination, as well as high resting pressures (Fig. 1b). Keyhole deformity was observed not only after LIS but also in patients without any prior anorectal interventions. The demographic data, duration to the diagnosis, complaints, and the modalities of treatment performed were collected for all the patients included in the study. Anal manometry was performed in all patients with the keyhole deformity.

Surgical Procedures LIS was performed for CAF in all patients with the open technique under local anesthesia via the supervision of the same surgeon. In the prone jackknife position with the buttocks taped apart, a 1-cm incision was created on the anal verge. The anal subepithelial and intersphincteric spaces were delineated with blunt dissection. LIS was generally performed to the level of the dentate line. Hemostasis was checked, and the operation was terminated. The patients were discharged on the same day. Sitz baths after each bowel movement were suggested for 1 week after the surgery. Antibiotics were not used at any time. The patients who underwent LIS for CAF were followed up in our coloproctology outpatient clinic at the postoperative 1 week, 2 months, 4 months, 6 months, 1 year, and then on a yearly basis. Only the observation of a

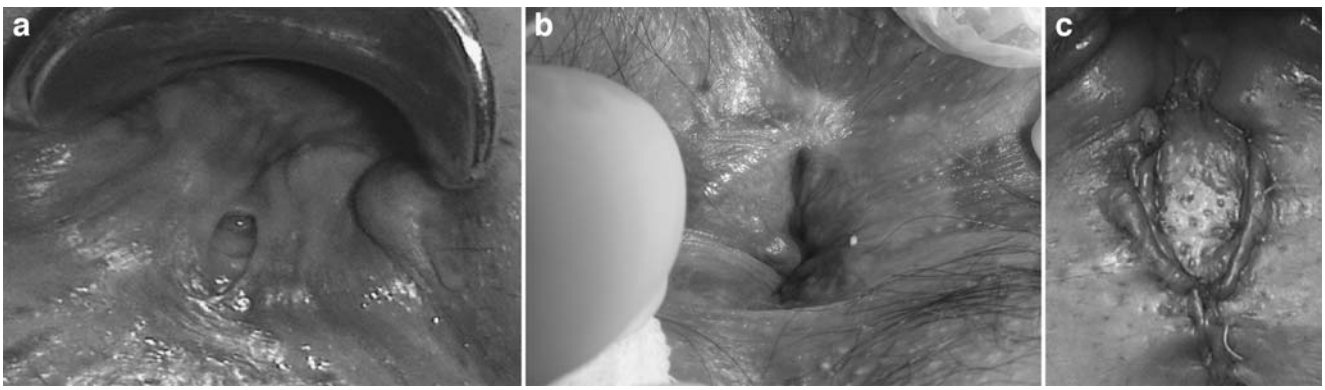

Figure 1 **a** A case with keyhole deformity after lateral internal sphincterotomy. **b** Nonhealing fissure. **c** Diamond flap reconstruction.

contracted and completely epithelialized scar or no signs of fissure (complete healing) was considered successful treatment, while all other definitions were regarded as failed cases (nonhealing).

Patients who were diagnosed to have keyhole deformity were initially managed conservatively for 6 months (diet changes, attention to stool consistency, enemas, and cotton pledgets). Patients who did not respond to conservative management were treated surgically. Advancement or diamond flap reconstructions were the two surgical treatment options performed for patients with keyhole deformity (Fig. 1c). Concerning defects greater than 1 cm, a diamond flap was preferred, while for defects smaller than 1 cm, an advancement flap was used. Full bowel preparation with phosphosoda was applied before the operations. In contrast with LIS, the lithotomy position was preferred. The surgical procedures were carried out under regional anesthesia, and a single dose of prophylactic antibiotics (cefuroxime 750 mg and metronidazole 500 mg) were given at induction. Before flap advancement, debridement of the base and edges of the deformity was carried out. Postoperative follow-up ranged from 6 to 44 months.

Results

Between January 2001 and January 2006, 926 patients were treated for CAF. One hundred of these patients received directly LIS as a patient preference. The remaining 826 patients initially received conservative management (including glyceryl trinitrate, botulinum toxin, etc.). In 150 of these cases, satisfactory results were obtained, while in 676 patients, conservative management failed, and LIS was performed. In this series, we noted eight recurrences and 28 nonhealing fissures, indicating to a treatment failure rate of 4.6%. This issue is out of our present topic. Stratification of the patients according to the type of previous treatment and the incidence of keyhole deformity encountered are summarized in Fig. 2.

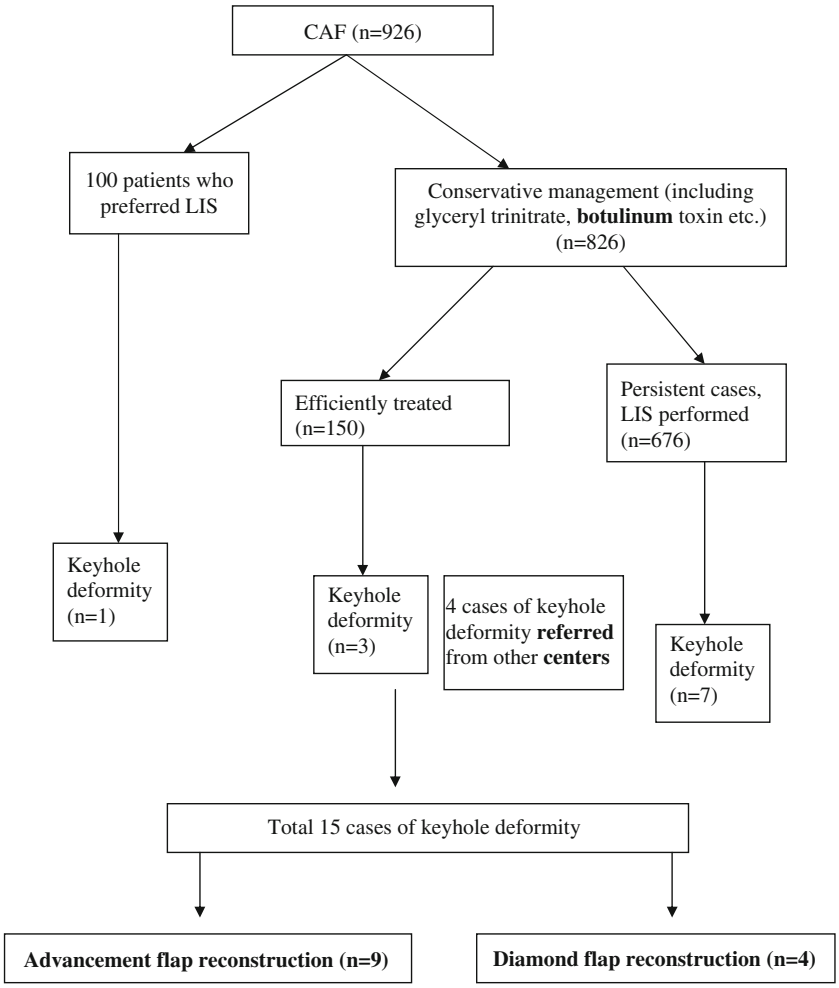

Figure 2 Stratification of the patients according to the type of management.

CAF: Chronic anal fissure
LIS: Lateral internal sphincterotomy

Table 1 Data Summarizing Characteristics of Patients with Keyhole Deformity

	KHD-LIS		NS-KHD	Total
	$n=8$[a]	$n=3$[b]	$n=4$	$n=15$
Mean age (range)	38 (17–75)	40 (19–54)	43 (30–60)	39 (17–75)
Gender (F/M)	5/3	2/1	3/1	10/5
Surgical procedure	7	2	4	13 (87%)
Advancement flap	5	1	3	9 (60%)
Diamond flap	2	1	1	4 (27%)
Conservative treatment	1	1	–	2 (13%)
Wound dehiscence	1	–	1	2 (15%)
Anal resting pressure (mmHg±SD)	44.2±14.3		42.5±11.2	
Anal squeeze pressure (mmHg±SD)	98.2±13.5		101.3±112.3	

KHD-LIS Keyhole deformity after lateral internal sphincterotomy, *NS-KHD* keyhole deformity without any intervention, *SD* standard deviation
[a] Keyhole deformity after lateral internal sphincterotomy performed in our clinic
[b] Keyhole deformity after lateral internal sphincterotomy performed elsewhere

Totally, 15 patients with significant keyhole deformity were treated, four of them being referred to our clinic from other centers during the study period. The fissure was localized in the posterior midline in all of the keyhole deformity cases. Among the patients with keyhole deformity who previously underwent LIS, the manometric evaluation revealed a resting pressure of 44.2±14.3 mmHg (mean±SD) and a anal squeeze pressure of 98.2± 13.5 mmHg (mean±SD). The patients who had no previous surgical interventions also had normal resting pressures. Data concerning the anal manometry results are summarized in Table 1. Three of the patients who were referred to our clinic for keyhole deformity had undergone surgery for CAF, and the remaining patient was managed conservatively. Nine patients (60%) underwent advancement flap technique, while four (27%) patients underwent diamond flap reconstruction. In the remaining two patients (13%), conservative treatment provided satisfactory relief of symptoms (moderate or no symptoms). In this series, 29 additional cases were noted to have posterior midline deformities, which were generally in the form of a slight depression/dimple with no inflammation. With moderate or no symptoms, these were not considered as significant keyhole deformities, and no treatment was intended.

A quality-of-life instrument was not used, and the decision to proceed with flap reconstruction was based on the patient's preference because of persistent, severe symptoms. After reconstructive surgery in 13 patients, wound dehiscence occurred in two cases (15%; Table 1). During a follow-up of 6–44 months, eight patients were symptom-free, while five declared satisfactory relief of symptoms, as summarized in Table 2. Therefore, the 85% rate of surgical success was associated with a 100% rate of good functional outcome.

Discussion

CAF is one of the most common anorectal disorders encountered in surgical practice.[12,13] Currently, LIS is the gold-standard treatment modality for CAF.[14] When the literature is reviewed, keyhole deformity is proposed to be a historical entity after posterior sphincterotomy. The pathophysiological mechanism underlying the deformity was proposed to be wide excision of the anoderm, posterior anal skin, and the subjacent muscle fibers.[10] However, current literature reveals that in patients with the diagnosis of CAF, keyhole deformity may also be observed after LIS or may be seen during the conservative management period, thus addressing a more complicated pathophysiologic mechanism.[10] In our study, the observation of this deformity after LIS or conservative management of CAF emphasizes the fact that this entity is not solely seen after posterior sphincterotomy or fissurectomy. In the present study, keyhole deformity was shown to be a rare complication of either surgical or conservative treatment for CAF. The patients usually present with the complaints of mucous discharge, pruritus, or soiling that can be misinterpreted as anal incontinence. However, this deformity is not associated with anal incontinence. The patients generally continue their daily activities without the need for consultation to the

Table 2 Data Summarizing the Outcome of Operated Patients

Patients	Satisfactory (%)	Full Response (%)	Total
KHD-LIS	3	6	9
NS-KHD	2	2	4
Total	5 (38%)	8 (62%)	13

KHD-LIS Keyhole deformity after lateral internal sphincterotomy, *NS-KHD* keyhole deformity without any intervention

physician, which may obscure the true incidence. Although almost all colorectal surgeons are aware of this rare entity, it is largely neglected by both the surgeons and the patients, mainly because the fissure pain does not exist anymore and the deformity (and the associated symptoms) may be difficult to differentiate from a nonhealing fissure or incontinence/soiling. The exact mechanism by which keyhole deformity occurs after surgical or conservative treatment of CAF is still unclear. Therefore, whether IAS spasm or altered perfusion may lead to defective wound healing is still obscure.

Keyhole deformities do occur after a variety of anal operations and anal trauma.[10] The posterior midline location of this deformity may be explained by the fact that the already reduced blood flow is altered further because of anal trauma or operations. Furthermore, surgical or conservative treatment performed for CAF may lead to altered blood supply and may alter wound healing. We hypothesize that both a nonhealing fissure and keyhole deformity are two edges of a spectrum of the same pathophysiologic process. Therefore, steps of fissure healing should be verified. Madalinski and Chodorowski[15] suggested that not all CAF heal in the desired direction, although a standard technique is performed. They stated that although the anal pressure dropped, some fissures remained nonhealed. For this reason, they postulated that certain vascular relaxing factors such as adenosine diphosphate, adenosine triphosphate, serotonin, thrombin, histamine, and substance P may act on anoderm and mucosal arterioles resulting in enhanced wound healing via nitric oxide and prostacyclin. On the contrary, in nonhealing cases, a series of mechanisms lead to smooth muscle contraction and, therefore, cause prolonged mucosal ischemia, which may be responsible for the altered wound healing.[15] Furthermore, the 15 cases with keyhole deformity in our study may be explained by deranged wound healing by the biochemical mechanism proposed by Madalinski and Chodorowski.[15]

The initial strategy for the management of the keyhole deformity should be conservative, by alteration of the diet, attention to stool consistency, use of enemas after bowel movements, and cotton pledgets. Few studies contain limited information about the treatment of keyhole deformity.[10] Surgical repair of the deformities in the anterior anal canal in women is usually associated with excellent results. Surgical repair of the deformities posteriorly, especially in the male, is difficult and, when undertaken, should be done with an appropriate warning to the patient that a good result may not be obtained. Avoidance of the defect is probably the most important factor in the equation.[10] In the present study, eight female patients were treated with the advancement flap technique and five male patients with advancement or diamond flap techniques. In two patients, a conservative approach was applied. It deserves emphasis that debridement and filling in the deformity with a healthy flap is highly successful in treating this disease entity. Smaller defects are satisfactorily treated with advancement (island) flaps. Bigger and relatively more complicated flap reconstructions, such as diamond flap reconstruction, may be indicated for bigger deformities.

Conclusion

Contrary to the classic literature, the keyhole deformity can be seen after treatment options applied for CAF. This entity is usually seen as a late complication of the treatment procedure and may be well tolerated by the patient without any well-defined symptoms. The treatment strategy is directed toward the degree of functional alteration.

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Outcome of and Risk Factors for Incisional Hernia After Partial Hepatectomy

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Abstract
Introduction This study was conducted to analyze differences among abdominal incisions, and risk factors for incisional hernia after partial hepatectomy.
Materials and Methods In 626 posthepatectomy cases, we analyzed retrospectively the distribution regarding the type of incision and assessed risk factors for incisional hernia.
Results Of the patients, 95 (15.2%) had median incisions, 233 (37.2%) had J-shaped incisions, 206 (32.9%) had right transverse incisions with vertical extensions in the midline from the subumbilical region to the xiphoid process (RTVE), and 92 (14.7%) had bilateral transverse incision with a vertical extension to the xiphoid process (a reversed T incision). The respective frequencies of incisional hernia after median, J-shaped, RTVE, and reversed T incisions were 6.3, 4.7, 5.4, and 21.7%, so that the difference between reversed T and other incisions was significant. A diagnosis of "no hernia" required a minimum follow-up of 12 months. The risk factors for incisional hernia were incision type, postoperative ascites, body mass index, repeat hepatectomy, and steroid use in multivariate analysis.
Conclusion The incidence of incisional hernia after reversed T incision was significantly higher than after other incisions. If incision extension is necessary, the midline incision should be extended from the subumbilical region.

Keywords Hepatectomy · Incisional hernia · Risk factor

Introduction

Incisional complications include not only incisional hernia but also wound dehiscence and wound infection. However, incisional hernia can occur long after surgery.

The risk factors for incisional hernia are age,[1] smoking,[2] nutritional status,[3] diagnoses of cancer, diabetes[4] or obesity,[5] and the nature of the surgical procedure (palliative or radical). With respect to abdominal procedures, several studies have also shown that type of incision plays a role. For example, compared to vertical abdominal incisions, transverse incisions are associated with a lower incidence of dehiscence, hernia, and overall wound complications.[6] However, only one report has been found about patients undergoing hepatic resection.[7]

The aim of this study was to analyze the differences among abdominal incisions and the risk factors for incisional hernia after hepatectomy.

Materials and Methods

Between January 1991 and June 2006, 684 consecutive patients who underwent elective liver resection at Yokohama City University Hospital were enrolled in this study. Patients who were concomitantly treated with the resection of other organs, resection and anastomosis of the bile duct, drainage, and resection and anastomosis of the digestive tract were excluded. Perioperatively, 5 patients died, and 53

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died of cancer recurrence within 1 year after surgery. These 58 patients were excluded from this study.

Type of Incision

A J-shaped incision was defined as a right transverse incision with a vertical extension at the midline to the xiphoid process. An RTVE incision was defined as a right transverse incision with a vertical extension at the midline from the subumbilical region to the xiphoid process. A reversed T incision was defined as a bilateral transverse incision with a vertical extension to the xiphoid process (Fig. 1).

Concerning the selection of the incision type for hepatectomy, a median or reversed T incision was performed for tumors located in the left lobe, a J-shaped incision for tumors located in the right lobe, and a reversed T or RTVE incision for large tumors (Table 1).

Intraoperative Procedure

The liver resections performed were defined according to the Couinaud classification.[8, 9] Liver resections combined with other major nongastrointestinal procedures (vascular resection, diaphragmatic resection, lung resection, adrenectomy, and lymphadenectomy) or associated with additional hepatic procedures (contralateral resection or ablation, or

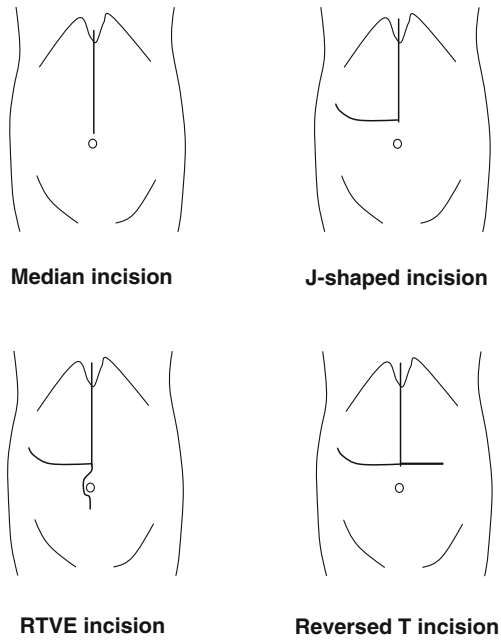

Figure 1 Types of incision. A J-shaped incision was defined as a right transverse incision with a vertical extension at the midline to the xiphoid process. An RTVM incision was defined as a right transverse incision with a vertical extension at the midline from the below the umbilicus to the xiphoid process. A reversed T incision was defined as a bilateral transverse incision with a vertical extension to the xiphoid process.

Table 1 Site of Incisional Hernia According to Abdominal Incision

Site	Median (n=95)	J-shaped (n=233)	RTVE (n=206)	Reversed T (n=92)
Right lateral abdomen	–	3	0	2
Trifurcation or bifurcation	–	3	6	11
Median area	6	5	5	5
Left lateral abdomen	–	–	–	2
Total	6	11	11	20

both) were included. Routine administration of prophylactic antibiotics was performed with the induction of anesthesia and then usually continued for 72–120 h after the completion of surgery.[10] The types of antimicrobial prophylaxis used were left to the judgment of the physician in charge.

Closure of Abdominal Wall

Closure of the abdominal wall muscle and fascia was performed using layered closure with an no. 1 interrupted silk suture or no. 1 Ethigard (Ethicon, Somerville, NJ, USA). Skin closure was done using a silk suture, nylon, or a skin stapler.

Postoperative Management

Postoperative management was similar for the entire cohort. All patients were monitored in the intensive care unit on the first postoperative night and were then transferred to a general ward. Postoperative pain control was performed by fentanyl citrate infusion via an epidural tube inserted during the operation in patients in whom the preoperative coagulation function was relatively well maintained, and the tube was, in principle, removed 3 days after the operation. For additional analgesia, Pentagin® or fentanyl was intravenously injected.

The remaining cavity was drained using large-bore silastic drains connected to a closed collecting system (suction pressure=10 cm H_2O). The drains were usually left in place until the drainage fluid was serous and the daily loss was below 100 ml. An open drainage system was sometimes selected in the early period (from January 1991 to March 1997).

Follow-up

A diagnosis of “no hernia” required a minimum follow-up of 12 months. No patients were lost to follow-up within 2 years. The duration of follow-up was 12 to 168 months, and the mean was 52.8 months. Until 2 years after operation, we performed a physical examination, including palpation every month, and took computed tomography (CT) scans every 3 months. From 2 to 5 years after operation, we performed a physical examination, including

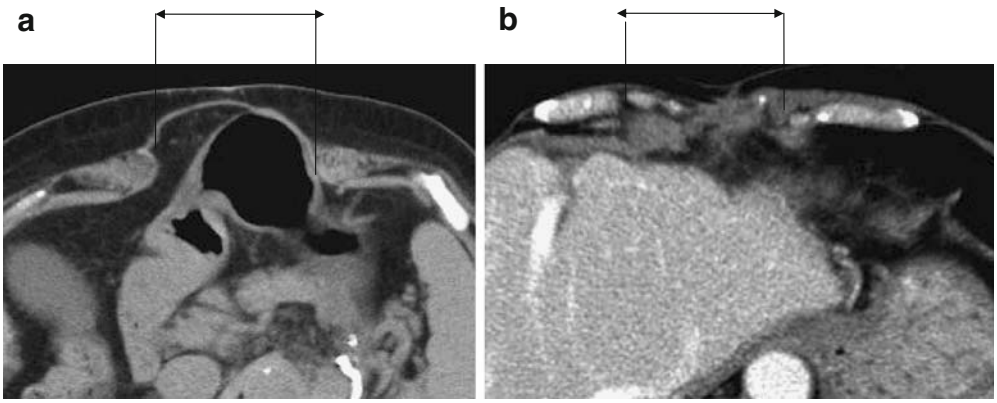

Figure 2 Computed tomograms of incisional hernias. In this study, not only incisional hernias that were covered with peritoneum and protruded from the abdominal wall (**a**) but also those in which fascial continuity of the abdominal wall was demonstrated by CT (**b**) were included in incisional hernias.

palpation every 2 or 3 months, and carried out a CT scan every 6 months. After 5 years, we performed physical examination, including palpation every 3 months, and did a CT scan every 6–12 months.

Diagnosis of Incisional Hernia

Incisional hernia was diagnosed based on a review of medical records and findings on CT. In general, a hernia is defined as a protrusion that is covered with the peritoneum and protrudes from the abdominal wall (Fig. 2a). In this study, when the fascial discontinuity of the abdominal wall was demonstrated by objective findings including palpation findings and CT-scans (Fig. 2b), even in the absence of a protrusion from the abdominal wall, the case was included in incisional hernias.

The definition of surgical site infection (SSI) followed that in the guidelines[11] for the prevention of surgical site infection issued by Centers for Disease Control and Prevention. Organ/space SSI occurred within 30 days after the operation; infection appeared to be related to the operation and involved any part of the anatomy (e.g., organ or spaces) other than the incision, which was opened or manipulated during the operation, and at least one of the following: (1) purulent drainage from a drain that was placed through a stab wound into the organ/space, (2) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space, and (3) an abscess or other evidence of infection involving the organ/space found on direct examination during reoperation or by histopathologic or radiologic examination. Generally, wound infection was defined as incisional erythema requiring antibiotics or an incision opened for grossly infected or culture-positive fluid.[12]

Postoperative Ascites

Ascites was considered intractable when definitely observed by diagnostic imaging techniques such as CT and ultrasonography more than 1 month after the operation, despite diuretic administration (furosemide, 60 mg/day; Soldactone®, 75 mg/day or more), after removal of the drain.

Patient demographics, disease-related variables, operative variables, and the outcome were analyzed and compared among the incision types. The risk factors for incisional hernia after hepatectomy were estimated.

Statistics

Results are expressed as the mean+SD. Continuous variables were evaluated using the unpaired Student's *t* test and the Mann–Whitney test. Categorical data were compared using the χ^2 test and Fisher's exact test, where appropriate. Multivariate analysis was performed with logistic regression analysis, which had been programmed in STAT-view version 5.0 software (SAS Institute Inc., USA). A level of $P<0.05$ was considered significant.

Results

From January 1991 to June 2006, hepatic resection was performed in 684 patients, 626 (91.5%) of whom met the inclusion criteria of this study. Among them, 95 (15.2%)

- Rate of incidence: 7.7%(48/626)
- Time before occurrence: 2-23 months, 9.5±5.2 months

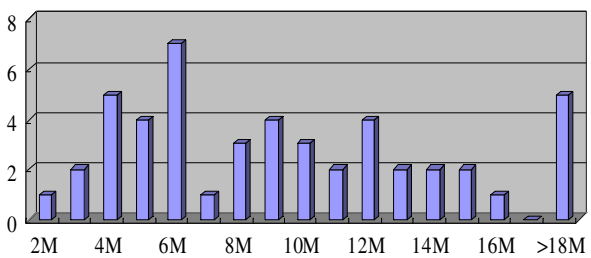

Figure 3 Incidence of incisional hernias. Of all patients, 48 (7.7%) had an incisional hernia. Incisional hernias developed 2–23 months (mean, 9.5 months) after hepatectomy.

Table 2 Patient Profiles

	Median	J-shaped	RTVE	Reversed T	*P* value
Number	95	233	206	92	
Age	63.3±10.1	61.9±11.6	61.5±11.0	61.6±9.7	0.6034
Sex (M/F)	54:41	155:78	143:63	69:23	0.0532
HCC/LM/Other	$36/50/9_{a}$	$108/99/26_{a}$	$82/119/5_{b}$	$37/47/8_{a}$	0.0050
Underlying disease (NL/CH/LC)	65/11/19	127/51/55	129/44/33	52/22/18	0.1091
DM (+/+/−)	73/8/14	166/34/33	127/41/38	58/17/17	0.0988
Smoking (+/+/−)	$27/13/55_{b}$	$107/50/76_{a}$	$98/34/74_{a}$	$40/13/39_{ab}$	0.0015
BMI	22.3±2.9	22.4±3.0	22.3±3.1	22.8±3.3	0.5648
Steroids (Y/N)	0/95	3/230	1/205	0/92	0.4198
Pulmonary dis. (Y/N)	4/91	8/225	11/195	6/86	0.6208
Alb	$4.05±0.46_{ab}$	$4.04±0.45_{a}$	$3.98±0.41_{b}$	$3.96±0.47_{b}$	0.0022
T-bil	0.77±0.36	0.77±0.39	0.77±0.35	0.76±0.36	0.9927
ICG15R	13.6±10.7	13.5±9.8	12.3±7.9	13.3±6.9	0.1365

HCC Hepatocellular carcinoma, *LM* liver metastasis, *NL* normal liver, *CH* chronic hepatitis, *LC* liver cirrhosis, *DM* diabetes mellitus, *BMI* body mass index, *Alb* albumin, *T-bil*, total bilirubin, *ICG15R* indocyanine green retention test

had a median incision, 233 (37.2%) had a J-shaped incision, 206 (32.9%) had an RTVE incision, and 92 (14.7%) had a reversed T incision. Perioperative mortality was identical in the four groups.

Of the total, 48 patients (7.7%) developed incisional hernia. Incisional hernias developed 2–23 months (mean, 9.5 months) after hepatectomy (Fig. 3). The site of hernias was frequently the trifurcation and median areas and infrequently the lateral abdominal area (Table 2).

Table 3 summarizes the association of demographics and preoperative variables with the incision type. Among the four incision types, there were no significant differences in terms of gender, primary disease, underlying disease, diabetes mellitus, body mass index (BMI), use of steroids, presence of lung disease, serum albumin, total bilirubin, and ICG 15. On the other hand, Table 4 summarizes the association of demographics and intraoperative and postoperative variables with incision types. The blood loss and transfusion volume were definitely smaller for the median and J-shaped incisions than for the reversed T and RTVE incisions. The resected proportion was significantly smaller for the median incision than for the other three types of incision. Although there may be period-associated differences, the use of silk and SSI were frequently observed for the RTVE and reversed T incisions. The incidence of postoperative ascites did not differ among the types of incision.

The respective frequencies of incisional hernia after median, J-shaped, RTVE, and reversed T incisions were 6.3, 4.7, 5.4, and 21.7%. The difference between reversed T and other incisions was significant (Table 5).

Risk Factors for Incisional Hernia After Partial Hepatectomy

Of the 626, 48 developed incisional hernia. A total of 21 independent clinical variables, including 11 preoperative

Table 3 Patient Profiles

	Median	J-shaped	RTVE	Reversed T	*P* value
Number	95	233	206	92	
Repeated Hx (Y/N)	8/87	20/213	20/186	15/73	0.1339
Op. length (min)	$317±149_{c}$	$360±120_{b}$	$480±143_{a}$	$445±139_{a}$	<0.0001
Blood loss (ml)	$700±708_{c}$	$1098±907_{b}$	$2175±2707_{a}$	$1926±3356_{a}$	<0.0001
Transfusion (ml)	$267±362_{a}$	$202±362_{a}$	$822±1261_{b}$	$622±1331_{b}$	<0.0001
Tumor diameter (mm)	$33.6±22.6_{c}$	$43.4±33.0_{b}$	$51.2±47.0_{ab}$	$58.9±57.8_{a}$	0.0009
Proportion resected	$17.3±10.2_{b}$	$32.1±19.1_{a}$	$32.4±20.8_{a}$	$28.7±24.3_{a}$	<0.0001
Suture (Silk/AS)	$44/51_{b}$	$37/196_{ab}$	$148/58_{a}$	$55/37_{b}$	<0.0001
SSI (Y/N)	$9/86_{c}$	$9/222_{a}$	$43/163_{ab}$	$12/80_{bc}$	<0.0001
Wound infection (Y/N)	4/91	5/228	9/197	4/88	0.5611
Ascites (Y/N)	2/93	14/219	13/193	7/85	0.3820

SSI Surgical site infection

Table 4 Incidence of Incisional Hernia According to Abdominal Incision

	Median (n=95)	J-shaped (n=233)	RTVE (n=206)	Reversed T (n=92)
Incidence (%)	6 $(6.3)_a$	11$(4.7)_a$	11 $(5.4)_a$	20$(21.7)_b$

P<0.01

and 10 surgical variables, were analyzed univariately as possible risk factors for incisional hernia. Eleven of these were significant: age, underlying disease, presence of diabetes mellitus, BMI, use of steroids, pulmonary disease, incisional type, repeat hepatectomy, proportion resected, use of absorbable sutures, and ascites (Table 6).

Multivariate analysis using a logistic regression model involving the 11 significant factors determined by univariate analysis identified five significant independent variables: BMI, use of steroids, incisional type, repeat hepatectomy, and ascites (Table 7). According to logistic analysis, if the reversed T incision was performed, the risk of incisional hernia would increase by 4.775 times.

Discussion

Wound complications such as infections, dehiscence, and hernia are a common cause of extended hospitalization, outpatient care, and increased costs associated with surgery.[13] Wound complications, especially incisional hernia, may have a broader impact, such as a delayed return to work, resulting in lost wages, and a decreased quality of life or performance status while patients are recovering at home after the operation. Therefore, avoidance of the development of incisional hernias may be useful for both patient well-being and cost-effectiveness.

Incisional hernias are one of the most common complications of abdominal surgery, with an overall estimated incidence ranging from 3 to 15.7% after abdominal operations.[14, 15] Generally speaking, the incidence of incisional hernia in Western countries is higher than that in Asia. There have been only a few studies on the incidence of incisional hernias after hepatic surgery. However, living-donor liver transplantation has been increasingly performed for terminal liver failure, and the incidence of incisional hernias are now being reported for the safety and quality of life of donors. Based on these reports, the incidence of incisional hernias was 3–20%.[16, 17] Because donors undergoing surgery are generally healthy, there are only a few donors with risk factors for the development of incisional hernias. However, the incidence was high.

Table 5 Risk Factors for Incisional Hernia after Hepatectomy (Preoperative)

	Hernia Gr. (n=48)	No hernia Gr. (n=578)	P value
Age	65.2±9.3	61.7±10.9	0.0321
Sex (M/F)	29/19	392/186	0.6636
Disease (HCC/LM/OT)	26/19/3	237/296/45	0.2065
Underlying disease (NL/CH/LC)	22/10/16	351/109/118	0.0428
DM (+/+/−)	9/16/23	93/84/401	0.0015
Smoking (+/+/−)	17/8/23	199/102/277	0.9818
BMI	24.5±3.7	22.2±2.9	<0.0001
BMI (25</>25)	23/25	100/478	<0.0001
Steroids	2/46	2/576	0.0014
Pulmonary disease (+/−)	7/41	22/556	0.0006
Serum albumin	4.02±0.37	4.03±0.44	0.8938
Serum T-Bil.	0.74±0.31	0.77±0.37	0.6320
ICG-R15	14.9±8.2	12.8±8.6	0.1092

HCC Hepatocellular carcinoma, *LM* liver metastasis, *OT* other liver disease, *NL* normal liver, *CH* chronic hepatitis, *LC* liver cirrhosis, *DM* diabetes mellitus, *BMI* body mass index, *ICG15R* indocyanine green retention test

Table 6 Risk Factors for Incisional Hernia after Hepatectomy (Intraoperative, Postoperative)

	Hernia Gr. (n=48)	No hernia Gr. (n=578)	P value
Incision type (Med/J-sharp/XX/R-T)	6/11/11/20	89/222/195/72	<0.0001
Repeat Hx (Y/N)	13/35	50/528	<0.0001
Op. duration (min)	412±156	419±145	0.7485
Blood loss (ml)	1298±1262	1531±2240	0.4786
Transfusion (ml)	313±712	486±1007	0.4611
Proportion resected (%)	21.9±15.3	30.5±20.4	0.0078
Tumor diameter (mm)	39.6±32.3	48.0±43.4	0.2182
Sutures (silk/non-silk)	19/29	323/255	0.0293
SSI (Y/N)	9/39	63/516	0.1003
Ascites (Y/N)	9/39	27/551	<0.0001

HCC Hepatocellular carcinoma, *LM* liver metastasis, *OT* other liver disease; *Hx* hepatectomy, *SSI* surgical site infection

Table 7 Multivariate Analysis of Factors Contributing to Postoperative Infections, by Logistic Regression Analysis

	Variable	ARR	P value
Incisional type	rT	4.775 (2.313–9.857)	<0.0001
Ascites	+	4.373 (1.590–12.029)	0.0043
BMI	>25	4.573 (2.279–9.173)	<0.0001
Repeat Hx	+	4.081 (1.774–9.388)	0.0009
Steroids	+	48.845 (5.413–440.797)	0.0005

Values in parentheses are 95% confidence intervals.
ARR Adjusted relative risk

Liver resection sometimes requires a wide incision. Many patients who underwent liver resection were concerned about wound complications, especially incisional hernia. Most studies addressing the optimal incision for hepatic surgery focused on whether a thoracoabdominal incision is beneficial.[18] However, thoracoabdominal incisions are associated with higher rates of pulmonary complications such as atelectasis, pneumonia, and pleural effusion. There are few data that address which abdominal incision is best suited for partial hepatectomy. D'Angelica et al.[7] reported that the common incisions utilized for partial hepatectomy have been the Mercedes incision and extended right subcostal (ERSC) incision. He reported that an ERSC incision provides adequate, safe access and is associated with fewer long-term wound complications. We generally use a median or J-shaped incision. However, for large tumors, the incision is extended to the left lateral abdomen (reversed T incision) or downward (RTVE incision). A reversed T incision is often used for large tumors in the left lobe and an RTVE incision for those in the right lobe. In the evaluation of incisional hernias in this study, the reversed T incision including the Mercedes incision should be avoided if possible due to the high incidence of postoperative incisional hernias.

The exact mechanism responsible for the higher rate of hernia development with a reversed T incision is unknown. It has previously been speculated that factors that predispose incisions to hernia include ischemia[19] and infection.[20] In our study, ischemia may have been an important, potentially avoidable cause because SSI was not a risk factor of incisional hernia. An area of relative ischemia at the trifurcation point from the midline fascia to anterior and posterior sheaths of the rectus abdominis may have contributed to impaired healing and led to the development of a hernia. Considering that the most frequent site of incisional hernias was the trifurcation point, ischemia may be the main cause. In addition, postoperative tension in the abdominal wall may have aggravated this area, resulting in a delay in wound healing. Thus, in hepatectomy, the addition of a transverse incision to obtain a better visual field is necessary, and the median incision should be continuous with the transverse incision. When a good visual field cannot be obtained by this method, the median incision should be extended downward. The Mercedes and reversed T incisions, which are transverse extensions, are associated with a higher incidence of hernias. Therefore, the incision of the left rectus abdominis should not be made except in unavoidable cases such as giant tumors of the left lobe.

We concluded that the incidence of incisional hernia after a reversed T incision is significantly higher than that on other incisions. If incision extension is necessary, the midline incision should be extended to the subumbilical region.

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Gingival Metastasis from Rectal Cancer

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Abstract We report a 51-year-old woman who had undergone surgical resection of Dukes'B rectal cancer. On postoperative day 30, she noticed a dark red swelling in the right upper gingival, for which immunohistochemical study of the biopsy specimen revealed metastasis from the rectal cancer.

Keywords Gingiva · Metastasis · Colorectal cancer

Case Report

A 51-year-old woman underwent Hartmann's procedure for poorly differentiated rectal carcinoma. On postoperative day 30, she noticed a dark red and tender swelling (10×15 mm) in the right fifth to sixth interdental gingiva (Fig. 1). Although the tumor was empirically diagnosed as epulis by a family dentist, biopsy revealed poorly differentiated adenocarcinoma, which was similar to the histology of the primary site. Imuunohistochemically, the staining was positive for cytokeratin (CK) 20 and negative for CK 7 (Fig. 2). Furthemore, the tumor cells showed negative immunostaining for estrogen, progesterone, and thyroid transcription factor-1 (TTF-1). We concluded the gingival tumor as the metastasis from the rectum cancer. The clinical course of the patient was very rapid. She suffered from dyspnea 2 months later, and died of local recurrence and malignant pleuritis.

Discussion

Metastatic cancers consist of only 1% of oral cancer.[1–7] The common locations of the primary site are the lung, the kidney, and the breast,[1–7] Most gingival metastatic tumors present as a firm polypoid mass, which mimics benign lesions such as hemangioma, pyogenic granuloma, and peripheral fibroma, and one third of them precedes clinical

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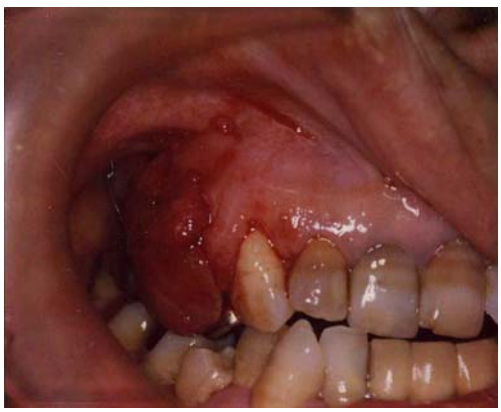

Figure 1 A dark red and firm nodule is present at right upper gingiva.

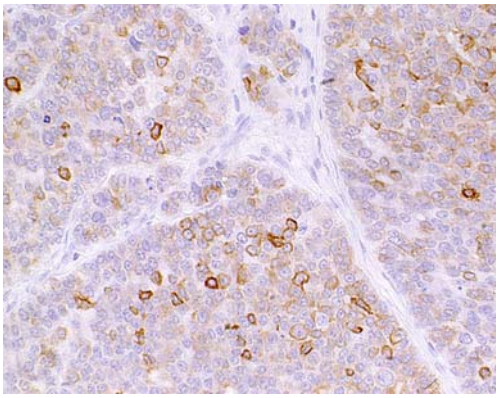

Figure 2 The staining was positive for cytokeratin (CK) 20 and negative for CK 7.

presentation of the primary lesion.[3] The tumor frequently accompanies pain, swelling, and bleeding, which mimic inflammation as seen in this patient.[1,2,4] The mechanism of metastasis to the oral cavity is mainly hematogenous spread.[1,3,6,7] When the oral metastasis is identified first, the prognosis is poor due to widespread metastasis of the tumor cells.[1,3–6]

There is no effective treatment for patients with oral cavity metastasis so far, and local surgical resection has been empirically chosen to avoid artification disorder or dysmasesis. Chemoradiation therapy is also performed for the management of general metastasis following the standard regimen targeted to the primary site. Identification of the primary site is mandatory to decide appropriate therapeutic strategy.

Since oral metastasis has no peculiar clinical characteristics as compared to benign or reactive tumors, a gingival lesion in a patient with a recent history of malignancy should undergo prompt biopsy to rule out gingival metastasis.

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CASE REPORT

Malignant Melanoma of the Gallbladder: A Report of Two Cases and Review of the Literature

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Abstract Melanoma metastatic to the gallbladder is rare. When present, it is often part of a widespread complex of metastases. Primary gallbladder melanomas are also extremely rare and can sometimes be difficult to distinguish from metastatic lesions. The optimal treatment for malignant melanoma of the gallbladder remains unclear, and prognosis is generally poor. We present here two cases of patients with metastatic lesions to the gallbladder. One patient presented with symptomatic cholelithiasis and was found incidentally to have a metastasis. Another patient had known a metastasis, but underwent curative resection of the only site of disease. We review the published literature for gallbladder melanoma, both primary and metastatic to determine the role of surgery in this disease.

Keywords Malignant melanoma · Metastatic melanoma · Gallbladder · Cholecystectomy

Introduction

Malignant melanoma is a highly unpredictable tumor, which can metastasize to any organ, including the gallbladder in 4–20%.[1–5] Additionally, there are several case reports of primary melanoma of the gallbladder.[6–9] Grossly and histologically, the distinction between primary and secondary lesions can be difficult because they share many similar characteristics.[10]

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Because of the rarity of melanoma of the gallbladder, optimal therapy is unclear. Cholecystectomy, especially in symptomatic patients, appears to prolong survival and improve the quality of life in many patients, even in the face of disseminated disease.[2,11] However, even with appropriate therapy, the diagnosis of melanoma of the gallbladder has a poor prognosis, with the mean survival ranging from a few weeks to several years.[6,11,12]

Case Presentations

Case Report No. 1

A 52-year-old white man with a past medical history of malignant melanoma presented with biliary colic on September 2004. In 1996, he was diagnosed with a 1.3-mm thick malignant melanoma on his left shoulder. A new 0.7-mm thick primary melanoma was removed from his back in 2002. Ultrasound at presentation revealed sludging and echogenic gallstones, without evidence of cholecystitis. A laparoscopic cholecystectomy was preformed for presumed cholelithiasis, and pathology incidentally revealed a polypoid mass consistent with malignant melanoma. The mass had a single attachment point to the mucosal surface with no evidence of invasion into the muscularis and stained positive for S100 and Melan A (Fig. 1). He subsequently developed widespread subcutaneous and

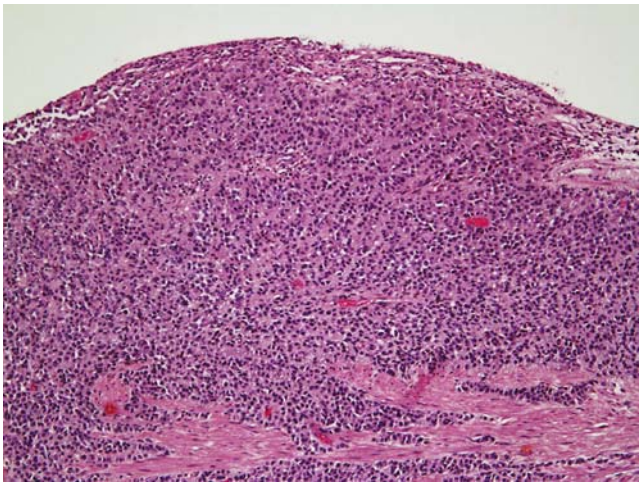

Figure 1 Polypoid mass of malignant melanoma expanding gallbladder mucosa (hematoxylin and eosin, ×100 original magnification).

lymph node metastases and was started on systemic chemotherapy. He is currently alive with disease 11.5 years after his original melanoma diagnosis and 36 months after diagnosis of metastatic disease.

Case Report No. 2

A 60-year-old white man presented with a subcutaneous nodule on his leg. Biopsy revealed melanoma in the dermis, and it was presumed to be metastatic from an unknown primary because all other possible sources (including ocular or other mucosal sites) were ruled out. A metastatic evaluation revealed a 4-cm gallbladder mass (Fig. 2) and a left axillary mass. He started systemic cytotoxic chemotherapy that led to regression of the leg nodule, but was complicated by severe thrombocytopenia. After resolution of his thrombocytopenia, the patient underwent laparoscopic cholecystectomy and left axillary lymph node dissection. Pathology of the gallbladder showed a necrotic mass 2.5×2×2 cm, which proved to be malignant melanoma. The lymph node dissection revealed malignant melanoma in 1 of 11 lymph nodes, which measured 4.5×2.2 cm, and was morphologically similar to the melanoma found in the gallbladder. The patient was free of new metastatic disease for ~14 months after surgery and then developed widespread metastatic disease to which he eventually succumbed 24 months later.

Discussion

The tumor biology of malignant melanoma is highly unpredictable. There may be aggressive disease causing death within months or an indolent course with recurrence long after the disease was thought to be cured.[4,13] Primary cutaneous melanoma can metastasize to any organ[12,14] and is known for its propensity for metastasis to multiple sites.[9,15] Melanoma commonly metastasizes to the small intestine-up to 60% of patients dying with malignant melanoma will have intestinal metastases at autopsy.[16] However, while melanoma metastatic to the gastrointestinal tract is common, isolated metastases to the gallbladder are rare, as most metastases are seen as part of widespread dissemination.[6,17]

Primary melanoma of the gallbladder was first described by Weiting and Hamdi in 1907.[7] Melanoma can develop wherever melanocytes, which migrate from the neural crest to all endodermal derivatives, are found. They are found in the retina, meninges, esophagus, intestines, along all organ capsules, the periadventitious layer of major blood vessels, muscle fascia, and the gallbladder.[11,17] Melanoma usually has a cutaneous origin; however, a cutaneous primary may undergo spontaneous regression.[13] Therefore, it may be very difficult to prove that a lesion is primary versus metastatic.

Patients with melanoma metastatic to the gallbladder are often asymptomatic. However, when they do have symptoms, it is often because of obstruction of the cystic duct by a mass, causing cholecystitis.[18,19] Patients may also present with right upper quadrant or epigastric pain, weight loss, nausea, or vomiting.[11,18,19] In a recent review of 13 patients from Memorial Sloan-Kettering Cancer Center (MSKCC), 7 patients were symptomatic.[20] One of our patients was symptomatic, and he was thought to have cholelithiasis causing his symptoms—the metastatic melanoma was an incidental finding. The other patient was asymptomatic, but as the gallbladder was one of only two sites of imageable disease after chemotherapy, a curative resection was performed.

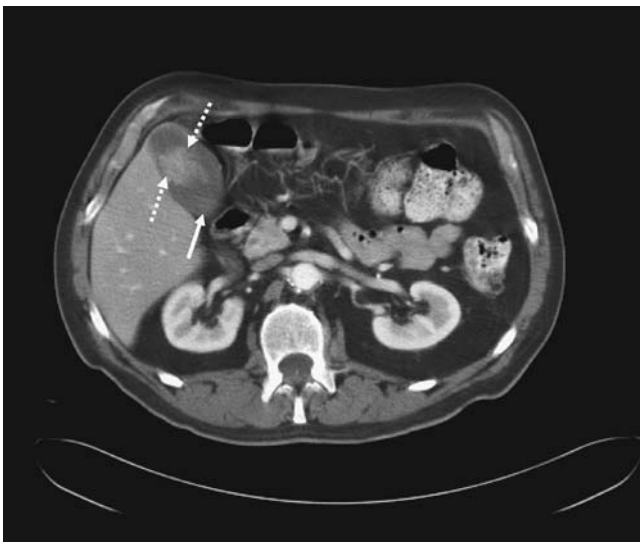

Figure 2 CT scan with intravenous and per os contrast demonstrates gallbladder (*solid arrow*) with 2.5 cm mass projecting into the lumen (*dashed arrows*).

Allen and Spitz were the first to establish criteria for distinguishing a true primary from a metastatic melanoma of the gallbladder, and Heath and Womack devised similar criteria.[8] They proposed that primary tumors must be: (1) solitary and arise from the mucosal surface; (2) papillary or polypoid; (3) display junctional activity (the presence of pigmented dendritic cells at the junction of the epithelium and lamina propria); and (4) have other sites excluded as the primary.[8] Of these, junctional activity is considered the most indicative of a primary lesion.[21] However, the absence of junctional changes in a primary lesion does not exclude the possibility of its being a primary because these cells may be destroyed by the rapid growth of the tumor.[9] Although it is often difficult to differentiate primary from metastatic lesions, it is generally accepted that the absence of melanoma in common primary sites, along with the presence of junctional activity, is sufficient evidence for a primary lesion of the gallbladder.[4,12] Our patient with the 'unknown primary' meets three of the four criteria, but junctional activity was not assessed. Therefore, because of the rarity of primary gallbladder melanoma and the lack of assessment of junctional activity make the diagnosis of a primary gallbladder melanoma unlikely.

Radiographic findings are useful in determining the location and nature of gallbladder masses. Ultrasound is the most useful, easy, and inexpensive modality for assessing both primary and metastatic lesions of the gallbladder.[21] Because masses have a lower density than gallstones, they do not produce the acoustic shadowing seen with gallstones.[3] If melanoma is present, computed tomography (CT) or ultrasound may show focal thickening of the gallbladder wall or intraluminal masses[3,11] (Fig. 2). Melanoma metastases are generally larger than 1 cm and attached to the gallbladder wall.[22] If the mass involves the biliary tree, ductal dilation and intraluminal masses may be visualized.[15] CT scan is useful for visualizing masses in asymptomatic patients. Magnetic resonance (MR) cholangiogram or MR imaging has been used in recent years, although the expected signal pattern of melanoma is inconsistent and may vary greatly within a single tumor.[15] Finally, although radiologic studies may be helpful in differentiating calculi from tumor, in many cases, the distinction may be impossible.

Because of the rarity of melanoma of the gallbladder, the optimal therapy is unclear. In many cases, the diagnosis is not made before surgery. Aggressive surgical therapy, including cholecystectomy, appears to prolong survival and improve the quality of life in many patients, even in the face of disseminated disease.[2,5] However, complete excision of tumor metastases is only feasible in approximately one third of patients.[12] In the analysis from MSKCC, the median survival of patients undergoing cholecystectomy was 12 months. Univariate analysis revealed the following factors to be prognostic of improved survival—presence of symptoms (p=0.0002), operative treatment (p=0.0005), and solitary metastasis (p=0.01).[20] Nevertheless, surgical resection even in the face of widespread metastatic disease has proven benefit for palliation.[11,12]

Even with appropriate therapy, the diagnosis of melanoma of the gallbladder has a poor prognosis. The mean survival times have ranged from a few weeks to several years, with the average survival for patients with primary lesions being 20.1 months and for metastatic disease being 8.4 months, with few patients surviving more than 2 years.[11] Both of our patients survived longer than 12 months after the diagnosis of gallbladder metastasis, with one being alive with disease 36 months later and the other being disease free for about 14 months and then dying of metastatic disease 24 months after cholecystectomy.

Finally, here is a word about laparoscopic surgery for metastatic disease. In the MSKCC series, three cholecystectomies were performed laparoscopically, and there were two instances of port site recurrence. In both of these patients, there were other sites of metastatic disease, and the gallbladder was placed in a specimen bag before removal and was not violated during the procedure.[20] There are other reports of laparoscopic cholecystectomy for metastatic melanoma to the gallbladder[17] with no clear indication of port site metastases. Both cases in our series were performed laparoscopically without evidence of a port site recurrence. There are clearly too few cases reported in the literature to make a recommendation for or against this practice—these cases should be handled individually.

Malignant melanoma of the gallbladder, whether it is primary or metastatic is a rare disease. It is often difficult to distinguish between primary and metastatic disease in the absence of an identifiable primary. In general, the prognosis of these patients is poor. However, in well-selected patients, an aggressive multidisciplinary approach to treatment of these patients, which includes surgery, immunotherapy, and chemotherapy, can improve survival.

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Duodenum-Preserving Subtotal and Total Pancreatic Head Resections for Inflammatory and Cystic Neoplastic Lesions of the Pancreas

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Abstract
Introduction For treatment of inflammatory and benign neoplastic lesions of the pancreatic head, a subtotal or total pancreatic head resection is a limited surgical procedure with the impact of replacing the application of a Whipple procedure. The objective of this work is to describe the technical modifications of subtotal and total pancreatic head resection for inflammatory and neoplastic lesions of the pancreas. The advantages of this limited surgical procedure are the preservation of the stomach, the duodenum and the extrahepatic biliary ducts for treatment of benign lesions of the pancreatic head, papilla, and intrapancreatic segment of the common bile duct. For chronic pancreatitis with an inflammatory mass complicated by compression of the common bile duct or causing multiple pancreatic main duct stenoses and dilatations, a subtotal pancreatic head resection results in a long-lasting pain control. Performing, in addition, a biliary anastomosis or a Partington Rochelle type of pancreatic main duct drainage, respectively, is a logic and simple extension of the procedure. The rationale for the application of duodenum-preserving total pancreatic head resection for cystic neoplastic lesions are complete exstirpation of the tumor and, as a consequence, interruption of carcinogenesis of the neoplasia preventing development of pancreatic cancer. Duodenum-preserving total head resection necessitates additional biliary and duodenal anastomoses. For mono-centric IPMN, MCN, and SCA tumors, located in the pancreatic head, total duodenum-preserving pancreatic head resection can be performed without hospital mortality and resurgery for recurrency. Based on controlled clinical trials, duodenum-preserving pancreatic head resection is superior to the Whipple-type resection with regard to lower postoperative morbidity, almost no delay of gastric emptying, preservation of the endocrine function, lower frequency of rehospitalization, early professional rehabilitation, and establishment of a predisease level of quality of life.
Conclusion The limited surgical procedures of subtotal or total pancreatic head resection are simple, safe, ensures free tumour margins and replace in the authors institution the application of a Whipple-type head resection.

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Keywords Inflammatory head mass · Cystic neoplastic lesion · Duodenum-preserving head resection

Duodenum-preserving pancreatic head resection has been introduced 1972 in surgical practice. The rationale to apply a duodenum-preserving pancreatic head resection is to avoid resection of the gastric antrum, preservation of the duodenum and the extrahepatic biliary ducts for benign inflammatory and neoplastic lesions.[1] The short-term benefits are low postoperative morbidity and mortality, and in the long-term outcome, major advantages are restoration of a pain-free status and maintenance of the endocrine and exocrine functions.[2–4] Comparing the early and late postoperative course after duodenum-preserving

Table 1 Criteria for Use of Duodenum-Preserving Subtotal and Total Pancreatic Head Resection for Inflammatory and Cystic–Neoplastic Lesions of the Pancreatic Head

Indications to Dudodenum-Preserving Subtotal and Total Pancreatic Head Resection		
Indications to subtotal head resection		
Chronic pancreatitis complicated by		
Inflammatory head mass		
Stenosis of the CBD		
Multiple stenoses and dilatations of PMD		
Severe narrowing of peripapillary duodenum causing gastric outlet syndrome		
Compression/stenosis of PV/SMV		
Pancreas divisum causing CP or recurrent acute pancreatitis		
Indications to duodenum-preserving total pancreatic head resection for adenoma, borderline lesion, and carcinoma in situ of cystic neoplasia:		
Cystic neoplastic lesions monocentric located in the head[a]		
All clinical symptomatic cysts		
Asymptomatic cysts		
IPMN	main duct lesions	
	branch duct lesion >2 cm	
MCN	lesion causing duct compression, growing, >2 cm	
SCA	>3 cm, growing	
SPsN	All	
Endocrine cystic lesions		

[a] Modified from Tanaka M, International Center for Guidelines, Pancreatology 2006;6:17–32[21]
CBD Common bile duct, *PMD* pancreatic main duct, *PV/SMV* portal vein, superior mesenteric vein, *IPMN* Intraductal, papillary mucinous neoplasia, *MCN* mucinous cystic neoplasis, *SCA* serous cystadenoma, *SPsN* solid pseudopapillary tumor

pancreatic head resection with the Whipple-type resection for chronic pancreatitis, results of four randomized prospective clinical trials have, as an objective, a significant superiority of the duodenum-preserving procedure regarding postoperative morbidity, maintenance of glucose metabolism, absence of delay of gastric emptying, low frequency of rehospitalization, professional rehabilitation, and overall improvement of quality of life.[5–9]

The rationale for a pancreatic head resection in chronic pancreatitis are (a) the head of the pancreas is the pacemaker of chronic pancreatitis,[10] (b) about half of the patients with chronic pancreatitis served for surgical treatment disclose an inflammatory mass in the head, (c) common bile duct stenoses are present in about 40–50%, (d) pancreatic main duct stenosis with prestenotic duct dilatation, pseudo-cystic lesions, calcifications, and duct stones are frequent in advanced disease. The clinical relevant abdominal pain syndrome is closely related to the degree of patho-morphologic changes in the pancreatic head. Rationale for total pancreatic head resection for cystic neoplasia are (a) complete removal of the lesion and (b) prevention of development of pancreatic cancer.[11]

The indications of duodenum-preserving pancreatic head resection in inflammatory and cystic neoplastic diseases of the pancreas are given in Table 1.

The surgical technique of duodenum-preserving subtotal head resection are based on four surgical steps:

1. Tunnelling of the portal vein below the neck of the pancreas with transection of the pancreatic head on the duodenal edge of the portal vein (Fig. 1).
2. Rotation of the pancreatic head in the ventral/dorsal position by 90° to the left, exposing the head mass for resection (Fig. 1).
3. Subtotal resection of the pancreatic head up to the intrapancreatic common bile duct but preservation of the dorsal capsule of the head and the posterior vessels (Fig. 2a,b,c).
4. Reconstruction with an excluded jejunal loop performing two anastomosis: duct-to-mucosa anastomosis with the left pancreas and a side-to-side anastomosis with the shell-like rest of the pancreatic head.

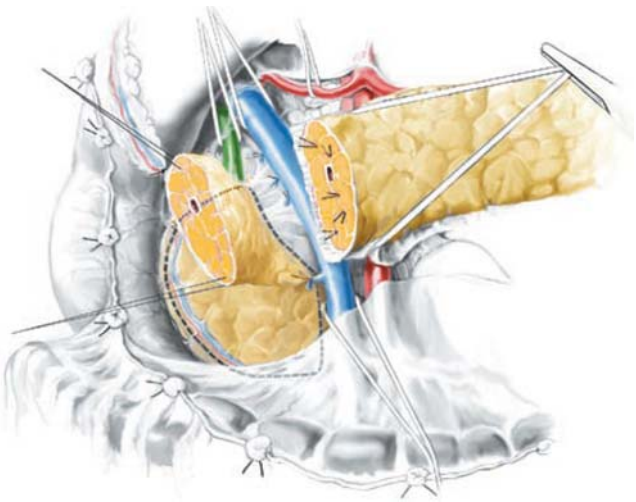

Figure 1 Duodenum-preserving pancreatic head resection after transection of the pancreatic neck, rotation in a ventral/dorsal position of the pancreatic head.

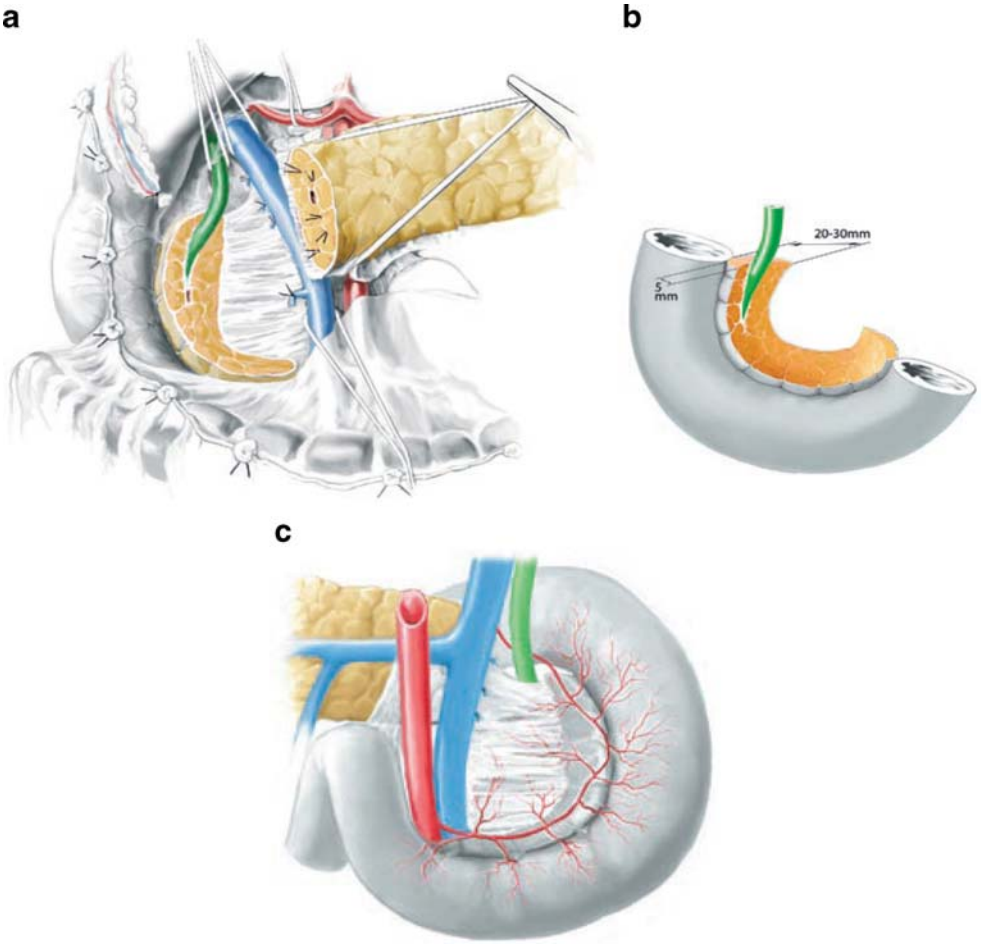

Figure 2 **a**–**c** Subtotal pancreatic head resection results in a shell-like rest between the common bile duct and the duodenum. The dorsal capsule and the dorsal gastro-duodenal and pancreatico-duodenal arcades are preserved (**a**). The shell-like rest of the pancreatic head has ventrally a distance of 5 mm and dorsally 2–3 cm to the duodenal wall (**b**). Preservation of the dorsal gastro-duodenal and pancreatico-duodenal arcades after subtotal pancreatic head resection is important (**c**).

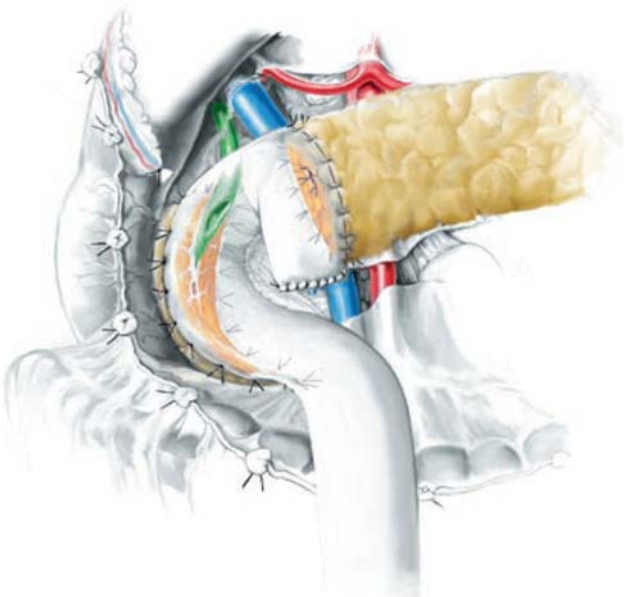

Figure 3 Duodenum-preserving subtotal pancreatic head resection with additional internal biliary anastomosis between the jejunal loop and the prepapillary common bile duct.[2]

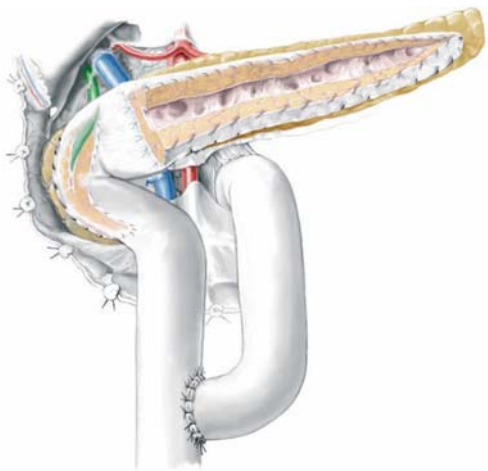

Figure 4 In chronic pancreatitis with multiple stenosis of the pancreatic main duct, an additional side-to-side duct drainage procedure using the Partington Rochelle technique with the first jejunal loop is performed.[11]

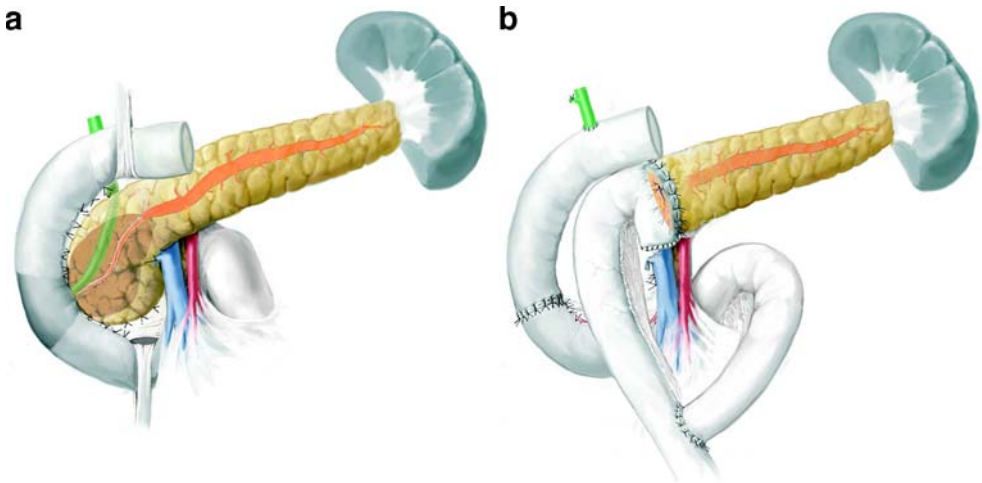

Figure 5 **a**, **b** Total pancreatic head resection with additional segment resection of the peripapillary duodenum (**a**). For reconstruction, the excluded upper jejunal loop is used creating a duct-to-mucosa anastomosis. In addition, anastomosis is done with common bile duct and post-pyloric duodenum (e-s); to restore the continuity of the duodenum an anastomosis (e-e) between proximal and distal duodenum is performed (Fig. 5b).

Two different modifications have been developed and published 1981[2] and 1987[12] based on the duct pathomorphology of the intrapancreatic, pre-papillary common bile duct, and the presence of multiple pancreatic main duct stenoses of the left pancreas. In patients suffering a common bile duct stenosis, frequently managed before surgery with biliary stentings, an internal biliary anastomosis is additionally created[2] (Fig. 3). Patients who show multiple pancreatic main duct stenoses and dilatations, a duct drainage procedure using a side-to-side anastomosis with the jejunal loop has been applied[12] (Fig. 4).

Several modifications of the duodenum-preserving techniques have later been published by other groups. The drainage procedure of Frey[13] and Izbicki[14] resembles the technique of the Partington Rochelle technique with partial resection of pancreatic head tissue by coring-out some tissue (~5 g wet weight) or ventral resection of tissue of the pancreas. The Bern modification avoids transection of the pancreatic neck and may result in subtotal pancreatic head resection.[15]

Table 2 Early Postoperative Course After Duodenum-Preserving Subtotal and Total Pancreatic Head Resection (The Experience of the Authors' Institution)

Parameter	Pat.	Type of Head Resection	Reop. (%)	Hospital mortality (%)	Citation
Chronic pancreatitis	128	Subtotal	5.5	0.8	Beger 1989[3]
Pancreas divisum	36	Subtotal	0	0	Schlosser 2005[24]
Cystic-neoplastic TM's	96	Total	3.8	0	Beger Review 2007[18]

Dudodenum-Preserving Total Pancreatic Head Resection for Cystic Neoplastic Lesions

A modification of the duodenum-preserving pancreatic head resection has been applied with increasing frequency in patients suffering neoplastic lesions located in the head.[11,16–20] Due to routine use of upper abdominal ultrasound and contrast-enhanced CT, cystic neoplastic lesions are increasingly diagnosed. Intra-ductal papillary mucinous tumors (IPMT), mucinous cystic tumors (MCT), and serous cyst adenoma (SCA) are the most frequent cystic lesions, less frequent are cystic forms of solid pseudo-papillary tumors (SPsT), acinus cell carcinomas, and endocrine and neuroendocrine neoplastic lesions. Clinically, most relevant cystic neoplasia are the IPMN and MCN. About 60% of the patients with IPMN develop a cystic lesion in the pancreatic head, but only up to 20% of the MCNs show single cystic head lesions, and one third of SCA's are located in the head.[21,22] The use of a duodenum-preserving total pancreatic head resection is determined by

Table 3 Modifications of Duodenum-Preserving Subtotal and Total Pancreatic Head Resection

Modifications
Duodenum-preserving subtotal pancreatic head resection (DPPHRs)
DPPHRs + biliary anstomosis (s-s)[2]
DPPHRs + PMD-drainage using, a jejunal loop (s-s)[12]
Duodenum-preserving total pancreatic head resection (DPPHRt)
DPPHRt + peripapillary segment of duodenum (e-e) + biliary anastomosis (e-s)[11,16–20]
DPPHRt + total pancreatectomy + segment of duodenum + biliary anastomosis (e-s), preservation of the spleen[23]
DPPPHRu of uncinate process + segment of postpapillary duondem (e-e)[11,18]

the nature and extent of the neoplasia. Goals of surgical treatment of a cystic tumor are complete extirpation, using frozen section investigations of the resection margins as intraoperative controls. In case of a combination of a cystic neoplasia having developed to an advanced pancreatic cancer, a Whipple-type resection including lymph node dissection is recommended. Patients with multicentric cystic lesions mostly identified preoperatively are candidates for application of a duodenum-preserving total pancreatectomy. The criteria of indication for duodenum-preserving total pancreatic head resections for cystic neoplastic lesions are given in Table 1.

Total pancreatic head resection for cystic neoplasia's are based on the following technical steps:

1. After a limited Kocher maneuver dissection of the duodenum and pancreatic head along the duodenal wall beginning at the post-pyloric duodenum towards the papilla major (Fig. 5a).
2. Dissection along the uncinate process towards the papilla major but preserving the vessels of the mesoduodenum. The anterior and posterior branches of the inferior pancreatico-duodenal artery running parallel to the infrapapillary duodenum are important to preserve[23] (Fig. 5a).
3. En bloc resection of the peripapillary duodenum with the pancreatic head. The rationale for segmental resection of the peripapillary duodenum are (a) the intrapancreatic common bile duct and the papilla of Vater yielding the blood supply from the dorsal branch of the superior gastro-duodenal artery are at risk for ischemia after ligation of the vessel during the dissection process and (b) to perform an oncologic complete extirpation of the neoplastic lesion which may have infiltrated in the duodenal wall.
4. To reconstruct the GI tract, three anastomoses have to be done: (a) a duct-to-mucosa anastomosis between the jejunal loop or the stomach, (b) a common bile duct-to-duodenum anastomosis, and (3) an anastomosis between proximal and distal duodenum (Fig. 5b).

The duodenum-preserving total pancreatic head resection including resection of a segment of the peripapillary duodenum is indicated for adenoma, borderline lesion and carcinoma in situ of cystic neoplastic lesions, and has been used for low risk T_1 cancer of the papilla and the prepapillary CBD. Total extirpation of a cystic neoplastic lesion of the pancreatic head is a cancer-preventive strategy.[18] This limited surgical procedure has been performed in most published series without hospital mortality and a low early postoperative morbidity.[18] However, incomplete extirpation of the neoplastic lesion using subtotal pancreatic head resection may result in a reoccurrence of the IPMN-tumor necessitating a Whipple-type procedure for resurgery.[18]

Patients who have preoperative signs of malignancy, jaundice, sudden onset of diabetes, intramural nods >5 mm, PMD >10 mm, CEA-level increased, are not candidates for a duodenum-preserving procedure, but for a Whipple-type resection.

Intraoperative frozen section of the operative specimen and the resection margins are most important for the surgical strategy: to apply limited or major oncologic resection.

Several modifications of duodenum-preserving total pancreatic head resection have been successfully applied[16–20] (Table 2). For location of the neoplasia in the uncinate process, a resection of the uncinate process is performed, including a segment of the postpapillary duodenum.[11] Patients suffering from multicentric IPMN- and MCN-lesions including head, body and tail, a duodenum-preserving total pancreatectomy with preservation of the spleen is a technically demanding procedure.[23] To avoid surgical exclusion of the first jejunal loop, the implantation of the left pancreas into the stomach performing a pancreas-gastricwall anastomosis is an elegant surgical technique with a low perioperative morbidity. Duodenum-preserving total pancreatic head resection (Table 3) without segmental resection of the duodenum and implantation of the left pancreas into the duodenum, performing a pancreatic duct-to-duodenum-mucosa anastomosis spares an additional Roux-Y procedure with the upper jejunal loop.[17]

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A Comprehensive Appraisal of the Surgical Treatment of Diffuse Esophageal Spasm

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Abstract Diffuse esophageal spasm is a motility disorder of undetermined cause. The optimal treatment remains controversial, and evidence-based data are lacking. Several medical treatment modalities have been proposed, but none has emerged as the treatment of choice. Patients who do not respond to medical therapy may be considered for surgical treatment. The surgical treatment of diffuse esophageal spasm is based on similar principles to the treatment of achalasia. A long esophageal myotomy is done to divide the hypertrophied circular muscle that is frequently noted in diffuse esophageal spasm. To protect against postoperative reflux, an antireflux procedure may be added. However, the surgical treatment of diffuse esophageal spasm has not been subjected to randomized clinical trials. The purpose of this article is to provide a review of the available literature regarding the surgical management of the diffuse esophageal spasm. In particular, we offer an appraisal of surgical outcomes, the effects of surgery on manometric and radiologic parameters (when available), complications, and mortality.

Keywords Esophageal myotomy · Esophageal spasm · Esophageal spastic disorders · Surgical treatment

Abbreviations

DES	Diffuse esophageal spasm
GER	Gastroesophageal reflux
HLES	Hypertensive lower esophageal sphincter
LES	Lower esophageal sphincter
NE	Nutcracker esophagus

Introduction

Diffuse esophageal spasm (DES) is a motility disorder of undetermined cause. The typical presentation includes recurrent episodes of chest pain or dysphagia and non-propulsive (tertiary) contractions seen radiographically. The diagnostic hallmark is identification of simultaneous contractions in the smooth muscle of the esophagus in at least 20% of wet swallows, alternating with normal peristalsis during esophageal motility.[1]

The optimal treatment of DES remains controversial and lacks evidence-based data. The controversy is caused in part by the rarity of the disease and the lack of understanding of its etiology, pathogenesis, and natural history. Multiple medical treatment approaches have been used,[2] but no single modality has emerged as an ideal therapy. Furthermore, no large randomized clinical trials of medical treatments are available.

Patients who do not respond to medical therapy occasionally are considered for surgical treatment. The surgical treatment of patients with spastic motility disorders of the esophagus, such as DES, is based on similar principles used for the treatment of achalasia.[3] A long esophagogastric myotomy is performed to divide the hypertrophied circular muscle that is frequently noted in DES. With this, it is expected that the uncoordinated contractions found are eliminated along with the characteristic radiographic findings and disabling symptoms. In contrast to achalasia, which has

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extensive literature supporting the beneficial outcome of surgery,[3–5] randomized trials evaluating surgical outcomes in DES are lacking.

The purpose of this manuscript is to provide a comprehensive review of the literature concerning the surgical management of DES. In particular, we focus on surgical outcomes, type of surgical procedures performed, the impact on manometric and radiologic parameters (when available), complications, and mortality.

Methods

A computerized search of the published literature was performed from 1966 to September 2007 using MEDLINE. We used the terms *diffuse esophageal spasm*, *therapy*, *surgery*, *laparoscopy*, and *myotomy*. A total of 37 articles were identified, and 28, published in English, were included. Furthermore, a manual search of the literature done by examining the references cited in above-mentioned articles identified 15 additional related papers, some of them predating 1966.

From these searches we selected 28 articles that contained original series of patients undergoing surgery for DES; the number of patients ranged from one to 63. These articles were exhaustively reviewed and patient data (number of subjects operated; basis for the diagnosis of DES; type of operation performed; surgical, manometric, and radiologic outcomes; mean follow-up period; and mortality) were compiled and analyzed. The remaining articles were not included because they were either review articles or did not report original outcomes of operated patients. We have organized our findings as follows: (1) major historical landmarks in DES; (2) the era of the 1960s after the advent of esophageal motility studies; (3) the period from 1972 to 1992 when either lower esophageal sphincter (LES)-sparing operations or antireflux surgery was added to surgical myotomy; (4) the advent of minimally invasive surgical laparoscopy in the 1990s; and (5) summary and conclusions.

Results

Historical Perspective—Medical and Surgical Milestones in the Treatment of DES

Figure 1 summarizes historical landmarks in the treatment of DES. The left column includes some major medical developments, and the right column shows some milestones in the surgical management of DES.

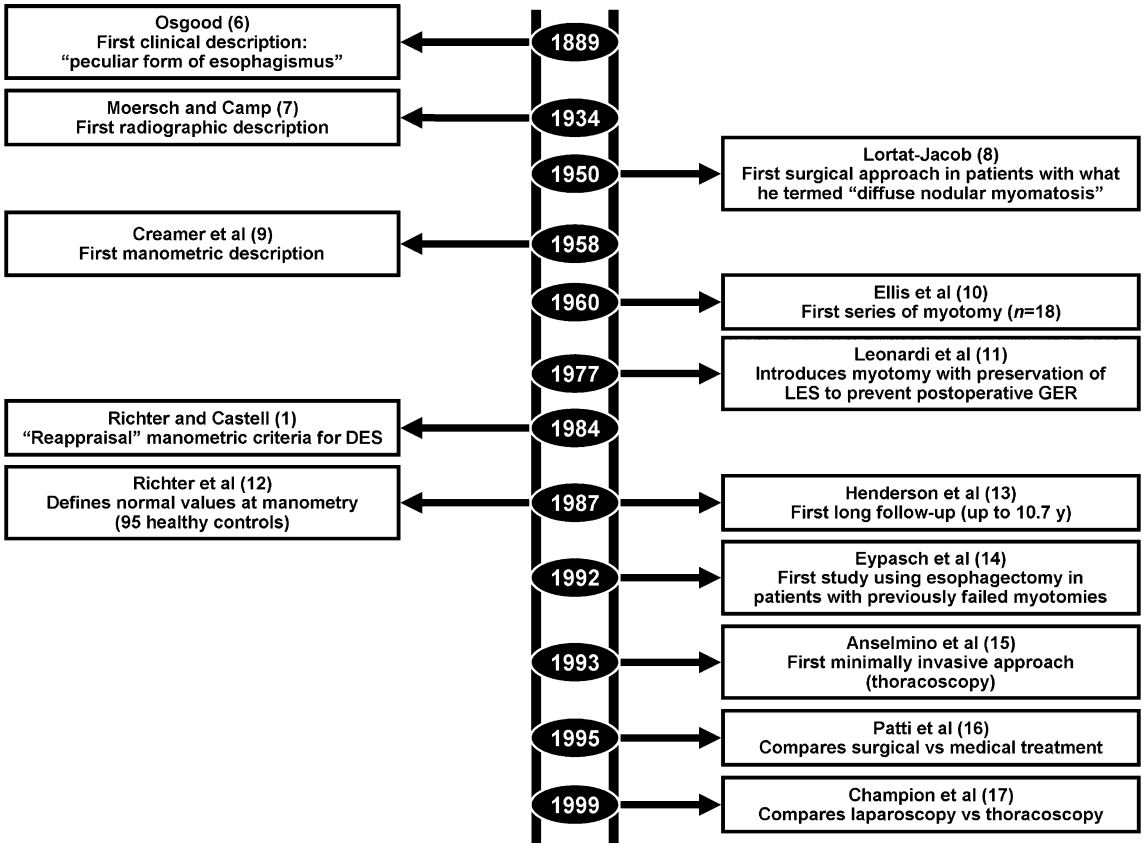

Figure 1 Medical (left column) and surgical (right column) historical landmarks in the diagnosis and treatment of DES. DES, diffuse esophageal spasm; GER, gastroesophageal reflux.

Medical Developments

The term *esophageal spasm* and its first clinical description are attributed to Osgood.[6] In 1889, he described six patients who had sudden and intense constriction in the epigastrium and dysphagia that he termed a "peculiar form of esophagismus".[6] In 1934, Moersch and Camp[7] published the earliest radiographic description, which was amplified by Van Exter and Keet.[18] In 1958, Creamer et al.[9] and Roth and Fleshler[19] in 1964 were credited with the earliest manometric descriptions. In 1984, Richter and Castell,[1] in a retrospective review of literature published to that date, noted that the most consistent manometric criterion was simultaneous contractions in the smooth muscle. In 1987, Richter et al.[12] defined normal manometric parameters in 95 healthy volunteers and confirmed that 20% or more simultaneous contractions in the distal esophagus was a feature not appreciated in healthy volunteers, lending further supporting evidence to the diagnostic criteria for DES.

Early Surgical Developments

Lortat-Jacob of Paris[8,20] is credited with the first report, in 1950, of surgical treatment of DES. In that pioneer work, four patients with what he termed "diffuse nodular myomatosis of the esophagus" were treated surgically. He performed a left thoracotomy to do a modified Heller myotomy extending proximally to the aortic arch and distally 2 cm onto the gastric wall with "good results." Although esophageal manometry was not available then, at least two patients in his series appear to have had clinical features consistent with a diagnosis of DES.[21]

Also during the 1950s, two studies reported on the surgical management of the esophagus for a spastic disorder that was likely unrecognized DES. In 1956, Sweet[22] defined a group of patients as having type II achalasia who presented with chest pain as the main complaint; they showed "curling" (a corkscrew appearance) of the esophagus and little evidence of esophageal dilation on esophagogram. He treated them with a modification of the Heller esophagomyotomy (and incidentally noted hypertrophy of the distal esophageal muscle at surgery).[22] Marston and Bradshaw,[23] in 1959, reported the clinical course and surgical management of a patient affected with what they termed as "idiopathic muscular hypertrophy of the esophagus." A patient presented with a longstanding history of chest pain, nausea, vomiting, and dysphagia; the esophagogram showed curling of the esophagus with a delay in the distal 6 cm that now would be suggestive of DES; motility studies were not available. The patient underwent an esophageal myotomy from the aortic arch to the cardia, and a tiny sliding hiatal hernia was also repaired.[23]

The Advent of Manometry and the First Surgical Series of DES in the 1960s

After the manometric recognition of DES in 1958,[9] Ellis and coworkers[10] presented in 1960 the first series of 18 patients who had a diagnosis of DES at manometry and were treated with a long esophagomyotomy. The proximal surgical limit was marked by extension of the disease on the basis of preoperative esophageal manometry; the distal limit was 1 to 2 cm onto the gastric wall. They added a hiatal hernia repair if a hernia was present. Fourteen patients had DES, four had DES and hypertensive lower esophageal sphincter (HLES) (defined as "exceeding more than 140 cm of water"), and two had an isolated HLES; seven patients also had a hiatal hernia. After a mean follow-up of 15 months (range, 6–35 months), 15 patients (83%) obtained symptomatic improvement ("seven excellent, seven good results, and one fair"). Postoperative manometry showed that the amplitude, duration, and repetitiveness of contraction were reduced, but simultaneous contractions persisted in the operated area. Repeat barium studies after surgery showed decreased amplitude, duration, and repetitiveness of the deglutition responses in the incised esophagus and loss of peristaltic activity.

In 1964, Ellis et al.[24] amplified their initial investigation on the effects of long esophagomyotomy in 33 patients with DES (including follow-up of patients previously described). Twenty-seven patients had DES, and six patients had DES plus HLES. Follow-up was a mean period of 40 months (range 12–78 months). Seventy-eight percent of the patients obtained at least some degree of symptomatic improvement; in 67%, this improvement was described as "excellent" and in 11% as "good." Manometric follow-up was available in half the subjects. A reduction in amplitude in the incised region was seen at manometry, and this was maintained during the follow-up period in all but one patient. There was also a decrease in the duration and repetitiveness of contractions, but no change in velocity of contractions or decrease in the rate of simultaneous contractions. The authors frequently noticed a lack of direct correlation between the postoperative motility pattern and the patient's symptoms. Barium swallow showed "dilation at the site of the myotomy," and 5 of 30 patients also had gastroesophageal reflux (GER) on barium testing. One death occurred in this series unrelated to the operation; a patient died from myocardial infarction at 1 year after surgery.

In 1966, Craddock et al.[25] described 12 patients with DES diagnosed on the basis of radiologic imaging in all and manometry in 11 (simultaneous contractions, although the report does not state what percentage of simultaneous contractions was observed). All patients initially underwent esophageal dilation; in only five patients who did not

respond to esophageal dilation or required frequent dilations was a long esophageal myotomy done. Improvement was achieved in all patients during a follow-up ranging from 3 to 144 months. Postoperative dysphagia in one patient required esophageal dilation. Manometry showed that "hypertonic, nonperistaltic waves were eliminated." The patients' radiologic appearance improved, but did not normalize.

Gillies et al.[26] in 1967 described a series of 21 patients diagnosed with DES on the basis of "synchronous, repetitive, spontaneous, prolonged and high pressure esophageal contractions." According to the authors, synchronous activity was present after "every swallow in all but one patient"; thus, on the basis of current manometric criteria, these patients most likely had achalasia instead of diffuse spasm.[1] Seven patients (unclear which had DES or achalasia) underwent myotomy because of the "severity of their symptoms." All improved with follow-up as long as 3 years after the operation. Repeat manometry showed persistent simultaneous activity, but of lower amplitude. Postoperative radiographic evaluations were not done.

Ferguson et al.[27] in 1969 reported 14 patients with DES (described by the authors as "giant muscular hypertrophy of the esophagus") who underwent Heller myotomy. The preoperative diagnosis was made on the basis of clinical and radiographic findings (preoperative esophageal motility available in only three patients). Follow-up was available in 13 of the 14 patients with a mean time of 57 months (range 6–72 months). Satisfactory results (no symptoms) were noted in 9 (69%) of 13 patients, fair results (occasional dysphagia not requiring dilation) in three patients (23%), and poor results (requiring a new esophageal myotomy) in one patient (8%). Postoperative motility (available in only 7 of 13 patients) showed unchanged simultaneous and repetitive contractions, although with a markedly decreased amplitude. The radiographic appearance continued to show disordered activity, but of lesser magnitude than that which occurred preoperatively.

Nicks[28] in 1969 described the outcome of 7 of 26 patients diagnosed with DES (radiologically and manometrically). Motility showed "simultaneous tetanic contractions of the entire esophagus," but again the actual percentage of simultaneous contractions was not reported, raising concern about achalasia in these subjects. All but one patient achieved complete relief of symptoms after a long myotomy. The patient who relapsed had been diagnosed with a hypertensive LES and had previously undergone a short myotomy limited to the sphincter. This patient became asymptomatic after reoperation to extend the myotomy proximally.

In summary, during the 1960s, six surgical series were published involving approximately 63 patients. It is possible that some of these series may have involved patients with achalasia rather than DES, based on our present accepted diagnostic criteria at manometry. Most studies included very small numbers of patients (range 5–33 patients). Taken together, these studies report a success rate that ranged between 69% and 100%. Only one death occurred (myocardial infarction 1 year after surgery), unlikely related to surgery; three patients required reoperation, and three patients had postoperative dilation. Despite improvement in symptoms, manometric incoordination and radiographic abnormalities persisted. Table 1 summarizes these case series.

The 1970s to the 1990s: Use of Antireflux Surgery and LES-Sparing Myotomy

Patients undergoing a myotomy are at risk for developing GER because the procedure may extend to the LES and cause a loss of the antireflux protective mechanism. In addition, some patients with DES may have coexisting reflux. Bombeck et al.[29] in 1972 were the first to report the results of antireflux surgery instead of a myotomy for the potential treatment of DES. Their prospective study included 63 patients classified into three groups: 28 with esophagitis alone, 24 with DES alone, and 11 with combined reflux esophagitis and DES. After 6 months of medical therapy, the patients were reevaluated clinically (to assess the resolution of spasm) and endoscopically (to evaluate the cure of esophagitis). The patients in whom medical treatment failed had surgery, commonly Nissen fundoplication, although some had Belsey or Hill type surgery. Patients were followed up for at least 1 year. In 10 patients with reflux alone who had surgery, esophagitis was healed and symptoms were resolved. Symptoms persisted in 5 of 6 patients with DES alone who had surgery, yielding a failure rate of 83%. Four of six patients with esophagitis-related DES continued to be symptomatic, although esophagitis was cured in all patients (a failure rate of 67%). Thus, this uncontrolled study suggested that in a small number of patients with DES, whether reflux was associated or unrelated, surgical treatment with an antireflux procedure alone resulted in a high failure rate. Postoperative manometry and barium studies were not reported.

During the ensuing years, investigators considered the addition of an antireflux operation to a Heller myotomy to avoid potential reflux (Figs. 2 and 3). In 1974, Henderson et al.[30] reported their initial experience in the surgical treatment of 21 patients with DES. In 12 of 21 patients, manometry demonstrated "total disordered motor activity in the lower two-thirds of the esophagus." Thus, these patients probably had achalasia, and only the remaining nine had DES. They performed extended myotomy (from 1 cm into the stomach and up to the aortic arch to avoid possible

Table 1 Surgical Series in the 1960s After the Advent of Manometry

Source	No. of Patients	Surgical Technique	Mean Follow-up, mo (Range)	Outcome[a]	Morbidity and Mortality
Ellis et al. 1960[10]	18	Long esophagomyotomy and hiatal hernia repair (allison) (n=7)	15 (6–35)	S: Improvement 83% M: Amplitude, duration, and repetitiveness reduced R: Decreased amplitude, duration, and repetitiveness of deglutition	Morbidity: 6 incisional pain (1 required rhizotomy); 3 dysphagia (1 required dilation) Mortality: 0
Ellis et al. 1964[24b]	33	Long esophagomyotomy	40 (12–78)	S: Improvement 78% M: Amplitude, duration, and repetitiveness reduced; simultaneous contractions not changed R: "Dilation in the region of myotomy"	Morbidity: 3 gastroesophageal reflux complications (2 strictures, 1 esophagitis); 1 hiatal hernia requiring surgery Mortality: 1 died at 1 y after operation (myocardial infarction), most likely unrelated to surgery
Craddock et al. 1966[25]	5	Long esophagomyotomy	NA (3–144)	S: Improvement 100% M: Elimination of hypertonic, repetitive, nonperistaltic waves R: Appearance improved	Morbidity: 1 postoperative dysphagia (required dilation) Mortality: 0
Gillies et al. 1967[26]	7	Esophagomyotomy	NA (up to 36)	S: Improvement 100% M: Synchronous activity persisted; pressure decreased, repetitive and spontaneous activity absent R: NA	Morbidity: None reported Mortality: 0
Ferguson et al. 1969[27]	14	Long esophagomyotomy	57 (6–72)	S: No symptoms 69%; occasional dysphagia 23%; poor outcome 8% M: Simultaneous and repetitive contractions still present, decrease in amplitude R: Continued disordered contractile activity	Morbidity: 3 dysphagia (1 required surgery) Mortality: 0
Nicks 1969[28]	7	Long myotomy	NA	S: Improvement 86% M: NA R: NA	Morbidity: 1 symptom recurrence (requiring extended myotomy) Mortality: 0

NA=not available.
[a] S=symptoms, M=motility, R=radiology.
[b] This series included the 18 patients reported in the 1960 report by Ellis et al.[18]

residual dysphagia related to a short myotomy), combined with Belsey repair in 17 patients (it is unclear which ones had DES or achalasia). Their overall results after 3 to 45 months (average, 23 months) of follow-up were defined as excellent in 19 of 21 patients. Four of these patients developed reflux, which was severe in two of them, and all four patients had a second surgical procedure, a modified Collis gastroplasty, which controlled the reflux in 2 of the 4 patients. One patient (lost to follow-up 18 months after surgery) developed symptomatic reflux, and another had prolonged gastric emptying. Esophageal motility was carried out 3 months after myotomy in 14 of 21 patients showing a marked reduction in the tone of LES and a reduction of the amplitude of distal esophageal motor activity. From this experience, the authors concluded that reflux is possible when an esophagomyotomy was performed even in the absence of hiatal hernia, thus reinforcing the importance of adding an antireflux operation. No barium studies were available after surgery.

The same group of researchers[31] in 1976 compared the results obtained in the previously described 17 patients treated with myotomy and Belsey repair and a second group of 17 who had myotomy, Belsey repair, and Collis gastroplasty. Eight of 17 patients in the first group developed reflux; none of the second group undergoing gastroplasty had GER. Of note again is that "16 of the 34 patients studied had total disorder of peristalsis," which suggests that nearly half their patients had achalasia. The

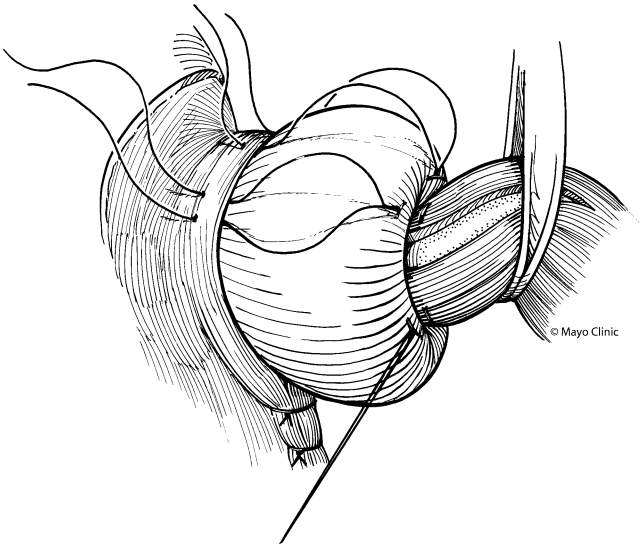

Figure 2 Thoracic view of a long myotomy with a Belsey fundoplication. (From Hinder RA, Rodriguez JA. Epiphrenic esophageal diverticula. In: Kelly KA, Sarr MG, Hinder RA, editors. Mayo Clinic gastrointestinal surgery. Philadelphia: Saunders; 2004. pp. 49–55. Used with the permission of Mayo Foundation for Medical Education and Research).

overall outcome after a mean follow-up of 40 months (range 20–50 months) was considered good or excellent in 28 (82%) of 34 patients. Specifically, 11 (65%) of 17 patients in the first group and all 17 in the second group were deemed to have a successful outcome at mean follow-up of 19 months (range 2–48 months). Eight patients in the first group (without a gastroplasty) developed GER, five requiring gastroplasty. Four patients having gastroplasty developed dysphagia, requiring dilation. Postoperative manometry was not done. Barium swallow studies after surgery showed GER in 47% of patients who had a Belsey procedure and in 14% who had a Belsey procedure plus gastroplasty.

In 1975, Flye and Sealy[32] described their experience with 11 patients with DES treated with long esophageal myotomy (in addition, two had a diverticulum of the lower esophagus excised, and six had an associated sliding hiatal hernia repaired). The diagnosis was based on characteristic esophagograms in all; only three underwent confirmatory esophageal motility studies. After surgery, six patients had "practically" no symptoms, and these results were considered excellent. Five had mild dysphagia and pain and were classified as having fair to good outcomes because their major symptoms were relieved. In three patients who underwent excision of a diverticulum, symptoms of regurgitation were relieved, but "mild dysphagia and pain" persisted. No manometric data were available postoperatively. Barium radiographic studies showed continued, but less disorganized, motor activity of the lower esophagus.

In 1977, Leonardi et al.[11] retrospectively reviewed 11 patients with a diagnosis of DES (radiographically and manometrically) in whom extended esophagomyotomy with preservation of the LES was performed to avoid an antireflux procedure. After a mean follow-up of 38.5 months (range 12–70 months), 10 of 11 patients had clinical improvement, and only one patient developed postoperative GER. Manometric follow-up was available in 10 patients, which showed decreased amplitude in the incised esophagus. In most, the repetitive and prolonged features of the abnormal contractions were replaced by spontaneous feeble waveforms. The mean resting LES pressure was reduced from 20 to 13 mmHg, but LES function was unaltered. This small study suggested that LES-sparing myotomy may be effective for DES while also preventing the occurrence of postoperative GER. Radiographic evaluations showed "slightly widened atonic area at the myotomy site." In this study, one death occurred at 1 year from a myocardial infarction, again unlikely related to surgery.

In 1982, McGiffin et al.[33] described eight patients with clinical and radiographic features of DES (esophageal manometry was available in only four of them). All patients underwent long esophagomyotomy with sparing of the LES, with immediate relief of symptoms and adequate passage of barium in all. Good results were achieved in six patients (75%) at follow-up ranging from 6 to 72 months; two patients had acute and transient recurrence of painful dysphagia, and another two developed slowly progressive recurrence of their dysphagia, requiring a modified Heller

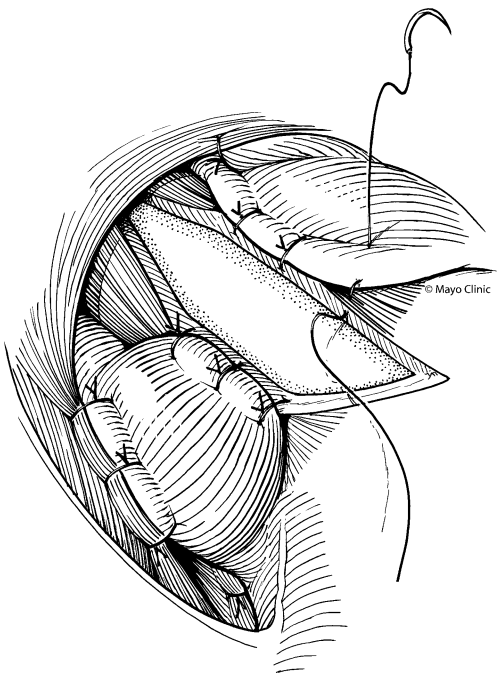

Figure 3 Abdominal view of a Heller myotomy with a Toupet fundoplication. (From Hinder RA, Rodriguez JA. Epiphrenic esophageal diverticula. In: Kelly KA, Sarr MG, Hinder RA, editors. Mayo Clinic gastrointestinal surgery. Philadelphia: Saunders; 2004. pp. 49–55. Used with the permission of Mayo Foundation for Medical Education and Research).

myotomy in one and esophageal dilation in the other. No postoperative motility studies were available. Barium tests showed "an inert esophagus with adequate drainage and no GER."

In 1982, Henderson and Ryder[34] evaluated 63 patients who underwent extended esophagomyotomy to the apex of the chest and distally through "the high pressure zone" of the LES. In addition to myotomy, a hiatal hernia repair was used for reflux control using different procedures: Belsey fundoplication in 20, partial fundoplication gastroplasty in nine, total fundoplication gastroplasty in 19, and modified short Nissen fundoplication in 15. In 60 patients, the diagnosis was made manometrically using the criteria of Vantrappen et al.[35]; three other patients were included in the series after "confirming esophageal muscle hyperplasia and motor spasticity at the time of surgery." Seven patients had no peristalsis at manometry, raising the concern of possible achalasia. Mean follow-up was 6 years (range 1–11.7 years). In patients who had Belsey fundoplication, 8 (38%) became asymptomatic, 2 (9.5%) had minor residual symptoms, and 10 (47.6%) had unsatisfactory results. In the nine patients who had partial fundoplication gastroplasty, 6 (67%) were asymptomatic, 2 (22.2%) had minor residual symptoms (mild reflux), and 1 (11.1%) had continuous severe reflux. In the 19 patients treated by total fundoplication gastroplasty, 12 (63.1%) were asymptomatic, 6 (31.5%) had minor residual symptoms, most of them had residual dysphagia, and 1 (5.2%) had major dysphagia. Of the 15 patients treated by a modified short Nissen fundoplication, 13 (86.5%) were asymptomatic and 2 (13.3%) had minor residual dysphagia. Thus, this series suggested that the addition of an antireflux surgical procedure to a myotomy (except for a Belsey procedure) seems effective, providing a high improvement rate with a modest rate of postoperative dysphagia or GER. Postoperative manometry, available in 70% of the patients, showed persistent "disordered motor activity in 96% of the subjects" and decreased LES pressures. GER was shown by barium swallow in three patients after a Belsey operation and two patients who had partial fundoplication.

Henderson et al.[13] also published in 1987 one of the series with the longest mean follow-up of 90 months (7.5 years) (range 5–10.7 years). Thirty-four patients, evaluated by radiology (82.4%) and manometry (62%) using the classification proposed by Vantrappen et al.[35], underwent surgery. The length of the myotomy was from the distal part of the LES to beyond the aortic arch to the apex of the chest (most proximal intrathoracic esophagus). To prevent GER in the 16 initial patients, a gastroplasty was added to a short fundoplication; in the latter 18 patients, the gastroplasty was avoided and the patients had a short Nissen fundoplication only. Thirty-two patients (94%) had a satisfactory response ("88% excellent results, 5.9% mild dysphagia"), and results in 2 (6%) were regarded as unsatisfactory or failures. Follow-up by radiology was available in 82.4% and with manometry in 62%. The manometry studies showed that the esophageal body contraction amplitudes were reduced in all patients. LES pressure was decreased in 13 patients and increased in six with a preoperative low pressure. Radiographic studies demonstrated "no recurrence of GER or hiatal hernia."

Ellis[36] in 1992 reported a series of 42 patients with chest pain; 28 received a diagnosis of DES (13 also had hypertensive LES), and the remainder had various non-DES-related spastic motility disorders. An esophagomyotomy was performed in 34, including those 28 with DES; the length of the myotomy was restricted to the affected esophageal portion previously demonstrated by manometry. They included LES in the myotomy only if it was hypertensive. This report includes no description of how the diagnosis of DES was established. The overall rate of improvement at median follow-up of 5.8 years was 70% for the entire group, but it is not specified how many of these patients had DES only. Only one patient developed postoperative reflux. The authors underscore the importance of LES-sparing myotomy unless the sphincter is hypertensive (ie, pressure greater than 45 mmHg). Neither manometry nor barium studies were available postoperatively.

Also in 1992, Eypasch et al.[14] presented a prospective study with 2 years of follow-up describing 19 patients with symptomatic DES unresponsive to medical treatment. The manometric criteria used were consistent with current-day criteria.[1] Eleven of the 19 patients had increased esophageal acid exposure. Fifteen of these patients underwent a long esophageal myotomy with an antireflux procedure (Dor). Four patients with multiple previous esophageal procedures (myotomies, antireflux surgeries) had an esophagectomy, with colon interposition in three and an esophagogastrostomy in another who had poor collateral colon blood supply. Eleven of 14 patients who had a myotomy had symptomatic improvement; 12 of 14 patients reported "definite improvement in eating ability and would have the operation again if faced with the decision." Manometry, both standard and 24-h techniques, showed a considerable reduction in the amplitude of esophageal body contractions, a decrease in the frequency of simultaneous contractions, and the elimination of multipeaked waves after myotomy. Improvement in the symptom scores in the patients who had esophagectomy (follow-up available in 3 of 4) was comparable, with the best improvement in subjects with myotomy. Postoperative barium studies were not available. On the basis of these results, the authors suggested the value of myotomy plus an antireflux procedure is comparable in outcome to an esophagectomy and colon interposition as the procedure of choice in patients with multiple previously failed myotomies. The small sample size of the

Table 2 Surgical Series of the 1970s to the 1990s Using Antireflux Surgery and LES Myotomy

Source	No. of Patients	Surgical Technique	Mean Follow-up, mo (Range)	Outcome[a]	Morbidity and Mortality
Bombeck et al. 1972[29]	12 (6 DES, 6 DES reflux)	Fundoplication: Nissen, Belsey, or Hill	≥12 (NA)	S: Improvement: DES 17%; DES and reflux 34%	Morbidity: Symptoms persisted: DES 83%; DES and reflux 67%
				M: NA	Mortality: NA
				R: NA	
Henderson et al. 1974[30]	21 (12 had probable achalasia	Extended esophagomyotomy and Belsey (n=17)	23 (3–45)	S: Excellent in 90%	Morbidity: Myotomy and Belsey: 4 reflux (2 requiring modified Collis gastroplasty) Overall: 1 with GER (lost to follow-up) and 1 prolonged gastric emptying
				M: LES tone and amplitude of distal esophageal motor activity reduced	
				R: NA	Mortality: 0
Flye and Sealy 1975[32]	11	Long esophagomyotomy and hiatal hernia repair: Belsey (n=3), Allison (n=3)	NA (up to 120)	S: No symptoms 55%; mild symptoms 45%	Morbidity: 5 dysphagia (1 required dilation)
				M: NA	
				R: Continued disorganized motor activity	Mortality: 0
Henderson and Pearson 1976[31b]	34 (16 had probable achalasia)	Long esophagomyotomy and Belsey (n=17) Long esophagomyotomy and Belsey plus Collis gastroplasty (n=17)	40 (20–50)	S: Overall improvement 93%; Belsey 65%; Belsey and Collis gastroplasty 100%	Morbidity: Belsey, 8 GER (5 required gastroplasty); Belsey and Collis gastroplasty, 4 dysphagia (required dilation)
			19 (2–48)	M: NA	
				R: GER 47% after Belsey; 14% after Belsey and Collis gastroplasty	Mortality: 0
Leonardi et al. 1977[11]	11	Long esophagomyotomy "with LES sparing"	38.5 (12–70)	S: Improvement 91%	Morbidity: 1 esophagitis; 1 heartburn
				M: Repetitive and prolonged waves replaced by spontaneous feeble waves; LES pressure and contraction amplitude decreased	Mortality: 1 (myocardial infarction at 1 y), probably unrelated to surgery
				R: Myotomy site slightly atonic	
McGiffin et al. 1982[33]	8	Long esophagomyotomy "with LES sparing"	NA (6–72)	S: Improvement 75%	Morbidity: 2 transient painful dysphagia; 2 dysphagia (1 required dilation; 1 required surgery)
				M: NA	
				R: "Inert esophagus" with adequate drainage, no GER	Mortality: 0
Henderson and Ryder 1982[34]	63 (7 probable achalasia)	Esophagomyotomy and Belsey (n=20)	72 (12–139)	S: Improvement: Belsey 38%; partial fundoplication 67%; total fundoplication 63%; Nissen 87%	Morbidity: Belsey: 10 GER; 8 dysphagia; partial fundoplication: 1 GER; total fundoplication: 6 dysplagia; Nissen: 2 dysphagia
		Partial fundoplication and gastroplasty (n=9)		M: Available in 70%; decrease in LES tone; disordered motor activity	Mortality: 0

Table 2 (continued)

Source	No. of Patients	Surgical Technique	Mean Follow-up, mo (Range)	Outcome[a]	Morbidity and Mortality
				rose from 80% (preoperatively) to 96% (postoperatively)	
		Total fundoplication and gastroplasty (n=19)		R: 2 hernia recurrence; 3 GER with Belsey; 2 GER with partial fundoplication	
		Nissen (n=15)			
Henderson et al. 1987[13]	34	Long esophagomyotomy and Nissen and Collis gastroplasty (n=16)	90 (60–127)	S: Improved in 94%	Morbidity: 2 thoracic duct fistula (1 required surgery); 1 residual pain and mild dysphagia; 3 dysphagia with gastroplasty (1 required colon interposition and several dilations)
		Nissen (n=18)		M: Available in 62%; contraction amplitude reduced	
				R: Available in 82%; "no recurrent hernia or GER"	Mortality: 0
Ellis 1992[36]	28	Esophagomyotomy (LES included only if hypertensive)	70 (median) (NA)	S: Improvement 70% M: NA	Morbidity: 1 GER; 5 persistent pain; 1 persistent dysphagia; 2 evolved into achalasia requiring LES myotomy
				R: NA	Mortality: 0
Eypasch et al. 1992[14]	19	Long esophagomyotomy and Dor (n=15)	24 (8–156)	S: Overall improvement 90%; esophagectomy 100%; myotomy 80%	Morbidity: Myotomy: 1 heartburn; 3 weight loss; 2 dysphagia; 3 chest pain; 4 regurgitation; esophagectomy: 1 heartburn
		Esophagectomy with colon interposition (n=4)		M: Amplitude and frequency of simultaneous contractions decreased, elimination of multipeaked waves	Mortality: 0
				R: NA	

DES=diffuse esophageal spasm, GER=gastroesophageal reflux, LES=lower esophageal sphincter, NA=not available.
[a] S=symptoms, M=motility, R=radiology
[b] This series included 17 patients reported in Henderson et al.[30]

study and the sample's highly selected nature must be taken into account when interpreting these results.

In summary, between 1972 and 1992, 10 surgical series were published involving 177 patients. The studies reported between eight and 63 cases. Data from these studies indicate that the success rate ranged from 17% to 94% with the use of antireflux techniques. The least improvement was noted with Belsey repair. The performance of a fundoplication alone without a myotomy[29] offered poor results and is not recommended. LES-sparing myotomy resulted in 75% to 91% improvement rate. Death occurred in a single case (myocardial infarction at 1 year follow-up, unrelated to surgery). Additional surgical procedures were required in 11 patients; seven patients required subsequent dilations. Similar to the series in the 1960s, despite apparent improvement in symptoms, persistent radiographic and manometric abnormalities were observed. Table 2 summarizes the case series of this era.

1993 and Beyond: Beginning the Era of Minimally Invasive Surgery

Shortly after the introduction of minimally invasive surgery for the treatment of esophageal disorders by Shimi et al.[37] in 1991, Anselmino et al.[15] in 1993 were the first to use minimally invasive surgery (thoracoscopic myotomy) for the treatment of DES. They treated one patient successfully with resolution of chest pain and added the Belsey

procedure to protect against reflux. Follow-up was limited to 4 months.

In 1994, Filipi and Hinder[38] described a series of five cases to illustrate the technical considerations and results of thoracoscopic esophageal myotomy for the treatment of esophageal spastic disorders, including three patients with DES (greater than 30% of esophageal body simultaneous waves at manometry), one with achalasia, and one with nutcracker esophagus (NE). Patients underwent myotomy (distal extension 1 cm beyond the apparent gastroesophageal junction and proximally to the level of the aortic arch), adding modified Dor fundoplication in all but one patient. Focusing on the three patients with DES, at 6 months' follow-up, two patients "had excellent to good results" and one patient developed postoperative dysphagia secondary to a paraesophageal hernia requiring correction by open thoracotomy. No postoperative manometry or radiographic studies were done.

In 1995, Patti et al.[16] published the results of a study comparing medical treatment with minimally invasive surgery (thoracoscopic myotomy) in patients with esophageal motility disorders. Follow-up was by telephone interviews every 3 months for a mean of 28 months (range 12–45 months). It appears that the total number of DES patients in this study was 11. They combined patients with DES and NE (manometrically documented). Of 30 patients with DES and NE treated medically, only 8 (26%) responded, as assessed by a symptomatic scale interview. Eight (80%) of 10 surgically treated patients had good to excellent results, but it is not possible to distinguish which ones had DES or NE. Manometric and radiographic studies were not done in the postoperative period.

Champion et al.[17] in 1999 reported a comparative analysis of thoracoscopic (n=12) versus laparoscopic abdominal (n=66) esophagomyotomy with fundoplication for patients with motility disorders. The motility disorders included were NE in 26, HLES in 25, achalasia in 14, and DES in 13. All were appropriately documented by contemporary manometric criteria. Specifically, among the 13 DES patients, three had a thoracic Belsey procedure, eight had an abdominal approach-8 Toupet and two Nissen. Mean follow-up was 19 months (range 6–40 months). The report did not provide concrete information as to the specific outcome for patients with DES, but the authors concluded that the "overall symptomatic relief for the entire group" was 81%, favoring the abdominal rather than the thoracic approach in this nonrandomized study with limited follow-up and patients with various motor disorders. No follow-up postoperative manometry or barium studies were reported.

In a subsequent study in 2000, Champion et al.[39] compared the outcomes of a laparoscopic esophagomyotomy with posterior fundoplication between groups of patients with primary motility disorders (achalasia in 12, NE in 12, HLES in 16, and DES in seven). After a mean follow-up of 30.3 months, 81.5% of patients with DES improved. Two patients (28.5%) developed persistent dysphagia or chest pain 6 weeks after surgery, and another patient (14.2%) had recurrent GER. There was no mortality or early morbidity. Late morbidity, more than 6 weeks after surgery, included chest pain in 10 patients (21%), GER in 3 (6%), and recurrent motility disorder (NE) in 2 (4%). The authors found no notable differences in outcomes among groups, although they offered limited data for each motility disorder. They did not perform motility or radiologic follow-up of patients.

In 2002, Nastos et al.[40] evaluated the effects of surgery in eight patients with esophageal spastic disorders plus a diverticulum and in eight patients with spastic disorders alone. Patients underwent manometric diagnosis and were diagnosed as having DES in 12, NE in three, and HLES in one. They performed long esophageal myotomy with an antireflux technique (Belsey in 12 and Nissen in four). The diverticulum disappeared into the myotomy zone in four patients; in two patients it was resected (diverticulectomy), and in another two patients it was suspended and attached to the layers of the transected muscle (diverticulopexy). After a mean follow-up of 81 months (range 12–168 months), patients with DES and associated diverticulum did better (86–100% improvement) versus those who did not have a diverticulum (50–62% improvement). Long myotomy and fundoplication reduced symptoms, and postoperative manometry showed decreased amplitude of contractions, but persistent coordination abnormalities in the distal esophagus. The LES pressure and relaxation "improved." Barium studies showed "clearance of tertiary waves," but stasis and dilation of the esophagus remained unchanged.

In 2005, Patti et al.[41] reported the results of a study in patients with primary esophageal motility disorders. Focusing only on the surgical approach of patients with DES, 19 of 49 patients diagnosed with DES were referred to surgery. They performed thoracoscopic myotomy in five patients and laparoscopic myotomy with fundoplication in 14 patients. The median follow-up was 125 months in the thoracoscopic group and 52 months in the laparoscopic group. Dysphagia was relieved in 80% after thoracoscopic myotomy and in 86% after laparoscopic myotomy. Chest pain was relieved in 75% of patients undergoing thoracoscopic myotomy and in 80% of patients undergoing laparoscopic myotomy. Operative and postoperative data (surgery time, time to diet, and length of hospital stay) were also better in the laparoscopic group, suggesting that laparoscopic myotomy is the treatment of choice in DES. Postoperative studies of manometry or barium tests were not available.

Table 3 1993 and Beyond: The Advent of Minimally Invasive Surgery

Source	No. of Patients	Surgical Technique	Mean Follow-up, mo (Range)	Outcome[a]	Morbidity and Mortality
Filipi and Hinder 1994[38]	3	Thoracoscopic esohagomyotomy and Dor fundoplication	6 (NA)	S: Improvement 67% M: NA R: NA	Morbidity: 1 heartburn, 1 dysphagia requiring surgery (paraesophageal hernia, inadequate crural closure) Mortality: 0
Patti et al. 1995[16]	11 (unclear how many DES vs NE)	Thoracoscopic myotomy (n=10) Laparoscopic, diverticulectomy, and partial fundoplication (n=1)	28 (12–45)	S: Improvement 80% M: NA R: NA	Morbidity: 20% GER; 1 symptom recurrence (requiring surgery); 1 symptoms remained unchanged Mortality: 0
Champion et al. 1999[17]	13	Compared abdominal to thoracic laparoscopic approach esophagomyotomy	19 (6–40)	S: "Overall" 81% favoring abdominal rather than thoracic approach M: NA R: NA	Morbidity: No apparent morbidity reported Mortality: 0
Champion et al. 2000[39]	7	Laparoscopic myotomy and partial fundoplication	30.3 (19–52)	S: Improvement 81.5% M: NA R: NA	Morbidity: 21% persistent chest pain, 6% GER Mortality: 0
Nastos et al. 2002[40]	16 spastic disorder alone in 8 and spastic disorder and diverticulum in 8); only 12 had DES (see text)	Esophagomyotomy and partial fundoplication (n=12)	81 (12–168)	S: Improvement by symptom Dysphagia: DES 62%; DES and diverticulum 86% Chest pain: DES 50%; DES and diverticulum 100%	Morbidity: 2 pulmonary complications (lobar atelectasis, pulmonary edema); 5 heartburn; 3 GER complications (stricture, ulcers, Barrett); 4 remained symptomatic (3 requiring esophagectomy)
		Total fundoplication (n=4)		M: Decreased contraction pressure; resting pressure and LES relaxation improved, persistent abnormalities in distal esophagus R: Clearance of tertiary waves; stasis and dilation remained	Mortality: 0
Patti et al. 2005[41]	19	Thoracoscopic myotomy (n=5)	125 (NA)	S: Improvement by symptom Dysphagia: Thoracoscopic 80%; laparoscopic 86% Chest pain: Thoracoscopic 75%; laparoscopic 80%	Morbidity: 1 perforation (laparoscopic repair) Symptoms persist Thoracoscopic: dysphagia 20%; chest pain 40%
		Laparoscopic myotomy and partial fundoplication (n=14)	52 (NA)	M: NA R: NA	Laparoscopic: dysphagia 14%; chest pain 21% Mortality: 0

DES=diffuse esophageal spasm, GER=gastroesophageal reflux, NA=not available, NE=nutcracker esophagus.
[a] S=symptoms, M=motility, R=radiology

In summary, during this period seven case series describing the laparoscopic surgical approach for the treatment of DES have been published involving approximately 69 cases (range 1–19). Improvement varied between 50% and 86%. No mortality was observed in these series. Surgical reintervention was required in six patients. Only one study[40] performed postoperative manometry and radiography showing decreased contraction amplitudes, but lack of

resolution of the disordered motility characteristic of DES. Table 3 summarizes the case series of this era.

A Recent Report

A publication in 2007 described the use of open laparotomy for DES. Leconte et al.[42] reported surgical results for 1998 through 2004. They used an extended myotomy (including the LES) with anterior fundoplication to treat 20 patients with severe DES via open laparotomy. All patients had barium swallow, endoscopy, and esophageal manometry. The diagnosis of DES was made on the basis of current criteria.[1] Patients were considered surgical candidates when they presented with a severe form of the disease defined on the basis of dysphagia score of 2 or higher (range 0–3) and quality-of-life impairment. In addition, "when LES pressure was above 70 cm H_2O, primary surgery was considered, and secondary surgery when LES pressure was below 70 cm H_2O after failure of endoscopic treatment." The surgical procedure consisted of an extended modified Heller myotomy (12–16 cm above the cardia and 2 cm below) associated with muscular crural closure and anterior fundoplication (Dor procedure). There were no postoperative deaths. Postoperative "relevant" morbidity was 5%; however, one patient showed delayed gastric emptying, and two patients had asymptomatic pleural effusions (15%). Overall median follow-up was 50 months (range 6–84 months). Global excellent or satisfactory results (graded according to symptomatic scores) were found in 16 (80%) of 20 patients, 18 (90%) of 20 patients with dysphagia, and all 20 (100%) of those with chest pain. Two patients with persistent symptoms at follow-up showed postoperative GER during pH testing. No postoperative manometry or barium studies were described.

Summary and Conclusions

Despite the recognition of DES for more than a century, its treatment remains challenging. Surgical series to date include few patients, different techniques, and variable periods of follow-up. Some studies seem to have included patients with achalasia. The difficulty of analyzing the available studies is compounded because the patients with DES have undergone extensive attempts at medical therapy. It is unknown what proportion of patients with DES reach this stage. It is also unclear what criteria should be used to define "medical failure." These observations raise the question of whether patients with DES treated earlier in the course of the disease with surgery would have a different outcome. Therefore, the surgical outcome must be viewed with the understanding that virtually all published series represent highly selected populations. For the most part, the published data suggest that the surgical outcome provides an overall beneficial effect, but outcomes are variable. In addition, there are no randomized clinical trials comparing the effects of medical and surgical therapies. Most surgeons have used a myotomy as the procedure of choice (usually combined with an antireflux procedure). The majority of series come from tertiary centers, highly skilled in the surgical treatment of diseases of the esophagus. Whether the good results reported in these series can be reproduced by surgeons outside referral centers is unknown. The surgical repair rarely induces restoration of normal peristalsis or complete resolution of the radiographic appearance. These data indicate that restoration of motility and relief of symptoms may not be related, and incidental dissection or division of intramural nerve fibers may account for symptom relief. The role of surgery in the management of patients with DES requires further study for better understanding of the neurosensory abnormalities observed in these patients. Controlled trials, however, may be difficult to do, given the rarity of the disorder.

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Adenoma of the Major Duodenal Papilla with Intraductal Extension into the Lower Common Bile Duct

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Abstract Although benign and malignant tumors of the major duodenal papilla can be detected endoscopically, definitive diagnosis of such lesions by histologic examination of biopsy specimens is sometimes difficult, especially in cases with intraductal extension into the bile duct or pancreatic duct. We herein report a case of adenoma of the major duodenal papilla showing an intraductal extension into the lower common bile duct that necessitated pylorus-preserving pancreaticoduodenectomy.

Keywords Adenoma · Major duodenal papilla · Intraductal extension · Pancreaticoduodenectomy · Lower bile duct

Case Report

A 62-year-old woman with an elevated lesion at the major duodenal papilla was admitted to our hospital for further examination and treatment. Laboratory values upon admission were within normal limits, and carcinoembryonic antigen and carbohydrate antigen 19–9 levels were within normal limits. Computed tomography (CT) showed an elevated mass, 1.5 cm in diameter, at the major duodenal papilla, and the lesion extended into the lower bile duct. Upper gastrointestinal endoscopy revealed a nodular elevated lesion at the major papilla, and endoscopic retrograde cholangiography (ERC) showed a filling defect in the lower bile duct, 1 cm in length; thus, intraductal extension into the lower bile duct was suspected (Fig. 1). Involvement of the major pancreatic duct was not observed with ERC. Intraductal ultrasonography was then performed, revealing an isoechoic mass at the major papilla continuing to the lower common bile duct. Celiac angiography showed no tumor stain, but CT angiography showed strong enhancement at the site corresponding to the tumorous lesion of the major papilla. A biopsy specimen from the papillary tumor consisted of tubules lined by tall columnar epithelial cells, and papillary growth with focal nuclear stratification was observed. No invasive growth was seen in this specimen, and adenoma was diagnosed. Positron emission tomography with fluorodeoxyglucose showed uptake at the tumorous lesion, suggesting malignancy. On the basis of these findings, a tumor of the major papilla with intraductal extension into the lower common bile duct was considered likely. Surgical treatment was planned, although malignancy was not diagnosed conclusively before surgery by repeated histologic examination.

Upon laparotomy, no ascites was seen, and no lymph node metastasis was detected. Pylorus-preserving pancreaticoduodenectomy (PD) with lymph node dissection was performed.

Gross examination of the resected specimen revealed an elevated lesion, 16×14 mm in the major papilla with intraductal extension into the lower common bile duct. The tumor appeared as a flat elevation, about 10 mm in length, and a region of polypoid protrusion accompanying surface nodularity in the lower common bile duct (Fig. 2). Histologically, the tumor comprised a proliferation of

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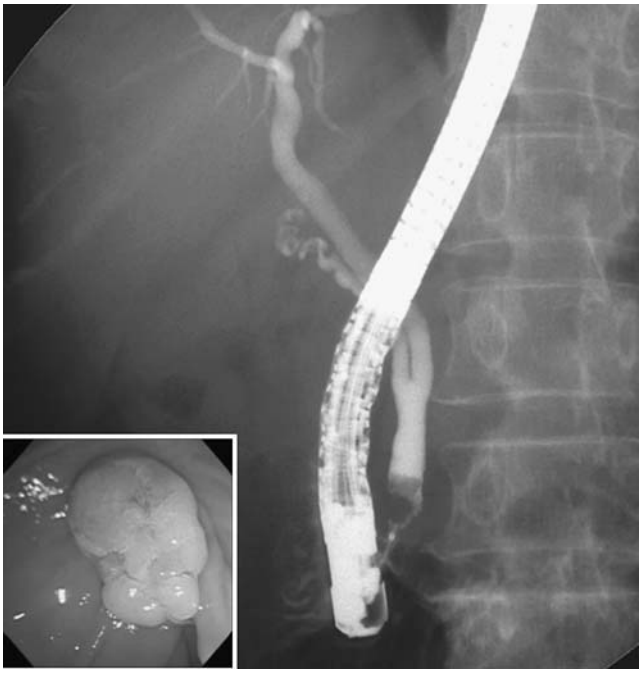

Figure 1 ERC showed a filling defect 1-cm long in the lower bile duct. A nodular elevated lesion (*inset*) was seen at the major duodenal papilla.

tubules lined by tall columnar epithelial cells with elongated nuclei with a focus of severe dysplastic change, but no invasive growth was observed (Fig. 3). Immunohistochemical study showed negative immunoreactivity to p53 stain. There was no metastasis in the dissected lymph nodes. From these histologic findings, the lesion was diagnosed as an adenoma with no conclusive evidence of malignancy.

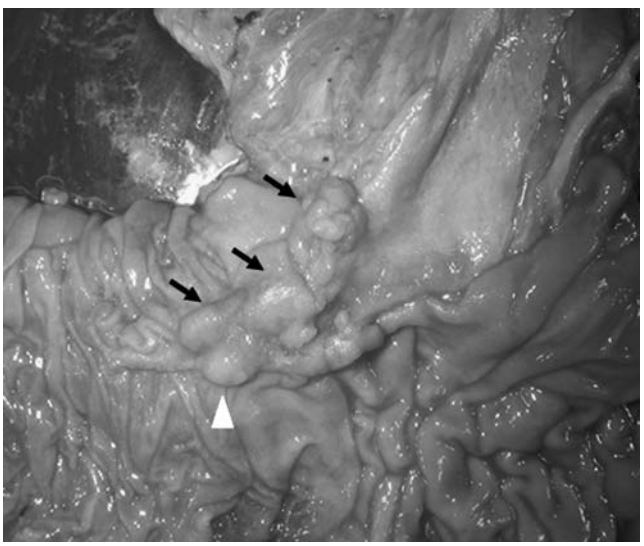

Figure 2 Gross appearance of the resected specimen. The elevated lesion of the major papilla extended directly into the lower bile duct. The tumor is indicated with the *black arrows*, and the major duodenal papilla is indicated with the *white arrowhead*.

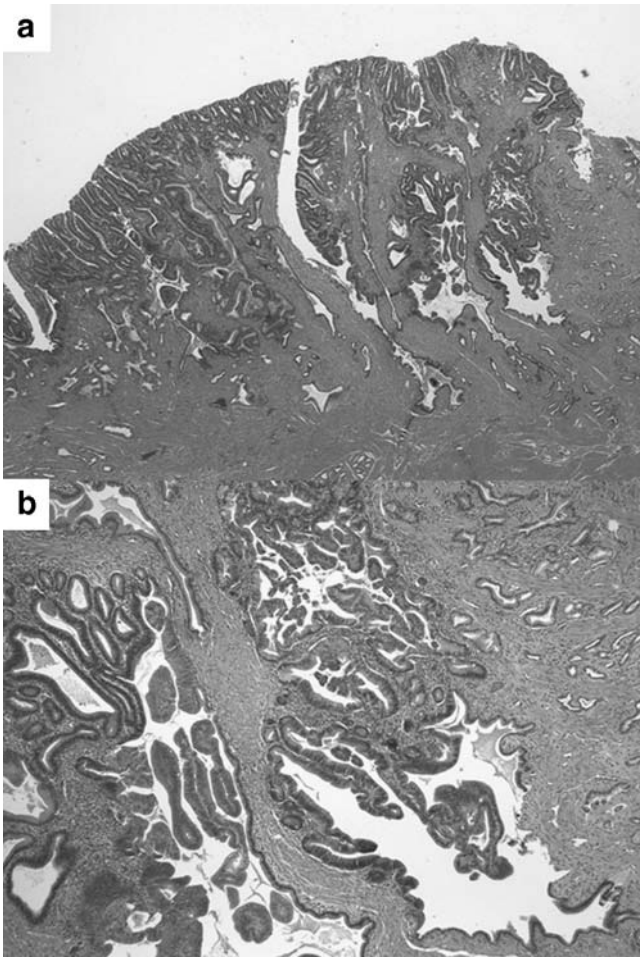

Figure 3 Histologic findings. **a** Proliferation of tubules lined by tall columnar epithelial cells is seen (hematoxylin and eosin stain, original magnification ×12.5). **b** Severe dysplastic change is apparent (hematoxylin and eosin stain, original magnification ×40).

Discussion

It is well known that adenoma of the major duodenal papilla has a potential for malignant transformation. The adenoma–carcinoma sequence seems to be as significant in the small intestine as in the large intestine, and adenoma progresses to carcinoma in up to 30% of cases.[1] The incidence of periampullary cancer is 200 to 300 times greater in patients with familial adenomatous polyposis than in the general population.[2] Nonetheless, neoplasms arising from major duodenal papilla have a relatively good prognosis after resection, showing better 5-year survival rate, from 35 to 46%, than either distal biliary (24 to 27%) or pancreatic head (15%) cancer.[3]

Although legions of the duodenal papilla are identified endoscopically, the definitive diagnosis is relatively difficult even with the use of biopsy. This is owing to the deceptive nature of the ampullary lesion: Adenocarcinoma is occasionally concealed deep within the tumor. The reported accuracy of preoperative biopsy for diagnosing

ampullary neoplasms ranges from 40 to 75%.[4] Up to 50% of villous adenomas at the papilla harbor a focus of adenocarcinoma at the time of diagnosis, and malignancy is likely when there is surface nodularity, increased friability, and spontaneous bleeding during endoscopic examination.[5] In our case, the biopsy specimen was taken from the surface of the major duodenal papilla, resulting in no evidence of malignancy, and it was technically difficult to perform precise biopsy of the protruded portion in the lower common bile duct. However, the morphologic and radiologic features of the lesion were strongly suggestive of malignant tumor with intraductal extension, and thus, surgical treatment was planned from the beginning.

There are an increasing number of reports on endoscopic management of adenoma of the major duodenal papilla. According to analysis of the long-term outcome and safety of endoscopic papillectomy in 103 cases of papillary adenoma at four pancreaticobiliary endoscopy centers, endoscopic treatment was successful in 80% of patients, and success was significantly associated with older age (54> years), smaller lesions (≤3 cm), and sporadic lesions vs genetically determined lesions.[6]

Open transduodenal ampullectomy is applied mainly to benign ampullary neoplasms. Clary et al.[7] reported that ampullary resection with frozen section evaluation is the best way to treat small benign ampullary neoplasms because morbidity associated with ampullary resection is lower than that with PD, and frozen section evaluation is accurate.[7] de Castro et al.[3] also recommend frozen section evaluation in patients undergoing local resection, and if an unexpected malignant neoplasm with advanced invasion exists, conversion to PD can easily be performed at the same time. However, there are limitations to the intraoperative frozen section diagnosis, and it is difficult to differentiate between submucosal and deeper invasion during examination of a frozen section.[3] The appropriate surgical management of high-grade dysplasia remains controversial and should be determined by weighing patient comorbidities against the radicality of the operative procedure.[4]

In general, extension of the tumor into deeper tissue layers, such as the distal common bile duct or pancreatic duct, is regarded as a contraindication for endoscopic resection with a curative intent.[8] Endoscopic resection of benign tumors of the duodenal papilla with intraductal growth has been reported; the rate of cure is 46% in cases with intraductal growth and 83% in cases without intraductal growth, respectively, and the rate at which curative open surgery was added after endoscopic treatment was significantly higher in cases with intraductal growth (37 vs 12%, $p<0.01$).[9] The indication for endoscopic treatment should still be carefully evaluated.

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Peripheral Cholangiocarcinoma with Endoluminal Tumor Thrombus in Main Bile Duct Mimicking a Klatskin Tumor

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Abstract

Background Peripheral cholangiocarcinoma with endobiliary thrombus could be confused with Klatskin tumor, eventually leading to inappropriate therapeutic decision.

Case report A 56-year-old man presented with an obstructive jaundice. Preoperative magnetic resonance imaging (MRI) showed a segment 7 liver tumor associated with a complete stop at the biliary bifurcation compatible with a Klatskin tumor. Surgical exploration revealed that biliary obstruction was caused by endobiliary tumor-related thrombus. A right hepatectomy was performed, allowing complete endobiliary thrombus extraction. At pathology, a T2N0 intrahepatic cholangiocarcinoma was demonstrated. No adjuvant chemotherapy was given and currently, 22 months after surgery, the patient remains disease free.

Discussion This case underlines the fact that intraductal growth of peripheral cholangiocarcinoma does not represent a contraindication for surgical treatment. MRI could be useful to differentiate such presentation of peripheral cholangiocracinoma from Klatskin tumor and orientate the surgical treatment.

Keywords Cholangiocarcinoma · Peripheral · Klatskin · Endobiliary · Thrombus · Surgery

Introduction

Intrahepatic or peripheral (IHCC) should be clearly differentiated from Katskin tumors, which involved the biliary bifurcation and required extended liver resection. We report herein a case of a patient with IHCC associated with obstructive jaundice caused by endoluminal thrombus in the main bile duct. In such presentations, confusion with Klatskin tumor could be made and magnetic resonance imaging (MRI) may be essential for accurate preoperative diagnosis.

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Case Report

A 56-year-old man was admitted with jaundice and right upper quadrant abdominal pain. MRI showed a 45-mm tumor in segment 7 associated with a complete stop on bile duct confluence, with separation of left and right anterior and posterior ducts, suggesting a Klatskin tumor. However, the bulging aspect of this interruption at the level of the left duct was found compatible with the presence of an endobiliary tumor thrombus (Fig. 1). Surgical exploration confirmed the diagnosis of peripheral cholangiocarcinoma with intraductal growth (type C classification of "Liver Cancer Group of Japan"[1]), and consecutively, in the absence of other tumor locations, a right hepatectomy was performed. When the right bile duct was opened at the end of parenchymal transsection, the entire tumor thrombus bulging until biliary main bifurcation was extracted (Fig. 2). Because of the presence of low-grade dysplasia at extemporaneous pathological examination of the right bile duct section margin, the main bile duct was resected up to the pancreas head and roux-en-Y hepaticojejunostomy on the left bile duct was performed. Histopathological examination of the specimen confirmed the diagnosis of

well-differentiated intrahepatic cholangiocarcinoma of 45 mm with endobiliary tumor thrombus in continuity, without nodal invasion (T2N0 from UICC classification). No adjuvant therapy was given and currently, 22 months after surgery, the patient remains disease-free.

Discussion

IHCC remains an uncommon liver cancer carrying a poor overall prognosis.[2] In the absence of extrahepatic dissemination, a complete surgical resection represents the only potentially curative option.[3] The particular form of peripheral cholangiocarcinoma presenting with obstructive jaundice has been rarely described.[4, 5] Jaundice in these cases could be related to tumor-associated thrombus, free-floating tumor debris or emboli, or mucobilia. In these last two instances, jaundice could be intermittent.[5] The case presented here illustrates that obstructive jaundice, caused by intraductal tumor growth from the intrahepatic cholangiocarcinoma, does not necessarily represent a harbinger of advanced disease and a contraindication for surgery. For treatment, this entity should be clearly differentiated from Klatskin tumors, in which the presence of direct tumor infiltration of the biliary bifurcation indicates extended resection including segments 1 and 4. As in the present case, accurate examination of MRI and identification of the characteristic bulging aspect of the endobiliary thrombus could be essential to differentiate peripheral cholangiocarcinoma with intraductal growth from Katskin tumor and therefore, to establish the surgical strategy.

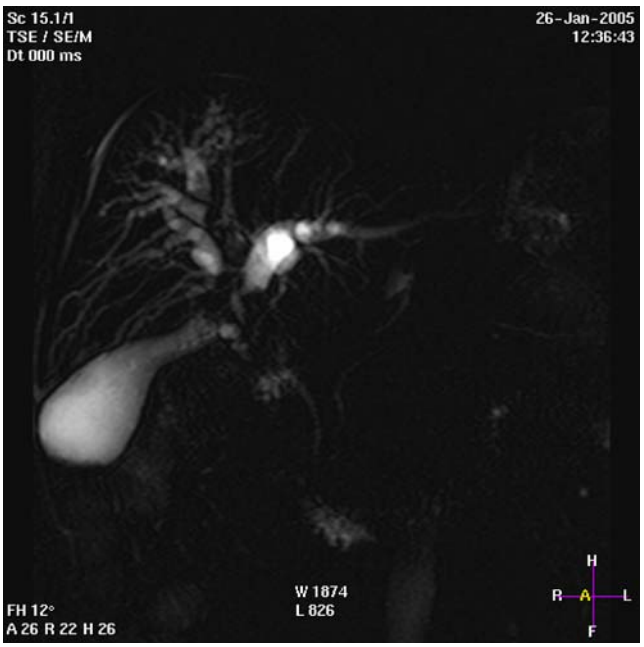

Figure 1 Magnetic resonance imaging showing an abrupt interruption at biliary confluence with division of anterior and posterior right ducts mimicking a Klatskin tumor. The bulging aspect of the obstruction in the left hepatic duct corresponds to tumor-related endobiliary thrombus.

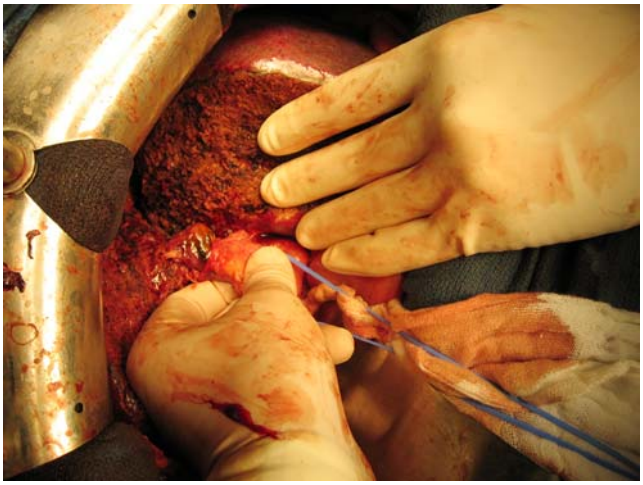

Figure 2 After parenchymal transsection, extraction of the biliary tumor thrombus by gentle manual pressure. The intrahepatic main tumor and tumor thrombus remained attached during the entire dissection.

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