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Predicting Stricture in Morbidly Obese Patients Undergoing Laparoscopic Roux-en-Y Gastric Bypass: A Logistic Regression Analysis

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Abstract Gastrojejunostomy stricture after Roux-en-Y gastric bypass occurs in 3 to 27% of morbidly obese patients in the USA. We questioned whether preoperative patient characteristics, including demographic attributes and comorbid disease, might be significant factors in the etiology of stricture. In this study from November 2001 to February 2006 (51 months), at a high-volume bariatric center, of the 1,351 patients who underwent laparoscopic gastric bypass, 92 developed stricture (6.8%). All but two were treated successfully by endoscopic dilation. All patients stopped nonsteroidal anti-inflammatory medications 2 weeks prior to surgery and did not restart them. The operative procedure included the use of a 21-mm transoral circular stapler to create the gastrojejunostomy; the Roux limb was brought retrogastric, retrocolic. In an effort to reduce our center's stricture rate, late in the study, U-clips used at the gastrojejunostomy were replaced by absorbable sutures, and postoperative H_2 antagonists were added to the treatment protocol. The change to absorbable polyglactin suture proved to be significant, resulting in a lower stricture rate. The addition of H_2 antagonists showed no significant effect. Following the retrospective review of the prospective database, univariate and multivariate logistic regression analyses identified factors associated with the development of stricture. Gastroesophageal reflux disease and age were each shown to be statistically significant independent predictors of stricture following laparoscopic gastric bypass.

Keywords Obesity · Bariatric surgery · Stricture · Gastric bypass · Gastrojejunostomy

Introduction

Bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB), has been proven safe[1,2] and effective in achieving long-term weight loss,[3,4] comorbidity reduction,[3,5] and enhancement of quality of life.[6] Since its introduction by Wittgrove et al. in 1994,[7] laparoscopic Roux-en-Y gastric bypass (LRYGB) has been shown to be as reliable as open RYGB[8–10] and less traumatic, requiring a briefer recovery time and shorter duration of stay.[11] It is effective in achieving comparable weight loss at 1 year[3,12–15] and is successful in reducing the comorbidities of morbid obesity.[3,9,13] Laparoscopic RYGB has surpassed other weight-loss methods for the morbidly obese in frequency of use in the USA.[14]

Laparoscopic RYGB is a technically demanding procedure with a lengthy learning curve of approximately 100 cases.[16,17] Gastrojejunostomy stricture following RYGB has been reported variously in 3 to 27% of patients.[12,16–19] Actual incidence of this complication is a function of the accuracy of its diagnosis and reporting[19] and has been shown to be relative to operative technique and surgeon experience.[20] Other known etiologies of stricture following LRYGB are tension on the anastomosis, foreign body reaction, technical error in creation of the anastomosis, marginal ulcer, and leak with associated scarring.[19]

In 2003, Perugini and colleagues published an analysis of preoperative predictors of complications.[20] They reported a 14.4% rate of gastrojejunostomy stricture (N= 27/188), greater than half of all complications. With

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multivariate analysis by stepwise logistic regression, they found that surgeon experience was the most significant predictor of complications in general (not of stricture specifically) and that sleep apnea and hypertension were also significant independent predictors of complications.[20] Perugini et al. cautioned that the factors they identified (experience, sleep apnea, hypertension) as predictive of complications in general might, in fact, " be specific for the complication of gastrojejunal stenosis".[20] Our study took up this question and, by univariate and multivariate logistic regression, analyzed preoperative predictors *specifically for stricture*.

Patients and Methods

Patients

A consecutive series of morbidly obese patients underwent LRYGB between November 12, 2001, and February 28, 2006 (51 months), in a dedicated, community-based, bariatric program awarded Center-of-Excellence status by the Surgical Review Corporation in 2005.

Institutional review board approval and informed consent were obtained prior to prospective data collection. In a retrospective analysis, preoperative patient characteristics, including whether the patient was taking any nonsteroidal anti-inflammatory medications on a chronic basis prior to surgery, were compared for two groups: those who developed gastrojejunostomy stricture (N=17/92, 6.8%) and those who did not (N=311/1,259, 93.2%). No patients were excluded from the study.

Patients where tested for *Helicobacter pylori* and treated if positive. Anti-inflammatory medications were withheld 2 weeks preoperatively and not resumed postoperatively. Procedures were performed by four bariatric surgeons. Stenosis, or stricture, indicated by progressive dysphagia, nausea, and vomiting, was diagnosed by endoscopy.

Surgical Technique

The procedure was performed using the transoral end-to-end anastomotic (EEA) technique similar to the Wittgrove technique.[10] Using a Veress needle to an intra-abdominal pressure of 15 mm Hg, abdominal insufflation was performed. The patient was placed supine, in the reverse

Table 1 Univariate Analysis to Identify Preoperative Patient Characteristics Associated with Stricture

Variable	Stricture Group [N (%)]	Nonstricture Group [N (%)]	P Value
No. patients (N=1,351)	92	1,259	
Age, mean (SD)	41.4 (11.6)	44.4 (10.4)	0.039[a]
Cardiac disease	6 (6.5)	107 (8.5)	0.885
Chronic depression	21 (22.8)	278 (22.1)	0.634
Chronic respiratory disease	22 (23.9)	318 (25.3)	0.766
Chronic venous insufficiency	53 (57.6)	692 (55.0)	0.347
Degenerative joint disease	89 (96.7)	1,209 (96.0)	0.893
Diabetes, type 2	26 (28.3)	307 (24.4)	0.184
Ethnicity, N (%)	–	–	0.145
Caucasian	76 (82.6)	1,122 (89.1)	–
Other	16 (17.4)	137 (10.9)	–
GERD	66 (71.7)	715 (56.8)	0.035[a]
Sex, N (%)	–	–	0.208
Female	81 (88.0)	1,042 (82.8)	–
Male	11 (12.0)	217 (17.2)	–
Hypercholesterolemia/hyperlipidemia	40 (43.5)	624 (49.6)	0.958
Hypertension	41 (44.6)	652 (51.8)	0.838
Infertility	11 (12.0)	96 (7.6)	0.732
Nonsteroidal anti-inflammatory medications	17 (18.5)	294 (23.4)	0.284
No. preoperative comorbidities	5.2 (2.0)	5.1 (1.9)	0.259
No. preoperative medications	4.6 (3.6)	4.2 (3.5)	0.088
Obstructive sleep apnea	43 (46.7)	564 (44.8)	0.415
BMI	48.5 (8.5)	49.2 (8.3)	0.202
Fasting blood sugar	111.5 (45.4)	108.9 (39.6)	0.779
HbA1C	6.2 (1.8)	6.1 (1.2)	0.150
Previous abdominal surgeries	1.2 (1.1)	1.2 (1.3)	0.754
Urinary stress incontinence	52 (56.5)	698 (55.4)	0.322

[a] Significance at the 0.05 level

Trendelenburg position, and six abdominal trocars were introduced. The angle of His was dissected, and a 15-ml balloon was passed transorally and placed at the esophagogastric junction. The lesser sac was entered just below the balloon on the lesser curve of the stomach. A 15- to 20-ml gastric pouch was created with the Endo GIA 45-mm stapler (Ethicon Endo-Surgery, Cincinnati, OH, USA), using an average of three firings. A guidewire was introduced through the anterior abdominal wall and an endoscope was passed transorally. Cautery was used to pass the snare through the pouch and grasp the guidewire. The anvil of the 21-mm EEA Stealth stapler (Ethicon Endo-Surgery) was attached to the guidewire and brought down through the mouth. The ligament of Treitz was identified, and, approximately 20 cm distally, the jejunum was divided. A 100-cm Roux limb was created for patients with BMI<55 kg/m^2, and a 150-cm Roux limb was created for patients with BMI≥55 kg/m^2. The jejunojejunostomy was stapled side to side, and closed with the Endo GIA stapler. The Roux limb was brought retrocolic, retrogastric through the lesser curve of the stomach. The EEA circular stapler was introduced through the abdominal wall and the gastrojejunostomy was stapled end to end. The posterior wall of the gastrojejuostomy lays on soft tissue that holds the left gastric and vagus nerve and does not need reinforcement. All techniques for reinforcing the gastrojejunostomy were instituted only in the anterior wall of the anastamosis as a second layer. The initial technique was to sew a continuous second layer of the gastrojejunostomy anteriorly with 3–0 polyglactin absorbable suture. The angle is often technically demanding. In October 2005, the procedure was modified to one in which the gastrojejunostomy was oversewn with two Nitinol "U" clips that revert to preformed circular memory when placed, without additional suture. In October of 2005, these U-clips were replaced with two interrupted 3–0 polyglactin absorbable sutures. Finally, in January 2006, the addition of H_2 antagonists for 90 days to the postoperative regimen was made. These technical changes were instituted in an attempt to lessen the stricture rate, which is followed monthly in our database.

Patients who experienced persistent postoperative nausea, vomiting, and intolerance to solid food were referred for upper gastrointestinal studies, followed by referral to the gastroenterologist for upper endoscopy. Patients with stricture were treated endoscopically with balloon dilation to a maximum of 15 mm.

Statistical Methods

Patient data were collected prospectively and included preoperative patient demographics and comorbidities, as well as postoperative complications extracted to identify potential influences on stricture rates. Variables included in the univariate logistic regression analysis are listed in Table 1.

The SPSS™ software package (version 14.0, SPSS, Chicago, IL, USA) was used to perform all statistical analyses. Statistical significance was set at $P<0.05$. Binary logistic regression analysis was used in both univariate and multivariate modeling to identify independent preoperative variables associated with the development of gastrojejunostomy stricture following LRYGB surgery. Univariate analysis using logistic regression was applied to identify significant associations with the dichotomous outcome variable (stricture). For comparison, Pearson chi-square test for categorical variables and Student's t test for continuous variables were used. A priori preoperative factors of research interest ($P<0.21$), as well as those found to be significantly associated with stricture ($P<0.05$), were entered into multivariate analysis using forward stepwise logistic regression. Likelihood ratio tests were used for variable selection.

In the initial analysis of preoperative characteristics by univariate logistic regression, age, number of comorbidities, number of medications, BMI, fasting blood sugar, HbA1C, and previous abdominal surgeries were classified as continuous variables. With the exception of sex and ethnicity (dichotomized to male/female and Caucasian/non-Caucasian, respectively), all remaining variables were dichotomized (yes/no). In the final multivariate forward stepwise logistic regression model, both age and BMI were redefined as categorical variables: age was coded to reflect four levels (≤35, 36 to 45, 46 to 55, and ≥55 years) and BMI was coded to reflect two levels (<50 and ≥50).

Results

From November 12, 2001, to February 28, 2006 (51 months), 1,351 patients underwent LRYGB at a single institution. Mean preoperative patient age was 44 years, mean BMI was 49 kg/m^2, 83% of patients were female, and mean preoperative weight was 305 lb. Patients were predominantly Caucasian (89%); 7% were Hispanic; 3% were African American; and 1% were of Native American, Asian/Pacific, and other ethnicities.

Operative technique was the same in all procedures, namely, a retrocolic, retrogastric, transoral, 21-mm, circular stapled gastrojejunostomy. Mean intraoperative time was 96 min and length of stay averaged 2.8 days; 97.6% of operations were accomplished laparoscopically and 2.4% were conversions to open procedures. There were two reoperations with revision of the gastrojejunostomy in the "stricture group." The first was in a patient who developed a leak immediately postoperatively and returned to the OR

for definitive management. The patient developed a stricture that was not amenable to dilation and, at 7 months, underwent a revision of her gastrojejunostomy. The second patient had a stricture that was dilated to 12–15 mm. Subsequent endoscopy showed no recurrent stricture. She continued to eat very large portions in multiple meals, developing recurrent bezoars that had to be cleared endoscopically. The pouch dilated over time, and even though the gastrojejunostomy was shown to be only large enough to pass an endoscope, we were obliged to revise the pouch to a smaller size. Since that time she has had no further problem with bezoars.

There were no deaths in the stricture group. In the "nonstricture group," early mortality was 0.2% (two deaths <31 days postoperatively); intermediate mortality, 0.3% (four deaths between 31 and 90 days postoperatively); and late mortality, 0.4% (five deaths >90 days postoperatively). Ninety-two patients (6.8%) were diagnosed with stricture and underwent subsequent endoscopic dilation. Seventeen of 92 stricture patients (18.5%) were on nonsteroidal anti-inflammatory medications prior to surgery, whereas 294 of the 1,259 (23.4%) nonstricture patients were on nonsteroidal anti-inflammatory medications prior to surgery (Table 1). The difference in stricture rates between these two groups was not significant.

Our rate of stricture (92/1,351, 6.8%) was in the range of rates previously reported by Higa et al. (5.3%), Schauer et al. (4.7%), and DeMaria et al. (6.6%), as compiled by Perugini[20], at the lower end of the national range of stricture prevalence. Other complications with the highest incidence were cholecystectomy (6.5% stricture group vs 3.0% nonstricture group), small bowel obstruction secondary to internal hernia (4.4 vs 1.9%), and intra-abdominal abscess (3.3 vs 2.0%). In the stricture and nonstricture groups, respectively, leakage occurred in 1.1 and 1.0% of patients, and port site infection occurred in 2.2 and 3.6% of patients. Peripheral neuropathy was 5.4% in the stricture group and 0.5% in the nonstricture group (Table 2).

Mean percent excess weight loss at 1 year following surgery was the same for both groups (−103.1 lb, 82.6% stricture group vs −115.8 lb, 82.0% nonstricture group). Mean numbers of medications were reduced from 4.6 to 1.6 and from 4.2 to 1.5 in the stricture and nonstricture groups, respectively, at the most recent postoperative examination.

By univariate logistic regression analysis, two preoperative characteristics were identified as factors associated significantly ($P<0.05$ level) with stricture: gastroesophageal reflux disease (GERD) ($P=0.035$) and age ($P=0.039$) (Table 1). In addition to GERD and age, BMI ($P=0.202$) and gender ($P=0.208$) were incorporated into the final multivariate analysis. In the first multivariate model (Table 3), with age defined as a continuous variable, forward stepwise multivariate logistic regression confirmed GERD ($P=0.006$, OR=1.917, CI=1.200–3.062) and age ($P=0.010$, OR=0.973, CI=0.953–0.993) to be independent factors associated with stricture. Seventy-two percent of all stricture patients were diagnosed with GERD prior to surgery, and the mean age was 41 years, whereas, in the preoperative nonstricture group, 57% were diagnosed with GERD and the mean age was 44 years.

In the second multivariate model (Table 3), age was classified as a categorical variable to refine our understanding of the impact of age on stricture. Using age group 1 (≤35 years) as the reference category, age groups 2 (36–45 years) and 3 (46–55 years) were significant at the 0.05 level [group 2, $P=0.015$ (OR=0.508, CI=0.294–0.877); group 3, $P=0.004$ (OR=0.431, CI=0.244–0.760)]. GERD remained significant ($P=0.005$; OR=1.963, CI=1.227–3.141).

Three postoperative complications were found to be associated significantly with the presence of stricture by univariate logistic regression, including readmissions within 30 days of surgery ($P=0.000$), peripheral neuropathy ($P=0.000$), and pneumonia ($P=0.031$). The postoperative multivariate model determined readmissions within 30 days of surgery ($P=0.000$, OR=4.381, CI=2.666–7.197) and peripheral neuropathy ($P=0.000$, OR=11.979, CI=3.423–41.929) to be statistically significant covariates of stricture.

Decreasing our rate of stricture by a protocol change to oversewing the gastrojejunostomy with polyglactin was

Table 2 Forward Stepwise Multivariate Logistic Regression Model for Complications of Stricture

Variable	Rate, *N* (%)		*P* Value	Odds Ratio (95% Confidence Interval)
	Stricture Group	Nonstricture Group		
30-day readmission	27 (29.35%)	109 (8.66%)	0.000[a]	4.381 (2.666–7.197)
Cholecystectomy	6 (6.52%)	38 (3.02%)	0.181	NS
Internal hernia	1 (1.09%)	35 (2.78%)	0.337	NS
Small bowel obstruction	4 (4.35%)	24 (1.91%)	0.500	NS
Intra-abdominal abscess	3 (3.26%)	25 (1.99%)	0.691	NS
Peripheral neuropathy	5 (5.43%)	6 (0.48%)	0.000[a]	11.979 (3.423–41.929)
Infection	2 (2.17%)	2 (3.57%)	0.151	NS

[a] Significance at the 0.05 level

Table 3 Significance and Odds Ratios for Age, GERD, Gender, and BMI in Multivariate Models to Predict Stricture

Variable	*P* Value	Odds Ratio (95% Confidence Interval)
Multivariate model #1[a]		
Age	0.010[b]	0.973 (0.953–0.993)
GERD	0.006[b]	1.917 (1.200–3.062)
Gender	0.324	NS
Preoperative BMI	0.086	NS
Multivariate model #2[c]		
Age overall	0.015	
Group 1: ≤35 years (reference category)		1
Group 2: 36–45 years	0.015	0.508 (0.294–0.877)
Group 3: 46–55 years	0.004	0.431 (0.244–0.760)
Group 4: >55 years	0.126	0.596 (0.308–1.156)
GERD	0.005	1.963 (1.227–3.141)
Gender	0.353	NS
Preoperative BMI	0.100	NS

[a] Age classified as a continuous variable
[b] Significant at the 0.05 level
[c] Age classified as a categorical variable

shown, by chi square analysis, to be a significant decrease, with the rate of 6.8% diminishing to 2.8% (P=0.028, OR= 0.358, CI=0.143–0.895). The second protocol adjustment, administration of an H_2 antagonist (prevacid) postoperatively, had no effect.

Discussion

Strictures contribute to almost half of all readmissions in the early perioperative period and require instrumentation and rehydration. They can also be associated with the development of a more serious complication, peripheral neuropathy, as is demonstrated by these data.

Specific intraoperative factors (e.g., surgeon experience) associated with stricture have been identified as causal by prior studies. Isolating preoperative factors that may be causally related to stricture may aid in minimizing this complication. In their study, Perugini et al. showed preoperative hypertension and obstructive sleep apnea to be predictive of complications in general; yet, they cautioned that their findings might have been confounded by their high rate of stricture.[20] By logistic regression analysis, our study found the variables of GERD and age to be significantly associated with a complication with one of the highest incidences—stricture. Our results are supportive of Perugini's findings, in that we did not find the same preoperative predictors of complications (hypertension, obstructive sleep apnea) significantly associated with stricture and the overall rate was significantly less.

The odds of developing stricture in patients with preoperative GERD were found to be nearly two times higher than those for patients without GERD. GERD is a known inflammatory condition of the upper gastrointestinal tract that specifically affects the lower esophagus and fundus. If present, this inflammation may predispose patients to more vigorous scarring of the gastrojejunostomy. During the period of the study, we began testing patients preoperatively for *H. pylori*. Patients who tested positive were treated preoperatively. In general, the micropouch used to create the gastrojejunostomy has been assumed to be almost devoid of acid-producing cells, and the rate of ulceration at the anastomosis at the time of endoscopy is low. It is clear, though, that adding H_2 antagonists for 30 days following surgery helps to decrease inflammation, and in addition, the polyglactin stitch may be less inflammatory in nature. Data were insufficient at study summary to demonstrate the statistical significance of administering H_2 antagonists; however, we are encouraged by the trend of fewer strictures.

Finding that younger rather than older age was associated with the development of stricture seems clinically counterintuitive. One reason for this is that age affects the small vessels' ability to provide necessary oxygenation to the anastomosis, and older patients are more likely overall to have diminished capability to oxygenate. In our center, maintenance on oxygen the night of surgery is standard; patients who require continuous positive airway pressure are started in the anesthesia recovery unit and are kept on supplemental oxygen until they can oxygenate in ambulating and resting modes at greater than 92%. However, as stated, in our first multivariate model, *older age* was shown to be slightly protective with respect to stricture. In the second multivariate model, designed to refine the interpretation of age effects on stricture, we found that the odds of developing stricture in those 35 years or younger were two times greater than those aged 36–45 years, and 2.32 times greater than those aged 46–55 years. The trend of age being protective against stricture leveled off and was not significant in those older than 55 years. More study of this finding is indicated.

Our original assumption that higher rates of central fat distribution in males might place greater tension on the

anastomosis predisposing male patients, particularly those with higher BMIs, toward stricture, may be in error. The effect of increased central fat on the anastomosis may not be injurious if meticulous technique is used to ensure a tension-free anastomosis. Also, the ischemic effects of diabetes, sleep apnea, and chronic respiratory disease at the gastrojejunostomy site may be insufficient, in themselves, to cause stricture.

It has been well documented that operative technique can contribute to increased stricture rates. Previous studies have reported fewer strictures with hand-sewn anastomoses than with stapled ones. Some authors have demonstrated that the 25-mm EEA stapler may be associated with fewer strictures that the 21-mm EEA stapler; we have a 6.8% stricture rate with the 21-mm EEA stapler. Further studies of stapling methodologies are warranted.

It has been proposed that stricture rates may be lessened by the creation of a larger gastrojejunostomy anastomosis. The effect on the restrictive element of the bypass and subsequent effect on weight loss long term has not been evaluated. We avoided excessive dilation to allow the patient to maintain as much restriction as possible. Using a protocol of minimal dilation to between 12.5 and 15 mm resulted in only one perforation and acceptable weight loss. In our study and those of others,[21,22] weight loss at 1 year is not hindered by dilation.

A limitation of this study is that is was retrospective. A prospective trial in which comorbidities were *not* controlled would not be feasible, although a prospective trial of H_2 antagonists may be of value. It is difficult to discern the effect of absorbable suture on stricture rates vs the effect of H_2 antagonists as their introduction to the protocol occurred in close proximity. The finding that readmissions within 30 days of surgery and postoperative peripheral neuropathy were statistically significant covariates of stricture most likely relates to the frequency of readmissions for peripheral neuropathy secondary to vitamin deficiencies following bariatric surgery.

The objective of this study was to reach back in the causal continuum, prior to the intraoperative effects of technique and surgeon experience, to identify other potentially salient contributors to postoperative stricture. This analysis of a large series of patients undergoing RYGB identified GERD and age as factors associated with gastrojejunostomy stricture.

Conclusions

Using absorbable suture at the gastrojejunostomy anastomosis appears to decrease stricture rates. As identified via multivariate logistic regression analysis, GERD and age are independent predictors of gastrojejunostomy stricture.

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Treatment of Gastric Adenocarcinoma May Differ Among Hospital Types in the United States, a Report from the National Cancer Data Base

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Abstract The concept that complex surgical procedures should be performed at high-volume centers to improve surgical morbidity and mortality is becoming widely accepted. We wanted to determine if there were differences in the treatment of patients with gastric cancer between community cancer centers and teaching hospitals in the United States. Data from the 2001 Gastric Cancer Patient Care Evaluation Study of the National Cancer Data Base comprising 6,047 patients with gastric adenocarcinoma treated at 691 hospitals were assessed. The mean number of patients treated was larger at teaching hospitals (14/year) when compared to community centers (5–9/year) ($p<0.05$). The utilization of laparoscopy and endoscopic ultrasonography were significantly more common at teaching centers ($p<0.01$). Pathologic assessment of greater than 15 nodes was documented in 31% of specimen at community hospitals and 38% at teaching hospitals ($p<0.01$). Adjusted for cancer stage, chemotherapy and radiation therapy were utilized with equal frequency at all types of treatment centers. The 30-day postoperative mortality was lowest at teaching hospitals (5.5%) and highest at community hospitals (9.9%) ($p<0.01$). These data support previous publications demonstrating that patients with diseases requiring specialized treatment have lower operative mortality when treated at high-volume centers.

Keywords Gastric cancer · Operative mortality · Hospital volume · Survival · NCDB

Abbreviations

AJCC	American Joint Committee on Cancer
CoC	Commission on Cancer
CHCP	Community Hospital Cancer Program
COMP	Community Hospital Comprehensive Cancer Program
NCDB	National Cancer Data Base
PCE	Patient Care Evaluation
THCP	Teaching Hospital Cancer Program
US	United States

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Introduction

Approximately 22,000 patients in the United States (US) will be diagnosed with gastric carcinoma in 2006, a number that pales in comparison to more common malignancies such as colorectal (172,000 new cases) and breast cancer (211,000 new cases).[1] Because of the relative infrequency of gastric cancer, most individual hospitals evaluate and treat a limited number of patients with stomach cancer, impairing the ability to develop expertise at many institutions. A lack of expertise may contribute to the dismal survival of gastric cancer in the US. In an earlier report from the National Cancer Data Base (NCDB), Hundahl et al.[2] observed a 5-year survival rate of 78% for stage IA, 58% for stage IB, 34% for stage II, 20% for stage IIIA, 8% for stage IIIB, and 7% for stage IV disease.

A recent report from the World Health Organization[3] shows a decline in the mortality of gastric cancer worldwide. However, the observed rate of decline in mortality is less in the US than what is observed for Japan. Factors that might contribute to the improved Japanese survival includes greater operative experience leading to more skilled surgeons, earlier diagnosis, different biologies of gastric cancer between countries, improved pathologic staging with stage migration (Will Rogers effect),[4] and the frequency of neoadjuvant or adjuvant chemoradiation therapy use.

These data highlight the need for improved treatment of gastric cancer to increase patient survival. A controversial way to accomplish this might be to limit gastric cancer care to high-volume centers, if the results were better at such sites. Evidence-based hospital referral has been adopted by some insurance companies and consortiums of large health care purchasers, such as the Leapfrog group, based on studies showing better outcomes for surgical services at high-volume centers.[5–7] Birkmeyer et al.[8] reported that Medicare patients had a lower operative mortality if they had cancer-related procedures (gastrectomy, esophagectomy, colectomy, pancreatectomy, cystectomy, nephrectomy, and pulmonary resection) or cardiovascular disease at a high-volume hospital. The Japanese have also found a similar pattern of improved survival after the treatment of gastric carcinoma at high-volume centers. Nomura et al.[9] reported 5-year survival rates to be significantly higher at centers with high surgical volumes (96–205/year), when compared to very-low-volume hospitals (1–28 cases/year).

To determine if patients treated for gastric cancer at high-volume and specialized centers in the US had better postoperative outcomes, we analyzed the preoperative evaluation and surgical treatment of gastric adenocarcinoma at three categories of hospitals, defined by the Commission on Cancer (CoC), namely, the Community Hospital Cancer Program (CHCP), Community Hospital Comprehensive Cancer Program (COMP), and Teaching Hospital Cancer Program (THCP). Data collected for the 2001 Gastric Cancer Patient Care Evaluation (PCE) by the NCDB were utilized.

Material and Methods

NCDB, Data Source, Case Selection, and Data Handling

The NCDB is a project of the American College of Surgeons (ACS) CoC. The NCDB was established in 1989 to serve as a comprehensive clinical surveillance resource for all forms of cancer diagnosed in the US and its operations have been supported in part by the American Cancer Society. In 2001, the database captured 73% of all newly diagnosed cancer cases in the US.

Data were submitted electronically in accordance with specified North American Association of Central Cancer Registries data transmission standards.[10] Hospital cancer registrars abstracted each case according to a standardized set of data elements and definitions as described in the CoC's *Registry Operations and Data Standards, volume II*.[11] The NCDB elements include patient characteristics: sex, age or date of birth, and race/ethnicity; tumor characteristics: primary site, histology, behavior, grade, and American Joint Committee on Cancer (AJCC), fifth edition stage groups; and first course of treatment: surgery, radiation, chemotherapy, and others. In addition to the annual call for data, a call for participation in a 2001 PCE was issued and 711 of the 1,423 CoC-approved institutions in the US responded. Cancer registrars were also asked to provide information describing additional diagnostic and treatment information, 30-day mortality, and patient comorbidities. Data quality checks were conducted at the local and the depository level.

Patient Population

The 2001 Gastric PCE included data submitted from 711 CoC-approved institutions in the US. Participating institutions submitted data for consecutive hospital admissions and clinic visits between January 1, 2001 and December 31, 2001. Patients eligible for participation had a "microscopically confirmed neoplasm of the stomach that was either diagnosed or initially treated at the reporting facility." Of 7,084 total patients, 6,099 (86%) were diagnosed with gastric adenocarcinoma. For this study, 52 patients were excluded because they were treated at nine institutions without a specialized hospital type, leaving 6,047 patients at 691 cancer program types for evaluation. This group comprises the study population.

Cancer Program Categories

Cancer programs were characterized as CHCP, COMP, or THCP. Community Hospital Cancer Programs diagnose and/or treat 100–650 cancer patients every year and will commonly refer patients to other institutions for diagnostic evaluation or treatment. A CHCP has neither a medical school affiliation nor residency programs but does posses a medical oncology unit or functional equivalent and infrequently participates in cancer research. Community Hospital Comprehensive Cancer Programs diagnose and/or treat more than 650 cancer cases per year, but are not associated with a medical school. A COMP may make outside patient referrals, has a medical oncology unit, and participates in cancer research. Teaching Hospital Cancer Programs are defined as facilities associated with a medical school that participates in the training of residents in at least four fields, two of which are medicine and surgery. A THCP offers a full range of diagnostic and therapeutic services on site and has an in-patient medical oncology unit. A THCP hospital also participates in cancer-related clinical research and has board-certified medical oncologists.

Statistical Analysis

All analyses were performed using the SPSS statistical software (SPSS for Windows, version 14.0; SPSS Inc, Chicago, IL, USA). Frequency distributions were calculated to get the mean number of cases by hospital category type. The chi-square (χ^2) test was used for comparisons of proportions across levels of categorical variables. When the overall test was significant, pairwise comparisons among the three hospital categories were also calculated to asses which hospitals differed in rates. The p values reported were adjusted for multiple comparisons using the Bonferroni adjustments.[12] Results were based on two-sided tests with a $p=0.01$ significance level, except where indicated. Where specific values were unknown, these cases were excluded from the analysis when appropriate.

A forward stepwise binary logistic regression model was used to evaluate the impact of age, stage, and comorbid burden on determination of type of treatment, i.e., the odds of "surgery, with or without other treatment" compared to the odds of nonsurgical treatment (radiation and/or chemotherapy). The Wald statistic was used to test significance. Exponentiated estimates of the beta coefficients were interpreted as the estimates for the effect (odds ratio) of a particular variable, controlling for the other variables in the equation. A receiver operating characteristic (ROC) curve was created to examine the prediction results. The true-positive probability was calculated to define the sensitivity of the classification rule and the true-negative probability was calculated to determine the specificity to summarize how well the model performed.

Confidentiality

Data reported to the NCDB are retrospective in nature. No patient or physician identifiers were collected as part of the study. Case identification information (facility identification number and local registry accession number) was collected for administrative purposes only. Analyses were reported only at the aggregate level to assist hospital cancer programs with quality assurance, rather than used to make decisions about individuals and their care.

The ACS has executed a business associate agreement that includes a data-use agreement, with each of its CoC-approved hospitals. Results reported in this study were in compliance with the privacy requirements of the Health Insurance Portability and Accountability Act of 1996 as reported in the Standards for Privacy of Individually Identifiable Health Information; Final Rule (45 CFR Parts 160 and 164).

Results

Treatment Volumes

A total of 691 cancer programs were included in the study: 258 CHCP sites, 267 COMP sites, and 166 THCP sites. Although 37.3% of the programs were CHCPs, only 22% ($n=1329$) of the cases were treated in this setting; 40.8% ($n=2,468$) of the cases came from COMPs; and 37.2% ($n=2,250$) of the patients came from THCPs. Community Hospital Cancer Programs saw on average of 5.2 cases/year; COMPs, 9.2; and THCPs 13.6. The THCPs treated more surgical patient on average (7.6 cases) than either the COMPs (5.3 cases) or the CHCPs (2.9 cases) (Table 1).

Patient Demographics

Men, 3,751(62%), and women, 2,296 (38%), were equally distributed across hospital types. The mean age in years was 69.3 and the median age 71 (18–103 years). Significantly more 70 and older patients were seen in CHCPs when compared to COMPs or THCPs ($p<0.01$). Significantly more 50 and younger patients were seen at THCPs when compared with CHCPs and COMPs ($p<0.01$) (Table 2).

The study population included 4,076 (67.4%) Caucasians, 827 (13.7%) African Americans, 533 (8.8%) Hispanic, 472 (7.8%) Asians, and 139 (2.3%) patients of other or unknown racial or ethnic background. Significantly fewer Caucasians were seen in THCPs when compared to

Table 1 Number and Percent of Cancer Programs, Number and Percent of Patients by Cancer Program, Mean Number and Range of All Cases by Cancer Program Type, Number and Percent of Surgically Treated Cases, and Mean Number of Surgical Cases and Range by Cancer Program Type

	Community Cancer Centers	Comprehensive Community Cancer Centers	Teaching/Research Hospitals	Total
Number (%) of cancer programs	258 (37.3)	267 (38.6)	166 (24.0)	691
Number (%) of patients in study	1,329 (22.0)	2,468 (40.8)	2,250 (37.2)	6,047
Mean number and range of all cases	5.2 (1–39)	9.2 (1–49)	13.6 (1–55)	
Number (%) of surgical cases	673 (20.5)	1,369 (41.8)	1,235 (37.7)	3,277
Mean number and range of surgical cases	2.9 (1–16)	5.3 (1–37)	7.6 (1–40)	

CHCPs and COMPs ($p<0.01$). THCPs saw significantly more African Americans than the other two types of cancer programs ($p<0.01$). Significantly more Asians were seen at COMP hospitals when compared to CHCP hospitals ($p<0.01$), but there was no significant difference when comparing the proportion of Asians in COMPs to the proportion found in THCPs.

A large percentage of this patient population did not have a documented AJCC Stage reported ($n=1,041$, 17.2%). Of those patients with a documented stage, more than 64.5% had advanced stage (stage III or IV) at presentation. The largest subgroup had stage IV disease ($n=2,118$, 35.0%). There were no significant differences in the stage at presentation between the different types of

Table 2 Patient Characteristics by Type Cancer Program

	Community Cancer Center *n* (%)	Comprehensive Cancer Center *n* (%)	Teaching/Research *n* (%)	Total *n* (%)
Gender				
Male	805 (60.6)	1,502 (60.9)	1,444 (64.2)	3,751 (62.0)
Female	524 (39.4)	966 (39.1)	806 (35.8)	2,296 (38.0)
Total	1,329	2,468	2,250	6,047
Age				
<50	106 (8.0)	207 (8.4)	264 (11.7)	577 (9.5)
50–69	402 (30.2)	865 (35.0)	836 (37.2)	2,103 (34.8)
70 and older	821 (61.8)	1,396 (56.6)	1,150 (51.1)	3,367 (55.7)
Total	1,329	2,468	2,250	6,047
Race/Ethnicity				
Caucasian	966 (72.7)	1,723 (69.8)	1,387 (61.6)	4,076 (67.4)
African American	143 (10.8)	278 (11.3)	406 (18.0)	827 (13.7)
Hispanic	120 (9.0)	206 (8.3)	207 (9.2)	533 (8.8)
Asian	78 (5.9)	218 (8.8)	176 (7.8)	472 (7.8)
Other	22 (1.7)	43 (1.7)	74 (3.3)	139 (2.3)
Total	1,329	2,468	2,250	6,047
AJCC stage				
O	2 (0.2)	8 (0.3)	2 (0.1)	12 (0.2)
I	13 (1.0)	28 (1.1)	26 (1.2)	67 (1.1)
IA	105 (7.9)	210 (8.5)	182 (8.1)	497 (8.2)
IB	118 (8.9)	218 (8.8)	178 (7.9)	514 (8.5)
II	160 (12.0)	286 (11.6)	242 (10.8)	688 (11.4)
III	6 (0.3)	12 (0.5)	12 (0.5)	30 (0.5)
IIIA	156 (11.7)	347 (14.1)	337 (15.0)	840 (13.9)
IIIB	47 (3.5)	96 (3.9)	97 (4.3)	240 (4.0)
IV	427 (32.1)	856 (34.7)	835 (37.1)	2,118 (35.0)
Unknown	295 (22.2)	407 (16.5)	339 (15.1)	1,041 (17.2)
Total	1,329	2,468	2,250	6,047

medical institutions. When specified, the most common location of the primary cancer was the cardia 27.4% (n=1,656), followed by the antrum 18.3% (n=1,107) and stomach, not otherwise specified (NOS) 17.9% (1,080) (Fig. 1). The distribution of tumor location was similar among all these categories of treatment institution.

Diagnostic Testing

Diagnostic evaluation included computed tomography (CT) of the abdomen (n=4,417, 73%) and pelvis (46.9%) over all hospital types. The abdominal CT suggested a diagnosis of cancer in 63.9% of patients at CHCP, 63.0% at COMP, and 68.2% at THCP. The CT of the abdomen was more likely to suggest cancer at the THCP when compared to the COMP (p<0.01), but no significant difference was noted between the THCP and the CHCP. Computed tomography of the pelvis was suggestive for cancer in 36.9, 38.1, and 42.6% at CHCP, COMP, and THCP, respectively. The differences across cancer programs were not significant (p>0.01). Only 15.6% (n=946) of these cases were evaluated with endoscopic ultrasonography. That procedure was used more often at THCPs (33.5%) when compared to both CHCP (13.8%) and COMP (17.6%) (p<0.01). 2-^{18}F-Fluoro-2-deoxy-D-glucose positron emission tomography (F18-FDG-PET) was rarely used at any type of hospital (4.6%). When done, THCPs were more likely to use the F18-FDG-PET than CHCP for diagnostic testing (p<0.01). No significant differences were noted between THCP and COMP use.

Intraoperative Assessment

Staging laparoscopy was performed significantly more often at THCPs (18.9%) than at COMPs (13.6%) or at CHCPs (10.5%) (p<0.01). No significant differences were seen between COMPs and CHCPs. Peritoneal lavage with cytology for the assessment of occult peritoneal disease was rarely used at THCPs, COMPs, and CHCPs with rates of 5.7, 4.3, and 2.7%, respectively. Significantly fewer peritoneal lavages occurred at CHCPs when compared to THCPs (p<0.01). No significant differences were found between THCPs and COMPs.

Surgical Treatment

Surgical intervention was undertaken for 54.2% (n=3,277) of the all patients in the study. At CHCP hospitals, 673 out of 1,329 (50.6%) patients were surgically treated, 1,369 out of 2,468 (55.5%) were surgical patients at COMP, and 1,235 out of 2,250 (54.9%) patients underwent surgery at THCP. When surgeries were grouped as less extensive or more extensive, significantly more extensive surgeries were performed at THCPs than at CHCPs (p<0.01); however, no significant difference was observed between COMPs and THCPs (p>0.01). More specifically, the most frequently recorded type of surgical resection was gastrectomy, NOS (overall, 21.7%; CHCP, 26.0%; COMP, 20.5%; and THCP, 20.6%) followed by distal gastrectomy (overall, 16.2%; CHCP, 15.6%; COMP, 17.3%; and THCP, 15.2%), and partial or subtotal gastrectomy (overall, 13.3%; CHCP, 12.2%; COMP, 12.7%; and THCP, 14.6%). A near total or total gastrectomy was uncommonly performed (overall, 5.7%; CHCP, 4.3%; COMP 5.7%; and THCP, 6.4%). After pathologic analysis, 83.5% of the entire surgical patient population had a resection with curative intent (R_0 resection), whereas 16.5% had a palliative resection (R_1 resection). The frequencies of R_0 and R_1 resections were similar (CHCP, 81.2/18.8%, COMP, 84.6/15.4%, and THCP, 83.6/16.4%) among all institutions and not statistically different between different types of institution (p=0.25).

Lymph node staging, a highly significant predictor of outcome, was evaluated using the number of lymph nodes examined after surgical resection. Analysis of at least 15

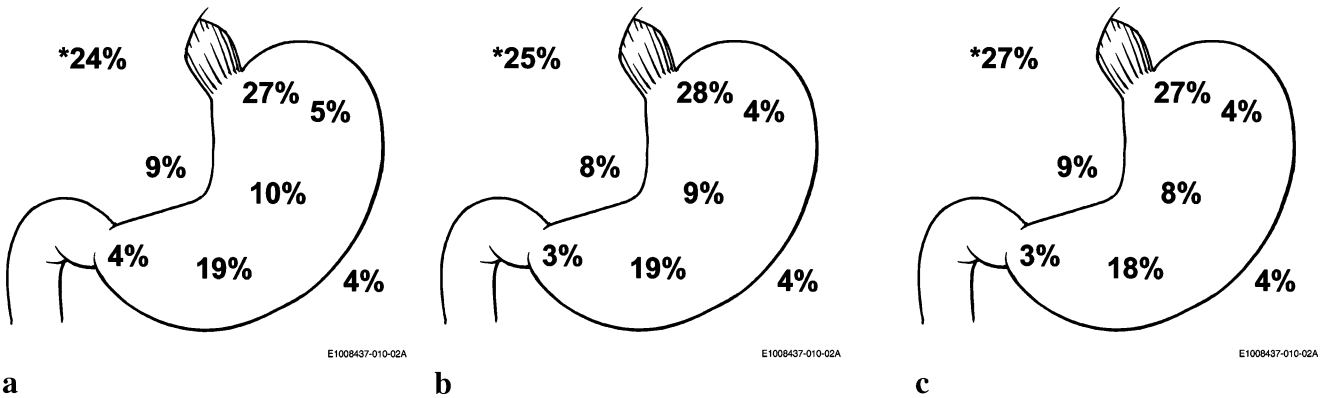

Figure 1 Location of cancer at presentation by cancer program types: **a** Community Hospital Cancer Program (CHCP), **b** Community Hospital Comprehensive Cancer Program (COMP), and **c** Teaching Hospital Cancer Program (THCP). Location of lesions: cardia, funds, body, antrum, pyloric, lesser curve, and greater curve by percent and others indicated by asterisk (C168, overlapping lesions and C169, stomach, NOS).

lymph nodes is required by the AJCC for accurate staging and exclusion of nodal metastases. Only 31.1% of patients at CHCPs, 31.0% at COMPs, and 38.4% at THCPs had more than 15 nodes examined ($p<0.01$). A large number of patients from each hospital type had an unknown number of lymph nodes pathologically evaluated (26.6% CHCP, 22.6% COMP, and 15.4% THCP), but THCPs had significantly better documentation of lymph node evaluation ($p<0.05$) (Fig. 2). A D1 lymphadenectomy with removal of only perigastric nodes was noted in 56.7% of surgically managed patients. Some patients had removal of some lymph nodes that are included in D2 or D3 nodes but most across all hospital types did not have a formal extended lymphadenectomy (Table 3).

Morbidity and Mortality

The prevalence of operative morbidity, specifically for postoperative hemorrhage, wound infection sepsis, and an anastomotic leak, was similar across all hospital categories (Table 4). Operative mortality, defined by 30-day mortality, was different among the institution types. Teaching Hospital Cancer Programs had the lowest 30-day mortality at 5.5%, compared to 7.9% at COMPs and 9.9% at CHCPs (Table 4). The proportional difference between THCPs and COMPs was not significant ($p>0.01$), whereas, when compared to CHCPs, THCPs had significantly fewer deaths within 30 days of surgery ($p<0.01$). For those that died within that 30-day period, no significant differences were found across all hospital types for stage ($p>0.01$) or age ($p>0.01$). In the logistic regression model stage was the most significant predictor of 30-day postoperative death ($p=0.0001$), followed by age ($p=0.0001$), and category of hospital ($p=0.004$). Stage IV patients were 2.6 times (99% confidence interval [CI]=1.6–4.3) more likely to die within 30 days of surgery; no other stage was significant ($p>0.01$). Patients in CHCPs were almost twice as likely to die within 30 days when compared to THCPs ($p=0.001$). Race and extent of surgery were not significant factors. The area under the ROC curve defined by the logistic model was 0.69 (99% CI=0.64–0.74), where 0.5 represents a nondiscriminatory result. Long-term 5-year survival data are unavailable for this patient population and will not be until the fall of 2007.

Neoadjuvant and Adjuvant Therapy

Approximately 38.9% of the surgical patients received chemotherapy; 30.5% received radiation therapy. Neither neoadjuvant radiation therapy nor chemotherapy was frequently provided at all hospital types, but highest, although not significant ($p>0.01$) at the THCPs when compared to CHCPs and COMPs (Table 5). Patients more frequently received adjuvant chemotherapy and radiation than neoadjuvant chemotherapy or radiation therapy at all the categories of hospitals. There were no statistically significant differences in the frequency of treatment with chemotherapy or radiation therapy by tumor stage between the hospital categories.

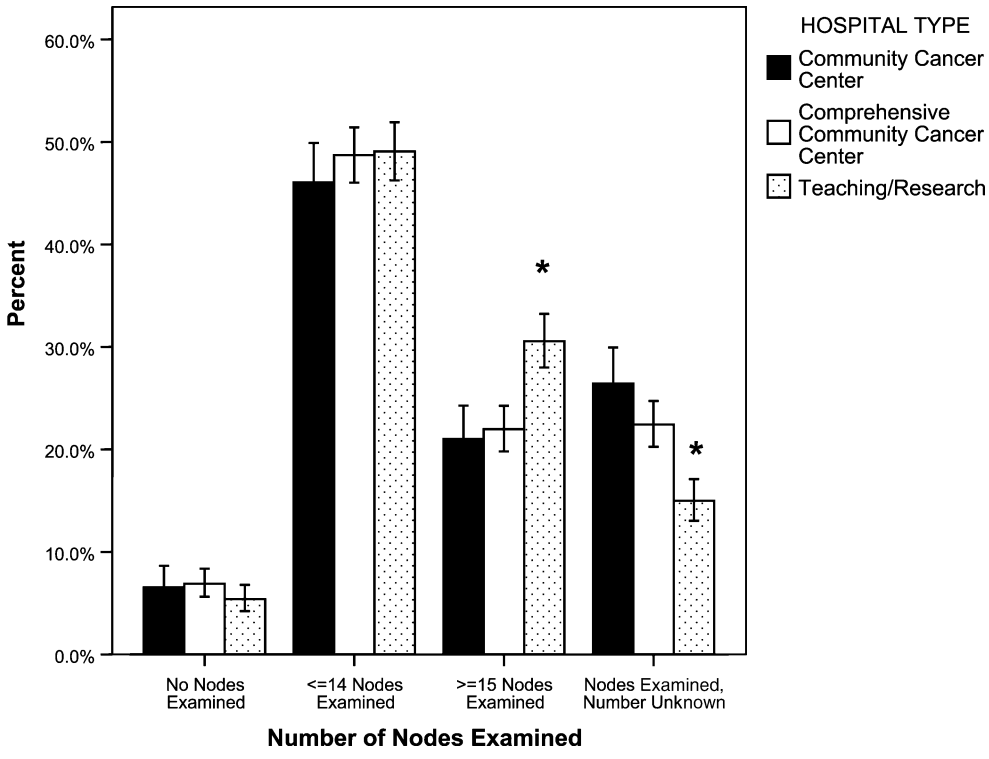

Figure 2 Percent of lymph nodes sampled at each hospital. CHCP = Community Cancer Center Program, COMP = Community Hospital Comprehensive Cancer Program, THCP = Teaching Hospital Cancer Program. $p<0.05$ (asterisk). Error bars: 95% CI.

Table 3 Lymph Nodes Sampled During Surgical Resection

Resected	Community Cancer Center *n* (%)	Comprehensive Cancer Center *n* (%)	Teaching/Research *n* (%)
Perigastric[a]			
Yes	367 (71.1)	775 (68.9)	715 (70.4)
No	149 (28.9)	350 (31.1)	301 (29.6)
Hepatic[b]			
Yes	21 (4.2)	68 (6.5)	70 (7.5)
No	478 (95.8)	979 (93.5)	867 (92.5)
Celiac[c]			
Yes	40 (7.9)	100 (9.5)	96 (10.1)
No	465 (92.1)	952 (90.5)	854 (89.9)
Splenic[d]			
Yes	14 (2.8)	49 (4.7)	52 (5.5)
No	481 (97.2)	988 (95.3)	887 (94.5)
Paraaortic[e]			
Yes	94 (18.8)	170 (16.8)	189 (20.2)
No	405 (81.2)	840 (83.2)	745 (79.8)

Comparison of column proportions did not include the unknown values in calculations.
[a] Perigastric unknown, $n=620$
[b] Hepatic unknown, $n=794$
[c] Celiac unknown, $n=770$
[d] Splenic unknown, $n=806$
[e] Paraaortic unknown, $n=834$

Discussion

When examining the current status of gastric cancer patient care in the US and seeking ways to improve survival, looking to the East for guidance is a reasonable strategy. The standards of gastric cancer therapy have largely been set by the practices of Japanese physicians and surgeons, in a large part, because of their large experience with this disease. In Japan, there are 104,000 new cases annually in a population of 128×10^6,[13] compared to the 22,000 cases

Table 4 Postoperative Mortality and Complications

	Community Cancer Center *n* (%)	Comprehensive Cancer Center *n* (%)	Teaching/Research *n* (%)
30-Day mortality[a]			
Yes	55 (9.9)	93 (7.9)	59 (5.5)
No	501 (90.1)	1,080 (92.1)	1,020 (94.5)
Bleeding[b]			
Yes	20 (4.2)	40 (3.9)	47 (5.1)
No	451 (95.8)	993 (96.1)	881 (94.9)
Wound infection[c]			
Yes	35 (7.4)	54 (5.2)	61 (6.6)
No	440 (92.6)	981 (94.8)	868 (93.4)
Sepsis[d]			
Yes	34 (7.1)	62 (6.0)	43 (4.7)
No	443 (92.9)	973 (94.0)	881 (95.3)
Anastomotic leak[e]			
Yes	32 (6.7)	68 (6.5)	64 (6.6)
No	447 (93.3)	979 (93.5)	884 (93.2)

Comparison of column proportions did not include the unknown values in calculations.
[a] 30-Day mortality unknown, $n=469$
[b] Bleeding unknown, $n=845$
[c] Wound infection unknown, $n=840$
[d] Sepsis unknown, $n=841$
[e] Anastomotic Leak unknown, $n=803$

Table 5 Radiation and Chemotherapy/Surgery Sequence

	Community Cancer Center # (%)	Comprehensive Cancer Center # (%)	Teaching/Research # (%)
Radiation[a]			
Neoadjuvant	23 (12.1)	53 (13.0)	68 (19.1)
Adjuvant	167 (87.9)	356 (87.0)	288 (80.9)
Chemotherapy[b]			
Neoadjuvant	36 (14.6)	71 (15.0)	87 (20.3)
Adjuvant	210 (85.4)	401 (85)	342 (79.7)

Comparison of column proportions did not include the unknown values in calculations.
[a] Radiation sequence unknown, $n=43$
[b] Chemotherapy sequence unknown, $n=128$

seen annually in the US in a population of 296×10^6,[1] an incidence that is more than 10 times greater than that of the US.

The high incidence seen in Japan has allowed the Japanese to develop surgical and medical strategies to improve mortality. However, several of the surgical principles practiced in Japan are difficult to incorporate into Western practices. Early detection programs in Japan have led to a significant decrease in mortality but this has not been replicated in the US because of the high cost to benefit ratio associated with the much lower incidence of gastric cancer in the US. A more controversial standard Japanese practice is the extended D2, D3, or even D4 lymphadenectomy performed for gastric cancer. Whereas extended lymphadenectomy has been associated with improved survival in Japan, with retrospective analysis, the value of this technique has not been proven in the West. Wanebo et al.,[14] in a retrospective study from the US, as well as Bonenkamp et al.[15] and Cuschieri et al.[16], in randomized controlled trials from The Netherlands and Great Britain, respectively, have reported a lack of survival benefit with D2 lymphadenectomy. Both Bokenkamp et al.[15] and Cuschieri et al.[16] observed significantly higher mortality rates among those patients that had a D2 resection of 10 vs 4% and 13 vs 6.5%, respectively. The operative mortality after a D2 resection is much lower in Japan with reported rates below 2%.[17,18] Kodera et al. from Japan reported an operative mortality rate of 0.8% from 523 patients in a D2 vs D3 study.[19]

Studies examining large national databases have found improved surgical mortality after gastrectomy for gastric cancer at high-volume centers. A study examined using the National Inpatient Sample reported on 23,690 hospitalized patients with a hospital discharge code of gastric cancer and any gastrectomy noted significant differences in mortality among hospital types. Very-low-volume hospitals (<4 cases/year) had a mortality rate of 8.9% compared with a rate of 6.4% seen at high-volume hospitals (>9 cases/year).[20] In a study by Birkmeyer et al.[21] of the Medicare population, the observed mortality rate was 13% at very-low-volume centers (<5 cases/year) compared to 8.7% at very-high-volume centers (>21 cases/year). Improved survival among high-volume hospitals was also reported in Swedish[22] hospitals that treated >20 surgical patients a year and German[23] hospitals that treated >50 patients/year.

The Japanese have also noted an association of lower patient survival rates among gastric cancer patients treated at low-volume centers when compared to high-volume centers. Nomura et al.[9] analyzed a database of more than 55,000 patients and grouped them into the following time periods: 1975–1979, 1980–1984, 1985–1989, and 1990–1994. He found "positive relationships between hospital volume and 5-year survival" but over time the survival benefit seen at high-volume centers decreased and persisted in comparison with the very-low-volume centers.

Not all authors, however, have observed improved survival at high-volume centers. A Dutch study evaluated the impact of patient volume on operative mortality and found no differences. This study analyzed 1,987 gastric cancer patients treated at 22 hospitals between 1987 and 1997.[24] A limitation of this study is the fact that only 1 of the 22 hospitals was a university hospital and the others were "general hospitals." Many of the participating hospitals were considered to be low-volume centers.

Interpretation of the Results

Our study had similar results to the aforementioned American, Japanese, and European studies. In this study, there was a marked improvement (>50%) in operative mortality at higher volume centers (≥14 cases/year) when compared to lowest volume institutions (≤5 cases/year). The average 30-day postoperative mortality at the low-volume community centers was almost 10%. The annual volume of gastric surgeries performed seems to be inversely related to 30-day postoperative mortality. On average 2.9, 5.5, and 7.6 gastric surgeries were reported from CHCPs, COMPs, and THCPs, respectively. Corresponding 30-day mortality was

9.9, 7.9, and 5.5%, respectively. There were no significant differences seen in postoperative morbidities such as wound infection and hemorrhage by hospital category. The logistical model revealed three predictors of perioperative mortality: stage IV disease, advanced age, and institution type. Patients that had surgery at a CHCP were twice as likely to die postoperatively compared to patients treated surgically at THCPs. Among those that died, there were no significant differences of stage or age at the different institutions.

Because the absolute differences in surgical case number among the hospital types were not vastly different, this observed difference in outcomes may be a reflection of the infrastructure of the institution rather than individualized surgeon skill. Centers affiliated with a medical school might have more experience with caring for the critically ill in the form of larger and better equipped intensive care units, resident and fellow coverage, newer technology, and more subspecialized physicians to help manage patient care. Unfortunately, we could not analyze the infrastructure for each hospital type nor look at surgeon-specific experience in this study as this was not a part of the study.

Clinical staging is affected by the sensitivity and specificity of the diagnostic studies performed during the preoperative evaluation. An assessment of staging at the different institutions revealed some major differences. Teaching hospitals were more likely to detect malignancy on a CT of the abdomen and pelvis than the other two hospital types. This might be a reflection on the quality of CT scans obtained and the experience of the radiologists. Preoperative utilization of endoscopic ultrasound was higher at teaching hospitals, a predictable finding given the recent adaptation of this technology and the expertise required to interpret these images.

In terms of pathologic staging, Karpeh et al.[25] previously reported that evaluation of more than 15 lymph nodes allows a better estimate of patient survival. In fact, a study by Smith et al.[26] found that overall survival was largely dependent on the number of nodes examined and found an increase in survival when up to 40 lymph nodes was assessed. We found that teaching hospitals did a significantly better job meeting this recommendation; however, even at THCPs only 38.4% of patients had greater than 15 nodes assessed. The D1 lymphadenectomy was the most common operation for of nodal dissection, probably as a result of controlled Western surgical trials showing no survival benefit from a D2 dissection. Only a limited number of patients had any D2–D4 nodes resected and usually without a standardized extended lymphadenectomy. A notable observation was that the percentage of D2–D4 lymphadenectomy performed at THCPs was not higher than what was observed at COMPs or CHCPs.

To improve and obtain accurate surgical staging of gastric cancer patients, current practice will have to improve and will be dependent upon both the excision of nodes by the surgeon and their retrieval from the specimen by the pathologist. Given so few patients had 15 or more nodes removed at the time of surgery, regardless of hospital type, this practice could be improved by surgeons and pathologists working together to achieve the goal of identifying at least 15 nodes followed by the proper documentation of the microscopic evaluation of these nodes in the pathology report. If intraoperative pathologic evaluation of the surgical specimen is possible and the lymph node sampling is inadequate, the surgeon should excise additional lymph nodes.

A strength of this study is the large number of patients and hospitals included in the study. This broad sampling of hospitals leads to a close approximation of the current practice of gastric cancer treatment in the US. The main shortcoming is that many of the critical data categories had at least 20% “unknown” responses, and may have biased the reported results of this study. In addition, analysis of hospital infrastructure or surgeon volume was limited by lack data availability in the database. Another limitation is that the 5-year survival information has not yet been documented; these data will provide long-term outcome by type of treatment center.

Conclusion

Data from the Gastric PCE project suggests that there is significant room for improvement in the surgical management of gastric cancer in the US. Most hospitals, regardless of category, do not document the evaluation at least 15 lymph nodes necessary to meet AJCC standards. With a little over one third of all patients having more than 15 lymph nodes examined, pathologic staging is less accurate and results of surgical and adjuvant therapy are likely to be worse. Significantly more patients had appropriate staging with the recommended number of nodes included in the lymphadenectomy at teaching centers than at nonacademic centers. Thirty-day mortality rates after gastric cancer resection were significantly lower at teaching centers, further establishing the recommendation that complex oncologic operations should be performed at high-volume centers to obtain better patient outcomes, corroborating the results of several previous studies. Long-term survival data will provide more information on effectiveness of treatment at each of the different institution types.

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DISCUSSION

Richard H. Bell, Jr. M. D. (Chicago Ill): Thank you, Dr. Reid-Lombardo. That was a nice presentation. This report deals with the thorny issue of where complex GI procedures are best done and by whom, and this is not an academic discussion, because in your data you suggest that there are about 500 preventable operative deaths per year in the United States for gastric cancer patients. The difficult question for me in all of this is identifying what is about large tertiary hospitals that results in better operative outcomes for complex GI cases. I think if we are going to argue for centralization, we need to understand the rationale for doing that. It is obviously a contentious issue.

So in this respect, I was disappointed a little bit with the way you examined your results, becaused you claimed that surgical volume predicts good outcomes, but this was really not a study of volume. You divided your hospitals based on structure and not on volume. You divided the hospitals based on their classification by the American College of Surgeons. And although you didn't show it, there was data in the manuscript that showed there were actually significant volume overlaps between the three categories. It was certainly not a clean distinction by volume. Some of the less complex hospitals in your study did as many operations as the tertiary medical centers, although their average number was smaller. So I thought this study would have been more illuminating if, in addition to what you look at, you had looked at volume as an independent variable in addition to structure. You actually have an unusual study here in that you can look at

both structure and volume. It may be that the structure of tertiary hospitals the better equipment, the higher per? forming ICUs, the resident coverage, all of these things are the primary driver of better outcomes.

From an educational point of view, this has implications in the sense that it would not do any good to do a better job of training community general surgeons to be more proficient in gastrectomy if the community hospitals is fundamentally a less capable environment for this type of operation. You have the data to lok at both structure and volume, and I wish you had done that perhaps in the future manuscript you will. Thank you.

Kaye Reid-Lombardo, M. D. (Rochester, Minn) Thank you, Dr. Bell. I definitely agree with you that it is less about volume, especially with gastric cancer, because, you are right, even at teaching hospitals the volumes are not that high. I think it has more to do with the infrastructure at each institution, as is being reported by many authors as well. I think factors such as ICU availability or the radiologic availability at each institution have more of an impact than the surgeon in and of him or herself. So I think this study will allow us to further examine things like infrastructure and see what the differences are and to make better recommendations based on that examination.

Michael A. Choti, M. D. (Baltimore, Md) Dr. Reid-Lombardo, I enjoyed your presentation and thank you for the opportunity to have reviewed the manuscript in advance. This is just another example of how the National Cancer Database can be a useful tool for analyzing a variety of cancer mangement question. This database is robust and different from SEER or other databases. I encourage others to utilize this resource.

I have two questions. The first, you report a surprisingly low number of palliative gastrectomies, yet you define this as margin positive resection and not based on symptomatic indications. While it is uncommon to have both proximal and distal positive margins, even in palliative resections, it is more common to have noncurative or R2 gastrectomy. In such cases the margins may be negative but residual disease is left behind as nodes or peritoneal implants. Were you able to see the difference between the margin positive and R2 resection?

The second question relates to the number of lymph nodes evaluated in this series. As you know, guidelines recommend histologic evaluation of at least 15 nodes. It was interesting how few gastrectomies in fact achieve greater 15 nodes. This number is significantly less than even colorectal cancer, where much attention has recently been given. Do you think in this case it is the pathol? ogist diligence as much as the extent of lymphadenectomy that is the problem? Or are we setting the bar to high with the recommendation of 15 or more nodes? Thank you.

Dr. Reid-Lombardo: Thank you for questions. To answer your first question, it aws difficult to analyze R2, and so that is why we difficult to analyze R2, and so that is why we evaluated based on margin status. I would have expected a higher palliative rate as well. We could not analyze that from the database. I think to improve on the lymph node sampling , the pathologist and surgeon must work hand in hand. The pathologist should analyze the resected specimen at the time that the surgeon is still in the operating room and provide feedback. If there are less than 15 nodes, then more node sampling should be done by the surgeon. Now, I know the western studies have not shown improved survival among patients with D1 and D2 rescted nodes, but sampling more nodes would almost seem to me to assure that we are doing a more extended lymphadenectomy. One way that we can achieve that goal is to have better discussion, and not only discussion, but the pathology report should clearly indicate how many nodes have been examined and how many are positive or negative. Thank you.

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Middle Segment Pancreatectomy: A Useful Tool in the Management of Pancreatic Neoplasms

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Abstract Small, benign, or low-grade malignant tumors located in the neck of the pancreas are usually treated with enucleation. However, if enucleation is too risky because of possible damage of the main pancreatic duct, standard pancreatic resections are performed. Such operations can lead to impaired long-term exocrine–endocrine function. Middle segment pancreatectomy consists of a limited resection of the midportion of the pancreas and can be performed in selected patients affected by tumors of the pancreatic neck. Middle segment pancreatectomy is a safe and feasible procedure for treating tumors of the pancreatic neck; in experienced hands it is associated with no mortality but with high morbidity, even if the rate of "clinical" pancreatic fistula is about 20%. Moreover, it allows a surgeon to preserve pancreatic parenchyma and consequently long-term endocrine and exocrine pancreatic function.

Keywords Pancreatic resection · Middle segment pancreatectomy · Pancreatic tumors · Surgical complications · Pancreatic function

Introduction

Whereas neoplastic lesion located in the pancreatic head or body-tail are usually resected by pancreaticoduodenectomy or distal pancreatectomy, tumors in the neck represent a real challenge for a surgeon. In these cases, standard or extended pancreatectomies performed for benign or borderline cases can determine the loss of a great amount of glandular tissue, significantly increasing the risk of diabetes, impaired exocrine function, and splenic loss.[1–6]

Enucleation would be an adequate alternative for small, benign, and low-grade malignant tumors, such as endocrine and cystic neoplasms of the pancreas. Unfortunately this conservative procedure cannot be always applicable. When the neoplastic lesion measures up to 2 cm or more, or it is encased within the pancreatic gland, enucleation is associated with a high risk of Wirsung's duct damage; moreover in the case of tumors with uncertain biological behavior this approach should be avoided because of the risk of tumor recurrence[1–5].

Letton and Wilson[7] reported for the first time in the English literature in 1959 two cases of traumatic mid-pancreatic transection followed by a reconstruction with a Roux-en-Y jejunal loop anastomized to the distal part of the gland. Dagradi and Serio,[8] from our own Department of Surgery, were the first in 1984 to propose middle pancreatectomy with an "oncological" indication, treating a pancreatic insulinoma. Subsequently, other authors reported cases of resection of the middle pancreas, of varying extent, using various terms such as "central pancreatectomy," "middle segment pancreatectomy," "segmental pancreatectomy," and "intermediate pancreatectomy."[9–13] The underlying indications for surgery ranged from chronic pancreatitis to benign, uncertain behavior, or low-grade malignant exocrine and endocrine neoplasms[1–19]. Different techniques were adopted for gastrointestinal reconstruction, including jejunal anastomosis of both the proximal and distal stump, or of only the distal stump, with pancreaticoduodenal or pancreaticogastric anastomosis.[1–21]

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Surgical Technique

The abdomen is entered through a midline incision. The gastrocolic ligament is opened, preserving the gastroepiploic vessels, and the pancreatic gland is exposed. The posterior peritoneum along the superior and inferior margin of the pancreas is incised. The superior mesenteric vein and the portal vein must be identified and their surfaces cleared below the gland. The plane between the superior mesenteric and portal vein should be teased apart. The splenic artery and vein are dissected free and separated from the gland. Some venous tributaries to the portomesenteric axis and some minor collaterals of the splenic artery can be ligated. Then, the posterior surface of the pancreatic neck is isolated from the portomesenteric axis and a ribbon is passed behind the gland to elevate it. Sutures are placed along the superior and inferior margins to indicate where the proximal and distal transection should be performed and to ligate those vessels running along the margins. The segment of the pancreas with the tumor is subsequently transected through a knife or a stapler to the left and to the right of the lesion. The cephalic stump is sutured with interrupted stitches after elective ligation of the Wirsung's duct or by means of a stapler. A small stent is placed in the main pancreatic duct while performing pancreojejunostomy or pancreogastrostomy; the stent can be left in place, even if in our experience we have never done it. Two closed-system suction drains are used to drain the cephalic stump of the gland and the pancreaticojejunostomy/pancreaticogastrostomy.

Discussion

It has been shown that standard pancreatic resections are nowadays associated with low mortality and morbidity if performed in high-volume centers by experienced surgeons.[22–24] It is remarkable that this type of surgery can lead to long-term complications, such as diabetes, exocrine insufficiency, and late postsplenectomy infection[25,26].

The incidence of postoperative exocrine and endocrine impairment is not predictable in patients with apparently "normal pancreas." Factors such as fibrosis of the remnant, Wirsung's duct obstruction, preexisting chronic pancreatitis, benign or malignant disease, and subclinical diabetes may play a role as "risk factors."[1–3] After standard left-sided resection there is an increased incidence of endocrine impairment and onset of diabetes reported from 17 to 85% of patients; it is reasonable that the extent of the resection is strictly related to the incidence of endocrine–exocrine long-term insufficiency[27–31].

For all these reasons, more conservative surgical techniques have been advocated for small, benign, or low-grade malignant tumors located in the neck of the gland, aimed for sparing, as much as possible, pancreatic parenchyma. Whenever neoplastic lesions are not small and superficial enough to be simply enucleated, middle segment pancreatectomy should be considerated.[1–6]

Middle segment pancreatectomy accounts for only 3% of the pancreatic resections performed at our institution and about 100 cases have been reported in the English literature[1–21,32–34]: this means careful selection of patients. In fact, the small number of patients who underwent this type of operation is related to different factors: specific localizations of the neoplasm, well-selected indications (benign or low-grade malignant tumors), and a distal pancreatic stump of at least 5 cm in length.

Some authors[1,3] have reported that this operation can be performed only in the case of small tumors (<5 cm in diameter); in our experience, although the mean diameter of the resected lesions was 27.4 mm, we have safely performed middle segment resection for tumor measuring more than 5 cm, harboring from the anterior face of the pancreas.

Middle segment pancreatectomy was also occasionally used for malignant disease: two islet cell carcinomas, one vipoma who subsequently developed hepatic metastases, one cystadenocarcinoma, and one carcinoma in situ[2,3,10–12].

In the past we have also performed this operation for malignant tumor but we had pancreatic recurrence of the tumor in two patients (one affected by metastasis and one by intraductal papillary mucinous neoplasms [IPMN] with in situ carcinoma); moreover, two patients with adenoma and borderline main duct IPMN had a tumor recurrence in the pancreatic gland. Thus, we believe that in patients affected by primary or metastatic malignant tumor, a standard resection would be more appropriate. Moreover, middle pancreatectomy in our experience should also be avoided in patients affected by IPMN, especially main duct type because of their potential malignity and the possibility to have different degrees of dysplasia along the Wirsung's duct in the same patients.

The surgeon must be sure to achieve tumor-free proximal and distal resection margins after performing middle segment pancreatectomy and, for this reason, frozen section examination is mandatory.

Middle segment pancreatectomy is a meticulous procedure. There is the possibility of leaks from both the closed cut edge of the head and the pancreaticojejunostomy, considering that in most patients we are dealing with a normal soft pancreatic texture with a small Wirsung's duct. Thus, not only great care must be taken in selecting the patients who will benefit from this operation, but also an experienced pancreatic surgeon working in a high-volume center is required for performing the procedure.[1–4,6,32,33]

Median pancreatectomy is reported to be associated with no mortality but with a high postoperative morbidity, above

all consisting of pancreatic fistula.[6] In our experience the "clinical" pancreatic fistula rates after pancreaticoduodenectomy and left pancreatectomy are 10 and 20%, respectively.[23,35–37] Between January 1990 and December 2005 61 patients underwent middle segment pancreatectomy at our institution. The incidence of pancreatic fistula—according to the International Study Group on Pancreatic Fistula definition[22]—was 51%. It is remarkable that most patients complained of Grade A fistula, which is a "biochemical" fistula without any clinical impact, whereas 13 patients (21%) developed a grade B or C fistula, which required prolonged in-hospital stay. In almost all patients the conservative management was successful; no one underwent reoperation and in four cases intraabdominal collections were treated with ultrasound-guided drainage. The mortality rate was zero.

The risk of developing a pancreatic fistula must be taken into account in the preoperative decision making; we believe that this risk is acceptable when the procedure is performed in a high-volume center and for patients with a long-life expectancy, such as young or middle-aged people affected by benign or low-grade tumors.

The most important advantage of middle segment pancreatectomy is the good endocrine and exocrine long-term function.[1–6,10] Iacono et al.[1] in a series of 13 patients demonstrated that postoperative oral glucose tolerance, pancreaticolauryl and fecal fat excretion were normal in all cases and they studied six patients pre- and postoperatively with oral glucose tolerance test showing no significant differences before and after surgery. Moreover, Sperti et al.[3] showed, in a review of the literature, no case of impaired endocrine function in 59 evaluable patients whereas exocrine function was reported to be normal in 56 out of 59.

Another advantage of this procedure is the possibility to preserve the spleen, preventing the risk of postsplenectomy sepsis and hematologic disorders, which is low but exists in an adult.[38,39]

In conclusion, middle segment pancreatectomy is a safe and technically feasible surgical approach for removing pancreatic neck tumors in well-selected patients; in experienced hands it is associated with no mortality but with high morbidity. Most of the complications do no require reoperation or prolonged in-hospital stay and can be successfully managed conservatively. Moreover, it allows the surgeon to preserve pancreatic parenchyma and consequently long-term endocrine and exocrine pancreatic function.

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An Innovative Option for Venous Reconstruction After Pancreaticoduodenectomy: the Left Renal Vein

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Abstract
Introduction Pancreatic ductal adenocarcinoma has a high mortality rate with limited treatment options. One option is pancreaticoduodenectomy, although complete resection may require venous resection. Pancreaticoduodenectomy with venous resection and reconstruction is becoming a more common practice with many choices for venous reconstruction. We describe the technique of using the left renal vein as a conduit for venous reconstruction during pancreaticoduodenectomy.
Methods The technique for use of the left renal vein as an interposition graft for venous reconstruction during pancreaticoduodenectomy is described as well as outcomes for nine patients that have undergone the procedure.
Results Nine patients, seven men, with a mean age of 57 years, have undergone the operation. There were eight interposition grafts and one patch graft. Mean operating time was 7.8 hours, and mean tumor size was 3.4 cm. Eight patients had node-positive disease, and six had involvement of the vein. Mean hospital stay was 14 days and perioperative morbidity included a superficial wound infection, delayed gastric emptying, ascites, and gastrointestinal bleeding in one patient each. Creatinine ranged from 0.8–1.1 mg/dl preoperatively and from 0.7–1.3 mg/dl at discharge. Mean follow-up was 6.8 months with normal creatinine values noted through the follow-up period. Two patients had died during follow-up from recurrent disease at 8.3 and 18.2 months after the operation.
Conclusions The left renal vein provides an additional choice for an autologous graft during pancreaticoduodenectomy with venous resection. The ease of harvesting the graft and maintenance of renal function distinguish its use.

Keywords Pancreatic cancer · Pancreaticoduodenectomy · Venous resection · Portal vein · Superior mesenteric vein · Left renal vein

Introduction

Pancreatic ductal adenocarcinoma has a high mortality rate[1], which approaches the incidence, and treatment options remain limited. For those patients diagnosed with pancreatic ductal adenocarcinoma, resection continues to offer the only chance for cure. Historically, involvement of local vasculature was considered a contraindication to pancreaticoduodenectomy (PD), with early experience associated with prohibitively high morbidity and mortality rates.[2] As surgeon experience has grown, morbidity and mortality rates have decreased, and at high-volume pancreatic surgery centers, invasion of local mesenteric venous structures is no longer a contraindication to resection. Venous resection occurs in up to 25% of patients undergoing PD at several centers.[3,4] Several techniques are described for reconstruction of the venous system after PD when necessary: primary lateral venorrhaphy, primary end-to-end anastomosis, and interposition grafting.[5,6] Both synthetic grafts and autologous vein grafts have been used, with several donor sites available.[3,7]

The goal of this report is to describe the use of the left renal vein as a conduit for venous reconstruction after PD with venous resection. Historically, the left renal

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vein has been used to repair the portal vein, hepatic vein, or inferior vena cava during resection of hepatic hilar carcinomas,[8–11] and its use offers distinct advantages for venous reconstruction during PD. Importantly, previous studies have demonstrated the safety of left renal vein ligation, specifically in relation to renal function.[12] We describe the technique of mesenteric venous reconstruction after PD with venous resection using a left renal vein graft and report on a group of patients that have undergone this repair.

Patient Selection and Technique

Contrast-enhanced computed tomography (CT) is used to evaluate a pancreatic head mass and its relation to vascular structures. CT accurately diagnoses mesenteric vein involvement, aiding in operative planning. The CT is also used to assess the length and caliber of the left renal vein, the status of the kidneys bilaterally, and the presence of the left gonadal and adrenal veins, which serve as collateral venous drainage. Additional imaging of the pancreas with endoscopic ultrasound (EUS) is frequently used to further evaluate the location and extent of any venous involvement.

After initiation of the operation, a Kocher maneuver allows assessment of tumor location and its relationship to the superior mesenteric artery (SMA), further assessing resectability. The lesser sac is entered by mobilizing the greater omentum off of the transverse colon through an avascular plane. The middle colic vein is followed centrally to identify the superior mesenteric vein (SMV) and the gastrocolic venous trunk. The gastrocolic venous trunk is routinely divided. (Fig. 1a) If venous resection is anticipated, to increase mobility, the middle colic vein and several other tributaries are ligated and divided. (Fig. 1b)

The superior border of the pancreas is approached by incising the gastrohepatic ligament. The right gastric and gastroduodenal arteries are routinely ligated and divided. Retraction of the common hepatic artery cephalad allows dissection of the portal vein (PV), thereby, allowing completion of the plane between the pancreas and the PV-SMV.

The gallbladder is dissected from the liver, and the hepatic duct is encircled near the cystic duct junction. If a pylorus-preserving PD is planned, the superior and inferior aspects of the duodenum are skeletonized, individually ligating the right gastroepiploic vessels. The ligament of Treitz is mobilized, and the proximal jejunum is divided. Sequential ligation and division of the bowel mesentery

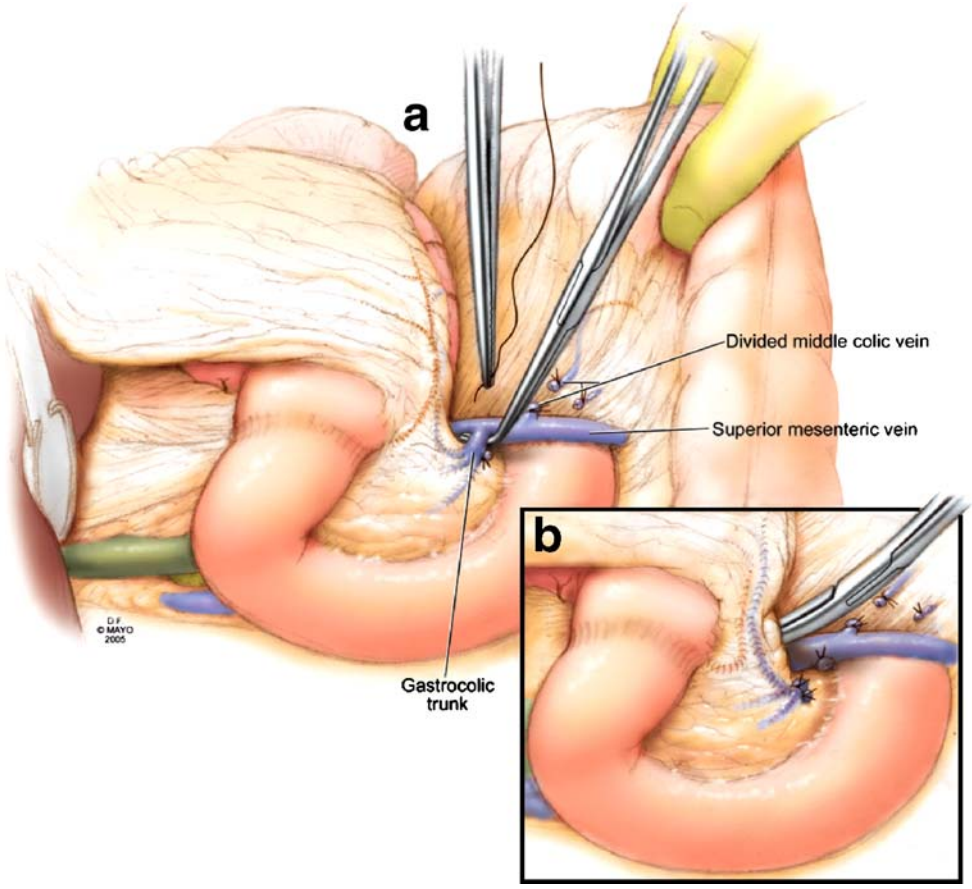

Figure 1 **a** Division of gastrocolic venous trunk and middle colic vein. **b** Mobilization of superior mesenteric vein in preparation of venous reconstruction.

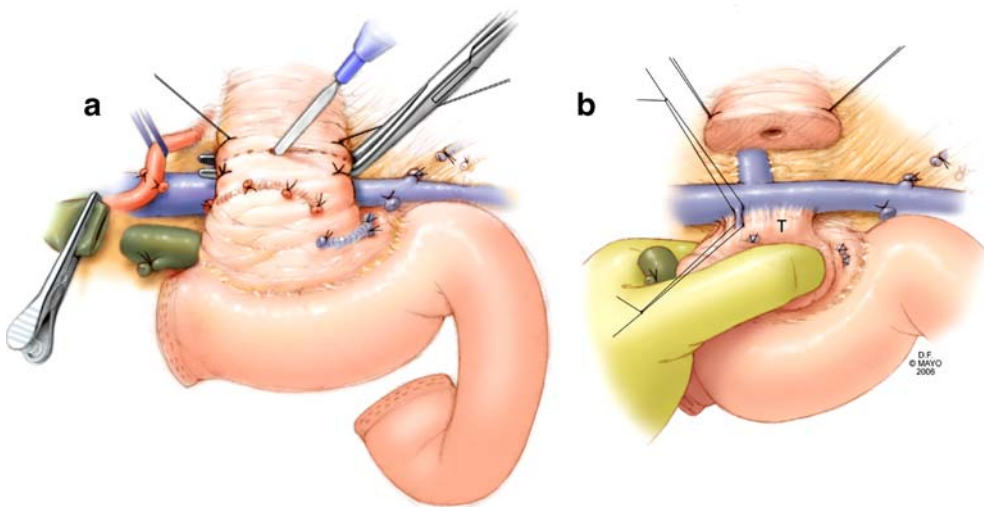

Figure 2 **a** The neck of the pancreas is transected over a clamp, thereby, protecting the portal vein from injury. **b** Venous tributaries to the portal vein are individually ligated while mobilizing the head and uncinate process of the pancreas.

exposes the uncinate process. The mobilized duodenum and jejunum are passed beneath the superior mesenteric vessels into the right upper quadrant.

Mobilization is now complete and transection begins at the duodenum approximately 3 cm distal to the pylorus. The bile duct is transected, and the margin is evaluated for malignancy. Stay sutures are placed on the superior and inferior borders of the pancreas to aid in retraction and hemostasis. The neck of the pancreas is transected over a clamp to protect the portal vein. (Fig. 2a) Reflection laterally allows visualization and ligation of venous tributaries. (Fig. 2b)

Often, venous invasion is not discovered until this juncture, and although some resections can be limited to tangential excision and primary lateral venorrhaphy, there are oncologic and vascular considerations that make other options, including segmental resection with primary end-to-end anastomosis or interposition grafting with autologous or synthetic material, advantageous. Early in our experience, we completed venous resection before division of the arterial branches and soft tissue along the right lateral aspect of the superior mesenteric artery (SMA) (Fig. 3a). More recently, we have altered our technique by performing the dissection of the retroperitoneal margin before venous resection. The advantages of this are to avoid the need for venous anastomosis before removal of the specimen, minimize venous occlusion time, and allow preservation of the splenic vein. This is accomplished by performance of a

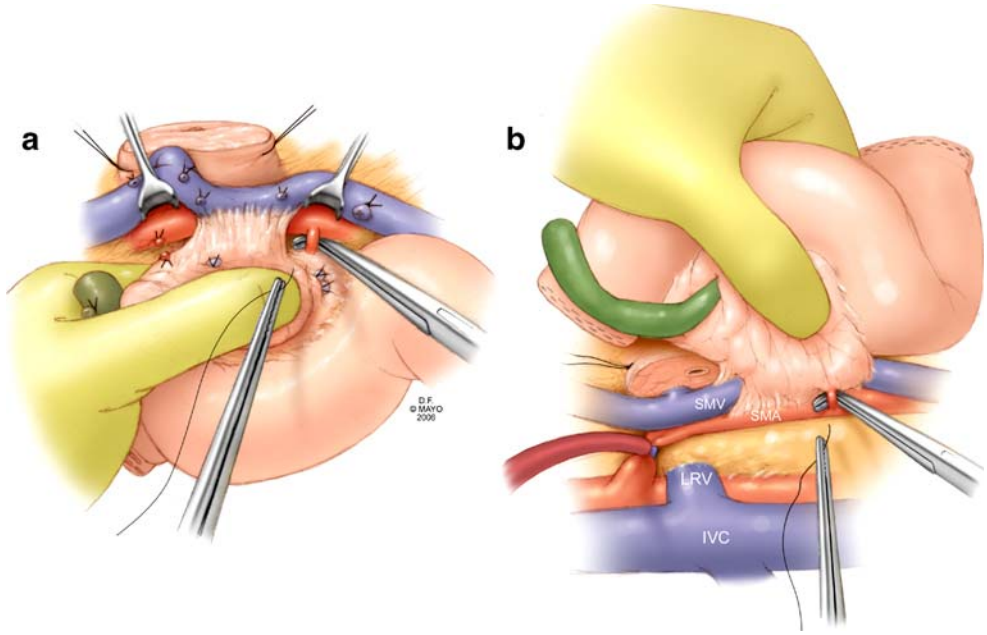

Figure 3 Dissection of the superior mesenteric artery proximal and distal to the area of venous invasion will limit total venous occlusion time after resection is performed. This can be approached anteriorly (**a**) or posteriorly (**b**) as necessary. Inflow occlusion of the SMA during posterior dissection is used selectively if maintenance of hemostasis is problematic.

generous Kocher maneuver and isolation of the superior mesenteric artery both at its origin and caudad to the uncinate process. The Kocher maneuver orients the superior mesenteric artery posterior to the PV-SMV and allows access for completion of the retroperitoneal dissection (Fig. 3b). Arterial branches coursing into the uncinate are sequentially clamped, divided, and ligated, thereby, completely freeing the pancreas from the SMA. The pancreatic head is then rotated back to its normal anatomic orientation, and it is at this juncture that a decision is made for primary end-to-end venous reconstruction or renal vein interposition grafting.

Mobilization of the portal vein superior to the pancreas and the peritoneum along the root of the small bowel mesentery may provide length for the SMV or PV segment. This is accomplished by ligating and dividing small branches to the SMV, PV, and splenic vein (SV). Although primary end-to-end anastomosis is preferred, if interposition grafting is necessary, autologous vein and specifically the left renal vein is utilized for two reasons. First, the vein may be exposed within the same operative field, thereby, eliminating a second operative field and dissection. Second, the caliber and wall thickness of the vein is similar to the portal vein in most instances, providing good handling and suturing properties. Harvest of the left renal vein is undertaken after the retroperitoneal dissection when the specimen remains attached to the portal vein segment only (before venous resection). This allows the best assessment of the need for interposition grafting and minimizes the amount of clamp time by harvesting the graft before SMA and venous occlusion.

The left renal vein is optimally exposed by extending the Kocher maneuver to the left and elevating the head of the pancreas. (Fig. 4a) The vein is divided at the junction of the left gonadal and left adrenal veins, always preserving these vessels as collateral venous outflow for the left kidney. The vein is divided again flush with the inferior vena cava. (Fig. 4b) This typically provides a 3- to 4-cm venous segment. For venous division, we prefer a linear stapling device. The vein segment is placed in heparinized saline and then can be used as an interposition graft. (Fig. 4c)

Vascular control includes the SMA with placement of a Rummel tourniquet (in addition to venous occlusion proximal and distal) and is obtained immediately before resection. This allows inflow occlusion during the resection and reconstruction, decreasing the amount of intestinal engorgement, thereby, facilitating an easier pancreaticojejunostomy. The patient is not systemically heparinized. Venous resection is done sharply to obtain a margin. (Fig. 5) If the specimen has not been entirely freed from the SMA, the remaining branches are now ligated. Communication between the surgical and pathological teams is crucial to fully evaluate the specimen. Of specific importance is the venous segment for margin status and invasion and the retroperitoneal (uncinate) margin. (Fig. 6) Frozen section analysis allows additional margin to be obtained if necessary before reconstruction. After completion of both anastomoses, intraoperative ultrasound is routinely utilized to evaluate the reconstruction for patency. After satisfactory venous reconstruction, the remainder of the gastrointestinal reconstruction is completed. (Fig. 7)

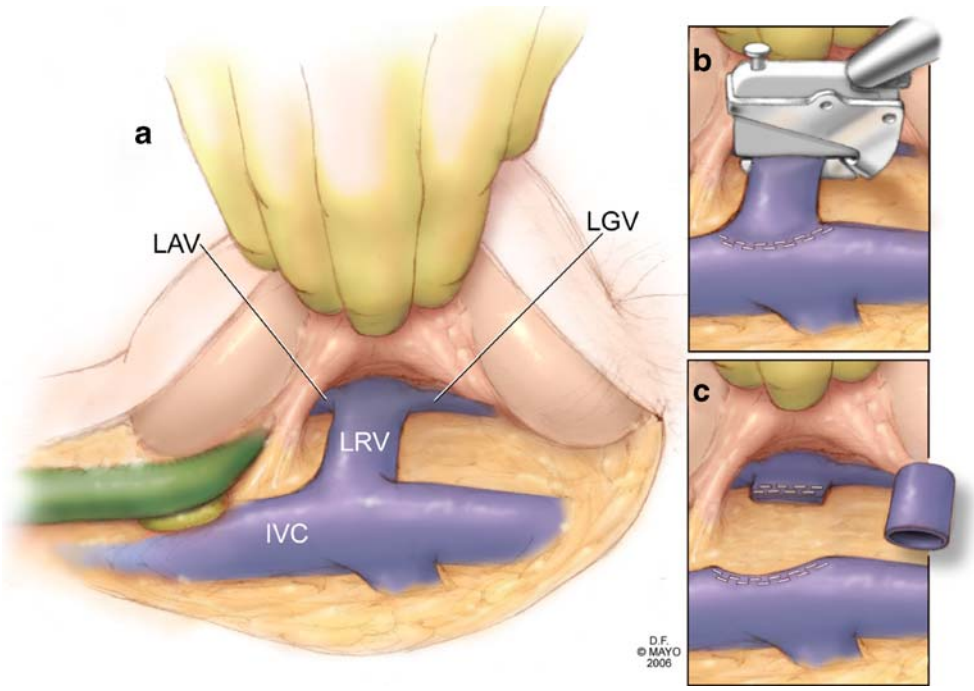

Figure 4 **a** The Kocher maneuver is extended to the left and elevation of the pancreatic head allows exposure of the entire left renal vein and the left adrenal and gonadal veins. **b** The vein is transected with a linear stapling device distal to the insertion of the left adrenal and gonadal veins and again flush with the inferior vena cava. **c** The left renal vein is used as an interposition graft to restore continuity to the mesenteric venous system.

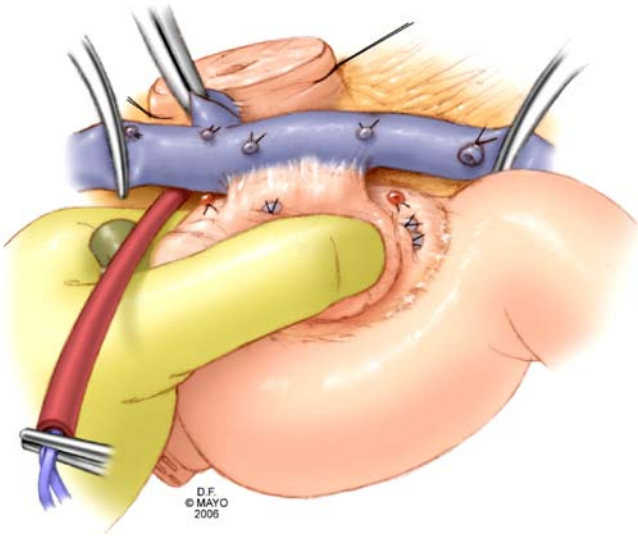

Figure 5 Vascular clamps are used to control the superior mesenteric vein, splenic vein, and portal vein before sharp dissection and resection of the involved venous segment. Inflow occlusion of the superior mesenteric artery during reconstruction reduces bowel engorgement.

Results

Nine patients have undergone reconstruction of the SMV-PV during PD with an autologous left renal vein graft. There were seven men and two women with a mean age of 57 years (range, 31–77). Preoperative abdominal CT had suggested mesenteric vein involvement in seven of the nine patients. EUS was completed in three patients. In one patient, EUS suggested there was no vein involvement, while in the remaining two patients, EUS did suggest involvement. Preoperative serum creatinine levels ranged from 0.8 to 1.1 mg/dl in these patients (normal values 0.9–1.4 mg/dl). Mean follow-up was 6.8 months.

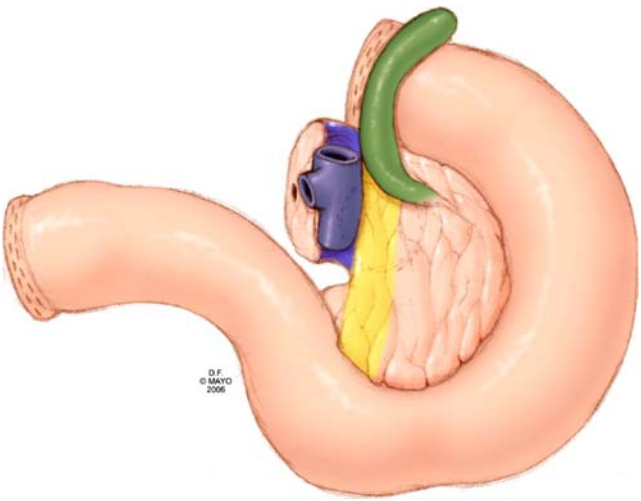

Figure 6 The specimen is carefully marked for all margins, including the venous segment margin. The portal vein groove and the retroperitoneal margin should be inked, and the venous segment should be evaluated histologically for malignant invasion (*posterior view*).

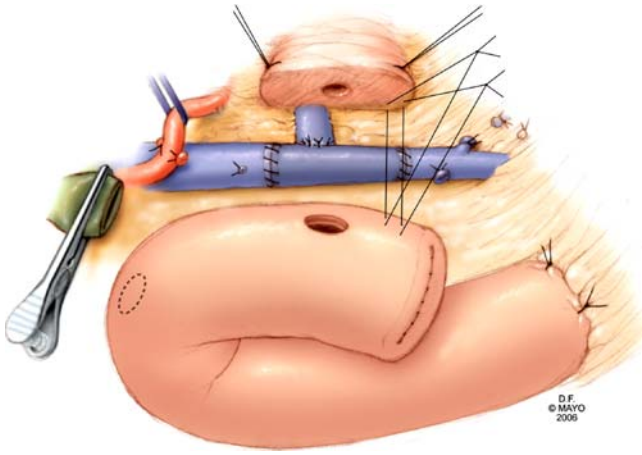

Figure 7 In the example shown, reconstruction of the PV-SMV confluence with an interposition graft utilizing left renal vein was performed initially, followed by reimplantation of the splenic vein into the graft (end-to-side) Gastrointestinal reconstruction is performed in a standard fashion after completion of venous reconstruction.

The procedure consisted of three standard PD and six pylorus-preserving PD. Venous reconstruction consisted of eight interposition grafts and one patch graft. The patch graft was located on the lateral edge of the SMV and PV. Five of the interposition grafts were placed in the SMV, inferior to the confluence. One interposition graft was placed between the SMV and PV with reimplantation of the splenic vein; an additional was placed between the SMV and PV without reimplantation of the splenic vein, and the final graft was in the portal vein. The mean operating time was 7.8 hours (range, 6.5–9.5). The mean tumor size was 3.4 cm (range, 2.2–5). The mean estimated blood loss was 1,300 ml (range, 350–2,500). Eight patients were found to have node-positive disease with six of these patients noted to have histological involvement of the venous segment,

Table 1 A Comparison of Creatinine Levels

Serum Creatinine Concentrations (mg/dL)			
Patient	Preoperative	Peak	Time of Discharge
1	1.1	1.1	1.1
2	1.1	1.4	1.1
3	1	1.5	1
4	0.9	1.3	1.1
5	1	1.3	1
6	0.9	1.3	1.3
7	0.8	0.9	0.9
8	0.8	1.1	0.9
9	0.8	0.8	0.7

while one additional patient had pathologically negative lymph nodes and no evidence of malignant invasion of the vein. In two patients, the uncinate margin was microscopically positive.

One patient was monitored overnight in the intensive care unit. There were no operative mortalities, and reoperation was not required in any of the patients. The mean length of hospitalization was 14 days (range, 9–29). Immediate perioperative morbidity included a superficial wound infection in one patient, delayed gastric emptying in one patient, and postoperative gastrointestinal bleeding in one patient. None of the patients experienced a pancreatic leak. No hematuria was noted. One patient was diagnosed with ascites and stenosis of the left renal vein interposition graft anastomosis 1 month after the operation. This patient had a congenitally cystic (nonfunctioning) left kidney. The left renal vein was reduced in caliber, but felt to be adequate for grafting at the time of the original operation. The patient underwent stenting of the graft by interventional radiology with resolution of her symptoms. Eight patients underwent adjuvant treatment, which included radiation therapy in six patients. None of the six patients receiving radiation therapy experienced a decrement in renal function after radiation therapy. Two patients had died 8.3 and 18.2 months after the operation of recurrent disease. Median survival has not been reached.

After discharge, all patients were evaluated with contrast-enhanced CT. All grafts were patent, and both kidneys were perfused well. Renal function was monitored by following serum creatinine levels. After the operation, creatinine levels transiently increased, but normalized by discharge. (Table 1) Creatinine values were available for a mean of 6.8 months postoperatively, with all levels within the normal range. One patient was anticoagulated with clopidogrel, while subsequent patients were treated with aspirin. Our current protocol is to treat all patients with daily aspirin if no clot is noted on the postoperative imaging, and heparin transitioned to coumadin if clot is noted.

Discussion

Venous resection and reconstruction is not uncommon during PD at high volume centers.[3,4] Involvement of the vein by malignancy is not always suggested preoperatively by imaging and is often discovered at a time during the operation after commitment has already been made to resection. This fact necessitates that the surgeon has a plan for completing the resection and reconstruction of the venous system.[13] Whereas many such cases can be completed with segmental resection and primary end-to-end anastomosis, a number will require either patch repair or interposition grafting. Other groups routinely use the internal jugular vein[3] or superficial femoral vein[14] as a conduit. While these groups have demonstrated good results with these conduits, the use of the left renal vein for autologous grafting offers some significant advantages and avoids the handling difficulties that can be encountered with the internal jugular vein and the risk of lymphedema or venous thrombosis that can be encountered with use of the superficial femoral vein.

The left renal vein provides a graft with good length, good caliber, and is easily accessible. The left renal vein typically provides a graft of 3–4 cm in length when harvested from the junction of the left gonadal and left adrenal vein proximally and the inferior vena cava distally, although some reports have indicated lengths up to 6 cm.[9] The caliber of the graft allows for excellent flow, as demonstrated by CT and Doppler ultrasound. The ease of harvesting the graft also is an important consideration. Exposure of the left renal vein can be accomplished through a standard PD incision, without requiring any further prepping, an additional incision, or the need for an additional operating team. Furthermore, use of the left renal vein leaves the patient with all possible routes of central venous access.

Importantly, the operation is tolerated well from a renal standpoint. Previous work demonstrated that good collateral flow and functional capacity of the left kidney is preserved despite ligation of the left renal vein. McCullough and colleagues reported that after a right nephrectomy and ligation of the left renal vein for malignancy, only one of three patients experienced transient renal insufficiency.[12] In our series, serum creatinine levels transiently increased after operation, but all normalized before discharge. Creatinine levels remained normal throughout follow-up.

Conclusions

Resection offers the only chance at cure for patients with pancreatic cancer, and potentially curative resection may require venous resection. When reconstruction of the venous system necessitates the use of interposition grafting, autologous vein interposition grafts are preferred. The left renal vein provides an additional choice for an autologous graft, and its use is distinguished by ease of harvest and maintenance of renal function. The use of the left renal vein for interposition grafting and patch repair should be considered by surgeons experienced in SMV-PV reconstruction during PD.

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Management of Massive Arterial Hemorrhage After Pancreatobiliary Surgery: Does Embolotherapy Contribute to Successful Outcome?

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Abstract Massive arterial hemorrhage is, although unusual, a life-threatening complication of major pancreatobiliary surgery. Records of 351 patients who underwent major surgery for malignant pancreatobiliary disease were reviewed in this series. Thirteen patients (3.7%) experienced massive hemorrhage after surgery. Complete hemostasis by transcatheter arterial embolization (TAE) or re-laparotomy was achieved in five patients and one patient, respectively. However, 7 of 13 cases ended in fatality, which is a 54% mortality rate. Among six survivors, one underwent selective TAE for a pseudoaneurysm of the right hepatic artery (RHA). Three patients underwent TAE proximal to the proper hepatic artery (PHA): hepatic inflow was maintained by successful TAE of the gastroduodenal artery in two and via a well-developed subphrenic artery in one. One patient had TAE of the celiac axis for a pseudoaneurysm of the splenic artery (SPA), and hepatic inflow was maintained by the arcades around the pancreatic head. One patient who experienced a pseudoaneurysm of the RHA after left hemihepatectomy successfully underwent re-laparotomy, ligation of RHA, and creation of an ileocolic arterioportal shunt. In contrast, four of seven patients with fatal outcomes experienced hepatic infarction following TAE proximal to the PHA or injury of the common hepatic artery during angiography. One patient who underwent a major hepatectomy for hilar bile duct cancer had a recurrent hemorrhage after TAE of the gastroduodenal artery and experienced hepatic failure. In the two patients with a pseudoaneurysm of the SPA or the superior mesenteric artery, an emergency re-laparotomy was required to obtain hemostasis because of worsening clinical status. Selective TAE distal to PHA or in the SPA is usually successful. TAE proximal to PHA must be restricted to cases where collateral hepatic blood flow exists. Otherwise or for a pseudoaneurysm of the superior mesenteric artery, endovascular stenting, temporary creation of an ileocolic arterioportal shunt, or vascular reconstruction by re-laparotomy is an alternative.

Keywords Hemorrhage · Pseudoaneurysm · Pancreato-biliary surgery · Transcatheter arterial embolization

Recent advances in surgical technique and postoperative management of major pancreatobiliary surgery have reduced the morbidity and mortality. However, the problem of life-threatening postoperative arterial hemorrhage caused by pseudoaneurysm rupture, although uncommon, has received little attention.[1–6] Immediate arteriography to identify the site of bleeding and subsequent treatment by radiological intervention have been the first approach for the last decade.[7–9] The efficacy of transcatheter arterial embolization (TAE) is well established.[8–18] Nevertheless, occlusion by TAE sometimes causes distal end-organ damage, even though bleeding has been controlled.[9–11] Indeed, complete interruption of hepatic inflow may lead to fatal hepatic necrosis, but risk factors for whole liver infarction have yet to be identified. Knowledge of which sites are associated with a high risk of hepatic necrosis

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would enable surgeons to choose an alternative to TAE, such as vascular reconstruction. Recent reports have documented an advantage of endovascular stenting over TAE.[19–22] We reviewed the records of patients who experienced massive arterial hemorrhage after pancreatobiliary surgery to help generate guidelines for the management of postoperative pseudoaneurysm rupture.

Patients and Methods

From January 1993 to December 2005, 351 patients underwent major surgery for malignant pancreatobiliary disease in the Department of Gastroenterological Surgery, Yokohama City University. The cases were pancreatic cancer (n=139), distal bile duct cancer (n=58), ampullary cancer (n=46), hilar bile duct cancer (n=47), advanced gallbladder cancer (n=42), and intrahepatic cholangiocarcinoma (n=19). Procedures included pylorus-preserving pancreatoduodenectomy (PPPD) in 113, conventional pancreatoduodenectomy (PD) in 84, distal pancreatectomy (DP) in 35, segmental resection of the pancreas in 4, total pancreatectomy in 6, bile duct resection with partial hepatectomy in 98, and PD combined with partial hepatectomy (HPD) in 11. Patients undergoing isolated bile duct resection or partial hepatectomy without bile duct resection were excluded. Except for the patients who underwent DP, all patients received biliary tract reconstruction and skeletonization of the hepatic arteries to complete lymphadenectomy within the hepatoduodenal ligament. Pancreatojejunostomy was created as an end-to-side, duct-to-mucosa anastomosis with a stenting tube, or via the pancreatic duct insertion technique with total tube drainage when the pancreatic duct was smaller than 3 mm. Hepaticojejunostomy was created end-to-side in a single layer.

Massive postoperative arterial hemorrhage was defined as bleeding requiring a transfusion of 2 or more units of packed red blood cells, an invasive intervention such as laparotomy or TAE and monitoring in the surgical intensive care unit within 24 h of the onset of hemorrhage. The medical records of these patients were analyzed retrospectively.

Results

Of the 351 patients who underwent a major procedure, 13 (3.7%) presented with massive postoperative arterial hemorrhage (10 men and 3 women; average age, 66±10 years). The demographic and clinical characteristics are summarized in Table 1.

After restoration of hemodynamic stability by volume loading, 10 of 13 patients underwent emergency panabdominal angiography visualizing the celiac axis (CA) and superior mesenteric artery (SMA) by standard Seldinger technique. The other three patients required emergency laparotomy without angiography because their clinical status was deteriorating.

Of the 10 patients who underwent angiography, an arterial pseudoaneurysm was detected in 7: right hepatic artery (RHA) in two, gastroduodenal artery (GDA) in three, common hepatic artery (CHA) in one, and splenic artery (SPA) in one. Three patients had extravasation in the area of the middle hepatic artery (MHA), proper hepatic artery (PHA), or GDA without a clear source of bleeding (see Table 1).

TAE was attempted in nine patients using various coil occlusion devices. Table 1 details the origin of bleeding and the sites of TAE. Complete hemostasis was achieved by TAE in five patients, but hemostasis was only temporary in four: two required a second TAE and two required laparotomy to control rebleeding.

Of the three patients with a pseudoaneurysm distal to the PHA, one received selective TAE of the RHA with a successful outcome (patient 1). A second patient had recurrent hemorrhage after TAE of the RHA and second TAE of the PHA was required. Unfortunately, the cluster of coils compressed the portal vein and portal flow was disrupted after the second TAE. This patient died of hepatic failure secondary to hepatic hypoperfusion (patient 2). The third patient had undergone extended left hepatectomy with resection of the RHA and had bleeding from the site of the RHA reconstruction (patient 3). If TAE had been performed at the RHA, inflow to the small remnant liver would be completely interrupted, and fatal hepatic failure would have been the most likely outcome. Instead, we re-operated, ligated the RHA, and created an ileocolic arterioportal shunt to supply the hepatic remnant. The patient survived without hepatic failure. However, portal hypertension developed because this shunt remained patent 6 months after reoperation, and the patient died of spinal metastasis 11 months after the initial operation.

In seven patients, the pseudoaneurysm was proximal to the PHA and involved the GDA or CHA. Two patients successfully underwent selective TAE of the GDA for a pseudoaneurysm that originated from the ligated GDA. One patient had a replaced RHA from the CA, which contributed to a favorable outcome (patient 4, Fig. 1). One patient underwent TAE of the CHA uneventfully because the hepatic inflow was narrowly maintained by the left subphrenic artery (patient 6, Fig. 2). In contrast, the patient who had extravasation of the PHA without a discrete source had intimal injury and occlusion of the CHA during angiography. The patient experienced a liver abscess that was difficult to treat and died of sepsis and cancer recurrence during a long hospital stay (patient 7). Of the three patients who underwent right hepatectomy, two had complete disruption of the inflow to the hepatic remnant by TAE of

Table 1 Baseline Characteristics of Patients

Case	Disease	Origin of bleed	Surgery	Interval (days)[a]	Site of TAE	Re-laparotomy	Cause of bleed	Outcome
1	Ampullary cancer	RHA	PPPD	10	RHA	No	Pancreatic leak	Alive
2	Gallbladder cancer	RHA and RHA	HPD	8 and 12	RHA and PHA	No	Minor injury	Hepatic failure died
3	Hilar bile duct cancer	RHA	Extended left hepatectomy	9	None	No	Unsuccessful reconstruction	Cancer recurrence, died
4	Gallbladder cancer	GDA	HPD	10	GDA	No	Pancreatic leak	Alive
5	Distal bile duct cancer	GDA	PD	11	GDA	Yes	Minor injury	Alive
6	Distal bile duct cancer	CHA	PPPD	24	CHA	No	Pancreatic leak	Alive
7	Distal bile duct cancer	PHA	PD	7	None	No	Pancreatic leak	Sepsis, died
8	Hilar bile duct cancer	GDA	Right hepatectomy	7	CHA	Yes	Minor injury	Hepatic failure died
9	Gallbladder cancer	MHA and GDA	Right hepatectomy	13 and 27	MHA and CHA	No	Pancreatic leak	Hepatic failure died
10	Gallbladder cancer	GDA	Right hepatectomy	7	GDA	Yes	Pancreatic leak	Hepatic failure died
11	Pancreatic cancer	SPA	DP	17	CA	Yes	Pancreatic leak	Alive
12	Intrahepatic cholangiocarcinoma	SPA	HPD	9	None	Yes	Minor injury	Hepatic failure died
13	Pancreatic cancer	SMA	PPPD	34	None	Yes	Pancreatic leak	MOF, died

TAE Transcatheter arterial embolization, *RHA* right hepatic artery, *PHA* proper hepatic artery, *GDA* gastroduodenal artery, *CHA* common hepatic artery, *MHA* middle hepatic artery, *SPA* splenic artery, *CA* celiac axis, *SMA* superior mesenteric artery, *PPPD* pylorus preserving pancreatoduodenectomy, *HPD* pancreatoduodenectomy combined with partial hepatectomy, *DP* distal pancreatectomy, *PD* pancreatoduodenectomy, *MOF* multiple organ failure

[a] Days from surgery to hemorrhage

the CHA, leading to fatal hepatic failure (patients 8 and 9), and one underwent unsuccessful TAE of the GDA and required a laparotomy. Vascular ligation at the pancreatic head was successful in achieving hemostasis, but hepatic failure secondary to hemorrhagic shock proved fatal 59 days after the initial surgery (patient 10).

Of the two patients with a pseudoaneurysm originating from the SPA, one underwent TAE of the CA with a favorable outcome because the pancreatoduodenal arcades around the pancreatic head maintained hepatic inflow after DP (patient 11, Fig. 3). The other patient underwent an emergency laparotomy. Complete hemostasis was achieved

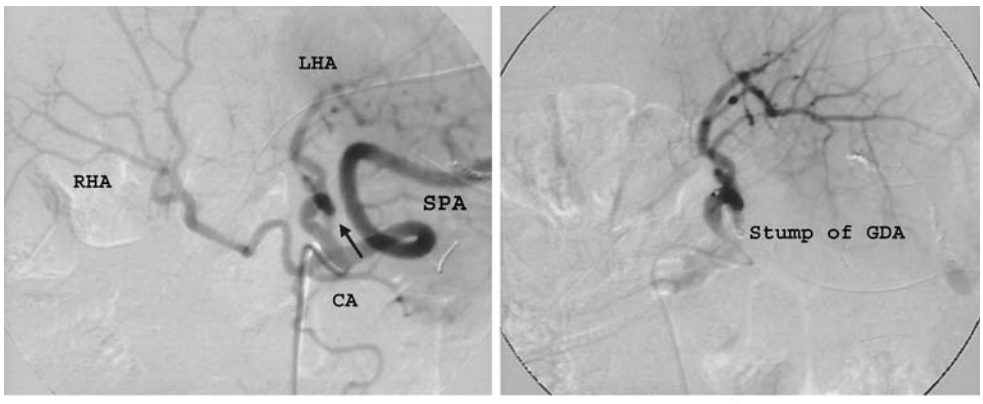

Figure 1 Case 3. A 74-year-old woman with advanced gallbladder cancer presented with massive hemorrhage 10 days after pancreatoduodenectomy combined with partial hepatectomy of the segments (Couinaud segments) IVb and V. Angiogram of the common hepatic artery [the right hepatic artery (RHA) replaced from the celiac axis (CA)] showed a pseudoaneurysm (*arrow*) originating from the stump of the gastroduodenal artery (GDA). (**a**) Complete hemostasis was obtained using transcatheter arterial embolization of this stump. The patient survived without hepatic failure because the hepatic inflow was maintained by the replaced RHA (**b**). *LHA* Left hepatic artery, *SPA* splenic artery.

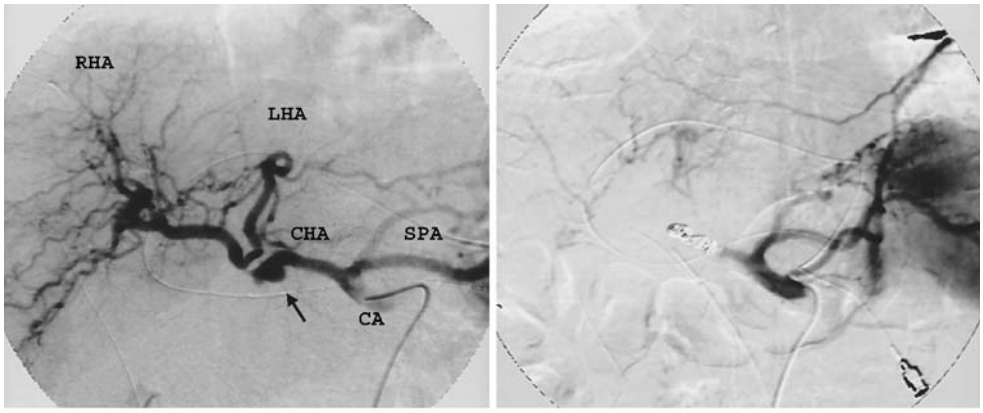

Figure 2 Case 4. A 69-year-old man who had undergone a pylorus preserving pancreatoduodenectomy for distal bile duct cancer had massive hemorrhage 24 days after surgery. Angiogram of the celiac axis (CA) showed a pseudoaneurysm (*arrow)* originating from the common hepatic artery (CHA) (**a**) Complete hemostasis was obtained using transcatheter arterial embolization proximally and distally to the origin of the pseudoaneurysm, but the proper hepatic artery was occluded. The hepatic arterial inflow was narrowly maintained via the left subphrenic artery (**b**). The patient had an uneventful course. RHA Right hepatic artery, *LHA* left hepatic artery, *SPA* splenic artery.

by ligation, but hemorrhagic shock resulted in subsequent hepatic failure (patient 12).

One patient with a pseudoaneurysm of the SMA underwent surgical resection with vascular reconstruction. However, the patient died of recurrent pancreatic cancer and multiple organ failure during the hospital stay (patient 13).

Seven of 13 patients died in the hospital; thus, the mortality rate for massive arterial hemorrhage was 54%, and the overall mortality rate was 2.0%.

Case reports of some patients are illustrated in Figs. 1, 2, and 3.

Discussion

Rupture of a pseudoaneurysm, although uncommon, can cause life-threatening hemorrhage even comparatively late after pancreatobiliary surgery.[1–6] This morbidity rate for pancreatectomy was reported to range from 2.0% to 4.6%.[4–6,11,12] A pseudoaneurysm is a pulsatile hematoma surrounded by fibrous tissue that communicates with the artery via a disruption of the arterial wall. It can rupture into the peritoneal cavity, the gastrointestinal tract, or biliopancreatic ducts through a point of weakness, most

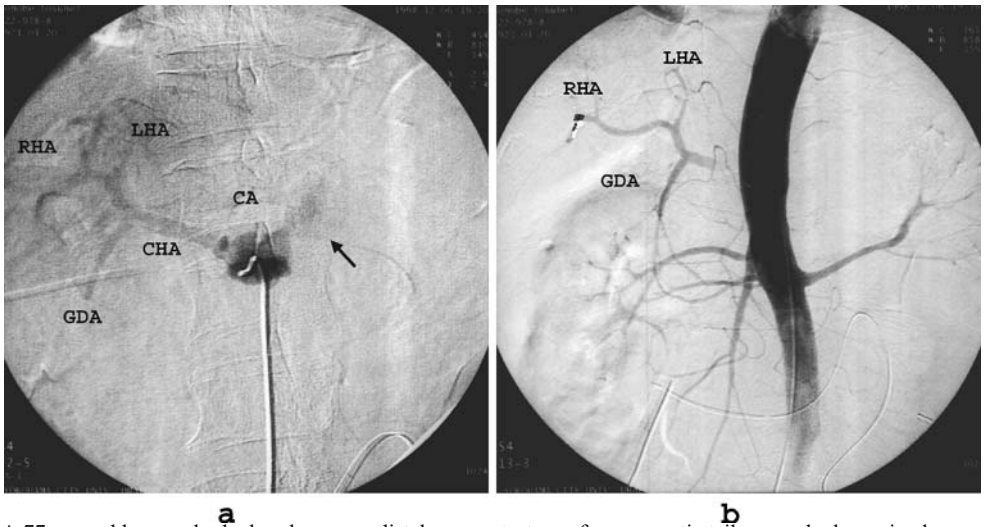

Figure 3 Case 8. A 77-year-old man who had undergone a distal pancreatectomy for pancreatic tail cancer had massive hemorrhage 17 days after surgery. Angiogram of the celiac axis (CA) showed a pseudoaneurysm (*arrow*) originating from the splenic artery (**a**). Hemostasis was obtained using transcatheter arterial embolization (TAE) of the CA. The common hepatic artery (CHA) was occluded by TAE but the hepatic inflow was maintained via the arcades of the pancreatic head from the superior mesenteric artery (**b**). The patient had a favorable course. *RHA* Right hepatic artery, *LHA* left hepatic artery, *GDA* gastroduodenal artery.

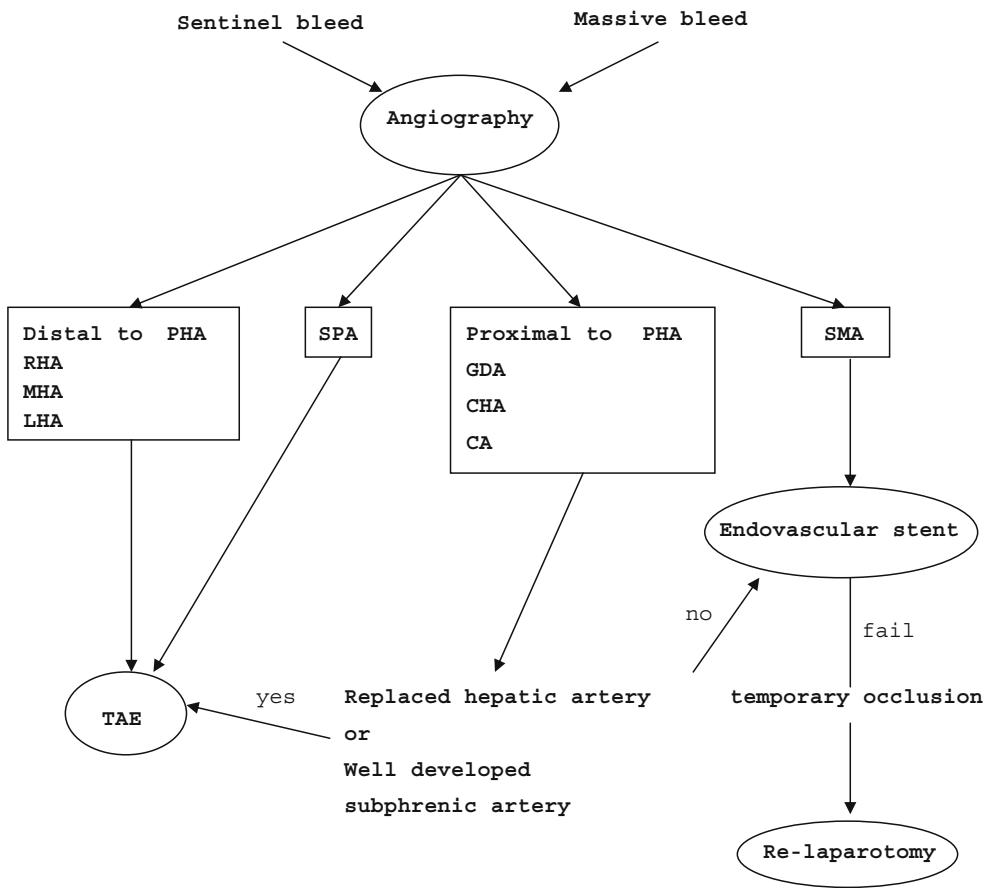

Figure 4 Scheme for an approach to the management of a pseudoaneurysm according to the site of bleeding. PHA Proper hepatic artery, RHA right hepatic artery, *MHA* middle hepatic artery, *LHA* left hepatic artery, *SPA* splenic artery, *GDA* gastroduodenal artery, *CHA* common hepatic artery, *CA* celiac axis, *SMA* superior mesenteric artery, *TAE* transcatheter arterial embolization.

commonly the anastomotic site. The Japanese Multi-institutional Study of 1,066 patients who underwent PPPD reported that the incidence of intra-abdominal hemorrhage was 3.5% and that of upper gastrointestinal hemorrhage was 3.2%.[23]

The etiology of pseudoaneurysm formation has yet to be clearly delineated. It is believed to be most commonly due to pancreatic fistula or anastomotic dehiscence.[1–4,10–12] However, pseudoaneurysm can develop far from the pancreatic cut surface, and there is no evidence of a pancreatic leak in some cases. It has been suggested that skeletonization of the visceral arteries may result in iatrogenic vascular injury (e.g., secondary to diathermy).[10,14] In three patients in our series, the etiology was thought to be a minor vascular injury that occurred during dissection (see Table 1). Previous reports found that the patients with massive arterial bleeding frequently had septic complications.[3,4,17] Therefore, both arterial injury and infection can contribute to massive arterial hemorrhage. Whether or not preoperative obstructive jaundice is an etiologic fact remains controversial.[3,24]

Some clinical studies found that a preliminary warning bleeding (sentinel bleeding) precedes major hemorrhage.[1,2,9–13] This sentinel bleeding probably indicates local infection and an anastomotic leak.[2] So, recognition of a sentinel bleeding and prompt intervention can be life-saving.

Angiography is necessary to identify the site of bleeding, and TAE is the treatment of choice to control massive bleeding and achieve hemodynamic stabilization. When performing TAE for a pseudoaneurysm, microcoils must be placed both proximally and distally to the origin, not within the pseudoaneurysm itself.[11,25]

When the origin of the pseudoaneurysm is distal to the PHA, left hepatic artery, RHA, or MHA, TAE should be highly selective to preserve the other branch to the liver. Selective TAE without devascularization of the other lobe provides optimal protection of the liver parenchyma (patient 1).[15] Nevertheless, superselective TAE frequently is not possible. Inadvertent occlusion of PHA, even when bleeding is controlled, may cause fatal hepatic infarction (patient 2).[10] Therefore, the success of superselective TAE distal to the PHA depends on the expertise of the radiologist.

Superselective TAE is difficult or even impossible for a pseudoaneurysm proximal to the PHA.[24] When the GDA is ligated close to its divergence from the CHA, you must embolize the CHA to obtain hemostasis. The proximal and

distal control of a bleeding pseudoaneurysm of the PHA or CHA usually results in complete occlusion of hepatic arterial flow. Fortunately, we successfully performed TAE of the GDA in patient 4 because the patient had the replaced RHA from CA, and it was unaffected by TAE. Even if the CHA is occluded, the prognosis is good when hepatic inflow can be maintained by a replaced hepatic artery,[6,13,14] but success is not uniform. In another case, hepatic inflow was narrowly maintained by the left subphrenic artery after TAE of the CHA (patient 6). A similar case has been described previously.[16] The liver can tolerate considerable arterial embolization because of its multiple collateral pathways, mainly via the subphrenic arteries. Unless the surgical procedure includes mobilization of both lobes of the liver, as long as the subphrenic arteries are well developed, TAE proximal to the PHA should lead to a successful outcome. However, TAE proximal to the PHA usually risks occlusion of the CHA with the attendant risk of necrosis and liver failure.[9,17] The authors believe that the presence of a few collateral pathways might make liver abscesses difficult to treat and may be associated with high morbidity and mortality rates (patient 7).[10] Complete interruption of arterial inflow to the remaining liver after major hepatectomy usually causes imminent hepatic failure (patients 8 and 9). Emergency laparotomy and vascular reconstruction are the most certain treatments for this type of bleeding, but preoperative angiography is highly recommended to identify the bleeding site, although surgery should not be excessively delayed. Endovascular stenting is another option in reestablishing the continuity of the bleeding artery, such as GDA, PHA, or CHA.[19–22] A covered stent makes it possible to arrest the bleeding, while preserving patency. Potential disadvantages include longer duration to obtain hemostasis than TAE, technical difficulties in negotiating tortuous arteries, and the risk of arterial rupture due to low flexibility and fragile vascular walls. In the case of a stented hepatic artery, the progressive occlusion of the stent due to intimal hyperplasia would not influence outcome because this process is gradual and allows for the formation of collateral pathways.[21] Therefore, a stent-graft delivered into a bleeding artery proximal to PHA may be the treatment of choice. When this procedure is technically difficult, vascular reconstruction should be performed after temporary occlusion by interventional radiology. When vascular reconstruction is difficult and ligation is required to obtain hemostasis, creation of an ileocolic arterioportal shunt is another option,[26] which we performed successfully in patient 3. Thus, the indications for TAE proximal to the PHA are limited to cases where the replaced hepatic artery exists or the subphrenic arteries are well developed.

Pseudoaneurysm originating from the SPA is well described as a complication of pancreatitis,[27,28] but this is an unusual source of bleeding after pancreatobiliary surgery. Selective TAE is indicated because ischemia of the spleen is rare. However, when the origin of the pseudoaneurysm is close to the CA, selective TAE proximal to the SPA is as difficult as the case of bleeding from the GDA. Therefore, when the SPA is divided in surgery, it may be better to leave the proximal part of the ligation site in some degree. TAE of the CA is contraindicated as it will completely interrupt hepatic arterial flow in most cases (patient 11).

When the origin of a pseudoaneurysm is the SMA, it may be extremely difficult or even impossible to preserve mesenteric arterial flow. Hence, resection of the pseudoaneurysm with vascular reconstruction is indicated (patient 11). Endovascular stenting may be an alternative deserving further study.

Hemorrhagic shock is a potentially fatal complication that may result in hepatic failure (patient 10). Rebleeding after TAE is a poor prognostic factor. As rebleeding is often due to a pancreatic leak or intraperitoneal septic condition, pancreatic drainage and loculated fluid collections are mandatory.[6] The management of anastomotic dehiscence after pancreatectomy, whether a completion pancreatectomy is necessary or not, is controversial.[1,6,29–33] When management of the dehiscence is difficult or when severe organ failure is present, completion pancreatectomy is probably necessary.[1,6,29–31]

Analysis of our experience and literature review suggests that management of a pseudoaneurysm must be individualized according to the site of bleeding (Fig. 4). We have developed a protocol for managing massive postoperative arterial hemorrhage and are evaluating it postoperatively in a prospective fashion. We hope to report the value of this approach in the future.

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Platelet Function in Acute Experimental Pancreatitis

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Abstract Acute pancreatitis (AP) is characterized by disturbances of pancreatic microcirculation. It remains unclear whether platelets contribute to these perfusion disturbances. The aim of our study was to investigate platelet activation and function in experimental AP. Acute pancreatitis was induced in rats: (1) control (n=18; Ringer's solution), (2) mild AP (n=18; cerulein), and (3) severe AP (n=18; glycodeoxycholic acid (GDOC) + cerulein). After 12 h, intravital microscopy was performed. Rhodamine-stained platelets were used to investigate velocity and endothelial adhesion in capillaries and venules. In addition, erythrocyte velocity and leukocyte adhesion were evaluated. Serum amylase, thromboxane A2, and histology were evaluated after 24 h in additional animals of each group. Results showed that 24 h after cerulein application, histology exhibited a mild AP, whereas GDOC induced severe necrotizing AP. Intravital microscopy showed significantly more platelet–endothelium interaction, reduced erythrocyte velocity, and increased leukocyte adherence in animals with AP compared to control animals. Thromboxane levels were significantly elevated in all AP animals and correlated with the extent of platelet activation and severity of AP. In conclusion, platelet activation plays an important role in acute, especially necrotizing, pancreatitis. Mainly temporary platelet–endothelium interaction is observed during mild AP, whereas severe AP is characterized by firm adhesion with consecutive coagulatory activation and perfusion failure.

Keywords Acute pancreatitis · Platelets · Leukocytes · Endothelium interaction · Microcirculation · Coagulation

Introduction

Acute pancreatitis (AP) is characterized by an inflammatory affection of the exocrine pancreatic tissue and disturbances of pancreatic microcirculation.[1] Depending on the severity of AP, irreversible perfusion failure with consecutive tissue hypoxia and necrosis can complicate the course of the disease and trigger systemic inflammatory and septic complications.[2] The pathophysiology of AP has been investigated with regard to microcirculatory changes in several studies.[1–5] Attention was paid especially to erythrocyte flow patterns, leukocyte–endothelium interaction, and rheological approaches to improve perfusion and inhibit irreversible tissue damage.[1,3–5] Leukocyte–endothelium interaction as an early event of the inflammatory response has been characterized as a key step in the pathophysiology of AP.[6] Besides, activation of the humoral coagulation cascade plays an important role in the development of microcirculatory disorders in AP.[7,8] However, the role of platelets as the cellular elements of hemostasis that can functionally link inflammatory cells and humoral coagulation factors has not been investigated.

The aim of this study was to investigate platelet activation and function in experimental AP.

Parts of the results of this study were presented at the congress of the German Surgical Society, Berlin (May 2004), the Digestive Disease Week (May 2004), and the Annual Meeting of the American Pancreatic Association, Chicago (November 2004).

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Materials and Methods

Animals The experiments were performed in 54 male Wistar rats weighing 270 to 335 g. Animals were fasted overnight with free access to water before the experiments. Care was provided in accordance with the guidelines published in the "Guide for Care and Use of Laboratory Animals" (National Institutes of Health, publication no. 85-23, 1985). Surgical anesthesia was induced with intraperitoneal injection of pentobarbital (25 mg/kg) and intramuscular injection of ketamine (40 mg/kg) for the procedures of catheter placement and induction of pancreatitis. Anesthesia during intravital microscopy was induced by intravenous injection of pentobarbital (10 mg/kg). Polyethylene catheters (inner diameter 0.5 mm) were placed in the right jugular vein and left carotid artery, tunneled subcutaneously to the suprascapular area, and brought out through a steel tether that allowed the animals' free movement and access to water during the experiments.

Monitoring blood samples Mean arterial pressure and heart rate were monitored during intravital microscopy by an electromechanical pressure transducer (Baxter Uniflow, Baxter Healthcare Cooperation, Deerfield, IL, USA). Arterial blood samples for determination of serum amylase were obtained before (baseline) and 24 h after (end point) pancreatitis was induced. Serum amylase was determined by standard laboratory methods (Hitachi automatic analyzer, Boehringer Mannheim, Germany).

Animal models Animals were divided into three groups. In each group, pancreatic microcirculation was evaluated in 12 animals by intravital microscopy, and morphological changes were assessed in six animals by histology. In the control group, animals underwent sham operation and received Ringer's solution only. Acute pancreatitis of graded severity was induced in the other groups either as mild or severe AP. Mild AP was induced by intraarterial infusion of cerulein (5 $\mu g\ kg^{-1}\ h^{-1}$) for over 6 h. Cerulein was reconstituted in saline solution, and infusion volume was 4 ml/kg/h. Severe necrotizing pancreatitis was induced by infusion of bile salt (glycodeoxycholic acid [GDOC] 2.5 mM/l) into the pancreatic duct in combination with intraarterial infusion of cerulein (5 $\mu g\ kg^{-1}\ h^{-1}$) for over 6 h as described by Schmidt et al.[9] in detail. Bile-salt infusion into the pancreatic duct was performed in a volume- (1.2 ml/kg), time- (5 min), and pressure- (30 mmHg) controlled manner.

In each of the models, animals received saline solution during the observation period (0.9%, 4 ml $kg^{-1}\ h^{-1}$). Intravital microscopy was performed 12 h after the induction of pancreatic injury, and histological changes and blood samples were assessed 24 h after the infusions were started.

Platelet preparation One milliliter of whole blood was withdrawn before intravital microscopy. Platelets were separated and stained according to the method originally described by Massberg et al.[10] Briefly, platelets were stained by rhodamine 6G and separated by 2 cycles of centrifugation under the addition of prostacyclin. After suspending and washing the separated platelets, blood cell count was performed to calculate the number of platelets per microliter and to rule out animal-specific differences in the number of platelets. Platelets were then reinjected, and intravital microscopy was performed.

Intravital microscopy The abdomen was reopened, and the pancreas was carefully exteriorized in a horizontal position through the midline incision after the animal was placed on the right side. The duodenal loop with the head of the pancreas was carefully fixed on an anatomically designed stage in a temperature-controlled (37°C) Ringer's bath. Afterward, intravital microscopy was performed as described below. The animals were killed after the completion of intravital microscopy by a pentobarbital overdose.

Erythrocyte and leukocyte assessment A 0.5 ml/kg of erythrocytes (hematocrit 50%) labeled with fluorescein isothiocyanate (FITC) as described before[11] was applied intravenously. In addition, 1 ml/kg of rhodamine-6G solution was applied intravenously to label leukocytes in vivo.[12] Intravital microscopy was performed after an equilibration period of 15 min using a fluorescent microscope (Leitz, Wetzlar, Germany) with a 20-fold water immersion objective. An epi-illuminescent xenon lamp with an excitation filter of 450–490 nm was used for visualization of FITC-labeled erythrocytes and an excitation filter of 540–630 nm for rhodamine-labeled leukocytes.

Platelet assessment After platelet reinjection, intravital microscopy was performed by an epi-illuminescent xenon lamp with an excitation filter of 540–630 nm.

Off-line analysis Images were transferred to a monitor and simultaneously recorded on a videotape recorder. In each animal, five capillary fields of the exocrine pancreas and five postcapillary venules (20–40 μm) were recorded for 1 min. Off-line analysis was performed using a specially designed computer program (Capimage, Dr. Zeintl, Heidelberg, Germany). Erythrocyte velocity and platelet velocity were determined for 10 cells in each capillary field and venule. Additionally, temporarily (rolling) and permanently (sticking) adherent leukocytes and platelets were determined in pancreatic venules and capillary fields. Rolling cells were defined as cells with less than 66% of red blood cell velocity, whereas sticking cells are those that were adherent to the vessel wall for the whole observation period.[13]

Table 1 Serum Parameters, Wet–Dry Ratio, and Histopathology

	Control	Mild AP	Severe AP
Serum parameters			
Amylase (U/l)	586±116	27,200±4,012*	27,317±3,220*
Thromboxane A2 [pg/50 µl]	15.3±10.3	47.8±12.1*	61.9±15.8*
Wet–dry ratio	2.87±0.79	6.96±0.95*	4.77±0.70
Histopathology			
Inflammation	0.25±0.42	1.31±0.08*	1.95±0.17*†
Necrosis	0.08±0.20	1.10±0.11*	1.70±0.23*†

*$p<0.05$ vs control group
†$p<0.05$ vs mild acute pancreatitis

Edema A portion of pancreatic tissue was trimmed of fat and weighed. Pancreatic water content was determined by the ratio of the initial weight (wet weight) of the pancreas to its weight after incubation at 60°C for 72 h (dry weight).

Histology The pancreas was immediately removed after killing and was fixed in 4% buffered formalin solution. It was then embedded in paraffin, cut, and stained with hematoxylin eosin. Histopathological evaluation was performed in a blinded fashion. For quantification of edema, inflammation, and necrosis, a modification of the scoring system originally described by Schmidt et al.[9] was used, ranging from 0 to 3 (no pathological changes to severe injury).

Assessment of thromboxane A2 Thromboxane A2 was measured in frozen serum by commercially available enzyme-linked immunosorbent assay (University of Freiburg, Germany).

Statistical analysis Results are shown as mean±SEM. Student's *t* test was used when the data had a normal distribution, whereas Kruskal–Wallis and Mann–Whitney tests were utilized when the distribution was not normal. Statistical significance was accepted at the 5% level ($p<0.05$).

Results

Serum amylase Twelve hours after the induction of AP, serum amylase increased significantly compared to control animals. Hyperamylasemia was comparable in both mild and severe AP indicating the presence of pancreatic cell damage. However, amylase was not a marker for the extent of tissue damage or disease severity (Table 1).

Serum thromboxane A2 Thromboxane A2, as a marker of platelet activation, showed significantly higher levels in both AP groups compared to control animals after 24 h. Thromboxane liberation correlated with severity of AP, with the highest levels being present in animals with necrotizing AP (Table 1).

Intravital microscopy Erythrocyte velocity decreased significantly in mild as well as severe AP in both capillaries and venules compared to control animals. Platelets showed comparable flow features. Flow velocity decreased under both AP conditions, with a highly significant decrease in severe AP in venules and capillaries (Table 2). These changes were paralleled by increased interaction between leukocytes and endothelium (Table 2). Platelet adhesion in capillaries and venules increased significantly in both mild and severe AP (Figs. 1 and 2). Reversible adhesion (rolling platelets) were comparable during both forms of AP, whereas the increase in irreversible adhesion (sticking platelets) depended on the severity of AP and showed peak platelet–endothelium adherence in necrotizing AP (Figs. 1 and 2).

Tissue edema (wet/dry ratio) Supramaximal cerulein stimulation induced a significant increase in pancreatic water content compared to control animals. In contrast, there was only a slight increase in tissue edema after GDOC treatment (Table 1).

Histopathology Control animals showed no histopathological changes after sham operation and 24 h infusion therapy. Histopathology of mild AP was characterized by significant edema formation, inflammatory tissue infiltration, and

Table 2 Results of the Intravital Microscopy

Intravital microscopy	Control	Mild AP	Severe AP
Erythrocyte velocity (capillary) (mm/s)	0.65/0.02	0.42/0.01*	0.36/0.01*
Erythrocyte velocity (venule) (mm/s)	0.93/0.11	0.77/0.17	0.58/0.10*†
Platelet velocity (capillary) (mm/s)	0.54±0.04	0.35±0.03*	0.29±0.03*
Platelet velocity (venule) (mm/s)	0.67±0.05	0.63±0.02	0.53±0.05*
Rolling leukocytes (capillary)	1.3±0.2	4.5±1.4*	9.0±1.7*†
Rolling leukocytes (venule)	1.3±0.2	14.8±1.2*	18.9±1.9*
Sticking leukocytes (capillary)	1.1±0.3	10.2±1.8*	7.2±0.7*
Sticking leukocytes (venule)	0.7±0.1	5.6±0.9*	13.5±2.0*†

*$p<0.05$ vs control group
†$p<0.05$ vs mild acute pancreatitis

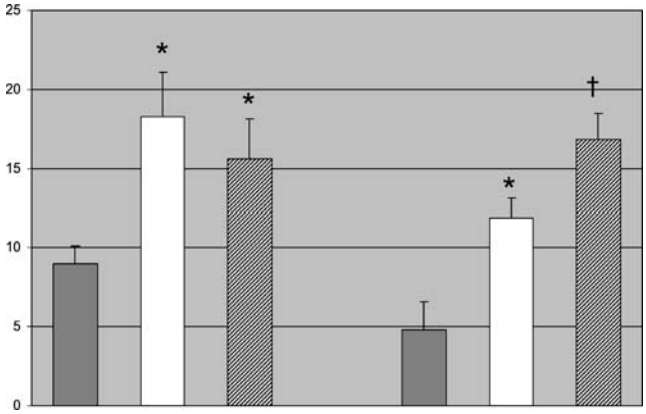

Figure 1 Intravital microscopy, capillary platelet adhesion (one per field). Control group (*gray*), mild acute pancreatitis (*white*), and severe acute pancreatitis (*striped*). Reversible platelet adhesion in mild and severe acute pancreatitis (*left columns*); irreversible platelet adhesion (*right columns*). *$p<0.05$ vs control group, †$p<0.05$ vs mild acute pancreatitis.

acinar cell necrosis. In severe AP, the changes regarding inflammation and necrosis were significantly more pronounced (Table 1).

Discussion

In the present study, we have investigated platelet function in experimental models of AP. We chose two animal models to induce a mild edematous or a severe necrotizing course of AP. Both models are established, well characterized, and have been used in numerous studies.[9,14,15] The induction of AP in these models results in a standardized grade of tissue damage, either mild or severe, with very little variance within each group. Therefore, the use of these models allows us to rule out the significant influence of preparatory or other methodological problems on the comparability of the results.

Analysis of platelet function by intravital microscopy has been established and standardized for examination of liver and small bowel perfusion by Massberg et al.[10] We have modified this method to investigate the pancreas.[15] In the present study, we could demonstrate that this method is not only suitable for the examination of healthy pancreas but also for the detailed analysis of pancreatic microcirculation in mild and severe AP.

Acute pancreatitis is characterized by an impairment of microcirculation due to an activation of inflammatory cells with a consecutive increase of leukocyte–endothelium interaction. These pathophysiological events mediate an inflammatory tissue infiltration, edema, and hemorrhagic lesions. While the inflammatory response is well investigated, the platelet function and the role of the coagulation cascade have not yet been investigated in detail.

It is well known that the inhibition of certain coagulatory steps, e.g., by applying hemodiluting or anticoagulatory substances, improves the outcome of AP.[16,17] Coagulation and hemostasis comprise two interacting pathways: humoral coagulatory factors leading to the activation of fibrinogen as the final step of the coagulation cascade and cellular factors, which are represented by activated platelets. Different mechanisms of platelet interaction are responsible for their physiological function, namely, interactions with endothelium, leukocytes, and humoral coagulatory and inflammatory proteins.[18,19]

In the present study, we could demonstrate that the platelet–endothelium interaction increases during AP and correlates with the degree of its severity. Comparable to leukocyte–endothelium interaction, temporary and permanent adhesions of platelets to the vessel wall were evident in our experiments. This correlates with the activation patterns that have been observed in vivo in ischemia models of the liver and the pancreas,[15,20] as well as in vitro.[21] Therefore, it seems likely that these activation patterns reflect the severity of the pancreatic affection, leading to reversible adhesion in mild AP and irreversible adhesion in more severe organ affection. Especially, the firm adhesion of platelets contributes to microcirculatory disturbances and may induce perfusion failure and tissue necrosis in the progression to severe AP. The significantly elevated thromboxane levels correlate well with platelet activation and microcirculatory failure observed during intravital microscopy. The increase in serum thromboxane elucidates one mechanism of our results as it executes a direct platelet stimulation and leads to the conversion of "resting" to "activated" platelets with the consecutive adhesive action. Furthermore, thromboxane does not only activate platelets but also acts as a complex pathophysio-

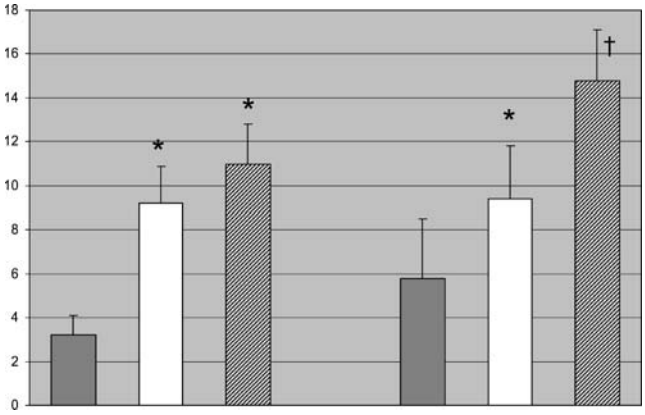

Figure 2 Intravital microscopy, venular platelet adhesion (one per 100 μm). Control group (*gray*), mild acute pancreatitis (*white*), and severe acute pancreatitis (*striped*). Reversible platelet adhesion in mild and severe acute pancreatitis (*left columns*); irreversible platelet adhesion (*right columns*). *$p<0.05$ vs control group, †$p<0.05$ vs mild acute pancreatitis.

logical mediator with multiple other targets. Its effects include leukocyte activation, upregulation of proinflammatory cytokines, and strong vasoconstricting effects. These are mediated via phosphatidylcholine and phosphatidylcholine-specific phospholipase-C pathway leading to a tonic contraction in smooth muscles and upregulating other vasoactive substances.[22,23] Especially, this vasoconstrictor mechanism may additionally contribute to perfusion failure in the course of AP as observed in our study. How far platelet inhibition itself could be an approach to attenuate the course of AP experimentally or clinically is hypothetical but should certainly be addressed to in further studies. Possible aims could be adhesion molecules such as selectins or platelet receptors and also synthesis of thromboxane and prostaglandins.

Platelet activation was accompanied by leukocyte activation in the present study. An interaction between these two cell types has been demonstrated by the different authors in the past.[24–26] Among others, P-selectin seems to be one of the most important adhesion molecules, which links the inflammatory and procoagulatory cascades and has the potency to activate leukocytes and platelets as the cellular elements of either pathway.[18,19,25,26] Besides their adherence to endothelial cells, activated platelets form stable aggregates with leukocytes. This results in a combined inflammatory and coagulatory contribution to thrombus formation and is also mediated by P-selectin and beta-integrins.[27–29] Especially, the formation of microthrombotic vessel occlusion with microcirculatory perfusion failure and consequent ischemia, hypoxia, and tissue necrosis was reflected by the intravital microscopic results in the present study.

Conclusion

The results of the present study show that activation and adhesion of platelets play an important role during AP. Platelet–endothelium and platelet–leukocyte interactions as well as thromboxane liberation show a correlation with the severity of experimental AP and seem to be of distinct importance in the progression from mild to severe necrotizing AP. A possible therapeutic use of these pathophysiological events should be evaluated in further studies.

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CD24 Expression is an Independent Prognostic Marker in Cholangiocarcinoma

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Abstract CD24 has been described as an adverse prognostic marker in several malignancies. This study evaluates CD24 expression in cholangiocarcinoma and correlates the findings with clinicopathologic data and patient survival. Between 1996 and 2002, 22 consecutive patients with cholangiocarcinoma were treated at our institution. Demographic data, SEER stage, pathologic data, treatment, expression of CD24, mitogen-activated protein kinase (MAPK), phosphorylated MAPK, and survival were analyzed. The majority of the tumors demonstrated CD24 (81.8%) and p-MAPK (87%) expression. A negative association was noted between the expression of CD24 and p-MAPK. Median survival for patients with low expression of CD24 was 36 months and high expression was 8 months. Median survival for patients who received chemotherapy with low CD24 expression was 163 months, and for seven patients with high CD24 expression, it was 17 months (p=0.04). With the addition of radiation therapy, median survival for patients with low expression of CD24 was 52 months and high expression was 17 months (p=0.08). On multivariate analysis, the use of chemotherapy (p=0.0014, hazard ratio 0.069) and the CD24 overexpression (p=0.02, hazard ratio 7.528) were predictive of survival. CD24 is commonly expressed in cholangiocarcinoma, and overexpression is predictive of poor survival and possibly of lack of response to chemotherapy and radiation therapy. These findings may improve selection of patients for the appropriate treatment modality and the development of CD24-targeted therapy.

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Introduction

Malignancies of the biliary tract are uncommon in the Western world. Two-thirds arise in the gallbladder and the remainder in the biliary tree or periampullary region. Cholangiocarcinoma or bile duct cancer is a rare but lethal malignancy with an incidence of 1–2 cases per 100,000 patients in the United States.[1] Clinicopathologic factors predictive of survival include curative resection, tumor stage and grade, serum bilirubin level <10 mg/dl, low CA19-9 level, hepatitis viral infection,[2–4] lymphovascular or portal vein invasion,[5] intrahepatic satellite lesions, inraductal papillary compvonent, tumor angiogenesis,[6] and DNA

ploidy.[7] Reports of molecular markers predictive of survival in cholangiocarcinoma include cluster of differentiation CD24,[8] MMP-2, TIMP-2,[9] cholinesterase level,[10] MUC-4,[11] cyclin D1,[12] VEGF-C,[13] p27,[14] p53, and p73.[15]

Recently, CD24 has been described in a wide variety of malignancies and shown to be a prognostic marker in several solid tumors including colorectal, stomach, lung, prostate, ovarian, and breast.[16–21] CD24 is a small, heavily glycosylated, mucin-like, cell-surface protein expressed in developing cells including pre-B cells, keratinocytes, and renal tubular epithelium.[22–24] It functions as an alternative ligand of P-selectin, an adhesion receptor expressed on activated endothelial cells and platelets which can enhance the metastatic potential of CD24-expressing tumor cells.[25–28] CD24 has apoptotic activity, and its cross-linking induces the sustained activation of p38 MAPK (mitogen-activated protein kinases)—the magnitude of which may determine the survival or death of pre-B cells.[29] An improved understanding of the molecular pathways involved in the pathogenesis and progression of cholangiocarcinoma will contribute to the development of targeted therapy.

This study correlates CD24 and MAPK expression with patient survival in cholangiocarcinoma with the objective of identifying a subset of patients who may benefit from targeted molecular therapy.

Patients and Methods

Clinical Data

After obtaining approval of the Institutional Review Board, a review of the tumor registry at Roswell Park Cancer Institute identified 31 consecutive patients with histologically proven cholangiocarcinoma between 1996 and 2002. Twenty-two patients had adequate tissue for further histopathologic studies and constitute the basis of this study. Medical records of these patients were reviewed for demographic data including age; gender; surveillance, epidemiology, and end results (SEER) stage at presentation; treatment; and survival from the time of diagnosis.

Immunohistochemical Staining

For most of the patients, diagnosis was established by examination of conventional hematoxylin and eosin (H&E)-stained slides and, in the remainder diagnosis, was confirmed with ancillary techniques including immunohistochemistry and special histochemistry with mucin and PAS stains. Uniform tissue fixation techniques were used for all patients. For each patient, a representative block containing adequate neoplastic and nonneoplastic tissue was selected. Five-micrometer tissue sections from these blocks were placed on charged slides and dried in a 60°C oven for 1 h. Upon return to room temperature, the slides were deparaffinized in three changes of xylene and rehydrated using graded alcohols. Endogenous peroxidase was quenched with 3% aqueous H_2O_2 for 15 min and washed with phosphate buffered saline with 0.05% Tween-20 (PBS/T). CD24 primary antibody was obtained from BD Biosciences (clone ML5) and used with the recommended incubation time and antigen retrieval procedures. The primary antibody used for MAPK was obtained from Cell Signaling and for phosphorylated/activated MAPK from Santa Cruz. After a PBS/T wash, 0.03% casein (in PBS/T) was used as a block for 30 min followed by the application of the primary antibody to the slides for an hour or overnight. Another PBS/T wash was followed by exposure to the biotinylated secondary antibody for 30 min. A third PBS/T wash was followed by exposure to the streptavidin–peroxidase complex for 30 min. A PBS/T wash was followed by the application of the chromogen DAB (DAKO, Carpinteria CA, USA) for 5 min. The slides were then counterstained with hematoxylin, rinsed with water, dehydrated, and cleared, and a coverslip was placed. The use of biomarkers, related controls, and interpretation of results using the Histoscore system for quantification of results have been described previously by our group.[30] Histoscore was defined as the product of the percentage of positive cells and the intensity of stain. The grade of positive staining depended upon the intensity of staining (0: no staining, 1: weak, 2: moderate, and 3: strong staining) and the percentage of cells stained. The final score was calculated as a sum of each stain intensity multiplied by the percentage of stained cells in the area of interest. For example: if tumor showed 50% weak, 30% moderate, and 20% strong staining, the score assigned was $(50 \times 1) + (30 \times 2) + (20 \times 3) = 170$.

Histological Grading

The cholangiocarcinoma tissue specimens were also stained by routine H&E stains. The specimens were graded based on the degree of tumor differentiation using the World Health Organization (WHO) system.

Statistical Analysis

Association between biomarker expressions in tumor tissue was investigated using the Kendall's tau. Biomarker expressions were classified as high and low based on whether their scores were above or below the median value, and survival between low and high expressions was compared using the log-rank test. The Kaplan–Meier method was also used to estimate the survival curves and median survival. The Cox's proportional hazards survival analysis was used in the multivariate analysis of survival

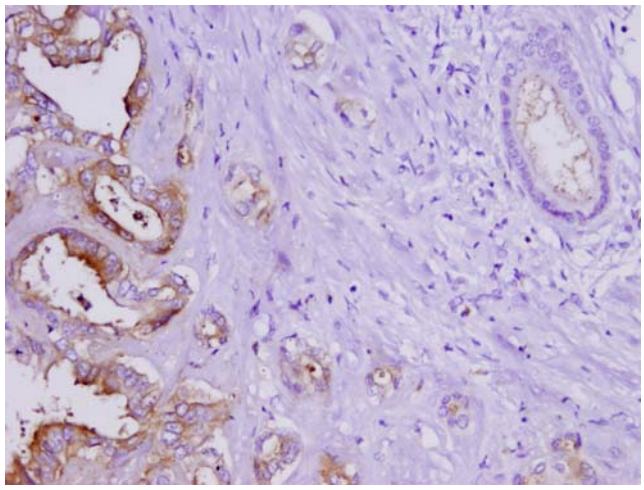

Figure 1 Moderately differentiated cholangiocarcinoma with overexpression of CD24. Normal bile duct (*right upper corner*) demonstrated weak apical staining, whereas neoplastic cells had strong apical and cytoplasmic staining (20×).

data to explain the effect of biomarker expressions together with other diagnostic parameters. Patient demographics including age, tumor grade, SEER stage, and treatment received were considered as possible parameters for explanatory variables in the model. All statistical tests were two-sided with statistical significance level at 5%.

Results

Patient Characteristics

Of the 22 patients included in the study, 7 were males and 15 females. The median age was 66.5 years (range: 35–77). SEER staging was local in 1 (4.6%), regional in 14 (63.6%), and distant in 7 (31.8%) patients. Differentiation of the tumor was classified as grade 1 in 3 (13.6%), grade 2 in 9 (40.9%), and grade 3 in 10 (45.5%) patients according to the WHO classification. Treatment for cholangiocarcinoma included surgery only (n=8), surgery and chemotherapy (n=5), surgery and radiation (n=1), chemotherapy only (n=2), and all three treatment modalities (n=5), and one patient did not receive any treatment.

Immunohistochemical Staining

Normal bile duct staining was used to set the score intensity. Most of the bile ducts were negative. Occasionally, they demonstrated weak focal and incomplete staining as seen in Fig. 1. The cholangiocarcinoma cells were scored as 1+ when they demonstrated weak expression of CD24, 2+ for moderate expression, and 3+ for strong expression of CD24. Figure 1 depicts cholangiocarcinoma positive for CD24 expression adjacent to normal biliary epithelium. The majority of the tumors demonstrated CD24 (81.8%) and p-MAPK (87%) expression. Immunohistochemical staining for these proteins was higher in malignant tissue in comparison to normal biliary epithelium. The pattern of staining was usually a combination of cytoplasmic and apical, and few specimens demonstrated the apical pattern only.

Relationship Between Biomarkers

A negative association was suggested between the expression of CD24 and phosphorylated/activated p-MAPK (Kendall's τ=−0.32408, p=0.0501).

Survival

Median survival was 36 months for nine patients with low expression of CD24 and 8 months for 13 patients with high expression of CD24 as shown in Fig. 2. The median survival for five patients who received chemotherapy with low CD24 expression was 163 months, and for seven patients with high CD24 expression, it was 17 months (Fig. 3, p=0.04). Median survival for four patients treated with radiation in the presence of low CD24 expression was 52 months, and it was 17 months for two patients with overexpression of CD24 (Fig. 4, p=0.08). Overexpression of CD24 continued to affect survival adversely despite the overall improvement noted with the addition of radiation therapy. Multivariate analysis using the Cox's proportional hazards survival analysis demonstrated that overexpression of CD24 (p=0.02, hazard ratio 7.528) and use of chemo-

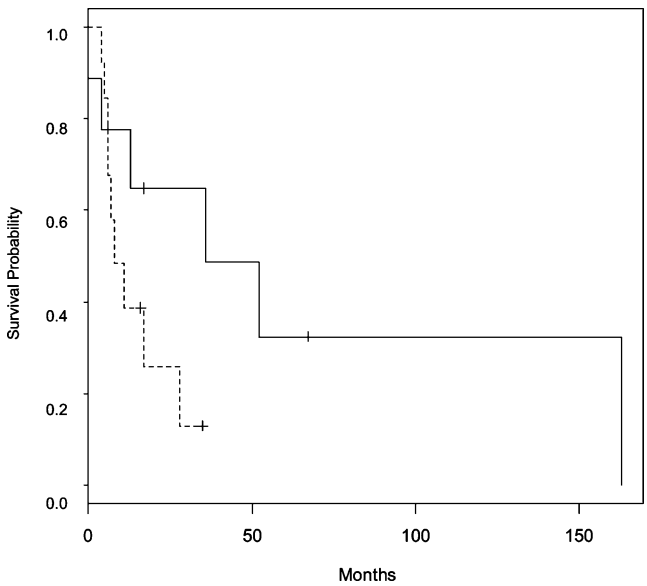

Figure 2 Kaplan–Meier survival curve for patients of cholangiocarcinoma with low and high levels of CD24 expression (n=22). p=0.02. Low CD24 (————), high CD24 (- - - - - - - - - - - -).

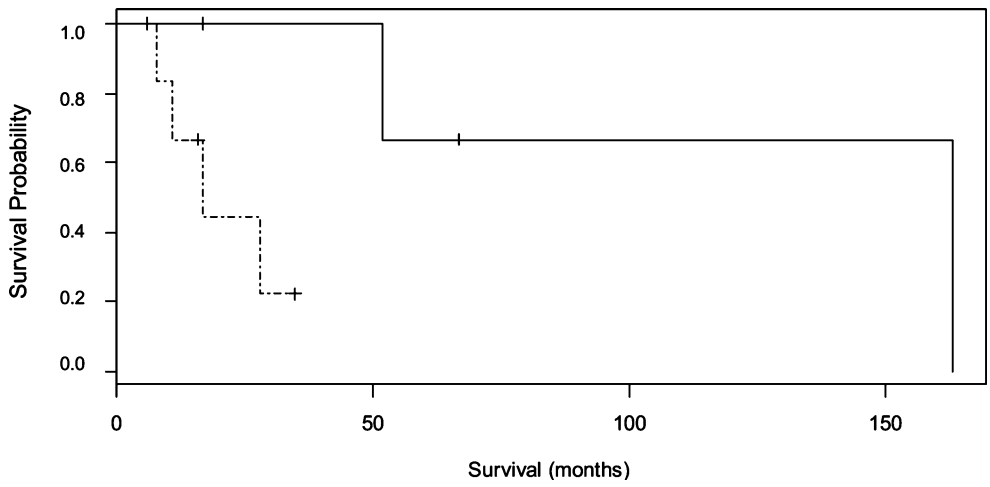

Figure 3 Kaplan–Meier survival curve for patients who received chemotherapy with low and high levels of CD24 expression (n=12). p=0.04. Low CD24 (————), high CD24 (– – – – – –).

therapy (p=0.0014, hazard ratio 0.069) were predictive of survival (Table 1). There was no significant association noted between survival and patient's age, sex, SEER stage, grade of the tumor, surgery, radiation therapy, or expression of MAPK.

Discussion

The physiologic function of CD24 is incompletely understood but it has been shown to increase tumor proliferation, cell adhesion, motility, invasion, and apoptosis.[22–24,31] Selectins are cell adhesion molecules involved in the rolling adhesion of leukocytes to endothelial cells and platelets under the shear forces of circulation, and P-selectin expressed by thrombin-activated platelets and endothelial cells is a major ligand for CD24 on carcinoma cells.[26,27] This suggests that CD24-expressing tumor cells can disseminate more readily due to their capacity to form thrombi with activated platelets or to adhere to endothelial cells. Friederichs et al.[28] have demonstrated that the carbohydrate sialylLex abundantly expressed on human cancers is essential for CD24-mediated rolling of tumor cells on P-selectin, and in its absence, human adenocarcinoma cells failed to arrest and colonize the lungs. CD24, a metastasis-associated protein, has been recently identified as a downstream target of Ral signaling.[32] Ral GTPases are important mediators of transformation, tumorigenesis, and cancer progression. Microarray by immunohistochemistry of a human bladder cancer identified CD24 as a novel Ral-regulated target and a prognostic biological marker.

In this study, 81.8% of patients with cholangiocarcinoma expressed CD24. Median survival for patients with overexpression of CD24 was significantly shorter, and the addition of chemotherapy improved survival. A negative association was noted between the expression of CD24 and p-MAPK. The use of chemotherapy in patients with low expression of CD24 was associated with a median survival of 163 months compared to 17 months in patients with a high CD24 expression (p=0.04). The use of radiation therapy in patients with low expression of CD24 was also associated with an improved survival than with over-

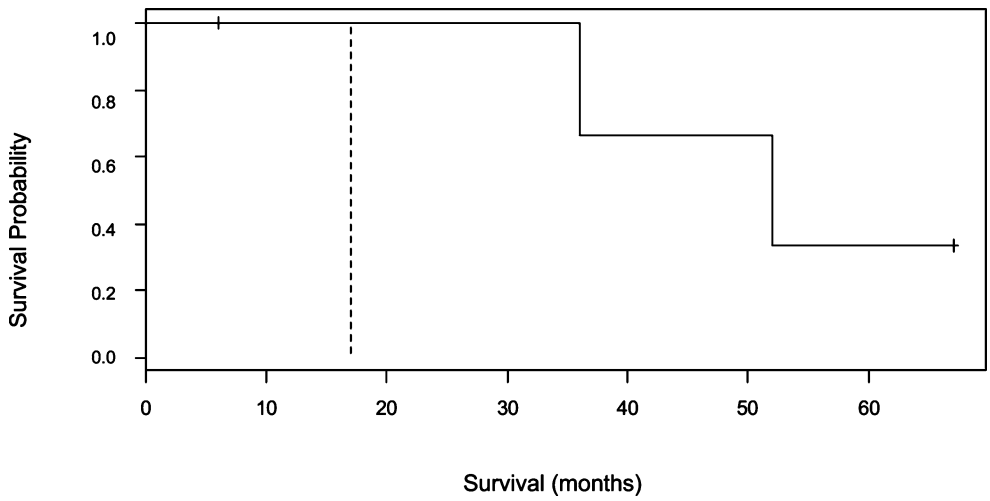

Figure 4 Kaplan–Meier survival curve for patients who received radiation therapy with low and high levels of CD24 expression (n=6). p=0.08. Low CD24 (————), high CD24 **(– – – – – –).**

Table 1 Prognostic Variables for Survival in 22 Patients with Cholangiocarcinoma

Variable	*n*	Median survival (months)	Survival (*p* value)	Multivariate analysis (*p* value)
Age				
<68	11	17 (8–36)	0.60	
>68	11	11 (5–52)		
Gender				
Male	7	12 (8–163)	0.52	
Female	15	17 (6–52)		
Grade				
1, 2	12	15 (6–52)	0.99	
3	10	11 (8–*)		
SEER stage				
1, 2	15	11 (6–52)	0.48	
3	7	28 (6–163)		
Chemotherapy				
No	10	6 (4–13)	0.0005	0.0014
Yes	12	52 (17–163)		
Radiation				
No	16	8 (6–28)	0.12	
Yes	6	44 (17–*)		
Surgery				
No	3	8 (0–28)	0.17	
Yes	19	17 (7–52)		
MAPK				
Low	10	17 (8–36)	0.68	
High	11	28 (5–163)		
P-MAPK				
Low	10	13 (8–52)	0.34	
High	11	36 (4–163)		
CD24				
<120	9	36 (13–163)	0.10	0.02
>120	13	8 (6–28)		

*The estimate was not provided because the upper limit of the survival curve had not reached a 50% failure rate.
CD denotes cluster of differentiation.
p-MAPK denotes phosphorylated form of mitogen-activated protein kinase.

expression of CD24 although the data did not attain statistical significance possibly due to the small number of patients in this series.

It has been reported by Taguchi et al.[29] that the cross-linking of CD24 induces apoptosis in Burkitt's lymphoma enhanced by a B-cell antigen receptor (BCR)-mediated signal. They observed that simultaneous cross-linking of pre-BCR clearly inhibited CD24-mediated apoptosis in pre-B cells. CD24 cross-linking also induces the sustained activation of p38 MAPK, and whether pre-B cells survive or die may be determined by the magnitude of MAPK activation. Consistent with these observations, the present study suggests an inverse association between CD24 and p-MAPK, and eventual cellular proliferation or apoptosis might be a consequence of the dominant effect in a complex interplay of opposing influences.[33]

Our data indicate that high expression of CD24 remains an adverse prognosticator despite the use of additional therapy. Chemotherapy and radiation were noted to provide maximal survival benefit to low expressors of CD24 although the data for the use of radiation was statistically insignificant probably due to the small number of patients in this study. Furthermore, correlation between CD24 expression and radiation sensitivity has been noted to vary with the cell type as in human small cell lung cancer, and radiation doses required to induce apoptosis of CD24-negative human ALL (acute lymphoblastic leukemia) cells were higher than those required for CD24-positive cells, suggesting that lack of CD24 surface antigen expression is associated with intrinsic radiation resistance.[34,35]

Hypoxia is a characteristic feature of tumor cells due to the sustained proliferation which progressively results in an acidic, nutrient-deprived, and hypoxic tumor microenvironment. Tumor oxygenation has been identified as an independent prognostic variable for locoregional control and overall survival following definitive irradiation for squamous cell carcinoma of the head, neck, and uterine cervix.[36,37] Recent reports have indicated decreased efficacy of chemotherapy under hypoxic conditions in several tumor types including pancreatic cancer and testicular tumors.[38,39] Because treatment failure was a consequence of hypoxia, the authors recommend novel treatment strategies aimed at improving tumor oxygenation or enhancing the treatment sensitivity of hypoxic tumor cells. Aimed at identifying potential oxygen-dependent markers in vascular endothelial cells for therapeutic intervention in tumor angiogenesis, Scheurer et al.[40] performed a broad-range transcriptomic analysis of selected extracellular matrix protein gene expression levels in human umbilical cord vein endothelial cells exposed in vitro to hypoxia for different time periods. They noted several genes transcriptionally upregulated including CD24 at late times of exposure to hypoxia, indicating that it was a useful marker of hypoxic activation in vascular endothelial cells. In the present series, low expressors of CD24 demonstrated greater survival benefit from chemotherapy and radiation than the high expressors, suggesting that its expression may be a marker for tumor hypoxia and response to therapy. This finding that shows that patients with low expression of CD24 may benefit from chemotherapy or radiation is of importance because it has been previously reported that adjuvant or palliative radiation had no effect on survival in patients with cholangiocarcinoma.[41] However, the small number of patients in the present series limits interpretation of data suggesting that CD24 overexpression may be predictive of lack of response to radiation or chemotherapy.

CD24 has been shown to be a prognostic marker for shortened survival and disease progression in several malignancies including colorectal, stomach, lung, prostate, ovarian, and breast cancers.[16–21] Weichert et al. report that in colorectal cancer, only the subset of patients with exceptionally strong cytoplasmic CD24 staining comprising 10% of their study group demonstrated a markedly shortened mean survival of 31.5 months compared to 67.5 months for the remaining patients.[16] They also reported that cytoplasmic CD24 staining pattern is prognostically more significant than the membranous pattern—the biological significance of which was unclear. Su et al. noted a 51% expression of CD24 by immunohistochemistry in intrahepatic cholangiocarcinoma as compared to the 81.8% in the present series. They reported CD24 expression and tumor stage as independently predictive of survival on multivariate analysis and suggested membrane-bound CD24 protein as a potential target for immunotherapy.[8]

In conclusion, overexpression of the molecular marker CD24 in cholangiocarcinoma is predictive of poor survival. CD24 overexpressors demonstrated a lack of response to chemotherapy and possibly radiation therapy although these observations were limited by the small sample size. Additional properties of tumor proliferation, invasion, metastasis, and apoptosis make CD24 a potent target for specifically directed molecular therapy and its overexpression a potential criterion in the selection of patients for the appropriate conventional treatment modality.

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Management of Hepatic Angiomyolipoma

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Abstract Preoperative diagnosis of hepatic angiomyolipoma is difficult, and the treatment for it remains controversial. The aim of this study is to review our experience in the treatment of hepatic angiomyolipoma and to propose a treatment strategy for this disease. We retrospectively collected the clinical, imaging, and pathological features of patients with hepatic angiomyolipoma. Immunohistochemical studies with antibodies for HMB-45, actin, S-100, cytokeratin, vimentin, and c-kit were performed. Treatment experience and long-term follow-up results are summarized. During a period of 9 years, 10 patients with hepatic angiomyolipoma were treated at our hospital. There was marked female predominance (nine patients). Nine patients received surgical resection without complications. One patient received nonoperative management with biopsy and follow-up. One patient died 11 months after surgery because of recurrent disease. We propose all symptomatic patients should receive surgical resection for hepatic angiomyolipoma. Conservative management with close follow-up is suggested in patients with asymptomatic tumors and meet the following criteria: (1) tumor size smaller than 5 cm, (2) angiomyolipoma proved through fine needle aspiration biopsy, (3) patients with good compliance, and (4) not a hepatitis virus carrier.

Keywords Angiomyolipoma · Hepatic angiomyolipoma · Liver tumor

Introduction

Hepatic angiomyolipoma (AML) is a rare mesenchymal tumor of the liver composed of smooth muscle cells, adipose tissue, and proliferating blood vessels. Since its first description by Ishak in 1976, approximately 200 cases have been reported in the English literature.[1] This type of tumor is usually seen in kidneys associated with tuberous sclerosis.[2] Definite pathologic diagnosis is made by identification of the three different components and HMB-45 positive staining.[3]

In the past, this tumor has been considered an entirely benign and slow-growing lesion without the possibility of malignant transformation. Therefore, several authors have suggested that this disease can be managed with conservative treatment.[4–7] However, since 2000, several reports have revealed that this kind of tumor can be malignant with evidence of recurrence.[8–10] Although the combination of ultrasonography, computed tomography (CT), magnetic resonance (MR) imaging, and angiography increases the accuracy in diagnosis of hepatic AML, the correct preoperative diagnostic rate of imaging studies has been reported to be less than 50%.[6,10–14] Even the postoperative pathologic diagnosis has been easily mistaken as hepatocellular carcinoma (HCC).[14,15] Many patients have been treated with surgical resection of the tumor. Therefore, the

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proper treatment of hepatic AML has remained controversial.

The purpose of this study is to retrospectively review the clinical, imaging, and pathological features of patients with hepatic AML treated at our hospital and to summarize our experience in the diagnosis and treatment of this disease. We also review the literature to highlight the important questions concerning hepatic AML: (1) Is hepatic AML a pure benign tumor? (2) What is the natural course of this tumor? Does the tumor size enlarge frequently during observation? (3) What difficulties exist in preoperative diagnosis with imaging studies and fine needle aspiration biopsy (FNAB)? (4) Is it proper for a hepatitis-carrier patient with hepatic AML to be treated with conservative management? (5) What are the criteria for patients with hepatic AML to be treated with surgical resection or conservative management?

Materials and Methods

The clinical, imaging, and pathological features of 10 patients with hepatic AML treated at the authors' institute were retrospectively reviewed. The follow-up information was obtained in each case. All tumor tissue was paraffin-embedded for routine hematoxylin and eosin (H&E) staining. Immunohistochemical assays were performed using a three-step indirect peroxidase complex technique with the following antibodies: HMB-45 (DAKO, dilution 1:40), actin (DAKO, dilution 1:50), S-100 (DAKO, dilution 1:800), cytokeratin (Biogenix, dilution 1:80), vimentin (DAKO, dilution 1:50), and c-kit (MBL, dilution 1:200).

Results

Patients and Clinical Data

Ten patients with hepatic angiomyolipoma were diagnosed at National Taiwan University Hospital from July 1995 to June 2004. There was marked female predominance (9/10). The median age was 44 years old with a range from 34 to 64 years. Most patients (60%) presented no symptoms and were detected incidentally by health check-ups or during medical exams for other diseases. Four of 10 patients had symptoms caused by the space-occupying effect of the tumors such as abdominal pain, abdominal fullness, and palpable mass, or other nonspecific symptoms such as fever, general malaise, or body weight loss (Tables 1 and 2). None of them had a history of renal AML or tuberous sclerosis. Two patients were hepatitis B-virus (HBV) carriers. The plasma levels of α-FP and CEA were within normal limits in all patients.

Imaging Studies

Based on the combined imaging studies of abdominal ultrasonography, CT, MR imaging, and angiography, the diagnostic accuracy of hepatic AML in this series was only 20% (Table 1). Other preoperative imaging impressions included hepatocellular carcinoma, angiosarcoma, hemangioma, and metastatic lesions.

Two other cases were diagnosed by fine needle aspiration biopsy (FNAB). The accurate preoperative diagnostic rate was 40% (4/10) after imaging studies and FNAB (Table 1).

Pathologic Study

All 10 patients had a single tumor. Five tumors were in the right lobe of the liver and four were in the left lobe. One tumor was located in the caudate lobe. Most tumor sizes were larger than 5 cm (70%). The median tumor size was 10.5 cm, ranging from 2.5 cm to 20 cm (Tables 1 and 2).

Gross pathology identified all tumors as a well-circumscribed, nonencapsulated tumor masses consisting of soft to elastic tissue. The cut surface in tumors varied from yellow to dark brown.

Table 1 Clinical Presentation of Hepatic Angiomyolipoma

Clinical Feature	No. of Patients
Age	34–64 years (median 44 years)
Gender (female: male)	9:1
Symptoms	
No symptom	6
Abdominal pain	2
Abdominal fullness	2
Palpable mass	1
Body weight loss	2
Malaise	1
Fever	2
Tumor location	
Right lobe	5
Left lobe	4
Caudate	1
Tumor size (cm)	
<5	3
5–10	1
>10	6
Preoperative diagnosis	
Angiomyolipoma	4(40%)
Based on radiological images	2
Based on tumor biopsy	2
Hepatocellular carcinoma	3(30%)
Angiosarcoma	1(10%)
Hemangioma	1(10%)
Metastasis	1(10%)
Associated liver disease	
HBV carrier	2

Table 2 Clinical Profile of Patients with Hepatic Angiomyolipoma

Case	Sex/ Age	Tumor Size (cm)/lobe	Symtoms/Signs	Incidental Finding	Treatment	Outcome/F/U Months
1	F/34	18/R	Nil	H/C	Atypical hepatectomy	Well/39 mon
2	F/34	10/R	Epigastralgia		Right lobectomy	Well/59 mon
3	F/37	13/L	Palpable mass, abdominal fullness, BW loss, fever		Extended left lobectomy	Dead/14 mon recurrent, liver and lung mets
4	F/40	20/R	Epigastralgia		Right lobectomy	Well/109 mon
5	F/42	7/R	Nil	H/C	FNAB and F/U	Lost F/U/6mon
6	F/46	11/L	Abdominal fullness, malaise, BW loss, fever		Left lateral segmentectomy	Well/40 mon
7	F/49	15/R	Nil	Exam of appendicitis	S56 segmentectomy	Well/37 mon
8	F/51	3/C	Nil	H/C	Caudate lobectomy	Well/40 mon
9	F/53	2.5/L	Nil	F/U echo due to colon cancer s/p	Left lateral segmentectomy	Well/33 mon
10	M/64	4/L	Nil	H/C	Left lobectomy	Well/32mon

H/C=health check-up, BW=body weight, F/U=follow-up, FNAB=fine needle aspiration biopsy, mon=month, mets=metastasis, s/p= postoperation

Histopathologic studies of these 10 tumors showed a picture of hepatic angiomyolipoma composed of myoid and vascular components with a variant content of fatty tissue. Hematopoiesis was noted in two cases. Immunohistochemical studies were performed in all patients except one (case 5). Most tumors were found positive for HMB-45 (10/10), SMA (4/9), S-100 (7/9), Vimentin (6/9), but negative for cytokeratin (0/9). Only three tumors were found positive for c-kit (Table 3).

Treatment and Follow-up

One patient (case 5) was confirmed with AML through fine needle aspiration biopsy. Nonoperative management with close follow-up was performed. However, this patient was lost after 6 months of follow-up. The other nine patients underwent hepatectomy with tumor resection. These nine patients, except for one patient (case 3), had no postoperative complications or disease recurrence, and were regularly followed up at our outpatient department, follow-up ranging from 32 to 109 months (Table 2). The very unusual patient (case 3) was a 37-year-old woman with a 13×9×9 cm, large tumor at the left lobe of the liver, receiving extended left lobectomy (Fig. 1a,b). Pathology revealed a picture of hepatic AML (Fig. 2a,b).

Unfortunately, 6 months later, ultrasonography showed recurrent hepatic lesions at the right lobe of the liver (Fig. 1c). MRI also confirmed a large tumor in the caudate lobe and numerous smaller nodules in the right lobe of the liver. Angiography also revealed multiple tumor stains (Fig. 1d). Fine needle aspiration biopsy was performed. The biopsy specimen was immunoreactive to HMB-45 antibody (Fig. 2c,d). The clinical and histologic picture demonstrated recurrent malignant hepatic angiomyolipoma. At the 11th postoperative month, chest CT scans revealed multiple metastatic nodules. Three months later, the woman died due to hepatic failure and renal failure.

Table 3 Immunohistochemical Study

Case	HMB-45	Actin	S-100	Cytokeratin	Vimentin	c-kit
1	++	−	++	−	−	+
2	++	++	+	−	+	+
3	++	−	++	−	+	−
4	++	++	−	−	+	−
5	++					
6	++	+	++	−	+	−
7	++	−	++	−	+	−
8	++	−	−	−	+	−
9	++	−	++	−	−	−
10	++	+	+	−	+	+

++: strongly staining, >30% positivity; +: weakly staining, 10~30% positivity; − no staining, or <10% positivity

Discussion

In the past, hepatic AML has been considered as a “benign” mesenchymal tumor. However, in 2000, Dalle reported the first case of malignant hepatic AML with vascular invasion

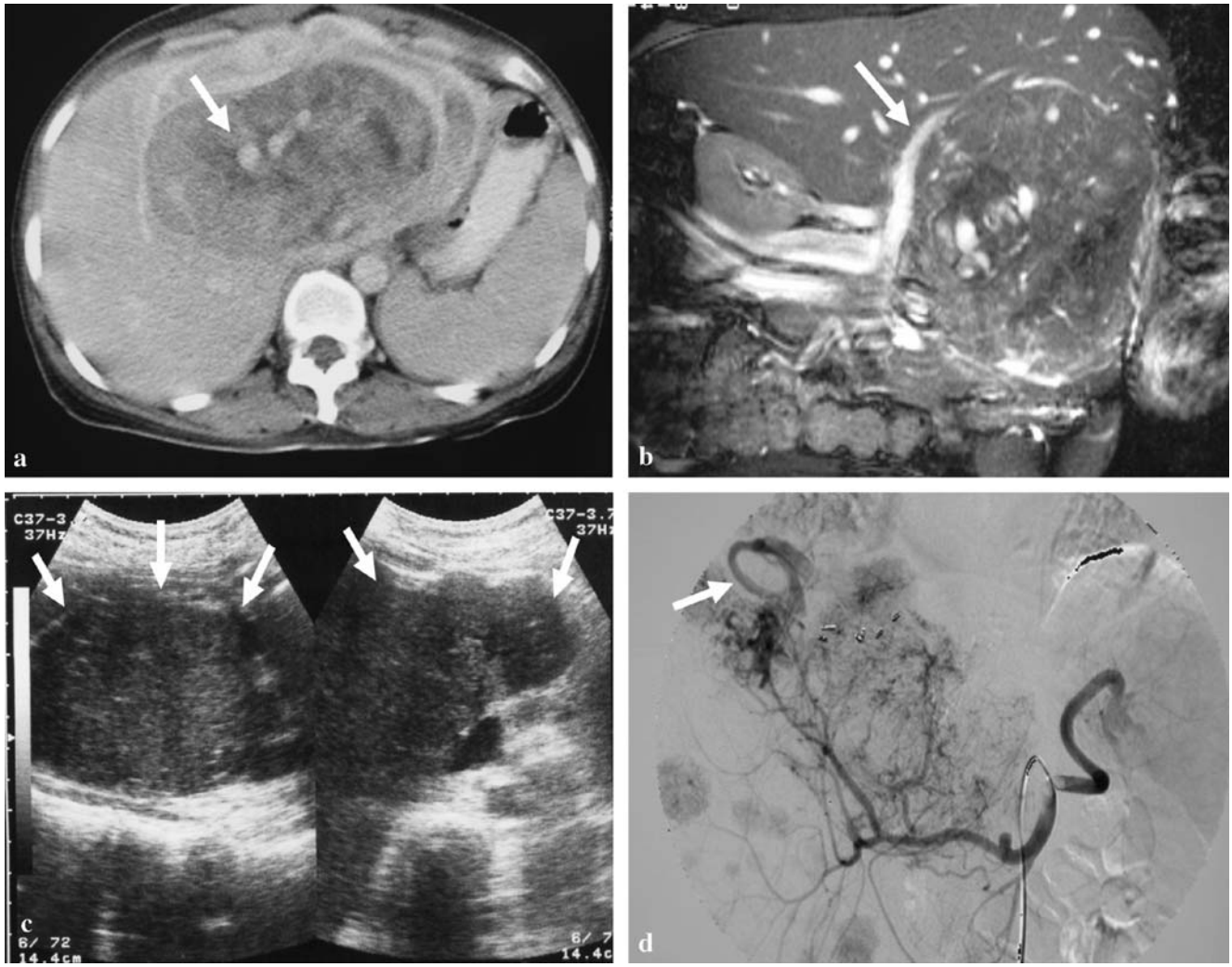

Figure 1 A 37-year-old woman (case 3) presented with fever and palpable abdominal mass. (a) The axial view of contrast-enhanced CT scans on portal venous phase shows a huge hepatic tumor at the left hepatic lobe with heterogeneous enhancement. Notice the engorged vessels within the tumor are vividly identified (arrow). (b) The MR coronal Tru FISP, fast imaging with steady-state precession. (TR/TE/FA=4.3/2.1/72°) shows engorged vessels in the tumor. The right portal vein (arrow) is displaced by the tumor. (c) After 6 months of extended left lobectomy, the abdominal ultrasonography reveals a huge recurrent tumor (arrows) in the previous location of left hepatic lobe, and numerous smaller tumors in the right lobe. (d) Celiac angiography also demonstrates the recurrent huge tumor and other multiple smaller ones in the right lobe of liver. Note the early drainage vein (arrow).

and recurrence with multiple liver metastases and suspected portal vein thrombosis 5 months after primary tumor resection.[8] Another two cases have been reported with hepatic recurrence after operation. One case was a 16-year-old girl with hepatic AML, receiving left lobectomy, with late recurrence noted 6 years after operation.[9] The other one was in the Flemming's report. Recurrent hepatic tumors were noted 3 years after operation.[10] Flemming also suggested that a proliferation index exceeding 3% and multicentric growth indicate a propensity for recurrence.

In this study, we reported a 37-year-old woman with left hepatic AML. A recurrent hepatic mass was noted 6 months after tumor resection, and multiple lung metastases were noted later. The patient died 14 months after diagnosis. To our knowledge, this case is the fourth reported case of recurrence in the literature, and the tumor in this case behaved as the most malignant one.[8–10] Therefore, hepatic AML should not be considered as an entirely benign tumor; at least, it has malignant transformation potential. Accordingly, conservative treatment should be performed carefully, especially for patients with poor compliance, who are unable to undergo a strict follow-up regimen.

There were few reports concerning the growth velocity of hepatic AML in long-term follow-up. In one retrospective study of 26 patients, there were six patients who were followed up for more than 1 year and finally decided to receive operation because of the enlargement of the lesions. In that study, the tumor size of one patient increased from 4 to 10 cm during the 5-year follow-up. Another patient had a tumor increasing from 1.5 to 5 cm in 13 years follow-up.[13]

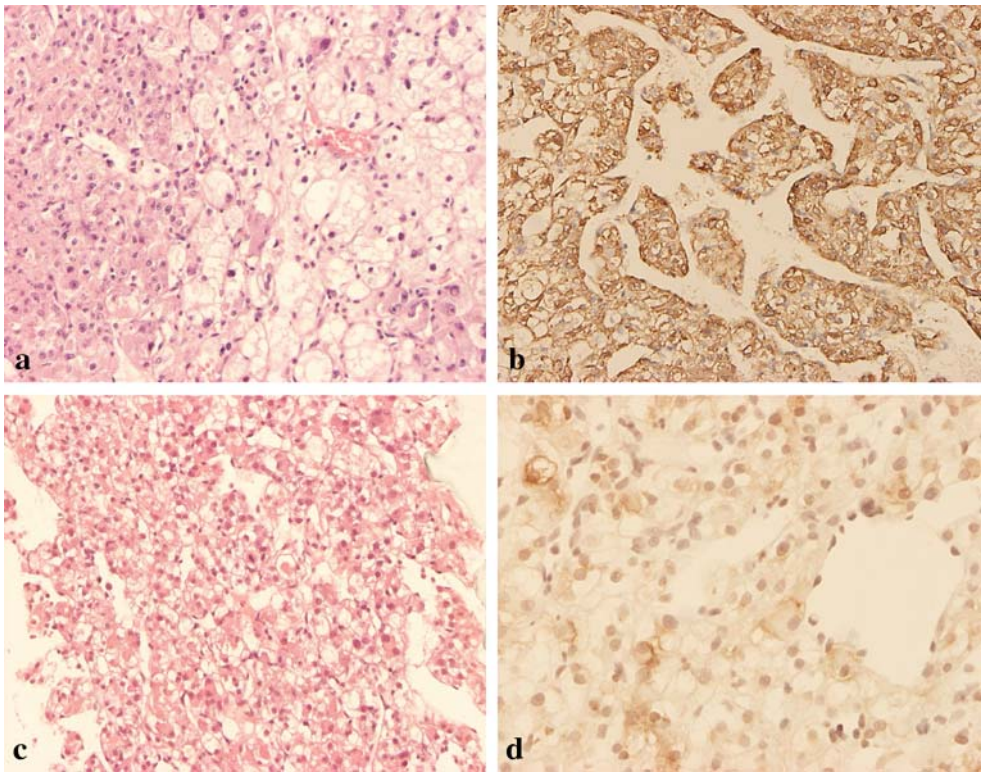

Figure 2 Microscopic appearance of the hepatic angiomyolipoma in case 3. (a) The primary tumor is composed of polygonal to spindle cells arranged in solid sheets or trabecular pattern with endothelial lining. Some of the tumor cells have eosinophilic cytoplasm, and some have large fat vacuoles. Some of the nuclei are bizarre, and some have large eosinophilic nucleoli (H&E stain, original magnification×100). (b) The tumor cells are strongly immunoreactive for HMB-45 (original magnification×100). Recurrent tumor was noted 6 months later, and the patient received fine needle aspiration biopsy. (c) Microscopically, it shows tumor cells with clear to ample eosinophilic cytoplasm arranged in trabecular pattern (H&E stain, original magnification×40). (d) Immunohistochemical staining shows the tumor cells are also positive for HMB-45 (original magnification×200).

In another case report of a 38-year-old patient, the tumor size enlarged from 8 to 14.4 cm over a 3-year follow-up period.[16] Irie also reported that a 40-year-old woman had hepatic AML with tumor size increasing in size from 4 cm to 7 cm during a 14-month follow-up period.[16]

Although hepatic AML seems slow-growing, the probability of tumor enlargement and hence an induced mass-compression effect is not uncommon in the long-term follow-up period. In the present series, the median age of patients was 44 years old, and 70% of patients were below 50 years. If all of these patients had received nonoperative management, the mass effect of tumor enlargement might have been presented during a long-term follow-up period, especially in younger patient groups with longer remaining years of life. Moreover, the difficulties and complications of operation at later years would increase when the tumor enlarges, especially for those patients with an original larger tumor (>5 cm).

Similar to the patients presented in this series, most patients with hepatic AML are not symptomatic.[12–14] Usually, these patients are diagnosed during health check-ups. Most symptoms are mass-compression effects including upper abdominal pain, abdominal fullness, and palpable mass. There are also some vague symptoms such as body weight loss, general malaise, and fever. In one review article with a collection of 52 patients, the incidence of symptoms or signs dramatically increased when tumor size was larger than 5 cm.[11] Twenty-one percent (4/19) of patients with a tumor smaller than 5 cm present symptoms/signs; however, the incidence increases to 64% (7/11) when tumor size is between 5 and 10 cm. The incidence increases to 89% when tumor size is larger than 10 cm. In our series, 40% (4/10) of patients were symptomatic, and all four of these patients had a tumor larger than 10 cm. Accordingly, we suggested that patients with tumor larger than 5 cm should receive tumor resection, because most patients in this group were predisposed toward being symptomatic.

The typical findings in imaging studies of hepatic AML are as follows: (1) heterogeneously hyperechoic mass in US, (2) heterogeneously low density with low attenuation value (less than −20 HU) in plain CT, (3) high intensity on T1 and T2 weighted MRI, and (4) hypervascularity and tumor stain on angiography.[12] Although a combination of US, CT, MRI, and angiography is able to increase the accuracy in preoperative diagnosis, hepatic AML usually shows various patterns in imaging studies. The differences in imaging studies occur because the relative proportions of vessels, muscles, and fatty tissue vary widely from one tumor to another. Consequently, hepatic AML is sometimes difficult to diagnose based on imaging studies.[17] Therefore, fine needle aspiration biopsy has been reported to be useful in the preoperative diagnosis of this tumor.[4,5,17,18]

However, more attention should be paid to the tumor's various morphologic appearances when minute samples are interpreted. With the combined tools of imaging studies and FNAB, the preoperative diagnostic accuracy has been smaller than 32% (ranging from 0 to 32%) in larger series.[6,10–15] In a collaborative study reported by

Tsui, including 30 cases from nine international hepatology centers, 50% were primarily misdiagnosed as carcinoma or sarcoma, either by imaging studies or by needle biopsy.[15] In Flemming's series, only one preoperative case was diagnosed correctly.[10] In the present series, only four preoperative cases (40%) were correctly diagnosed by combined imaging studies and FNAB.

Definite pathologic diagnosis of this tumor is usually made by identification of the three different components of smooth muscle cells, adipose tissue, and blood vessels. HMB-45 positive staining of myoid cells has been used as a pathologic characteristic of hepatic AML.[3,19] Because of the rarity and pleomorphism of the histological features of hepatic AML, histologic diagnosis may be difficult, especially with needle biopsy. Many features in AML can mislead the unwary pathologist to a diagnosis of hepatocellular carcinoma: polygonal cells in trabecular arrangement, peliosis, nuclear pleomorphism, prominent eosinophilic nucleoli, deficient reticulin framework, presence of glycogen, eosinophilic globules, and tumor necrosis.[14] In Zhong's series of 2000, none of the 14 cases were correctly diagnosed before operation. Furthermore, five cases were misdiagnosed as hepatocellular carcinoma or sarcoma by pathologists, even after operation. Therefore, we should be cautious when using FNAB as a diagnostic tool.

In an endemic area of hepatocellular carcinoma such as Taiwan,[20] conservative management is risky because cases of fat-rich minute hepatocellular carcinoma will make the differential diagnosis more difficult. Furthermore, Chang reported one case with hepatic AML and concomitant hepatocellular carcinoma.[21] In this series, two patients were carriers of hepatitis B virus with a high risk for hepatoma formation. Not only would these hepatitis-carrier patients bear more risk, but physicians would also bear more risk and psychological pressure during a long-term follow-up period if conservative management were adopted.

Because of the small patient number, we could not get definitely conclusive management suggestions solely from the results of this retrospective study. But a combination of our experience and a review of the literature, we suggest all symptomatic patients should receive surgical resection for hepatic angiomyolipoma. Conservative management with close follow-up is suggested in patients with asymptomatic tumors and meet the following criteria: (1) tumor size smaller than 5 cm, (2) angiomyolipoma proved through fine needle aspiration biopsy, (3) patients with good compliance, and (4) not a hepatitis-virus carrier.

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Liver Transplantation Across Rh Blood Group Barriers Increases the Risk of Biliary Complications

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Abstract
Background Cold ischemia time and the presence of postoperative hepatic arterial thrombosis have been associated with biliary complications (BC) after liver transplantation. An ABO-incompatible blood group has also been suggested as a factor for predisposal towards BC. However, the influence of Rh nonidentity has not been studied previously.
Materials Three hundred fifty six liver transplants were performed from 1995 to 2000 at our hospital. BC incidence and risk factors were studied in 345 patients.
Results Seventy patients (20%) presented BC after liver transplantation. Bile leakage (24/45%) and stenotic anastomosis (21/30%) were the most frequent complications. Presence of BC in Rh-nonidentical graft–host cases (23/76, 30%) was higher than in Rh-identical grafts (47/269, 17%) (P=0.01). BC was also more frequent in grafts with arterial thrombosis (9/25, 36% vs 60/319, 19%; P=0.03) and grafts with cold ischemia time longer than 430 min (26/174, 15% vs 44/171, 26%; P=0.01). Multivariate logistic regression confirmed that Rh graft–host nonidentical blood groups [RR=2 (1.1–3.6); P=0.02], arterial thrombosis [RR=2.6(1.1–6.4); P=0.02] and cold ischemia time longer than 430 min [RR=1.8 (1–3.2); P=0.02] were risk factors for presenting BC.
Conclusion Liver transplantation using Rh graft–host nonidentical blood groups leads to a greater incidence of BC.

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Keywords Liver transplantation · Biliary complications · Rh nonidentity

Introduction

Biliary complications (BC) after liver transplantation (LT) are still a significant cause of morbidity and mortality.[1,2] Hepatic arterial thrombosis, long ischemia time, inadequate exposure of the biliary epithelium to the preservation solution, and chronic rejection have been associated with BC.[3–5] However, complications may also occur in the absence of these pathogenic factors. The expression of donor ABH antigen in the vascular and biliary epithelium of hepatic allografts has been linked to higher risk of biliary and arterial complications, especially in ABO-incompatible grafts.[6] However, the influence of Rh nonidentity in LT has not been analyzed until now.

The aim of this study is to analyze the incidence of BC after LT, to define their etiological risk factors, and to study the influence of Rh nonidentity on presentation of BC after LT.

Materials

Three hundred and fifty-six (n=356) liver transplants were performed at our hospital between January 1995 and November 2000. Eleven were excluded from the study because important data were missing (n=345). The study was closed on May 2001 with a 6-month-minimum graft follow-up. The procurement procedure was based on the rapid flush technique.[7] After reperfusion of the allograft, cholecystectomy was performed, the donor bile duct being divided just above the cystic duct junction in most cases. Biliary anastomosis was performed with interrupted stitches of 6-0 Polydioxanone suture Ethicon® (Johnson & Johnson, Brussels, Belgium). The biliary reconstruction technique was end-to-end anastomosis in the majority of LTs (315 patients, 91%). T-tubes were used in four patients due to diameter discrepancy between the biliary ducts of the donor and the recipient. If the primary disease affected the biliary tract, or if technical factors made end-to-end anastomosis difficult, Roux-en-Y-hepaticojejunostomy was performed (25 out of 345, 7%). The outcome was assessed in terms of biliary and arterial complications and patient status (alive, retransplanted, or dead). BCs were studied routinely with abdominal ultrasonography at day 1 post LT, weekly before discharge from hospital and monthly thereafter or when there was clinical or biochemical suspicion of BC, and this was confirmed with magnetic resonance cholangiography, percutaneous transhepatic cholangiography, or endoscopic retrograde cholangio-pancreatography when necessary. The immunosuppressive regimen was based on quadruple sequential therapy with antilymphocyte globulin, Sandimmune Neoral® (Novartis, Basel, Switzerland), steroids, and azathioprine in most patients, as reported elsewhere.[8] Cellular rejection was diagnosed according to histological criteria.[9]

Statistical analysis Chi-squared analysis was used to compare dichotomous variables and the presence of BC. Variables that were statistically significant in the univariate analysis were introduced in a multivariate logistic regression analysis. Other known risk factors for developing BC were introduced into the model as covariates: donor age, acute rejection, and chronic rejection. Variables with $P>0.05$ were excluded from the final equation. Kaplan–Meier estimates of the rate of BC for both groups and the results were compared with a log-rank test.

Results

Perioperative data and surgical details The preservation solutions used were the University of Wisconsin solution in 332 (97%), Celsior solution in 5 (1%), and histidine-tryptophan-ketoglutarate solution in 8 (2%). Twenty grafts (6%) were shipped by another team. The study of donor risk factors demonstrated that there was no hemodynamic instability (systolic pressure lower than 60 mmHg for more than 1 h) in 265 cases (77%), and that the main cause of death was traumatic head injury (129/36%). Donor Rh blood group was positive in 301 (87%) and negative in 44 cases (13%). Recipient Rh blood group was positive in 284 (82%) patients, and negative in 61 (18%). Rh blood groups of donor and recipient were positive to positive in 255 cases (74%), positive to negative in 46 (13%), negative to positive in 30 (9%), and negative to negative in 14 (4%). Donors and recipients had identical Rh in 269 cases (78%) and nonidentical in 76 (22%). The donor ABO blood group was A in 157 (46%), B in 29 (8%), AB in 19 (5%), and O in 140 (41%), while recipients were A in 161 cases (46%), B in 34 (10%), AB in 20 (6%) and O in 130 (38%). The ABO groups of transplanted grafts and hosts were identical in 97% of cases (335 patients) and compatible in 10 cases. There were no cases of incompatible grafts.

During postoperative development, 25 LTs presented arterial thrombosis (7%). Eight grafts presented primary nonfunction and were retransplantated (2.2%), and 43 presented initial poor function that recovered spontaneously (12%).[3] Biopsy-proven acute rejection was diagnosed in 66 grafts (19%) after transplantation, with development to chronic ductopenic rejection in 8 (2%).

BCs and Rh mismatch BCs appeared in 70 of the 345 patients (20%). Cross-tabs were built to analyze differences between the grafts that suffered BCs and the rest. Both groups were similar in terms of donor preoperative evaluation and support, recipient descriptive data, and surgical terms. The incidence of BC in nonidentical Rh graft–host cases (23/76; 30%) was significantly higher than in cases of identical Rh graft–host (47/269; 17%, P=0.01). Cases of arterial thrombosis after LTs and ischemia time longer than 430 min were also associated with a higher incidence of BC (Table 1).

Multivariate Analysis of Risk Factors for BCs

In multivariate analysis, arterial thrombosis presented an adjusted relative risk (aRR)=2.6, CI 95%=(1.1–6.4) (P=0.02), cold ischemia time aRR=1.8 (CI 95% =1–3.2) (P=0.02), and Rh graft–host nonidentity aRR=2 (CI 95%=1.1–3) (P=0.02) were confirmed as independent risk factors for BC. Other variables included in the initial

Table 1 Demographics and Major Complications Occurring in Both Groups Studied, Chi-square Test

	BCs (n=70)	No BCs (n=275)	Chi-square
Donor data			
ABO blood group			0.2
A	25/157 (16%)	132/157 (84%)	
B	6/29 (21%)	23/29(79%)	
AB	6/19 (32%)	13/19(68%)	
O	33/140 (24%)	107/140 (76%)	
Rh blood group			0.4
Positive	59/301 (19%)	242/301 (81%)	
Negative	11/44 (25%)	33/44 (75%)	
Sex			0.4
Male	51/233 (22%)	182/233 (75%)	
Female	19/110 (17%)	91/110 (83%)	
Donor age			0.4
≤70 years	66/320 (20%)	254/320 (80%)	
>70 years	4/25 (16%)	21/25 (84%)	
Recipient data			
Rh blood group			0.2
Positive	54/284 (19%)	230/284 (81%)	
Negative	16/61 (26%)	45/61 (74%)	
Rh D-R crossing			0.1
Positive–positive	45/255 (18%)	210/255 (82%)	
Positive–negative	14/46 (30%)	32/46 (70%)	
Negative–positive	9/30 (30%)	21/30 (70%)	
Negative–negative	2/14 (14%)	12/14 (86%)	
Rh D-R identity			0.01
Identical	47/269 (17%)	222/269 (83%)	
Nonidentical	23/76 (30%)	53/76 (70%)	
ABO blood group			0.4
A	27/161 (17%)	134/161 (83%)	
B	7/34 (20%)	27/34(80%)	
O	30/130 (23%)	100/130(77%)	
AB	6/20 (30%)	14/20 (70%)	
ABO D-R identity			0.4
Identical	67/335 (20%)	268/335 (80%)	
Nonidentical	3/10 (30%)	7/10 (70%)	
Sex of recipient			0.4
Male	48/214(22%)	166/214 (78%)	
Female	22/130(17%)	108/130(83%)	
Recipient age			0.2
<60 years	41/221 (18%)	180/221 (82%)	
≥60 years	29/124 (24%)	95/124 (76%)	
Diagnosis			0.3
Choleostasis	2/14(15%)	12/14(85%)	
Cirrhosis	32/162 (20%)	130/162(80%)	
Hepatocarcinoma	27/103(26%)	76/103(74%)	
Other etiology	1/18(5%)	17/18(95%)	
Re-OLT	7/39(18%)	32/39 (89%)	
Other tumors	1/9(11%)	8/9 (89%)	
Surgical data			
Cold ischemic time			0.01
≤430 min	26/178 (15%)	148/178 (85%)	
>430 min	44/171 (26%)	127/171 (74%)	
Type of anastomosis			0.6
Termino-terminal	64/315(20%)	251/315(80%)	
Graft evolution data			
Arterial thrombosis			0.03
Yes	9/25 (36%)	16/25(64%)	
No	60/319 (19%)	259/319(81%)	
Initial poor function			0.6
Yes	10/43 (23%)	33/43 (77%)	
No	60/302 (20%)	242/302 (80%)	
Primary nonfunction			0.1
Yes	0	8/8 (100%)	
No	70/336 (20%)	266/336 (80%)	
Acute rejection			0.4
Yes	11/66(17%)	55/66(83%)	
No	59/279(21%)	220/279(79%)	
Chronic rejection			0.5
Yes	1/8(12%)	7/8(88%)	
No	69/337 (20%)	268/337(80%)	

OLT orthotopic liver transplantation

analysis were nonsignificant (Table 2). Kaplan–Meier estimator and log-rank test confirmed these findings (P= 0.01, Fig. 1). To discard the possible association between the Rh match and the two other risk factors, we demonstrated that arterial thrombosis had similar incidence in Rh-nonidentical grafts (3/75, 4%) and in Rh-identical grafts (22/269, 8%; P=0.1). Moreover, grafts with long ischemia times (>430 min) had similar incidence in the Rh-nonidentical (42/76, 55%) group and in Rh-identical patients (129/269, 48%; P=0.1).

Type and Management of BCs

BCs were diagnosed in 70 patients. Biliary duct anastomosis stricture was the main complication, presented clinically,

Table 2 Biliary Complications

	Univariate logistic regression	Multivariate logistic regression
Donor age >70 years	0.5	0.7
Rh D-R identity identical nonidentical	0.01; 2(1.1–3.6)	0.02; 2 (1.1–3.6)
Cold ischemic time >430 min	0.01; 1.9(1.1–3.3)	0.02; 1.8(1–3.2)
Arterial thrombosis (yes)	0.04; 2.4(1–5.7)	0.02; 2.6 (1.1–6.4)
Acute rejection (yes)	0.4	0.4
Chronic rejection (yes)	0.5	0.5

Univariate and multivariate logistic regression.

with (7/10%) or without postoperative leak (21/30%). Solitary leaks (17/24%), ischemic-type BCs (ITBC) with arterial thrombosis (6/9%), ITBC without arterial thrombosis (10/14%), and lithiasis (9/13%) were also related complications. The therapeutic approach was surgical in 23 patients (33%), endoscopic in 20 (28%), retransplantation in 11 (16%), and conservative treatment in 16 (23%).

Chi-square test was performed to analyze differences between the type of BC and the three risk factors found. As would be expected, arterial thrombosis was identified in all the cases of ITBC with thrombosis, in a higher percentage than the other BCs ($P<0.001$). However, the different types of BCs were not associated with long ischemia time ($P=0.2$) or Rh-identity ($P=0.4$).

Finally, chi-square test was also performed to analyze differences among the three BC risk factors and medical management. The therapeutic approach regarding Rh-mismatch was similar in both groups ($P=0.3$). Retransplantation was a frequent approach in arterial thrombosis management (4/9, 40%; $P=0.04$). Interestingly, when the BC was presented in grafts with short ischemic time (<430 min), management by surgery (10/26, 38%) or an endoscopic approach (10/26, 38%) were sufficient, and it was not necessary to retransplant. However, when the BC arose in a graft with a long ischemic time (>430 min) the management

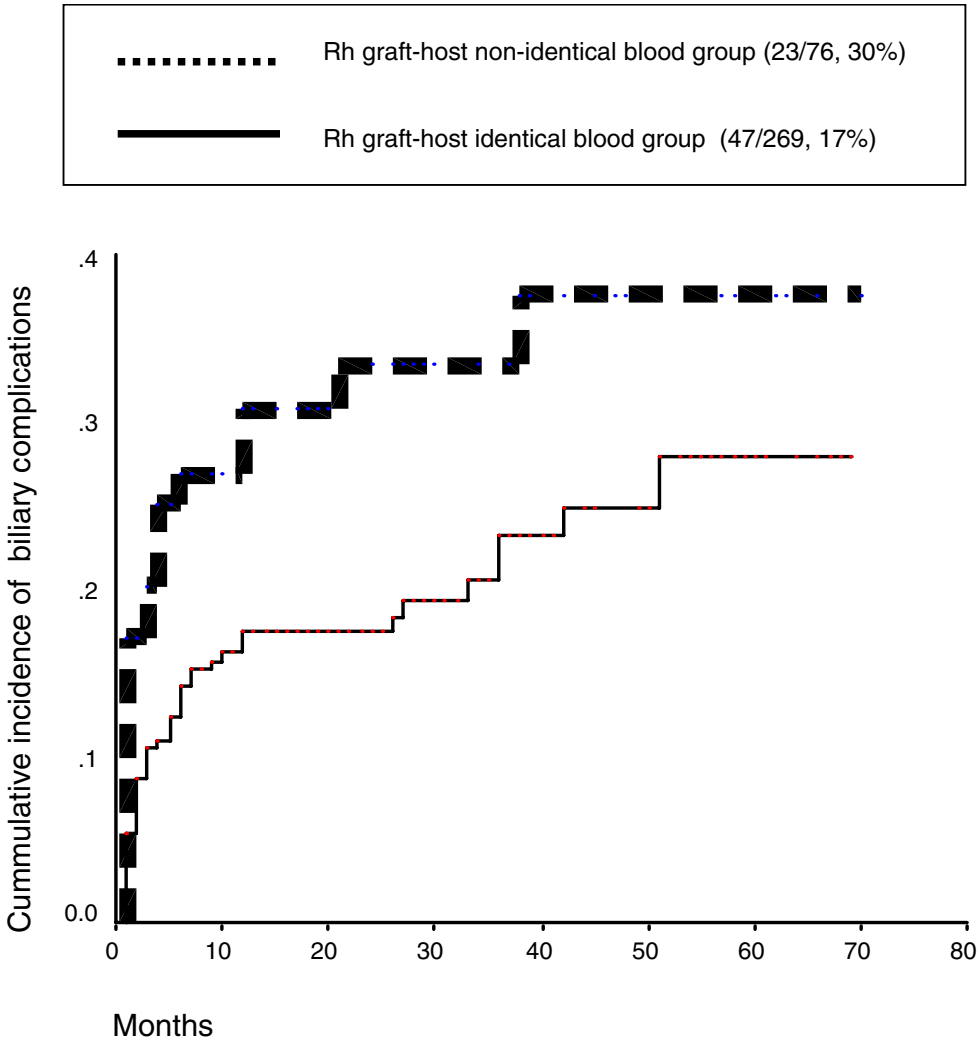

Figure 1 Kaplan–Meier estimates for the onset of BCs for nonidentical Rh graft–host ($P=0.01$).

was more aggressive, with 29% of patients (13/44) needing surgery and 25% (11/44) needing retransplantation.

Discussion

Etiopathogenesis of BC

Currently, orthotopic liver transplants are performed with good results at several centers without taking the donor–recipient Rh relationship into account. In fact, no prior work has shown greater morbidity or mortality after the usage of Rh-incompatible liver grafts. However, it was in studying the causes of BC in our grafts in prior studies that we began to suspect the existence of a possible relationship between BC and Rh incompatibility. First, we observed a greater rate of BC in the presence of preservation lesions in postreperfusion biopsies.[10] Thus, we found that the biliary epithelium is very sensitive to changes during preservation. Second, the description of lesions like ITBC,[11] to which surgical technique does not contribute as a primary cause, led us to suspect possible immunological pathogenesis of the BC. Lastly, it is paradoxical to find that, while surgical technique is improving and satisfactory results are achieved in liver transplants, BCs are still a problem, leading us to suspect that there are unidentified factors that cause them. The arterial thrombosis and long cold ischemia time were independent risk factors for developing BC, as was expected and reported by others.[11,12] In our study we have demonstrated that even though BC in grafts with short ischemia can be resolved with surgery or endoscopy, the prognosis of BC was worse in cases of long ischemic grafts requiring retransplantation.

Relationship Between ABO and Rh in Liver Transplants

As for the donor–recipient ABO relationship, the usage of ABO-incompatible grafts has been discouraged due to the high rate of BC and poor graft survival.[6,13,14] In the Sanchez-Urdazpal study,[6] 82% of the 18 ABO-incompatible grafts presented BC in comparison with 6% of the control group, while Farges,[14] published slightly better results several years later with BC of 54%. Therefore, these grafts are used in extremely urgent cases when there is no other possible alternative. Immunological phenomena, such as rejection,[3] may also lead to biliary strictures. In the same way, the ABO system was shown to cause more BC and worse graft survival in LT.[6,13–15] However, Rh nonidentity seems to have better tolerance and is not a cause of graft refusal when a donor appears. Surprisingly, our study demonstrated a higher incidence of BC in the Rh-nonidentical group.

Some authors[16,17] reported low rates of alloimmunization in Rh-negative recipients of Rh-incompatible transfusion after LT. It was suspected that immunosuppressant drugs modified the immunosuppressive response.[16] However, debate still exists as to whether the D barrier can be crossed in LT. Previous studies of ABO barrier and BC suggested the hypothesis of an immunological injury to the bile duct epithelium, and the expression of ABH antigens in the donor 150 days after transplantation.[6] However, the D antigen is only expressed in erythrocytes.

The nonidentical Rh group has two mismatch possibilities: positive donor to a negative recipient or negative donor to positive recipient. In the first case (positive to negative) the immunologic mechanism is easy to understand because the humoral anti-D (Rh) response may be responsible for the graft injury.

The other subgroup (negative to positive) may have a different pathogenic explanation. Bryan et al.[17] hypothesized that two mechanisms could be involved in the same process in kidney transplantation: other Rh antigenic loci (C and E) and histocompatibility antigenic crossings. A negative liver graft in a positive recipient with lymphatic cells and tissues predisposes to cellular response against it. Finally, the biliary tract can probably suffer immunological damage, and thus further BC. Therefore, while the results of the study lead to suspicion of an immunological pathogenesis, the mechanism is still unclear.

In conclusion, Rh-nonidentical LT involves a higher rate of BCs. Future studies should examine the influence of Rh donor and blood group on graft development. Finally, our results suggest that there is a summation effect of BC risk factors. In our opinion, Rh-nonidentical liver grafts should not undergo a very long ischemia time.

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Does Microvascular Invasion Affect Outcomes After Liver Transplantation for HCC? A Histopathological Analysis of 155 Consecutive Explants

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Abstract Macroscopic vascular invasion (macroVI) is associated with poor outcomes after liver transplantation (LT) for hepatocellular carcinoma (HCC). Whether microvascular invasion (microVI) is associated with the same adverse prognosis is unclear. One hundred and fifty-five consecutive patients with confirmed HCC after LT from March 1991 to 2004 at our institution were reviewed. Patients had to satisfy Milan criteria to be accepted for LT. They were followed with surveillance images every 3 months while on the waiting list. Disease-free survival (DFS) and overall survival (OS) were evaluated by Kaplan–Meier analysis. Demographic, tumor, and histopathologic characteristics were tested for their prognostic significance. Median follow-up after LT was 30 months. Overall graft survival rates were 87, 74, and 65% at 1, 3, and 5 years, respectively. All recurrences (22/155, 14%) developed within 4 years after LT with an overall 5-year DFS of 79%. Vascular invasion, either microVI or macroVI, was more likely in patients with multicentric HCC ($n \geq 3$, $p < 0.001$) and larger tumor size >4 cm ($p = 0.04$). Tumor size >5 cm ($p = 0.04$), advanced pathological TMN stage ($p = 0.007$), microVI ($p = 0.001$), and macroVI ($p < 0.001$) predicted poor tumor-free survival on univariate analysis, but only macroVI was significant in multivariate analysis (hazard ratio 54.2, 95% confidence interval 11, 266). Furthermore, only macroVI was a significant predictor of mortality after LT ($p = 0.01$). Macrovascular invasion is strongly associated with high rates of recurrence and diminished survival after LT whereas microVI is not an independent risk factor.

Keywords Hepatocellular carcinoma · Vascular invasion · Liver transplantation · Recurrence · Microvascular invasion

Introduction

In 1996, Mazzaferro et al.[1] documented excellent survival results after liver transplantation (LT) in a highly selected group of patients with hepatocellular carcinoma (HCC) with a single tumor <5 cm or as many as three tumors, each smaller than 3 cm. Recent studies have shown that selected patients who do not meet these criteria can still be cured with a transplant; the challenge now is to decide which factors, other than size and number, carry a sufficiently poor prognosis to deny transplantation.[2–5]

Gross vascular invasion or radiological evidence of tumor invasion in major veins is a known determinant of poor outcome after resection or transplantation for HCC and is an absolute contraindication to LT.[4–13] Macrovascular invasion (macroVI) or gross vascular invasion of major portal or hepatic veins evident visually at time of transplant or on pathological evaluation may also be a predictor of recurrence after LT.[14] Whether microvascular invasion (microVI), defined as microscopic tumor invasion in smaller intrahepatic vessels identified on pathologic analysis, or macroVI should also be considered a contraindication to LT is controversial. Both types of tumor invasion are difficult to determine pre-LT; therefore, their significance remains uncertain.

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Several published studies have found histopathological factors, namely, poorly differentiated grade, microVI, and macroVI, to be independent predictors of poor survival after LT.[4,11,15–17] We have previously shown that microVI is an independent predictor of early recurrence after resection for HCC.[5] The purpose of this study was to determine if microVI, macroVI, and other pathological factors are associated with tumor recurrence after LT and examine the outcomes thereafter. If these factors are predictors of poor tumor-free survival, then how can we attempt to identify these variables before transplant?

Patients and Methods

One hundred fifty-nine consecutive patients with confirmed HCC on liver explant pathology after LT from October 1991 to October 2004 at our institution were reviewed from a prospective database. The cohort includes 32 patients (20%) with incidental tumors. Patients had to satisfy Milan criteria and have no radiologic evidence of gross vascular invasion to be accepted for LT. Four patients were omitted from analysis for recurrent hepatitis B virus (HBV) before antiviral therapy; after 1991, hepatitis B immune globulin, lamivudine, or combination therapy was used. Patients with known HCC were followed every 3 months while on the waiting list with either an ultrasound or triphasic computed tomography (CT). Patients with HCC were eligible for deceased donor whole organs (n=149) and split (n=0) or living donor LT (n=6).

Patient, tumor, operative, and treatment characteristics were evaluated using a prospective clinical database and review of all pathological explants. The stage, size, and histopathology of the tumor were determined by analysis of the liver explant. Patients were staged based on the explanted specimens using the TNM staging classification of the American Liver Tumor Study Group[18]. Tumor size was measured as the largest diameter of the major tumor in centimeters. MacroVI was defined as gross vascular invasion into major portal vessels or hepatic veins identified either intraoperatively or on pathologic explant, whereas microVI was determined on pathologic analysis as microscopic vascular invasion of small vessels within the parenchyma of the liver. Pretransplant therapy was used in selective cases; if waiting time was determined to be longer than 6 months, patients commonly underwent radio frequency ablation as a bridge to LT. This was performed in an attempt to keep patients within Milan criteria while on the LT waiting list. Postoperative immunosuppression was similar in all patients and consisted of cyclosporine or tacrolimus and steroids.

After LT, patients were followed with Q3 monthly alpha-fetoprotein (AFP) and CT along with standard post-LT evaluation. Recurrences were defined as new nodules diagnosed by CT with confirmed biopsy in most cases. Overall survival (OS) was death as a result of any cause after LT. Patients were followed until death or study closure (arbitrarily denoted as October 1, 2004). Data was collected until May 1, 2005 to ensure at least 6 months of follow-up for all patients.

Statistical Package for Social Sciences software (SPSS, Inc., Chicago, IL) was used for data analysis. Statistical comparison of categorical and continuous variables was performed using the χ^2 test and Mann–Whitney U test, respectively. All data was reported as median with range, mean ± SD or interquartile range (IQR) when appropriate. Analysis of patient OS and disease-free survival (DFS) was performed according to the Kaplan–Meier method. Patient survival in different groups was compared using the log-rank test. All variables with a p value less than 0.1 were then included in a multivariate analysis applying the Cox multiple backward stepwise model.

Results

Patient Characteristics

Of the 1,070 LTs performed during the 13-year period from 1991 to 2004, 159 patients (14%) had HCC. After omission of 4 patients because of recurrent HBV before the antiviral therapy era, 155 patients were included in this analysis (Table 1). The average waiting time for LT was 7 months. There was no perioperative mortality. The median age was 57 years (range 28–70) and the majority of patients were men (79%). The median age of all patients who underwent LT for any cause was 51 years (range 16–71). The most common causes of end-stage liver disease and HCC were hepatitis C virus (HCV) (n=79; 51%), alcoholic liver disease (n=34; 22%), and HBV (n=25; 16%). Selected patients underwent pre-LT therapy, most commonly radio frequency or percutaneous ethanol ablation (ablation, 23%), but the majority of patients received no treatment before LT (72%). Use of ablation did not result in any adverse outcomes in this series of patients who underwent eventual LT.

Histopathological Analysis

The pathologic features for the 155 explants are shown in Table 2. The median number of tumors was 2 (range 1–20) and 18% were bilobar. The median size of the largest tumor was 2.6 cm and most tumors were graded as well or moderately differentiated (74%). Gross macroVI was evident in 3.9% (6/155) of the explants on pathologic examination, whereas 21% (33/155) of explants had the

Table 1 Pretransplant Demographics of 155 Patients with HCC Who Underwent LT

Pretransplant Criteria	*N*=155	*p* Value
Median age (range)	57 (28–70)	0.48
Sex		0.38
Male	123 (79%)	
Female	32 (21%)	
Cause of liver disease		0.10
HCV	79 (51%)	
HBV	25 (16%)	
Alcohol	34 (22%)	
Cryptogenic	7 (4.5%)	
Alpha-1 antitrypsin	6 (3.9%)	
NASH	2 (1.3%)	
PBC	2 (1.3%)	
Pretransplant therapy		0.67
Ablation	36 (23%)	
Resection	6 (3.9%)	
TACE	1 (0.6%)	
EBRT	1 (0.6%)	
None	111 (72%)	

The *p* values were determined by log-rank test as predictor of DFS after Kaplan–Meier analysis.
NASH = nonalcoholic steatohepatitis, PBC = primary biliary cirrhosis, EBRT = external beam radiation therapy

presence of microVI. Using the pathological TNM classification, 31 patients (20%) had stage I tumors, 69 patients (44%) had stage II tumors, 26 patients had stage III tumors (17%), and 29 patients had stage IV tumors (19%). Patterns of advanced stage were most often because of multifocal HCC or three or greater in number (40%).

Vascular invasion was associated with both the number and size of tumors. Liver explants, with either microVI or macroVI, had more tumors (3.8 vs 2.0, $p<0.001$) and were larger in size (3.6 cm vs 2.8 cm, $p=0.04$) compared to those without vascular invasion. Specifically, if microVI or macroVI was present on histopathology, 64 and 100% of the tumors, respectively, were outside of the Milan criteria or were TNM stage III or IV. Histological grade was not associated with either type of vascular invasion; 85% of patients with either type of vascular invasion had favorably differentiated tumors. Ablation did not affect the rate of vascular invasion, either microVI or macroVI, in this series. Eleven of 33 patients (33%) with vascular invasion on explant analysis had undergone ablation of their tumor.

Predictors of Recurrence and Survival

The 5-year disease-specific survival was 79% (Fig. 1a). All recurrences developed within 44 months after LT. The 1-, 3-, and 5-year overall graft OS rates were 87, 74, and 65%, respectively (Fig. 1b). Only 22 patients (14%) developed tumor recurrence after LT with a median follow-up of 30 months (range 6–144 months). Eighty-six percent of patients (122/155) are currently alive and free of cancer. There was no difference in OS in patients with incidental tumors compared to those with known HCC (data not shown), but a significant difference was observed in DFS (5-year OS rate 94 vs 74%, $p=0.02$).

The median time to recurrence for the 22 patients who developed recurrent HCC was 16.3 months (IQR 8.0–28). Tumor size >5 cm ($p=0.04$), pathological TMN stage ($p=0.007$), microVI ($p=0.001$), and macroVI ($p<0.001$) were found to be independent predictors of tumor-free survival. Patients with tumor size of 5 cm or larger had a 5-year DFS of 48 vs 82% for those with tumors smaller than 5 cm. Advanced TMN stage was also associated with poor recurrence-free survival after LT (Fig. 2). Twenty-one of the 22 patients (95%) who developed HCC recurrence were found to have either microVI ($n=15$) or macroVI ($n=6$) on pathological analysis. This accounts for 68% (15/22) of all patients with microVI and 100% (6/6) of patients with macroVI in the entire study. Patients with macroVI had a median DFS of only 7.1 months compared to a more favorable DFS in patients with microVI or no vascular invasion (median not achieved) (Fig. 3). No significant differences in DFS based on age, sex type, hepatitis status, tumor grade, bilobar disease, tumor number, ablative therapy, or type of transplant were found on univariate analysis. Pre-LT therapy did not result in any improvement in DFS or OS after LT (data not shown).

In a multivariate analysis including factors with an influence on DFS, only macroVI (hazard ratio [HR] 54.2, 95% CI 11.03–266.4) was identified to be predictive (Table 2). This was confirmed with a Cox backward stepwise model of multivariate analysis (data not shown).

Discussion

In this study, we report our experience with LT for HCC with a specific focus on pathological factors affecting long-term outcomes. Overall survival rates of LT for HCC were 87, 74, and 65% at 1, 3, and 5 years, respectively, with a median follow-up time of 30 months. The overall recurrence rate was 14% with 79% 5-year disease-specific survival. Patients with incidental tumors had similar OS rates as those with known tumors consistent with previous reports,[8,9,14,15,19] but in this study, a significant difference was found in DFS. Our studies suggest that large tumor size (>4 cm) and multiple tumors (≥3) correlate with an increased incidence of vascular invasion and may provide a surrogate marker for entities that are often difficult to detect before LT.

Recurrence rates after LT may not simply reflect only size and number as suggested in the initial Milan series, but may be a complex interplay of host- and tumor-related

Table 2 Pathologic Characteristics of 155 Liver Explants

Characteristic	*N*=155	*p* Value	HR (95% CI)
No. of tumors			
Median (range, cm)	2 (1–20)	0.23	
<3	126 (81%)		
>3	29 (19%)		
Bilobar	32 (21%)	0.15	
Size			
Median (range; cm)	2.6 (.1–16)	0.04	0.47 (0.14,1.61)
<5 cm	145 (94%)		
>5 cm	15 (10%)		
Stage			
I	31 (20%)	0.007	1.17 (0.39,3.50)
II	69 (44%)		
III	26 (17%)		
IV	29 (19%)		
Positive lymph nodes	3 (2.0%)	0.31	
Vascular invasion[a]			
Microscopic	33 (21%)	0.001	3.16 (0.92,10.93)
Macroscopic	6 (4%)	<0.001	54.2 (11.03,266.4)
None	121 (78%)	[b]	1.0[c]
Grade			
Well/mod	115 (74%)	0.36	
Poor	13 (9%)		
N/A[d]	27 (17%)		
Margins			
Positive	2 (1%)	0.25	
Negative	153 (99%)		
Incidental tumor	34 (22%)	0.19	

The *p* values were determined by chi-square test or log-rank test of variables after Kaplan–Meier analysis (univariate). HR (95% CI) represents multivariate analysis of factors affecting recurrence after resection.

[a] Five of six patients had characteristics of both microvascular and macrovascular tumor invasion.

[b] Reference category for comparison

[c] Reference category for each categorical variable is assigned HR=1.0.

[d] Not available in the analysis

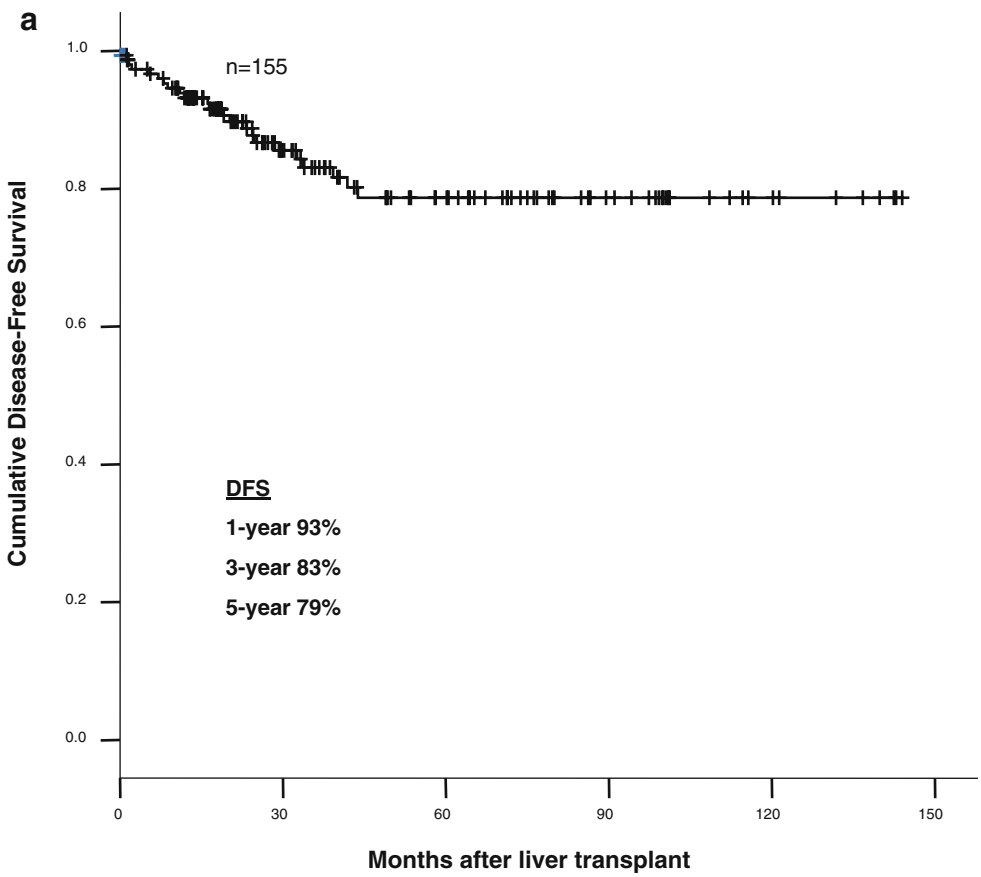
factors, which are still largely unknown.[20] This report suggests that tumor grade, size, number, and microVI do not influence outcome after LT for HCC; only the presence of macroVI appears to be associated with poor outcomes on multivariate analysis. MacroVI and microVI were more commonly found in multicentric (three or more) and large (>4 cm) HCC. Furthermore, 21 of 22 recurrences had evidence of either microVI or macroVI on pathologic examination. Because we are unable to identify these biologic factors preoperatively, markers of histopathologic or biologic variables that predict poor outcomes are extremely important.[14,20–22]

MacroVI was shown to be an independent predictor of tumor recurrence after LT in some studies.[4,9,10,14] The Pittsburgh group found that microVI and major vascular invasion was associated with increased risk of recurrence by multivariate analysis.[4,8] In a report of 344 patients with HCC treated by LT, microVI and macroVI were associated with 4.4- and 15-fold increased risk of recurrence, respectively.[8] Shetty et al.[14] found that macroVI, but not microVI, was a significant predictor of DSF and OS after LT for HCC. In this study, microVI is associated with higher stage and recurrent tumors, but does not appear to be an independent factor for survival.

The role of microVI on posttransplant recurrence and survival outcomes for HCC still remains unclear. Several published studies have found poorly differentiated histological grade or microVI to be independent predictors of impaired survival after LT.[11,15–17] Jonas et al.[11] found vascular invasion and histological grade to be the only statistically significant independent predictors of poor survival after LT in 120 patients. In their study, only poorly differentiated tumors larger than 5 cm predicted the presence of microVI. But other studies involving LT and HCC were not able to corroborate poor results regarding microVI.[3,14,23,24] The close relationship between histological grade and microVI may explain why microVI is often eliminated in multivariate models for analyzing tumor recurrence prognostic factors that include histological grading and vice versa.[4,8,11,15,23,25,26] Multiple tumors, larger tumors, and higher grade of differentiation have all been shown to be associated with microVI after resection for HCC. Esnaola et al.[13] reported that tumor size greater than 4 cm and poorly differentiated/undifferentiated histopathologic grade increased the odds of microVI by 3 and 6.3-fold, respectively, but these tumors were primarily in Child class A cirrhotic.

The degree of fibrosis and scarring of the liver may play a significant role in the biological behavior and significance of microVI and macroVI. We have previously shown that microVI was a significant predictor of early recurrence and death after resection for HCC in cirrhotic patients.[5] Most recurrences were intrahepatic and away from the staple line, suggesting that liver mobilization and manipulation may cause progression of microVI or a new tumor has developed in the presence of ongoing oncogenic stimulus from cirrhosis. For these reasons, prognostic factors for LT from resection studies should be interpreted with caution and a possible rationale why microVI is so important after resection but not after LT.[12,13] Lack of manipulation of the liver and intrahepatic dissection may be a potential explanation for the lack of importance of microVI with LT.

Because of the importance of histological features of HCC, some have advocated pre-LT biopsy to examine grade, vascular invasion, and genetic typing.[13,15,20] Complications of needle biopsy such as tumor tract seeding and lack of sensitivity have made routine biopsy unfavorable.[27] In our experience, needle biopsy was a poor predictor of microVI



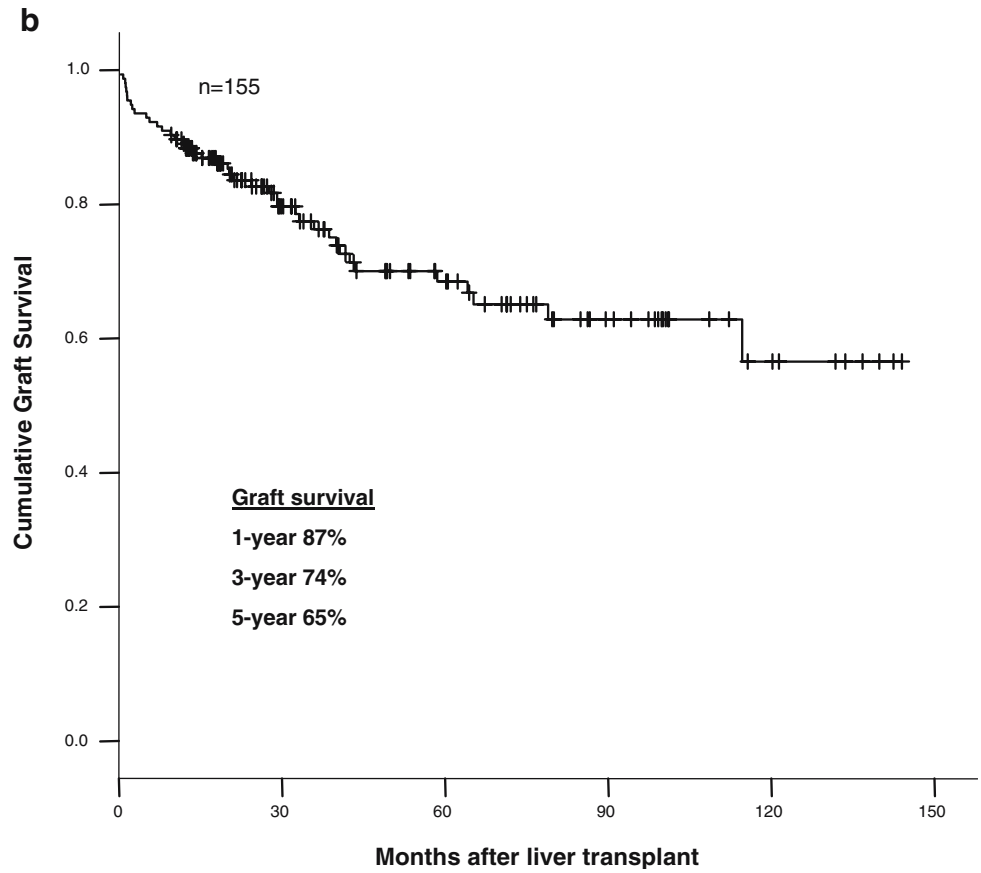


Figure 1 **(A)** Disease-free survival after LT for HCC of 155 patients. **(B)** Overall graft survival after LT for HCC of 155 patients.

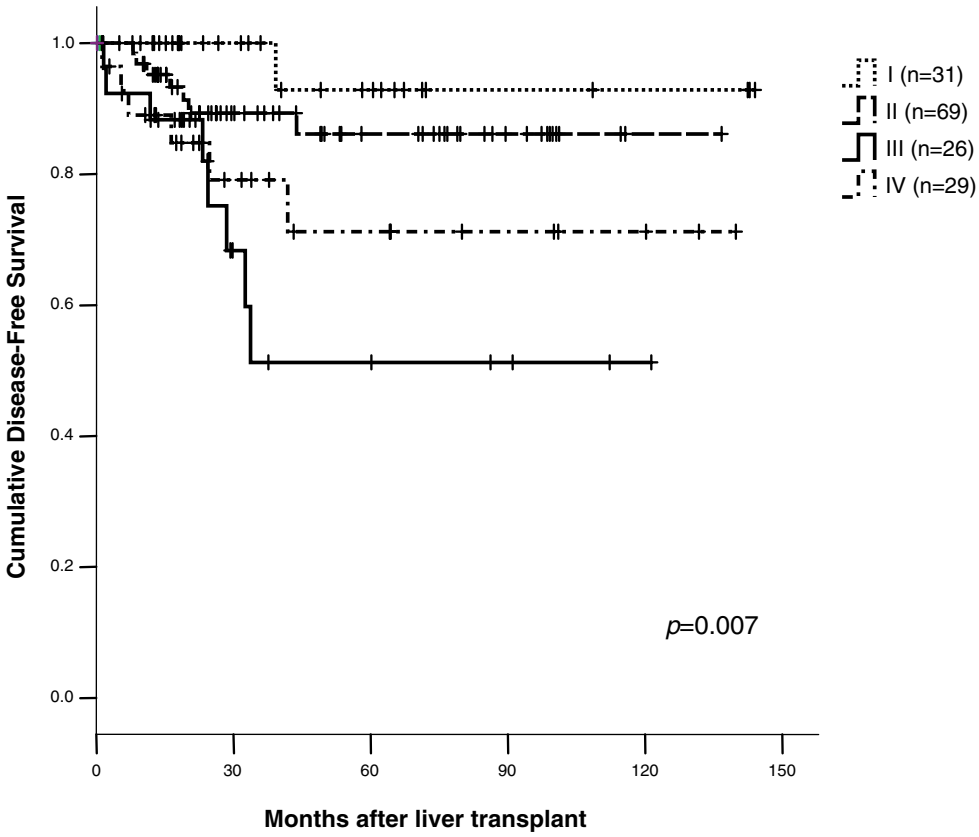


Figure 2 The effect of TNM stage on DFS after LT for HCC.

or macroVI, and therefore was not considered in our pre-LT work-up for HCC (data not shown).

There are several limitations to this study and therefore some of the results should be interpreted with caution. The need to standardize grading systems for HCC has long been recognized and would allow us to determine if tumor grade is indeed an important prognostic marker for recurrence and survival. Few tumors in this study were graded as poorly

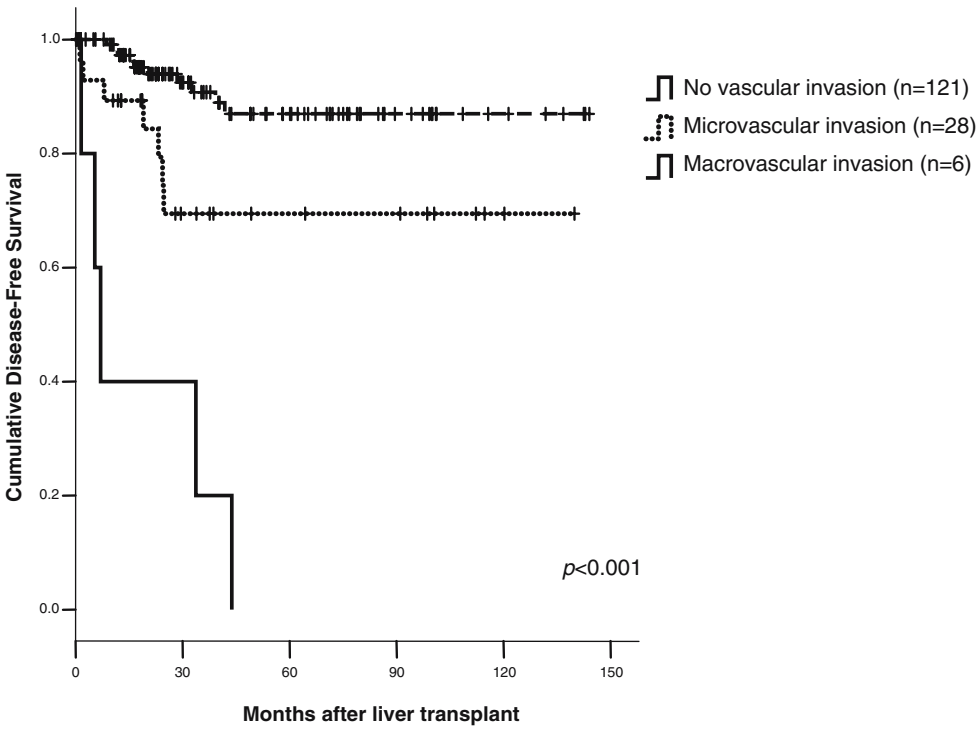


Figure 3 The effect of vascular invasion on recurrence-free survival after LT for HCC.

differentiated; moreover, in 27 patients, their grade was not determined. Results from histopathological analysis are often met with inherent biases from the pathologist and comprehensive evaluation of the whole liver explant may vary among pathologists and institutions. Finally, with very few tumors containing macroVI, strong conclusions about prognostic characteristics concerning macroVI cannot be made in this report. Whether microVI is a harbinger of macroVI or in some way correlated with a more aggressive form of HCC remains unclear.

The use of pathological and biological features of the tumor may allow us to identify those patients who are at increased risk of recurrence; then these patients should be considered for adjuvant therapy before evidence of a recurrence. Because vascular invasion is more common in multicentric (>3) HCC or large tumors (>4 cm), we propose shortening the interval of pre-LT imaging in patients with these tumors to identify vascular invasion or rapid growth of the tumor before LT. Genetic testing of tumors before LT may be a novel method to predict other prognostic factors affecting recurrence.[20] Several studies have reported improved posttransplant survival in HCC patients with transcatheter arterial chemoembolization (TACE) or systemic therapy,[28–31] but overall results for adjuvant chemotherapy post-LT were disappointing.[32] Because of small numbers, this would be best done in a multicenter-randomized trial. We are currently evaluating the role of tumor size and number in our allocation system in LT for HCC to determine their respective predictive value for prognosis.

In summary, LT for HCC can be performed with acceptable survival outcomes. A single tumor characteristic alone does not appear to determine prognosis or outcome. In the present study, macroVI alone was associated with very poor outcomes after LT. Extending criteria of LT for advanced HCC is possible only with better patient selection using improved pre-LT staging and identification of histopathological biological markers such as macroVI that would preclude LT.

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The Role and Limitations of 18-Fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG-PET) Scan and Computerized Tomography (CT) in Restaging Patients with Hepatic Colorectal Metastases Following Neoadjuvant Chemotherapy: Comparison with Operative and Pathological Findings

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Abstract
Background Recent data confirmed the importance of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the selection of patients with colorectal hepatic metastases for surgery. Neoadjuvant chemotherapy before hepatic resection in selected cases may improve outcome. The influence of chemotherapy on the sensitivity of FDG-PET and CT in detecting liver metastases is not known.
Methods Patients were assigned to either neoadjuvant treatment or immediate hepatic resection according to resectability, risk of recurrence, extrahepatic disease, and patient preference. Two-thirds of them underwent FDG-PET/CT before chemotherapy; all underwent preoperative contrast-enhanced CT and FDG-PET/CT. Those without extensive extrahepatic disease underwent open exploration and resection of all the metastases according to original imaging findings. Operative and pathological findings were compared to imaging results.
Results Twenty-seven patients (33 lesions) underwent immediate hepatic resection (group 1), and 48 patients (122 lesions) received preoperative neoadjuvant chemotherapy (group 2). Sensitivity of FDG-PET and CT in detecting colorectal (CR) metastases was significantly higher in group 1 than in group 2 (FDG-PET: 93.3 vs 49%, $P<0.0001$; CT: 87.5 vs 65.3, $P=0.038$). CT had a higher sensitivity than FDG-PET in detecting CR metastases following neoadjuvant therapy (65.3 vs 49%,

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$P<0.0001$). Sensitivity of FDG-PET, but not of CT, was lower in group 2 patients whose chemotherapy included bevacizumab compared to patients who did not receive bevacizumab (39 vs 59%, $P=0.068$).
Conclusions FDG-PET/CT sensitivity is lowered by neoadjuvant chemotherapy. CT is more sensitive than FDG-PET in detecting CR metastases following neoadjuvant therapy. Surgical decision-making requires information from multiple imaging modalities and pretreatment findings. Baseline FDG-PET and CT before neoadjuvant therapy are mandatory.

Keywords Colorectal liver metastases · FDG-PET · Neoadjuvant chemotherapy

Introduction

The liver is the most common, and often the only, site of distant metastases from colorectal cancer (CRC).[1] Hepatic resection is the only effective therapy for a subset of patients with CRC metastatic to the liver, and is associated with 5-year survival rates ranging from 25 to 40%.[2–5] From 60 to 65% of patients will, however, develop recurrent tumors after hepatic resection, indicating that they had harbored unrecognized intra- or extrahepatic tumor foci at the time of liver resection.[6] Moreover, several studies report unresectable disease in 40–70% of patients that undergo laparotomy for liver resection.[2,7,8] These data indicate that better patient selection is needed to avoid unnecessary operations. There are several potential ways of improving patient selection, one of which is the administration of neoadjuvant therapy followed by reevaluation and better preoperative staging.

Positron emission tomography with the glucose analog 18-fluoro-2-deoxy-D-glucose (FDG-PET) is a sensitive diagnostic tool for the detection of colorectal metastases. Approximately 25% of patients are discovered to have new intra- or extrahepatic tumors on FDG-PET performed after standard imaging.[9–13] Screening with FDG-PET before hepatic resection for CRC significantly improves the survival rates of resected patients, probably by improving patient selection.[14]

The role of neoadjuvant chemotherapy to down-stage nonresectable liver metastases and to improve outcome following hepatic resection of resectable liver metastases is an evolving concept, but one that is not yet established. With the recent application of new chemotherapeutic agents, such as irinotecan, oxaliplatin, and bevacizumab, improved response rates can be achieved and the use of these agents in the neoadjuvant setting would appear to be especially relevant for patients with nonresectable disease or patients with high risk of recurrence.[15–18]

The aim of our study was to examine the effect of neoadjuvant chemotherapy for hepatic colorectal metastases on CT and FDG-PET/CT findings and to define the role of these imaging techniques in this setting. To do so, we compared CT and FDG-PET/CT findings with histopathological reports.

Patients and Methods

Patients

Patients with colorectal liver metastases were assigned to receive either an immediate liver resection (group 1) or neoadjuvant chemotherapy (group 2). The criteria for neoadjuvant treatment were:

1. Nonresectable tumors due to size, location, and number and assessment of the surgical team that complete (R0) resection was not technically possible.
2. High risk of recurrence according to the Memorial Sloan–Kettering Cancer Center (MSKCC) clinical risk score to assess risk of recurrence.[19] Specifically, patients with two or more risk factors [number of metastases >1, disease-free survival <12 months, carcinoembryonic antigen (CEA) levels >200 ng/ml, metastases from the colonic tumor to regional lymph nodes, size of the largest metastases >5 cm] were assigned to neoadjuvant treatment.
3. Presence of extrahepatic disease.
4. Oncologist's preference—this applied to patients with MSKCC >2 that were referred from other hospitals for immediate surgery. The decision not to administer neoadjuvant therapy was not necessarily in agreement with our policy.
5. Patient's preference—patients who refused neoadjuvant therapy were assigned to immediate surgery when feasible.

Neoadjuvant Chemotherapy

Treatment consisted of a neoadjuvant chemotherapeutic combination of 5-fluorouracil, leucovorin, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Seventeen patients (35%) were also given bevacizumab. Most of the group 2 patients were given neoadjuvant irinotecan unless they were enrolled on a multicenter study whose protocol consisted of the administration of neoadjuvant oxaliplatin.

Staging

Before undergoing neoadjuvant chemotherapy, all group 2 patients underwent a triphasic contrast-enhanced CT scan, and a FDG-PET/CT was performed in 30 (62.5%) of them. All 75 patients in group 1 and group 2 underwent FDG-PET/CT and abdominal CT before liver surgery. The time interval between the last course of chemotherapy and the FDG-PET/CT scan

was at least 2 weeks, and surgical exploration took place within 1 month following the FDG-PET/CT scan in most of the cases. Because we used an integrated PET/CT technique, precise anatomical localization could be achieved and confirmed with the standard triphasic abdominal CT findings.

PET/CT

The patients were asked to fast for at least 4 h before undergoing PET/CT. Earlier lab tests had shown that they all had glucose levels <150 mg%. The patients received an intravenous injection of 370–666 MBq (10–18 mCi) of ^{18}F-FDG. Data acquisitions by an integrated PET/CT system (Discovery LS; GE Medical Systems, Milwaukee, WI, USA) were performed within 60–120 min after injection. Iodinated oral contrast material was given to opacify loops of the bowel on the CT image. Data acquisition was as follows: CT scanning was performed first, from the head to the pelvic floor, with 140 kV, 80 mA, a tube rotation time of 0.5 s, a pitch of 6, and a 5-mm section thickness, which was matched to the PET section thickness. Immediately after CT scanning, a PET emission scan that covered the identical transverse field of view was obtained. Acquisition time was 5 min per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation (Xeleris, Elgems, Haifa, Israel).

Studies of all patients were retrieved and read in consensus by two experts (U.M. and E.E.-S.). All suspected sites of metastatic disease showing an increased FDG uptake were recorded. The location of hepatic lesions was recorded according to the Couinaud segmental classification.

Hepatectomy

All patients without extensive extrahepatic disease underwent surgical exploration and intraoperative ultrasound (IOUS). Resections of all metastatic sites were performed by either anatomic or R0 nonanatomic resection, with a tendency toward maximal parenchymal preservation with nonanatomic resections.

Complete radiological response to neoadjuvant chemotherapy was defined as the complete resolution of all metastatic sites according to the CT and PET-CT. In these cases, careful palpation and IOUS were performed in search of remaining tumor or scarring. When there was no evidence of either, the tumor sites were resected according to the findings on the original imaging (i.e., before any response to neoadjuvant treatment).

Detection of Hepatic Metastases

To define the sensitivity of CT and FDG-PET/CT for liver metastases, imaging results were compared with the presence and size of liver lesions as demonstrated and measured by histopathological reports.

Results

Patients

Between June 2002 and September 2005, 75 patients with 155 suspected metastatic lesions from a primary CRC underwent hepatic resection in our department. Group 1 included 27 patients with 33 lesions who underwent immediate liver resection and group 2 included 48 patients with 122 lesions who first received neoadjuvant chemotherapy before subsequently undergoing liver resection. The patient's profiles are outlined in Table 1. Table 2 lists the operative procedures that were performed in the two groups.

Detection of Hepatic Metastases

The overall findings, the sensitivity, specificity, and accuracy of triphasic contrast-enhanced CT and FDG-PET/CT in the detection of viable liver metastases compared to the pathological results are presented in Table 3. FDG-PET and CT had a statistically significant higher sensitivity in detecting liver metastases in patients who did not receive chemotherapy compared to patients who received chemotherapy (Table 3). Statistical analysis also revealed that triphasic contrast-enhanced CT had a

Table 1 Study Patients' Profiles

	Group 1 (n=27)	Group 2 (n=48)	P value
Sex ratio (F/M)	0.50	0.92	0.22
Mean age, years (std deviation)	66 (9.8)	61.25 (10.9)	0.06
Site			
Colon	9 (71%)	32 (66%)	0.74
Rectum	8 (29%)	16 (33%)	
LN metastases (Duke's >B in colonic specimen)	81.5%	82%	0.73
No. of liver tumors (mean) (std deviation)	1.19 (0.4)	2.52 (1.9)	0.0001
Max tumor diameter (largest) (std deviation)	3.53 cm (2.84)	3.9 cm (1.84)	0.49
Extrahepatic disease (no. of patients)	7	9	0.56
Prior liver resection	4	6	1
Mean MSKCC risk score (range)	1.82 (0–4)	2.48 (2–5)	0.003

Group 1, immediate hepatic resection; Group 2, hepatic resection following neoadjuvant chemotherapy
LN=lymph node

Table 2 Operative Procedures

Operative procedure (no. of patients; lesions)	Group 1 (n=27)	Group 2 (n=48)
Right hepatic lobectomy	5	8
Left hepatic lobectomy	4	4
Central hepatectomy	0	3
Right trisegmentectomy	1	0
Nonanatomic resections	15	29
Left lat segmentectomy	2	2
Explorative laparotomy (no resection)	0	2

Group 1, immediate hepatic resection; Group 2, hepatic resection following neoadjuvant chemotherapy

higher sensitivity than PET/CT in detecting colorectal metastasis following neoadjuvant treatment (65.3 vs 49%, respectively, $P<0.0001$), but not in patients who did not receive neoadjuvant therapy (87.5 vs 93.3%, $P=0.625$).

Four of the six false-positive (FP) results on FDG-PET involved patients who had previously undergone hepatic resection. These lesions were discovered on follow-up FDG-PET/CT. Uptake was observed along the resection site, and these patients underwent nonanatomic liver resections for suspected locally recurrent lesions. Pathologic evaluation failed to reveal any tumor cells. The positive predictive value of FDG-PET/CT for metastasis recurrence in the resection site was only 33%, and specificity was 60%.

Sensitivity of FDG-PET in the detection of colorectal metastasis correlated with the size of the metastasis (Table 4). Average size of the metastases in the two groups was 33.9 mm (standard deviation 19) in group 1 and 18.9 mm (standard deviation 19) in group 2, $P<0.0001$.

We also compared the sensitivity of CT and FDG-PET for patients who received FOLFIRI or FOLFOX (n=31) with patients who received the same regimen plus bevacizumab (n=17). The results are outlined in Table 5. We found that the sensitivity of FDG-PET, but not of CT, was lower in patients who received bevacizumab, although the difference did not reach statistical significance.

Table 3 FDG-PET and CT—Comparison With Pathological Results

	Group 1 n=33	Group 2 n=122	P value
PET			
TP	29	48	
True negative (complete response)	–	20	
FP	2	4	
FN	2	50	
Sensitivity	93.3%	49%	<0.0001
Specificity	–	83.3%	
CT			
TP	28	64	
True negative (complete response)	–	18	
FP	1	6	
FN	4	34	
Sensitivity	87.5%	65.3%	0.038
Specificity	–	75%	

Group 1, immediate hepatic resection; group 2, hepatic resection following neoadjuvant chemotherapy

Detection of Extrahepatic Metastases

In group 1, there were one FP result for extrahepatic disease (suspected recurrence in colonic anastomosis, abdominal wall), one true-positive (TP) result (recurrence in mesocolic lymph nodes), and one false negative (FN) result (in a patient with peritoneal metastases). In group 2, there was one FP result (for suspected peritoneal metastasis), three TP results (recurrence in paraaortic lymph nodes and solitary lung metastasis), and two FN results (for peritoneal metastases).

Discussion

The role of neoadjuvant chemotherapy followed by hepatectomy for colorectal liver metastases has not yet been clearly established. New chemotherapeutic agents, including irinotecan, oxaliplatin, and the biologic agent bevacizumab, have yielded improved response rates in the treatment of advanced CRC. These agents may have a potential role in the neoadjuvant setting for down-staging both nonresectable disease to resectability[15,16] and resectable disease, probably mostly for patients with high risk of recurrence.[17] Our policy is to administer neoadjuvant treatment to patients with nonresectable disease, those with extrahepatic disease, and those with resectable disease who have two or more risk factors according to the MSKCC clinical risk score.[19] One of the theoretical benefits of neoadjuvant treatment is that patients who develop additional extrahepatic or intrahepatic metastases during this time period are spared a futile major operative procedure. Accurate staging before the beginning of neoadjuvant treatment and restaging following the treatment are crucial for optimal patient selection.

The standard preoperative staging of patients with colorectal liver metastases includes combined abdominal CT and chest x-ray or chest CT. It was recently demonstrated that FDG-PET as a complementary staging method improves the therapeutic management of patients with colorectal liver metastases.[20] Preoperative screening with FDG-PET results in an increased survival rate of patients who undergo liver resection.[14] This can be explained by the

Table 4 Sensitivity of FDG-PET: Correlation With Tumor Size

Tumor size	<1 cm	1–3 cm	>3 cm
Group 1 sensitivity (total no. of lesions)	33% (n=3)	100% (n=15)	92% (n=13)
Group 2 sensitivity (total no. of lesions)	17% (n=35)	78% (n=41)	100% (n=22)

Group 1, immediate hepatic resection; group 2, hepatic resection following neoadjuvant chemotherapy

detection of occult intra- and extrahepatic metastatic disease, thus obviating futile explorations. In the current study, the sensitivity of FDG-PET/CT following neoadjuvant therapy was only 49% compared to a sensitivity of 93.3% in patients who did not receive neoadjuvant treatment (P<0.0001). The influence of the chemotherapeutic drugs on the sensitivity of FDG-PET in detecting extrahepatic metastases is not known, but we could assume that it is influenced in a similar way. This may result in a higher-than-expected rate of nonresectable disease discovered at the time of laparotomy and more extrahepatic recurrences following resection. In our series, only three of the 48 patients (6.25%) who received neoadjuvant chemotherapy were found to have nonresectable disease (one had diffuse liver metastases and two had peritoneal spread) that was not discovered preoperatively by either abdominal CT or FDG-PET/CT. We believe that one of the reasons for the high operability rate is the fact that a significant number of patients underwent a baseline FDG-PET/CT before the administration of neoadjuvant chemotherapy. We therefore recommend performing a baseline FDG-PET scan for all candidates for liver resection before the administration of neoadjuvant treatment. A longer follow-up is needed to assess the results of our application of this protocol.

Table 5 FDG-PET and CT in Patients who Received Chemotherapy With or Without Bevacizumab: Comparison With Pathological Results

	Bevacizumab −	Bevacizumab +	P value
PET			
TP	29	19	
True negative (complete response)	17	3	
FP	2	2	
FN	20	30	
Sensitivity	59%	39%	0.068
CT			
TP	33	31	
True negative (complete response)	13	5	
FP	6	0	
FN	16	18	
Sensitivity	67%	63%	0.9

The decreased sensitivity of FDG-PET/CT in detecting liver metastases should also be a consideration when planning the extent of liver resection. We believe that the extent of resection should be guided by additional imaging modalities, including abdominal CT and IOUS, in patients who received neoadjuvant treatment. In our series, triphasic contrast-enhanced abdominal CT had a higher sensitivity than FDG-PET/CT in detecting colorectal metastasis in patients who received neoadjuvant chemotherapy (65.3 vs 49%, P< 0.0001). The higher sensitivity of CT alone compared to FDG-PET/CT in detecting small colorectal metastasis has been reported by Ruers et al.,[20] and this may be even greater in patients who received chemotherapy. An attractive solution is the integrated PET/CT scanner on which a diagnostic triphasic abdominal CT scan can be performed at the same setting as the PET scan.

There are several possible explanations for the decreased sensitivity of FDG-PET/CT in the detection of colorectal metastases following neoadjuvant therapy:

1. Size of the lesion. The sensitivity of FDG-PET in detecting colorectal metastasis was reported as being directly related to the size of the lesions.[20] We found similar results in our series (Table 4). The average size of the metastases following neoadjuvant treatment was significantly smaller than that in patients who did not receive chemotherapy (33.9 mm in group 1 and 18.9 mm in group 2, P<0.0001). Two FN results in group 1 and 32 in group 2 involved tumors smaller than 1 cm. We can assume that one of the main reasons for the decreased sensitivity of FDG-PET following chemotherapy is the decrease in size of the metastases.
2. Chemotherapy and "metabolic shutdown." It has been demonstrated that the sensitivity of FDG-PET is diminished in cancer patients who undergo the examination less than 2 weeks following the administration of chemotherapy,[21] presumably due to a temporary metabolic "shutdown." Although the scans in our study were done with a minimal interval of 2 weeks from the last course of chemotherapy, partial response to therapy may have caused decreased FDG uptake in metastatic lesions, making them undetectable in comparison to the physiological background uptake of FDG in the liver. This may have been a contributing factor to the FN results in our series. We found a lower sensitivity of FDG-PET (but not of CT) in detecting liver metastases following regimens including bevacizumab compared to regimens that did not include bevacizumab, although the difference did not reach statistical significance. This result may have significant clinical implications; however, it needs to be verified in larger series.

3. Time interval between the FDG-PET and surgery. In our series, two patients with FN results (two hepatic lesions) underwent surgery more than 2 months after FDG-PET was performed. Viable tumors were discovered at the site of the original metastases which had disappeared on FDG-PET following neoadjuvant treatment. Although it is conceivable that the relatively long interval between FDG-PET and surgery may have contributed to the FN results, we believe that these tumors may have been FN due the small size of the lesions following partial pathological response to chemotherapy.
4. Nonavid tumors. PET avidity of the tumors can be assessed only in patients who undergo a baseline FDG-PET before neoadjuvant treatment. It has been reported that FDG-PET is less sensitive for mucinous adenocarcinoma.[22] In our series, ten FN results (lesions) were in patients with nonavid mucinous adenocarcinoma (sensitivity 37.5%).

There were two FP results in group 1 and four FP results in group 2. Four of the six FP results were in patients who had undergone a previous hepatic resection, for which follow-up FDG-PET detected uptake in the same location of the resected metastasis. These patients underwent nonanatomic resections of the "lesions." The pathological examination revealed only foreign body reaction without any tumor cells. In our current study, FDG uptake in the tumor bed following previous resection had a positive predictive value of 33% (2/6). The specificity of FDG uptake in the tumor bed for recurrence was 60%. We believe that FDG uptake in the tumor bed following a previous liver resection is not specific for tumor recurrence, especially if the CEA levels are normal. Nguyen et al. demonstrated that FDG uptake may be high in various granulomatous lesions,[23] possibly explaining the FP results along resection margins. Therefore, biopsy or follow-up should be considered in these cases.

Conclusions

The sensitivity of FDG-PET in detecting colorectal hepatic metastases decreases significantly following neoadjuvant chemotherapy. This may result in a higher-than-expected rate of nonresectable disease discovered at the time of laparotomy and in more extrahepatic recurrences following resection. We recommend staging patients with a "baseline" contrast-enhanced FDG-PET/CT both before and after the administration of neoadjuvant therapy. The extent of hepatic resection should be guided by systematic integration of data from all additional imaging modalities (abdominal CT, IOUS), as well as by the original imaging findings (before the neoadjuvant treatment). We recommend resection of all metastases that achieved complete radiological response, whenever technically possible. Longer follow-up and further studies are required to justify neoadjuvant treatment and screening with FDG-PET/CT in patients with colorectal metastases to the liver who are at high risk of recurrence.

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Conflict of interest statement None declared

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Duodeno-Gastric-Esophageal Reflux—What is Pathologic? Comparison of Patients with Barrett's Esophagus and Age-Matched Volunteers

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Abstract
Introduction The aim of the study was to analyse pH- and bile-monitoring data in patients with Barrett's esophagus and in age- and gender-matched controls.
Subjects and Methods Twenty-four consecutive Barrett's patients (8 females, 16 males, mean age 57 years), 21 patients with esophagitis (10 females, 11 males, mean age 58 years), and 19 healthy controls (8 females, 11 males, mean age 51 years), were included. Only patients underwent endoscopy with biopsy. All groups were investigated with manometry, gastric and esophageal 24-h pH, and simultaneous bile monitoring according to a standardized protocol. A bilirubin absorption >0.25 was determined as noxious bile reflux. The receiver operator characteristic (ROC) method was applied to determine the optimal cutoff value of pathologic bilirubin levels.
Results Of Barrett's patients, 79% had pathologic acidic gastric reflux (pH<4 >5% of total measuring time). However, 32% of healthy controls also had acid reflux ($p<0.05$) without any symptoms. The median of esophageal bile reflux was 7.8% (lower quartile (LQ)–upper quartile (UQ)=1.6–17.8%) in Barrett's patients, in patients with esophagitis, 3.5% (LQ–UQ= 0.1–13.5), and in contrast to 0% (LQ–UQ=0–1.0%) in controls, $p=0.001$. ROC analysis showed the optimal dividing value for patients at more than 1% bile reflux over 24 h (75% sensitivity, 84% specificity).
Conclusion An optimal threshold to differentiate between normal and pathological bile reflux into the esophagus is 1% (24-h bile monitoring with an absorbance >0.25).

Keywords Reference value bilitec · Bile reflux · Acid reflux · Barrett's mucosa · Esophagus · Spectrophotometry

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Introduction

The incidence rates for adenocarcinoma (AC) of the esophagus and gastric cardia have risen rapidly in Western industrialized countries.[1] Besides nicotine and alcohol abuse, nutritional factors, high body mass index, acidic gastric reflux, and Barrett's esophagus are believed to be critical factors of carcinogenesis.[2–4] Recent studies have shown that the presence of biliary reflux in combination with acidic gastric reflux damages the esophageal mucosa and causes complications of gastro-esophageal reflux disease (GERD), e.g., development of Barrett's mucosa (BM).[5,6] Duodeno-gastric reflux into the esophagus (DGER), in particular, appears to be important to the pathogenesis of Barrett's esophagus.[7] Prolonged esophageal aspiration studies have documented increased bile acids in patients with severe esophagitis and Barrett's esophagus.[8] Eighty percent of patients with Barrett's

esophagus on proton-pump inhibitors show a normal esophageal pH profile, but 60% show abnormal esophageal exposure to bile as measured by Bilitec 2000.[9]

In the past, direct and prolonged quantification of duodenoesophageal reflux has been difficult to achieve. Now, bilirubin concentration can be directly measured by spectrophotometry, based on the specific absorption at a wavelength of 453 nm. Biliary reflux can be measured with a transnasally passed, ambulatory fiberoptic probe (Bilitec 2000), which records bile absorption. A number of papers have already been published on the exposure of the esophagus[10–13] and stomach[14–16] using this technique. However, in these studies, the control patients were between 25 and 35 years old. In clinical practice, patients with Barrett's mucosa tend to be older. In addition, the authors of each study used varying reference values to measure biliary reflux in the esophagus, making comparison of the measured values difficult.

The aim of the present study was to analyze data of pH and bile monitoring in a collective of healthy age- and gender-matched controls and patients with Barrett's esophagus.

Subjects and Methods

Subjects

Selection of controls was carried out according to a strict protocol. Healthy volunteers treated from 1999 to 2000 between the ages of 40 and 60 years were included in the study. None of the controls were on acid suppressing or gut motility medications, had a history of upper gastrointestinal disease, had undergone upper or major abdominal surgery, or had had therapeutic endoscopic procedures of the upper gastrointestinal tract. Diagnostic endoscopy and barium swallows were not performed, but gallstone disease was excluded by ultrasound scan.

From 1999 to 2002, 24 patients with histologically confirmed Barrett's mucosa were included in the study. For additional comparison, we include a group of patients with esophagitis (stage I to III according Savary and Miller) without Barrett's esophagus, which had the same diagnostic procedures before planned laparoscopic fundoplication. During the aforementioned time span, 21 patients age older than 40 years were available for this study. Exclusion criteria were history of esophageal, gastric, or biliary surgery, history of abdominal or thoracic radiotherapy, or presence of peptic ulcer disease, active gastrointestinal bleeding, esophageal or fundic varices, esophageal or upper small intestine chronic disease, or neoplastic disease. All drugs potentially affecting gastrointestinal motility and secretion were discontinued at least 1 week before the study.

Upper Gastrointestinal Endoscopy

All patients underwent classical upper gastrointestinal endoscopy. If sedation was necessary, intravenous administration of propofol (up to 200 mg) was normally used, or occasionally, midazolam (up to 5 mg) was used. During endoscopy, the presence and extent of esophagitis, Barrett's esophagus, and hiatal hernia was noted. Biopsies were taken from the Barrett's mucosa.

Ambulatory Esophageal/Gastric pH and Bile Monitoring

All groups underwent esophageal manometry and 24-h pH and simultaneous bile monitoring using a standardized protocol. Ambulatory pH monitoring was performed using a transnasally inserted antimony pH electrode with a separate skin reference electrode (Synetics Medical, Stockholm, Sweden). The data were stored on a portable digital recorder (Digitrapper MkIII, Synectics Medical Stockholm, Sweden). Before each study, the pH probe was calibrated in buffer solutions of pH 7 and 1. An episode of acid reflux was defined as a decrease in esophageal pH to less than 4 for more than 10 s.

To quantify duodeno-esophageal reflux, a transnasally passed, ambulatory fiberoptic spectrophotometer (Bilitec 2000, Synectics, Sweden) was used. The system consists of a miniaturized probe of 1.5-mm diameter that carries light signals into the esophagus and back via a plastic fiberoptic bundle. Before each study, the probe was calibrated in water. Corresponding to the current literature, a bilirubin absorption >0.25 was used as a reference for noxious biliary reflux.[14]

The bile and pH probes were taped together and passed transnasally into the esophagus and stomach, as described in detail elsewhere.[17] The upper tips of the probes were positioned 5 cm above the upper border of the lower esophageal sphincter as defined by esophageal manometry. The distal pH electrode and fiberoptic sensor were placed in the fundus of the stomach, 10 cm distal to the lower esophageal sphincter (Fig. 1). Controls and patients were asked to follow a strict protocol of three meals per day, with no liquids between meals. Recumbent phases of recording were permitted only at night. Patients were asked to keep a diary recording of the exact nature of meals, the supine and erect phases of measurement, and the sensations of heartburn and regurgitation.

The simultaneous biliary and pH monitoring was done with administration of a colorless "white diet" (WD) including liquid and solid foods with a maximum in vitro bile absorbance of 0.25 [absorbance scale ranging from 0 (plain water) to 1 (total screen)]. The meals included water, milk, toast, potatoes, chicken, dry biscuits, and fish.

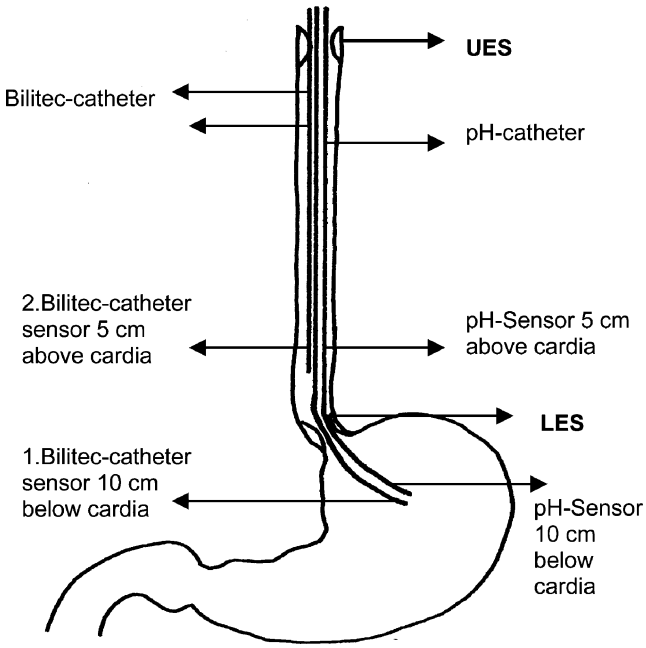

Figure 1 Position of the pH- and bilirubin-probes in the stomach and in the esophagus. (UES=upper esophageal sphincter; LES=lower esophageal sphincter).

Data Acquisition and Interpretation

After completion of the measurements, probes were withdrawn from the patients, and data were stored via interface on an IBM-compatible computer equipped with Polygram® software (Medtronic). The data of each second of the 24-h measurements were used for analysis. To assess the presence of gastric or esophageal biliary reflux, the percentage of time when absorbance was greater than 0.25 was calculated for the following periods: total supine, upright, and postprandial. The postprandial period was defined as 2 h after the end of meals. The percentage of time with esophageal pH lower than 4 and median gastric pH and the percentage of time with gastric pH measuring 1, 2, 3–7, and >7 was also calculated for the above periods. The mean duration of the ambulatory pH and Bilitec monitoring study was 22 h, 40 min in patients and 23 h, 44 min in the controls.

Statistical Analysis

The SPSS (version 11.0, Chicago, Illinois) program was used to analyze the results. For graphical presentation, we used the program MedCalc for Windows, (Version 9.0, MedCalc Software, Belgium). Median, interquartile range (IQR or 25th to 75th percentile) values were established. The nonparametric tests (Mann–Whitney and Kruskal–Wallis analysis) were used to assess the relationship between variables. Box and Whisker plots were used to present some of the data. In these plots, the box represents the IQR, and the Whiskers represent the highest and lowest values. Outliers are also plotted, defined as more than 1.5 times the IQR from the 75th centile. Extreme values were defined as more than three times the IQR from the 75th centile.

A receiver operator characteristic (ROC) curve was used to find a cutoff value for optimal sensitivity and specificity according Zweig and Campbell.[18] The area under the curve (AUC) as a measurement of diagnostic performance of the test was used. The results are given as point with the 95% confidence interval (95% CI) and graphically for presentation of all data. As the positive group, we used the patients with Barrett's mucosa, and the negative test group was defined by the healthy volunteers. A nonparametric distribution of the area under the curve was assumpted.

The assumptions for calculation of the required sample size were alpha=0.05, beta=0.80, and that a test is only valid for daily use if less than 20% of the healthy controls and at least 80% of the patients have positive test results. The calculated sample size for each group was 20.

Ethics

The study protocol was approved by the ethics committee of the University of Cologne. Each subject gave written informed consent.

Results

Twenty-four patients with Barrett's esophagus (mean age: 58 years), 21 patients with esophagitis (mean age: 57 years), and 19 healthy controls with a mean age of 51 years were included in the study. Patients with BM showed esophagitis grade 0 (4 cases), grade I (12 cases), and grade II (8 cases). The control group of patients with esophagitis showed nine cases with grade I, eight cases with grade II, and three cases with grade III. Demographics of patients and volunteers are displayed in Table 1 (the data of one volunteer was not usable due to technical problems).

Acidic Gastric Reflux (AGR)

Patients with Barrett's esophagus, 19 of 24 (79%) and 20 of 21 control patients with esophagitis (95%) had pathologic AGR [pH<4 in >5% of total measuring time (TMT)], but also 6 of the 19 healthy controls (32%) showed pathologic AGR without any symptoms (p=0.002). During the TMT, the median AGR was 10.6% for Barrett patients and 3.2% for controls (p<0.01). In particular, measurements of long acid reflux (LAR), defined as reflux pH<4 lasting longer than 5 min, showed significant differences between patients and controls. Pathologic AGR was found in patients during

Table 1 Demographic Data of Patients with Barrett-Mucosa or Esophagitis and Healthy Volunteers

Parameters	Patients with Barrett's Esophagus (n=24)	Patients with Esophagitis (n=21)	Controls (n=19)	Significance Pat. with Barrett vs Controls
Age (median)	57 years	58 years	51 years	–
Min–max	29–75 years	42–77 years	39–62 years	
Gender m:f	16:8	11:10	11:8	n.s.
BMI (median) min–max	27.0 kg/m^2 (18.6–33.1)	26.9 kg/m^2 (17.9–31.5)	24.1 kg/m^2 (19.62–27.34)	p=0.003
Smokers (%)	n=5 (20.8)	n=4 (19.0)	n=6 (31.6)	n.s.
No alcohol %	n=3 (12.5)	n=5 (23.8)	n=5 (26.3)	n.s.

BMI Body mass index

both the supine and upright fasting measuring periods. In contrast, pathologic AGR in healthy controls occurred only in the upright position (Table 2).

24-h Intragastric pH and Bile Monitoring

Gastric pH monitoring showed no significant differences between patients and controls for all measuring periods (Table 3). Gastric bilirubin exposure, indicating biliary reflux, was significantly more frequent in patients than in controls during all measuring periods (Table 3). Biliary exposure in the supine position typically occurred during the early hours of the morning during sleep, represented by increased absorbance over 2–3 h, with a rapid return to baseline values around the time the subject resumed the upright position. Over the same time period, gastric pH monitoring showed increased pH levels to greater than 2 (Fig. 2).

Bilirubin Exposure of the Esophagus

Over the TMT, the median of esophageal biliary reflux was 7.8% for patients with Barrett's esophagus (LQ–UQ=1.6–17.8%) and 3.5 (LQ–UQ=0.1–13.5) for control patients, in contrast to 0% for the controls (LQ–UQ=0–1.0%), p=0.001). Figure 3 shows that esophageal bile monitoring in patients with Barrett's esophagus and healthy controls varied during the total measuring and supine periods.

The receiver operating curve, plotting the true positive rate (patients with Barrett's esophagus identified by bilirubin exposure) in function of the false positive rate (healthy controls with high bilirubin exposure) is shown in Fig. 4. With an area under the curve of 0.78 (95% CI=0.56–0.89), the ROC analysis of biliary monitoring showed the optimal value for patients at 1% of the TMT [75% sensitivity (95% CI=53–90%), 84% specificity (95% CI=60–96%)]. Therefore, the cutoff value to distinguish normal vs pathologic biliary reflux using 24-h biliary monitoring in the esophagus (absorbance threshold >0.25) should be fixed at 1% of TMT.

Barrett patients, 18 of 24 (75%), 15 of 21 control patients with esophagitis (71%), and 3 of 19 controls (16%) showed biliry reflux into the esophagus more than 1.1% of the TMT (p<0.001). Using this cutoff value, none of the controls, 10 of the control patients (48%), and 11 of 24 Barrett's patients (46%) had pathologic bilirubin exposure during sleep.

Discussion

The results of our study confirm that patients with Barrett's esophagus have significantly more frequent duodenogastric reflux into the esophagus than age- and sex-matched healthy controls. In addition, this reflux, measured by acid and bilirubin exposure, remains longer in the esophagus, especially during sleep.

The role of acid and nonacid reflux into the esophagus as a causative factor of symptoms and mucosal lesions has been addressed in a number of studies. Not only the

Table 2 Median of Acidic Gastric Reflux into the Esophagus in Patients with BM or with Esophagitis and in Healthy Controls

Parameters	Patients with Barrett's Esophagus (n=24) [median (LQ-UQ)]	Patients with Esophagitis (n=21) [median (LQ-UQ)]	Controls (n=19) [median (LQ-UQ)]	Significance Pat. with Barrett vs Controls
Percentage of total measuring time pH<4 (%)	10.6 (6.2–38.3)	19.9 (1.6–71.7)	3.2 (0.9–5.5)	p=0.01
Percentage of upright measuring time pH<4 (%)	11.7 (6.03–6.4)	18.9 (8.7–60.8)	2.4 (0.9–6.1)	p<0.05
Percentage of supine measuring time pH<4 (%)	10.9 (0.4–27.1)	6.3 (0.0–13.3)	0.3 (0.0–4.2)	p=0.004

LQ Lower quartile, *UQ* upper quartile

Table 3 Results of 24-H Intragastric pH and Bile Monitoring in Patients with Barrett Esophagus and Healthy Controls

Parameters	Patients (n=24) [Median (LQ–UQ)]	Controls (n=19) [Median (LQ–UQ)]	Significance
Median of intragastric pH during TMT	1.3 (1.0–1.4)	1.4 (1.1–1.7)	n.s.
Bilirubin exposure percentage (%) of TMT	7.8 (1.6–17.8)	0.0 (0.0–1.0)	p=0.001
Bilirubin exposure percentage (%) of upright time	6.9 (0.1–12.9)	0.0 (0.0–1.3)	p<0.01
Bilirubin exposure percentage (%) of supine time	2.0 (0.0–28.6)	0.0 (0.0–0.0)	p=0.001

LQ Lower quartile, *UQ* upper quartile, *TMT* total measuring time

duration, but possibly the composition of the reflux, is instrumental in the development of such lesions.[13] Twenty-four-hour intragastric bile monitoring has provided the clinician with unequivocal evidence of excessive duodenogastric reflux (DGR) in 41% of patients with endoscopic esophagitis, gastroesophageal reflux (GER) symptoms, and gastric symptoms suggestive of DGR.[19] Reflux of duodenal contents into the stomach, especially postprandially, is a physiological event;[20] however, biliary reflux is a large contributor to mucosal lesions in the whole stomach.[21]

In our study, the control group of patients with different grades of esophagitis showed no significantly different measurements of acidic or bile reflux into the stomach or the esophagus compared to Barrett's patients. This may be caused by selection of patients with esophagitis, which were candidates for fundoplication, but both groups of patients differed significantly compared to healthy controls.

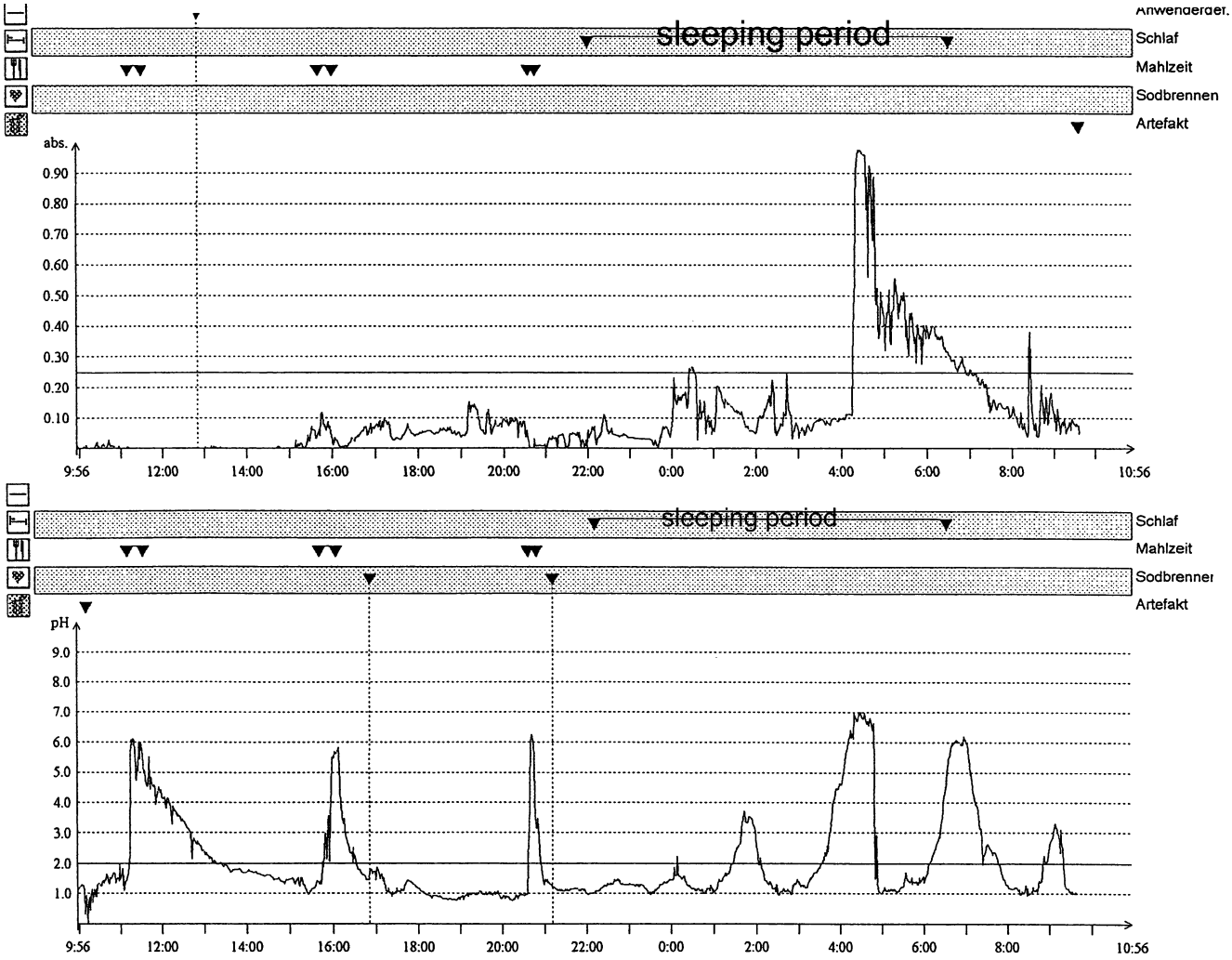

Figure 2 24h intragastric pH- and bile monitoring in a patient with Barrett's esophagus demonstrating the duodenogastric reflux in the early morning. a. Bilitec®-monitoring, b. pH-monitoring.

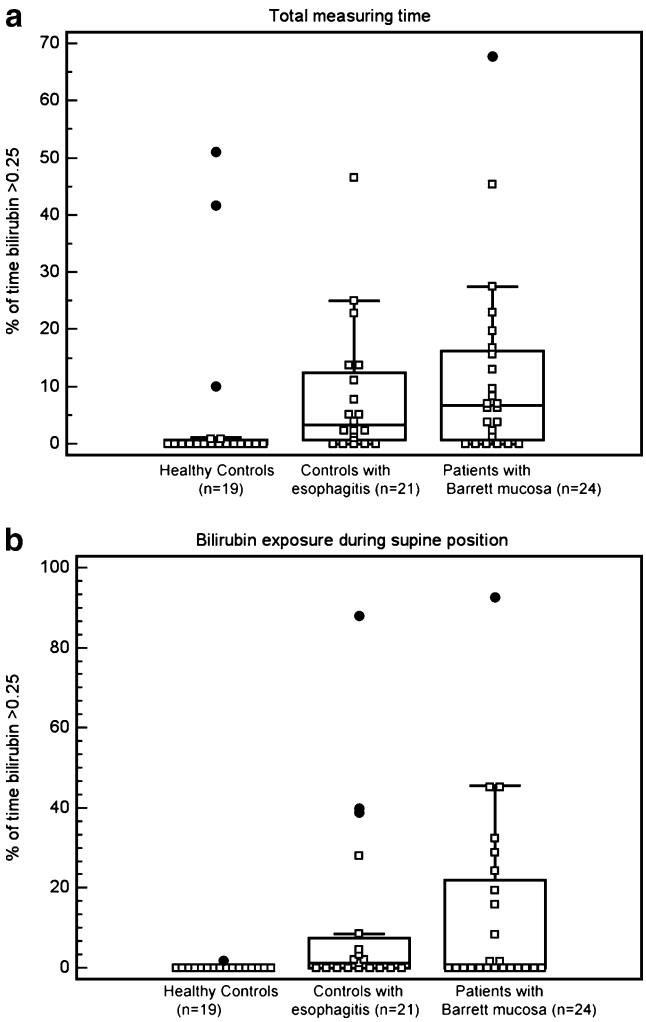

Figure 3 Results of the esophageal bile-monitoring in 24 patients with Barrett's esophagus, 21 patients with esophagitis and 19 healthy controls a) total measuring period (Kruskal-Wallis Test=0.01) b) supine period (Kruskal-Wallis Test p=0.01).

Therefore, our results are of great clinical relevance especially for preoperative diagnostic.

Marshall et al. compared healthy controls to patients with different grades of reflux-esophagitis and Barrett's esophagus with regard to bile measurements in the stomach.[22] In this study, the average age of the control patients was 25 years, and that of the patients in Groups I, II, and III was 42, 50, and 60 years, respectively. The bilitec-probe was positioned 10 cm below the lower esophageal sphincter (LES). The threshold of bilirubin absorbance was 0.14, and although no difference was found between groups over the TMT, gastric bilirubin exposure was higher in the supine than in the upright position. In the current study, the control group was older than that of the Marshall study. More duodeno-gastric reflux was recorded in both study and control patients during all periods of measurement. These findings may be due to improved study conditions.

We used an esophageal threshold of 0.25 for bilirubin absorbance. Fein et al.,[14] in an in vitro study of absorption of different white meals, showed that the least food interference during bile monitoring was measured with an absorbance > 0.25.

Tack et al. reported the influence of meal consistency on Bilitec measurement results in healthy subjects.[23] They compared two groups of young controls. The subjects took either liquid meals only, not absorbing light of the same wavelength as bilirubin, or solid food, avoiding diets that interfere with bilirubin absorbance. The authors found significant differences between the two groups using a bilirubin absorbance threshold >0.14 with a median percentage (interquartile range) over the TMT of 10.9 % (6.7–19.3) for solid meals and 0.3% (0.0–2.8) for liquid meals. Major meal artifacts were present in two-solid-meal (10%) and no-liquid-meal subjects. In our study, we found such a meal artifact in one patient and one control, but the values of bilirubin absorbance were lower than 0.25, and therefore, not relevant to our results.

It is not unusual for gastro-esophageal reflux to contain bile, duodenal, and pancreatic secretions. Utilization of the Bilitec spectrophotometric probe has demonstrated a higher prevalence of abnormal esophageal bilirubin exposure in patients with Barrett's metaplasia when compared to those with erosive injury or without signs of esophagitis.[6,8,10,13] In those studies, patients were consistently older than volunteers included in the control group. However, other studies have shown an increased prevalence of gastro-esophageal reflux with age.[24] For these reasons, we studied

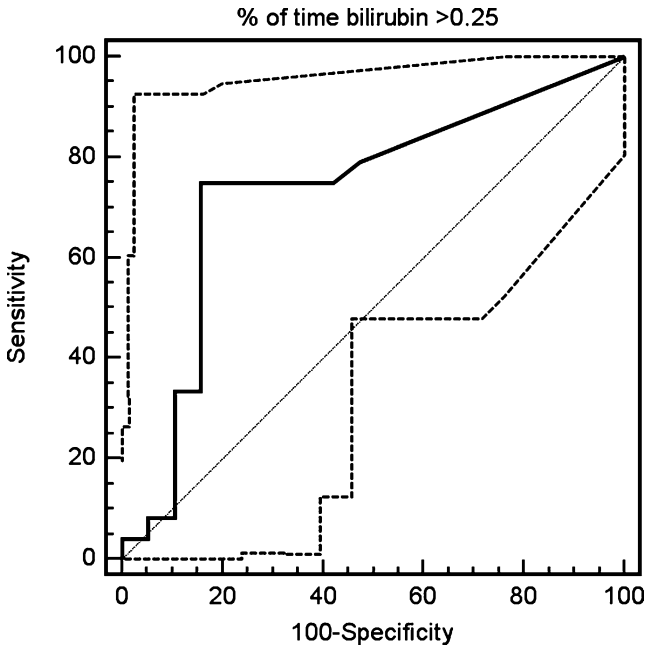

Figure 4 ROC-curve with 95% confidence intervals for pathologic bile-monitoring in patients with Barrett esophagus compared to age and sex matched healthy controls.

age and sex matched healthy controls and patients with Barrett's esophagus or with esophagitis. We found pathologic acid and biliary reflux of the esophagus in one-third of the controls. Perhaps, this may be caused by artefacts or by violation of the protocol by the volunteers. But in a previous published study, we could show that younger healthy controls had no such pathologic reflux.[17] Possibly, these phenomena are caused by relaxations which occur more often in older people. In contrast, nearly all patients with Barrett's esophagus (87%) and all patients with esophagitis (100%) showed pathologic acidic reflux and/or bile reflux measured with combined pH and bile monitoring. Bile reflux into the esophagus during sleep, in particular, was only found in patients with BM or with esophagitis.

In our study, we measured the intragastric pH and the bile reflux from the duodenum into the stomach (DGR). The median of the intragastric pH was similar in both groups. But patients with Barrett's esophagus had significantly longer duodenogastric reflux during the 24-h measuring period than controls. More DGR was demonstrated at night than during the day in both groups of study patients and in healthy controls. This could be associated with an alkaline shift in the pH, according to previously published studies.[25–27] The precise mechanism by which nocturnal DGR occurs and the roles posture plays remain unclear.

Bowrey et al. were unable to establish either gastro-esophageal or duodenogastric reflux as the predominant cause of inflammation in gastric cardiac mucosa with use of the Bilitec 2000 device.[16] This is understandable, as the amount of reflux into the stomach (DGR) does not necessarily correlate with DGER into the esophagus. In this study, the authors demonstrated more DGR in females during the supine period, while males presented more DGER. At the same time, there was no correlation between bile levels in the stomach and esophagus. The controls were, however, much younger than the patients. We found significant differences in bile measurements of the stomach and esophagus between BM patients and controls. In contrast to Bowrey et al., we saw more DGER in females during the supine period and more DGR in male patients.

In contrast, Banki reported similar esophageal exposure to refluxed acid and bilirubin in females and in males with Barrett's mucosa.[28] Pfaffenbach et al.[29] studied esophageal bile and acid reflux in patients with long segment Barrett's esophagus (LSBE), short segment Barrett's esophagus (SSBE) and patients with gastro-esophageal reflux disease (GERD). Subjects underwent esophageal manometry and simultaneous 24-h pH and bile monitoring (Bilitec 2000) with an absorbance value >0.2 for 10.9% of the total period. GER did not differ between the groups. However, DGER differed between patients with LSBE (14.7%), SSBE (2.1%), and GERD (2.1%).

In summary, the analysis of reference values of esophageal acid and bile-reflux measurements in a collective of healthy, age- and gender-matched controls compared to patients with BM led to the following conclusions:

1. Although about 30% of the healthy controls showed acid reflux in pH monitoring, patients with BM had significantly more acid reflux during all measured periods.
2. Healthy controls did not have relevant duodeno-gastric-esophageal reflux measured by bilirubin absorbance. Especially during the supine period, there was no bile reflux.
3. The optimal threshold for pathological bile reflux is 1.1 % (bile monitoring with an absorbance of 0.25).

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The Extended Learning Curve for Laparoscopic Fundoplication: A Cohort Analysis Of 400 Consecutive Cases

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Abstract Many studies have looked at the learning curve associated with laparoscopic Nissen fundoplication (LNF) in a given institution. This study looks at the learning curve of a single surgeon with a large cohort of patients over a 10-year period. Prospective data were collected on 400 patients undergoing laparoscopic fundoplication for over 10 years. The patients were grouped consecutively into cohorts of 50 patients. The operating time, the length of postoperative hospital stay, the conversion rate to open operation, the postoperative dilatation rate, and the reoperation rate were analyzed. Results showed that the mean length of operative time decreased from 143 min in the first 50 patients to 86 min in the last 50 patients. The mean postoperative length of hospital stay decreased from 3.7 days initially to 1.2 days latterly. There was a 14% conversion to open operation rate in the first cohort compared with a 2% rate in the last cohort. Fourteen percent of patients required reoperation in the first cohort and 6% in the last cohort. Sixteen percent required postoperative dilatation in the first cohort. None of the last 150 patients required dilatation. In conclusion, laparoscopic fundoplication is a safe and effective operation for patients with gastroesophageal reflux disease. New techniques and better instrumentation were introduced in the early era of LNF. The learning curve, however, continues well beyond the first 20 patients.

Keywords Laparoscopic Nissen fundoplication · Learning curve

Introduction

It is well known that there is a learning curve associated with laparoscopic Nissen fundoplication (LNF) for gastroesophageal reflux disease (GERD).[1,2] A number of studies have shown a decrease in the number of complications with surgical experience and with modifications to the surgical technique of fundoplication over time. Watson et al.[2] showed that the individual surgeon's complication rate and conversion rate were highest in the first five procedures and stabilized after the first 20 operations. There are, however, few studies with large patient numbers showing the learning curve of a single surgeon and his/her trainees. We have evaluated this learning curve in our series of 400 consecutive patients undergoing laparoscopic fundoplication.

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Materials and Methods

Between January 1993 and August 2002, 400 patients (262 males, 138 females) [mean age: 42.9 years (range 9–86)] underwent laparoscopic fundoplication in a District General Hospital. All procedures were performed or supervised by a dedicated upper gastrointestinal surgeon. Several trainees became the primary surgeons later in the series under direct supervision once they were deemed to have the appropriate laparoscopic skills. The indications for operation were: symptomatic GERD despite prolonged medical therapy; intolerance of medical therapy due to side effects; and volume regurgitation or patient preference for surgery.

Data were collected prospectively on a handheld computer database (Psion, Psion Ltd., England). All patients underwent preoperative endoscopy and 24 h ambulatory esophageal pH monitoring. After the first 75 cases, all

patients also underwent stationary esophageal manometry using a standardized technique.

The operative technique was modified during the course of the study as new equipment became available. Initially, five 10-mm abdominal ports were used: toward the latter half of the study, two 5-mm and three 10-mm ports were used. For the first 35 patients, a 0° laparoscope was used: all subsequent operations were carried out using a 30° laparoscope. The lower esophagus was mobilized from the crural arch. All patients underwent division of the short gastric vessels initially using individually applied ligaclips: after case 215, a harmonic scalpel (Ethicon, Endosurgery, UK) was used. In the first 40 patients, the crura were repaired (using 2/0 silk) only if a hiatal defect and a hernia were present. After this, all patients underwent crural approximation. A loose wrap of 1–2 cm length was constructed over a 56 French gauge bougie using nonabsorbable sutures (initially silk; later "0" Ethibond) incorporating the anterior esophagus. During the period of the study, 63 patients, who were included in the fourth to seventh cohorts, underwent a laparoscopic partial posterior fundoplication as part of a randomized trial.[3] These patients were included in this study, as there was no difference in symptomatic outcome, complication rate, or operative time between this group and those undergoing a 360° fundoplication. Fourteen pediatric patients underwent an LNF throughout the series. The surgical technique used was the same in adult and pediatric populations. Patients were encouraged to mobilize immediately and commenced on oral fluids, followed by a light diet, as soon as tolerated.

The overall patient group was divided into eight cohorts of 50 consecutive patients. These cohorts were analyzed separately to compare the following: (1) patient demographics, (2) preoperative symptom length, (3) operative time, (4) length of postoperative hospital stay, (5) conversion to open operation, (6) reoperation rate, (7) postoperative dilatation rate, and (8) perioperative mortality or other early (within 6 months) postoperative complications.

Results

The mean age, weight, and length of preoperative symptoms for each group was similar (see Table 1). This table also shows an overall decrease in the amount of time to accrue each cohort throughout the study period. There was a steady decrease in the mean operative time throughout the study period from 143 min in the first cohort to 86 min in the last cohort (Fig. 1). The mean postoperative hospital stay was reduced from 3.7 days (range 2–25) to 1.2 days (range 1–5) from the first to the last cohort. There were no perioperative deaths.

Figure 1 also shows the rate of conversion from laparoscopic to open fundoplication, the reoperation rate, and the postoperative dilatation rate.

Conversions to Open Operation

The conversion rate in the first cohort of 50 patients was 14%. Compared to this, only one conversion was required in the last 250 patients in the series, and this was necessitated by equipment failure rather than surgical difficulties. Other conversions were undertaken for hemorrhage from short gastric vessels (seven patients), port-site bleeding (one patient), splenic bleeding (one patient), difficult access (two patient), instrumental esophageal perforation (one patient), and adhesions from previous surgery (two patients).

Patients Needing Postoperative Dilatations

In the first 50 patients, 8 of them (16%) needed endoscopic balloon dilatation for persistent dysphagia or gas bloat syndrome between 10 days and 3 months postoperatively. They were dilated between one and three times. Nine patients (18%) were dilated in the second cohort between 9 days and 10 months postoperatively on one to four occasions. In the

Table 1 Demographics and Length of Preoperative Symptoms in Patients Undergoing Fundoplication for GERD

	Patient Numbers							
	1–50	51–100	101–150	151–200	201–250	251–300	301–350	351–400
Time period to accrue cohort (months)	29	21	12	11	11	12	11	10
Mean age (years) (range)	36.3 (13–70)	41.6 (9–82)	43.9 (13–64)	44.5 (12–86)	44.3 (15–66)	43.9 (17–66)	45.4 (18–74)	45.1 (15–81)
Sex (M:F)	34:16	38:12	28:22	32:18	29:21	29:21	34:16	35:15
Mean weight (kg) (range)	71.1 (44–102)	75.7 (29–98)	76.1 (49–104)	74.3 (30–102)	79.5 (51–120)	79.3 (44–103)	78 (48–103)	80.4 (53–100)
Mean preoperative symptomatic period (months) (range)	91 (8–420)	85 (6–540)	106 (3–480)	92 (4–516)	106 (4–430)	96 (12–360)	141 (6–1,152)	140 (4–1,152)

third cohort, six patients (12%) underwent dilatation between 1 week and 7 months, whereas in the fourth cohort, five patients (10%) were dilated between 3 weeks and 2 months postoperatively. They were all dilated once or twice. Two patients (4%) had two dilatations each between 2 and 9 months in the fifth cohort. No dilatations were needed by the last 150 patients to undergo laparoscopic fundoplication.

Patients Needing Reoperation

Figure 1 illustrates a decline in the number of patients requiring reoperation from seven patients (14%) in the first 50 to three patients (6%) in the last 50 patients. Table 2 shows the number of reoperations that took place for any given reason in our overall patient group. It also highlights the number of reoperations that occurred within 3 months of the original fundoplication.

In the first cohort, five patients underwent reoperation for mediastinal "wrap" herniation between 9 and 80 months postoperatively. Two patients required revisional surgery; one underwent a Watson fundoplication, whereas the other undertook a redo Nissen fundoplication at 2 and 6 months, respectively, for persistent dysphagia failing to respond to endoscopic dilatations. One reoperation for "wrap" herniation was attempted laparoscopically but was converted to an open procedure. All other reoperations were carried out as open procedures.

In the second cohort, three patients were reoperated on "for mediastinal "wrap" herniation and wrap disruption at 2, 30, and 47 months postoperatively: one by open surgery and two laparoscopically. One patient underwent laparoscopic conversion of a 360° to 270° "wrap" for "gas bloat" at 11 months despite two endoscopic "wrap" dilatations.

Table 2 Total Number and Timing of Patients Undergoing Reoperation after Laparoscopic Fundoplication

Cause of Reoperation	Total Number of patients	Early (within 3 months)	Late (after 3 months)
Mediastinal wrap herniation	16	1	15
Persistent reflux	1		1
Dysphagia despite dilatation	2	1	1
Gas bloat	3		3
Perforation of wrap	1	1	
Port-site hernia	1		1

There was one reoperation in the third cohort of patients for gas bloat 92 months later. The wrap was found to be mildly attenuated and was taken down laparoscopically. In the fourth cohort, one patient underwent laparoscopic conversion to a 270° "wrap" for "gas bloat" syndrome 12 months later, and one patient was converted from a 270° to a 360° wrap for a persistent reflux. Two patients underwent open reoperations in the fifth cohort: one for a perforation of the "wrap" at 4 days, the other for a port-site hernia repair at 9 months.

In the sixth cohort, two patients underwent a redo LNF for wrap herniation and disruption at 23 and 36 months postoperatively. In the seventh cohort, two patients were found to have a wrap herniation, and one patient was found to have a large crural defect with wrap herniation at 18, 19, and 23 months, respectively. All underwent redo LNF; the patient with the large crural defect had a hiatal mesh placed.

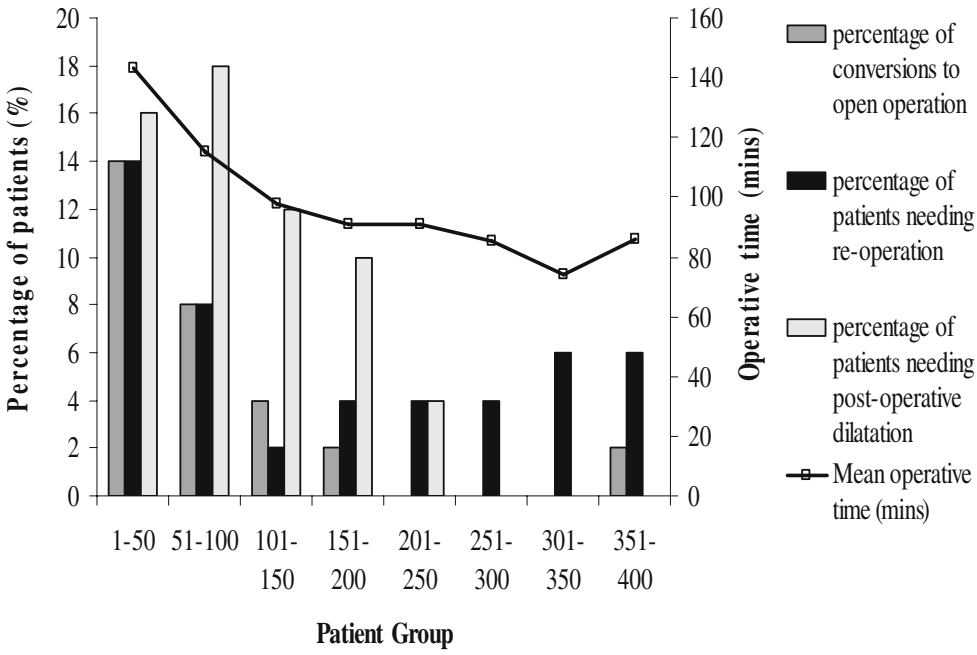

Figure 1 Showing operative conversions to open procedure, rates of reoperation, and rates of dilatation in patients undergoing laparoscopic fundoplication for GERD.

In the last cohort, three patients underwent redo LNF (two with hiatal mesh placement) for wrap herniation at 20, 27, and 36 months postoperatively.

Discussion

The postoperative complications most commonly associated with open fundoplication are dysphagia and gas bloat syndrome. The advent of the laparoscopic approach to fundoplication, first described in 1991,[4] has introduced a number of procedure-specific complications, including pneumothorax, pneumomediastinum, major-vessel injury, mesenteric thrombosis, and gastrointestinal perforation.[5]

The first prospective randomized study comparing laparoscopic and open Nissen fundoplication[6] showed similar complication rates and a better symptom outcome in those who had undergone laparoscopic surgery. There has, however, been a concern as to the severity of the reported complications in the laparoscopic approach.[7]

Before the commencement of this study, the surgeon had a 6-year experience with open fundoplications. In the early 1990s, formal courses were not available to learn laparoscopic fundoplication: consequently, the surgeons pioneering this procedure were mentored for the first few cases. After this, the surgeon would operate independently.

Our study shows that as the surgeon's experience of laparoscopic fundoplication increases, the mean operating time becomes comparable to that of an open operation. The mean postoperative length of stay in hospital was 1.2 days in the last 50 patients compared with an average stay of 7 days in those having an open fundoplication.[8] The decrease in postoperative length of stay in hospital, which was seen throughout this series, can be partly attributed to increased knowledge of recovery from laparoscopic procedures and from patient feedback of their postoperative recovery.

The high conversion rate to an open operation in our first 50 patients (14%) can be attributed to the surgical learning curve and poorer quality equipment leading to reduced quality of vision and the reduced ability to secure bleeding. Similarly, high conversion rates were seen in other early laparoscopic series.[9,2] Only 1 of the last 150 patients needed conversion to an open procedure, and this was due to equipment failure. One patient underwent a splenectomy (0.3% of all patients) due to splenic bleeding, which is comparable to other studies.[10] This compares with a splenectomy rate of 3.6% in open Nissen fundoplications in one study.[6] Of the 15 patients requiring conversion throughout the series, 14 were in the preharmonic scalpel era. Nine of these were converted due to bleeding. The harmonic scalpel has greatly enhanced the ease of fundal mobilization in comparison to the application of individual ligaclips to the short gastric arteries. A decreasing trend in conversion rate can, however, be seen within the first four cohorts before the introduction of the harmonic scalpel.

The number of patients undergoing endoscopic dilatation decreased significantly from 17% in the first 100 patients to none in the last 150 patients. This was probably due to a number of factors. First, none of the last 250 patients had symptomatic "wrap" disruptions/slippages causing dysphagia. The patients who were found to have wrap herniation presented with heartburn and not dysphagia. Secondly, it is now recognized that early dysphagia (less than 2 months postoperatively) is present in a significant proportion of patients but settles with time without the need for intervention.[11] The exception to this is in children who are less tolerant of dysphagia after laparoscopic fundoplication and hence are more likely to require early endoscopic dilatation.[12] Two studies[12,13] have shown dilatation success rates of 56 and 67%, respectively, in resolving postfundoplication dysphagia. The study by Malhi-Chowla et al.[13] also found that the only symptom that responded to dilatation was dysphagia.

Throughout the series, two patients had been reoperated on for persistent dysphagia beyond 2 months. Both were in the first 25 cases, and both were found to have bowstringing of the wrap due to lack of division of the posterior gastric bands. One was converted to a Watson fundoplication, whereas the other underwent a redo Nissen fundoplication. Our low incidence of dysphagia may be in part due to the laparoscopic operation used. Hunter et al.[14] showed that the incidence of early and late persistent dysphagia is significantly lower in both LFNs and Toupet fundoplications than in Rosetti–Nissen fundoplications.

Two patients had undergone reoperation for gas bloat syndrome: both were converted to a 270° posterior wrap and are now either asymptomatic or mildly symptomatic.

All patients in this study had been followed up for a minimum of 4 years. Overall, 6% of our patients required reoperation because principally of wrap herniation. After the first 40 operations, a routine posterior crural approximation was carried out with nonabsorbable sutures to reduce the incidence of thoracic "wrap" migration. Two studies[15,16] have emphasized the importance of a crural repair in reducing the incidence of postoperative paraesophageal hiatus hernia. Basso et al.[17] have proposed a mesh repair of the hiatus to prevent "wrap" migration after finding that in several reoperations, the sutures approximating the crura had cut out with consequent wrap herniation.

Paraesophageal wrap herniation is more common in laparoscopic than in open fundoplication.[16] Several reasons have been proposed for this: (1) the tendency to extend esophageal dissection further into the thorax,[18] (2) the increased risk of breaching the left pleural membrane during dissection,[19] and (3) the reduced postoperative pain allowing increased abdominal pressure when vomiting/coughing

in the laparoscopic procedure.[16] Wu et al.[20] found that routine division of the short gastric arteries and posterior closure of the crura during LNF significantly reduced wrap slippage/migration. This is the procedure that we have undertaken since the 40th patient. Despite of this, 5% of the last 150 patients underwent reoperation (all for heartburn due to wrap herniation). Smith et al.[21] have also concluded that wrap herniation is now the most common mechanism of failure requiring a redo fundoplication.

Of the eight patients reoperated on in the first cohort, only one procedure was attempted laparoscopically. All reoperations are now attempted laparoscopically where possible. This change in approach has occurred with increasing laparoscopic experience. Several studies[22,23] have shown that laparoscopic reoperations are not only possible and safe but also produce good results.

Several studies[24,25,26] have now shown a 90% satisfaction rate at 5-year follow-up after LNF. Our own study[25] on patient satisfaction 2–8 years postlaparoscopic fundoplication revealed that once over the initial problem of early postoperative dysphagia, the satisfaction rate was 91%. Furthermore, 90% remained free of significant reflux symptoms, and only 14% were subsequently taking regular antireflux medication. This has changed little throughout the course of the series.

Our results show a decreasing trend in operative time, postoperative hospital stay, conversion rate, postoperative dilatation rate, and reoperation rate with increasing surgical experience and improved technology. Another factor in this improvement may be due to the increased frequency with which this procedure was performed with time.

Conclusion

Dysphagia is the Achilles' heel of laparoscopic antireflux surgery. To avoid this, the authors have routinely divided the short gastric vessels. This has led to an increased rate of conversion owing to hemorrhage especially during the period when individual ligaclips were used. Short gastric vessel division may, in addition, increase the rate of wrap herniation and clip or thermal injury to the gastric fundus leading to perforation.

The high rate of reintervention in the first two cohorts would not be acceptable a decade later. It must be recognized that at the start of this series, the visual acuity of the optical systems and the quality of the instrumentation were both substantially inferior to those of today. Furthermore, there were no formal training courses available. The pioneers of advanced laparoscopic surgery had to suffer high conversion and complication rates in laparoscopic cholecystectomy,[27] antireflux,[2] and groin hernia surgery.[28,29]

When introducing complex techniques, surgeons tend to underestimate the learning curve: both of themselves and of their institution. Only by maintaining prospective data can these problems be identified and recognized.

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Impact of Solitary Involved Lymph Node on Outcome in Localized Cancer of the Esophagus and Esophagogastric Junction

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Abstract Node-positive esophageal cancer is associated with a dismal prognosis. The impact of a solitary involved node, however, is unclear, and this study examined the implications of a solitary node compared with greater nodal involvement and node-negative disease. The clinical and pathologic details of 604 patients were entered prospectively into a database from1993 and 2005. Four pathologic groups were analyzed: node-negative, one lymph node positive, two or three lymph nodes positive, and greater than three lymph nodes positive. Three hundred and fifteen patients (52%) were node-positive and 289 were node-negative. The median survival was 26 months in the node-negative group. Patients (n=84) who had one node positive had a median survival of 16 months (p=0.03 vs node-negative). Eighty-four patients who had two or three nodes positive had a median survival of 11 months compared with a median survival of 8 months in the 146 patients who had greater than three nodes positive (p=0.01). The survival of patients with one node positive [number of nodes (N)=1] was also significantly greater than the survival of patients with 2–3 nodes positive (N=2–3) (p=0.049) and greater than three nodes positive (p<0001). The presence of a solitary involved lymph node has a negative impact on survival compared with node-negative disease, but it is associated with significantly improved overall survival compared with all other nodal groups.

Keywords Lymph node · Esophagectomy · Lymphadenectomy · Survival

Introduction

Carcinoma of the esophagus carries a dismal prognosis, and for patients presenting with localized resectable disease, multivariate analysis has established that the presence or absence of involved lymph nodes confers the greatest prognostic significance.[1] In surgical management, the extent and type of lymphadenectomy undertaken varies from no formal lymphadenectomy to two and three field dissection.[2–5] The presence and extent of lymph node involvement is important as selective approaches may be considered depending on the nodal stage at presentation. In early tumors, for instance, the sentinel node concept initially developed in melanoma and breast cancer was explored to help identify patients who may not require lymph node dissection.[6–8] The advent of minimally invasive esophagectomy may also highlight the need to subselect patients for lymphadenectomy.[9]

In the observations of the senior author (JVR), patients with solitary involved lymph nodes may achieve good outcomes, and this hypothesis was evaluated in this analysis of a large prospective database. We report herein that the cohort with a solitary node involved had cancer outcomes closer to node-negative disease than other node-positive subgroups, and suggest that this represents a distinct prognostic subgroup.

Patients and Methods

The study population consisted of all patients with tumors of the esophagus and esophagogastric junction who underwent surgical resection, either alone or preceded by

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neoadjuvant chemoradiation, between 1993 and 2005. Patients receiving multimodal therapy received cisplatin, 5-fluorouracil, and external beam radiotherapy (40–44 Gy, 2–2.67 Gy/fraction) as previously described.[10] Data concerning the clinical and pathologic parameters for all patients was obtained from a detailed prospective database maintained by a full-time data manager. Pathologic parameters analyzed included the location of the tumor, tumor morphology, i.e., adenocarcinoma or squamous cell carcinoma, histological differentiation (grade), TNM staging, number and site of involved lymph nodes, and R classification after surgical resection. Staging of tumors was performed according to the American Joint Committee on Cancer TNM system.[11]

A subtotal esophagectomy was performed with a sutured anastomosis either in the right thorax (two-stage) or neck (three-stage). All cases underwent a formal abdominal lymphadenectomy and mediastinal lymph node dissection up to and including the subcarinal nodes. Thoracic nodes were submitted separately to abdominal nodes.

Statistical Analysis

Data are presented as frequencies, means, and percentages. ANOVA was used for comparison of the four demographic groups. Survival probability was estimated using the Kaplan–Meier method. Survival was calculated from the date of clinical diagnosis to date of death or date last seen. In the multivariate analysis, independent prognostic factors for survival were determined by using a Cox regression hazard model. Two analyses were performed, one for all patients and the other exclusive to node-positive patients. All statistical analyses were performed using Stata software (version 9.1 for Windows, Statcorp, TX). A p value <0.05 was considered statistically significant.[12]

Results

Patients/histology

Six hundred and four patients underwent surgery for localized malignancy of the esophagus or esophagogastric junction. The mean age was 62±10.4 (median=64, range 56 to 70). Four hundred and twelve (68%) patients were men. The mean number of lymph nodes examined per specimen was 12±6 (median=10, range=6 to 55). Two hundred and eighty-nine patients (48%) had node-negative disease [number of nodes (N)=0], 84 (14%) had one node positive (N=1), 84 had two or three nodes positive, and 147 (24%) had greater than three nodes positive (N>3). In patients with one involved node, in all cases the node was adjacent to the tumor, mediastinal for esophageal tumors, and periesophageal or along the left gastric artery for junctional tumors (Tables 1 and 2).

Two hundred and two patients (33%) had multimodal therapy and 402 patients (67%) had surgery alone. Of the multimodal cohort, 129 (64%) were ypN0 on histopathologic assessment, 28 (14%) had one node positive, 24 (12%) had two to three positive nodes, and 21 (10%) had greater than three positive nodes. The attainment of an R0 resection was significantly greater in patients with none or one node involved compared with both other groups ($p<0.05$). The majority of patients in all groups had pT3 tumors, 48% in the pN0 group compared with 71, 64, and 82% in the N=1, N=2–3, and N>3 groups, respectively ($p<0.05$). One hundred and forty (62%) of the squamous cell carcinoma cohort were node-negative (N=0) compared with 140 (39%) of cases with adenocarcinoma (39%) ($p<0.05$).

Table 1 Demographics of Nodal Subgroups

Histologic Data	N=0 (n=289)	N=1 (n=84)	N=2–3 (n=84)	N>3 (n=147)
Tumor site (%)				
Lower esophagus	138 (47)	39 (46)	37 (44)	57 (39)
EG junction	80 (28)	35 (42)	33 (39)	75 (51)
Middle esophagus	55 (19)	10 (12)	12 (14)	11 (7)
Upper esophagus	16 (6)	0	2 (3)	4 (3)
Morphology (%)				
Adenocarcinoma	140 (48)	51 (61)	57 (68)	113 (77)
Squamous cell carcinoma	140 (48)	29 (35)	25 (30)	32 (22)
Others	9 (4)	4 (5)	2 (1)	2 (1)
Treatment (%)				
Multimodal therapy	129 (44)	28 (33)	24 (29)	21 (14)
Surgery alone	161 (56)	56 (76)	60 (71)	125 (86)
Residual tumor (%)				
R0: no residual tumor	250 (86)	71 (85)	64 (76)	108 (73)
R1: residual tumor found	39 (13)	13 (15)	19 (23)	39 (27)
Rx: unknown	1 (1)	–	1 (1)	–
Pathological stage (%)				
Stage 0	53 (18)	–	–	–
Stage I	59 (20)	1 (1)	–	–
Stage II	170 (59)	21 (25)	25 (30)	16 (11)
Stage III	5 (2)	58 (29)	53 (63)	110 (76)
Stage IV	1 (1)	4 (5)	6 (7)	20 (13)
pT stage (%)				
Tx	3 (1)	0	2 (3)	1 (0.5)
Tis	12 (4)	0	0	0
T0	40 (14)	1 (1)	2 (3)	2 (1)
T1	56 (19)	5 (6)	4 (5)	3 (2)
T2	35 (12)	16 (19)	18 (21)	12 (8)
T3	138 (48)	60 (71)	54 (64)	120 (82)
T4	6 (2)	2 (3)	4 (5)	8 (5)

EG = esophagogastric

Table 2 Histology of Nodal Subgroups

Histologic Data	*N*=0				*N*=1				*N*=2–3				*N*>3			
	Adeno		SCC		Adeno		SCC		Adeno		SCC		Adeno		SCC	
	n=140		*n*=140		*n*=51		*n*=29		*n*=57		*n*=25		*n*=113		*n*=32	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Tumor site																
Lower Esophagus	64	(46)	66	(47)	19	(52)	15	(52)	23	(40)	13	(52)	39	(35)	17	(53)
EG Junction	73	(52)	6	(4)	31	(10)	3	(10)	33	(58)	0	0	74	(65)	1	(3)
Middle Esophagus	3	(2)	52	(37)	1	(28)	8	(28)	1	(2)	10	(40)	0	0	10	(31)
Upper Esophagus	0	0	16	(11)	0	(10)	3	(10)	0	0	2	(8)	0	0	4	(13)
Treatment																
Multimodal	80	(57)	46	(34)	23	(45)	5	(17)	20	(35)	4	(16)	19	(13)	3	(10)
Surgery alone	60	(43)	93	(66)	28	(55)	24	(83)	37	(65)	21	(84)	94	(87)	28	(90)
Path stage																
Stage 0	29	(21)	18	(13)	0	0	0	0	0	0	0	0	0	0	0	0
Stage 1	42	(30)	15	(10)	1	(2)	0	0	0	0	0	0	0	0	0	0
Stage 2	66	(47)	102	(73)	15	(29)	4	(14)	19	(33)	5	(20)	15	(13)	1	(3)
Stage 3	2	(1)	4	(3)	32	(63)	24	(83)	35	(61)	17	(68)	82	(73)	27	(84)
Stage 4	0	0	1	(1)	3	(6)	1	(3)	3	(6)	3	(12)	16	(914)	3	(10)
Unknown	1	(1)	0	0	0	0	0	0	0	0	0	0	0	0	1	(3)
pT stage																
Tx	2	(1)	1	(1)	0	0	0	0	0	0	2	(8)	0	0	1	(3)
Tis	9	(6)	0	0	0	0	0	0	2	(4)	0	0	0	0	0	0
T0	19	(14)	17	(12)	1	(2)	0	0	3	(5)	0	0	2	(2)	0	0
T1	39	(29)	15	(11)	4	(8)	0	0	14	(24)	0	0	3	(3)	0	0
T2	16	(11)	19	(14)	12	(23)	3	(10)	36	(63)	4	(16)	11	(10)	1	(3)
T3	53	(38)	84	(60)	33	(65)	26	(90)	2	(4)	17	(68)	91	(80)	28	(88)
T4	2	(1)	4	(2)	1	(2)	0	0	0	0	2	(8)	6	(5)	2	(6)

Adeno = adenocarcinoma, SCC = small cell carcinoma, EG = esophagogastric

Survival

The median survival for all patients was 20 months at a median follow-up of 19 months (3–167). Patients who were node-negative (*N*=0) had a median survival of 26 months (Table 3), compared with 16 months when one node was positive (p=0.03). Patients who had two to three nodes positive had a median survival of 11 months, and 8 months in patients who had greater than three nodes positive (p=0.01; *N*=2–3 vs *N*>3). The survival of patients with one node positive (*N*=1) was significantly greater than the survival of patients with 2–3 nodes positive (p=0.04) and the cohort with greater than three involved nodes (p<0.0001).

The 1-, 3-, and 5-year survival of the pN0 group was 78, 51, and 44%, respectively (Fig. 1). Where one node was involved, survival was 67, 41, and 35%, respectively. Where two to three nodes were involved, the 1-, 3-, and 5-year survival was 57, 25, and 13%, respectively, and where greater than three nodes were involved, this was 40, 14, and 8%, respectively.

Univariate analysis (Table 3) revealed nodal status, pT stage, pathologic stage, and R status as predictors of survival. Multivariate analysis revealed nodal status alone to significantly (p<0.0001) impact on survival. By this analysis the hazards ratio increased from 1.08 for one involved node to 1.42 for two to three involved nodes, and 1.84 for greater than three nodes.

Excluding node-negative patients, univariate analysis (Table 4) revealed pT stage, pathologic stage, R status, and number of nodes as predictive of survival. By multivariate analysis (Table 5), pathologic stage (p=0.010) and number of nodes were significant determinants of survival. Compared with the cohort with one involved node, the hazard ratio for two to three nodes was 1.56 (p=0.049) and 2.06 (p=0.007) for greater than three nodes.

Discussion

Cancers of the esophagus and esophagogastric junction are aggressive tumors, which are typically diagnosed at an advanced stage of disease progression.[13] This large retrospective review of a tertiary center's experiences over 12 years highlights the importance of lymph node involve-

Table 3 Univariate and Multivariate Analysis: All Patients

Variables	No. of Patients	Median Survival (moths)	*p* Value[a] (Univariate)	HR	95% CI[a]	*p* value[b] (Multivariate)	HR	95% CI
Treatment								
Surgery only	401	13	0.077	1		–	–	–
Multimodal	203	19		0.84	0.69–1.02			
Tumor site								
Upper esophagus	25	16	0.371	1		–	–	–
Middle esophagus	87	14	0.946	0.98	0.58–1.66			
Lower esophagus	268	14	0.658	1.16	0.69–1.81			
EG junction	224	14	0.624	1.13	0.69–1.84			
Depth of invasion								
T0	57	55	<0.001	1		0.652	1	
T1	68	26	0.537	1.16	0.73–1.83	0.472	0.71	0.21–2.3
T2	81	26	0.419	1.20	0.77–1.85	0.573	1.11	0.31–3.94
T3	373	11	<0.001	2.28	1.60–3.26	0.871	1.40	0.79–2.41
T4	19	7	<0.001	4.34	2.46–7.68	0.649	2.59	1.42–4.08
No. of nodes								
0	289	26	<0.001	1		<0.001	1	0.63–1.87
1	84	16	0.038	1.36	1.02–1.82	0.774	1.08	0.83–2.43
2–3	84	11	<0.001	1.91	1.45–2.52	0.202	1.42	1.07–3.18
>3	147	8	<0.001	2.61	2.08–3.29	0.027	1.84	
Histology								
Squamous	361	14	0.916	1				
Adenocarcinoma	224	13	0.596	1.05	0.87–1.28	–	–	–
Other	19	26	0.483	0.80	0.44–1.48			
Stage								
0	53	55	<0.001	1		0.118	1	
I	63	55	0.747	0.92	0.56–1.51	0.576	0.68	0.18–2.59
II	230	20	0.037	1.49	1.02–2.17	0.508	1.55	0.42–4.69
III	225	10	<0.001	2.71	1.86–3.95	0.527	1.68	0.34–5.58
IV	31	6	<0.001	6.16	3.72–10.2	0.182	3.14	1.14–7.76
Residual tumor								
R0	492	17	<0.001	1		0.052	1	
R1	110	8		1.70	1.37–2.12		1.25	0.99–1.58

[a] χ^2
[b] Cox regression
HR = hazard ratio, CI = 95% confidence intervals, EG = esophagogastric

ment in the prognosis of these tumors. The study shows that the presence of a solitary node, although a significantly negative factor compared with pN0 disease, is associated with significantly improved median and 1-, 3-, and 5-year survival compared with cohorts of patients with greater nodal involvement. The 5-year survival, for instance, was 35% compared with 13 and 8%, respectively, for cohorts with two to three positive nodes and greater than three positive nodes.

There is no uniform consensus on the number of lymph nodes that must be sampled. In a study by Ito et al.,[3] the median number of lymph nodes examined per specimen was 6 (range 0 to 35) and only 20% of patients had at least 15 lymph nodes examined. In this study, the median number of lymph nodes examined per specimen was 12 (range 6 to 55), and 24% of the patients had at least 15 lymph nodes examined. These results appear consistent with practice in the United States where an analysis of the National Cancer Database indicated that only 18% of patients undergoing surgery for gastric cancer have more than 15 lymph nodes analyzed.[14] In this Unit, lymph node clearance involves a D2 dissection of abdominal nodes, and wide mediastinal clearance to the carina and paratracheal node dissection if they appear involved. No cervical dissection is performed, consistent with recommendations from another group.[15] It is acknowledged that variation in lymph node yield may mask stage migration, particularly in a retrospective analysis, but the standardization of lymphadenectomy is likely to minimize the impact of this potential bias.

The association between extent of nodal involvement and outcome is well described.[16–18] No study to our

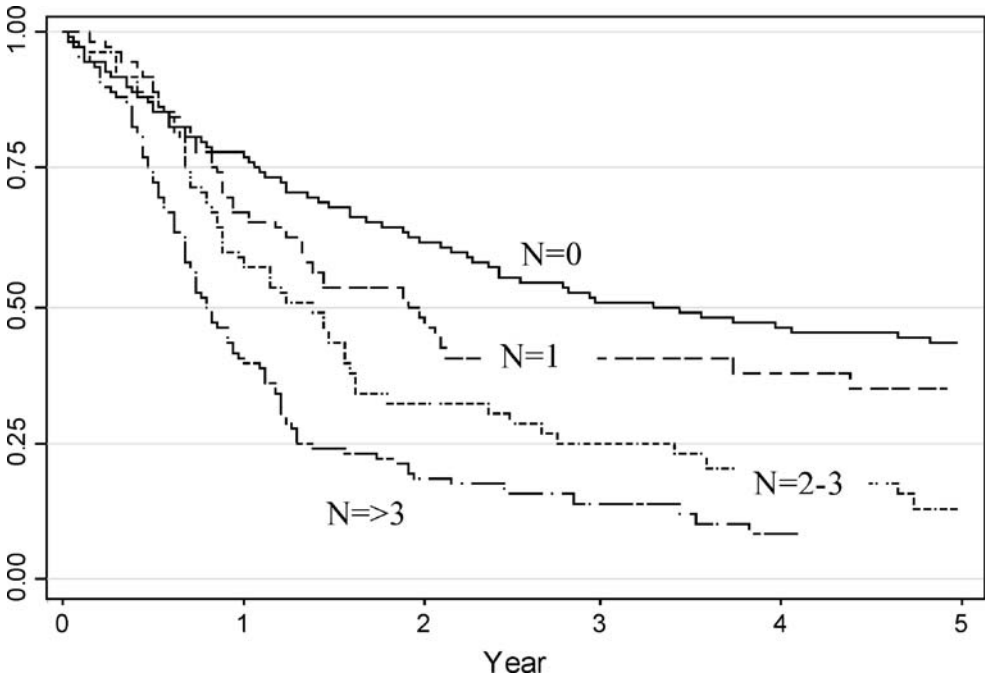

Figure 1 Overall survival by number of nodes positive.

Table 4 Univariate Analysis: Node-positive Alone

Variables	No. of Patients	Median Survival (moths)	*p* value[a] (Univariate)	HR	95% CI
Treatment					
Surgery only	241	11	0.234	1	0.63–1.11
Multimodal	74	11		0.84	
Tumor site					
Upper esophagus	9	18	0.650	1	
Middle esophagus	32	10	0.556	1.31	0.54–3.18
Lower esophagus	130	10	0.183	1.75	0.77–3.98
OG junction	144	12	0.350	1.48	0.65–3.36
Depth of invasion					
T0	5	11	0.001	1	
T1	12	8	0.917	1.06	0.33–3.41
T2	46	24	0.176	1.12	0.43–1.78
T3	235	11	0.757	1.43	0.74–2.14
T4	14	5	0.157	2.23	0.74–6.78
Histology					
Squamous	86	11	0.638	1	
Adenocarcinoma	221	11	0.638	1.07	0.81–1.40
Other	8	3	0.848	1.07	0.49–2.35
Stage					
1–II	63	19	<0.001	1	
III–IV	251	10		2.01	1.43–2.83
Residual tumor					
R0	259	12	0.035	1	
R1	61	9		1.33	1.02–1.73
No. of nodes					
1	84	17	<0.001	1	
2–3	84	13	0.021	1.67	1.06–2.29
>3	147	9	<0.001	2.53	1.50–3.62

[a] χ^2

HR = hazard ratio, CI = 95% confidence intervals

Table 5 Mutivariate Analysis: Node-positive Only

Variables	*p* value[a] (Multivariate)	HR	95% CI
Depth of invasion			
T0		1	
T1	0.544	0.82	0.31–1.75
T2	0.679	1.23	0.74–1.81
T3	0.313	1.49	0.99–2.21
T4	0.202	1.83	1.39–3.24
Stage			
I–II	0.010	1	
III–IV		1.59	0.82–3.06
No. of nodes			
1		1	
2–3	0.049	1.56	1.21–2.35
>3	0.007	2.06	1.51–2.82
Residual tumor			
R0	0.283	1	
R1		1.22	0.80–1.79

[a] Cox regression
HR = hazard ratio, CI = 95% confidence intervals

knowledge has previously focused on the impact of one positive node on outcome in esophageal cancer. The observation, however, of the unique prognostic significance of a solitary involved node was recently reported.[19] In a study of 187 patients with esophageal adenocarcinoma treated with neoadjuvant chemoradiotherapy, Gu et al.[19] at the MD Anderson observed from their analysis that patients with a solitary involved node had better overall and relapse-free survival compared with other nodal groups. Moreover, the 5-year survival outcomes and 2-year relapse-free survival was not significantly different from the node-negative cohort. Although in our series survival figures were better for node-negative patients than patients with a solitary involved node, the overall pattern of outcome data in our series is consistent with the report from the Anderson group, with prognosis in this cohort closer to node-negative than other node-positive subgroups.

The clinical implication of this finding is not clear at this time, but it should, at minimum, encourage a more optimistic view of patients who have a solitary lymph node identified after adequate lymphadenectomy, as approximately 35% of patients with this pathologic stage may be cured. In the future, it is possible that advances in endoscopic US staging, fluorodeoxyglucose PET, and sentinel node assessment may improve pre- and intra-operative assessment of nodal involvement, defining node-negative, solitary involved node and micrometastatic-involved subgroups, and selective lymphadenectomy and minimally invasive approaches may be evaluated in these situations. This demands prospective evaluation, but it may be noteworthy that all involved nodes in the solitary involved node cohort were close to the primary site and may possibly have been identified as sentinel nodes.

In conclusion, this study shows that in a large cohort of patients, lymph node status and the number of lymph nodes positive at the time of surgical resection is directly linked to survival. Extensive nodal involvement is confirmed as carrying a dismal prognosis, but greater optimism is justified where a solitary involved lymph gland defines the pN stage after an adequate lymphadenectomy.

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Factors Affecting Morbidity and Mortality of Roux-en-Y Gastric Bypass for Clinically Severe Obesity: An Analysis of 1,000 Consecutive Open Cases by a Single Surgeon

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Abstract
Introduction Determinants of perioperative risk for RYGB are not well defined.
Methods Retrospective analysis of comorbidities was used to evaluate predictors of perioperative risk in 1,000 consecutive patients having open RYGB by univariate analyses and logistic regression.
Results One hundred forty-six men, 854 women; average age 38.3±11.2 years; mean BMI 51.8±10.5 (range 24–116) were evaluated. Average hospital stay (LOS) was 3.8 days; 87% <3 days. 91.3% of procedures were without major complication. The most common complications were incisional hernia 3.5%, intestinal obstruction 1.9%, and leak 1.6%. 31 patients required reoperation within 30 days (3.1%). A 30-day mortality was 1.2%. Logistic regression evaluating predictors of operative mortality correlated strongly with coronary artery disease (CAD) ($p<0.01$), sleep apnea ($p=0.03$), and age ($p=0.042$). BMI>50 (0.6 vs 2.3%, $p=0.03$) and male sex were associated with increased mortality (1.3 vs. 4.0%, $p=0.02$). Sex-specific logistic regression demonstrated males with angiographically proven CAD were more likely to die ($p=0.028$) than matched cohorts. Age ($p=0.033$) and sleep apnea ($p=0.040$) were significant predictors of death for women.
Conclusion Perioperative mortality after RYGB appears to be affected by sex, BMI, age, CAD, and sleep apnea. Strategies employing risk stratification should be developed for bariatric surgery.

Keywords Obesity · Morbid obesity · Roux-en-Y gastric bypass · Morbidity · Mortality

Introduction

Obesity is currently the number one public health problem in the United States, affecting one-third of all Americans (http:/www.surgeongeneral.gov/topics/obesity). Approximately 5 to 8% have clinically severe or morbid obesity and are candidates for bariatric surgery.

This obesity epidemic has been accompanied by a geometric rise in the number of bariatric surgical procedures. The American Society for Bariatric Surgery (ASBS) estimates that the number of bariatric surgery procedures has increased from approximately 20,000 in 1996 to over 140,000 in 2004 (http://www.asbs.org). During this period, membership in the ASBS has also increased fivefold, suggesting that many more surgeons are performing these procedures. The most common bariatric procedure performed in the United States is Roux-en-Y gastric bypass (RYGB).[1]

The explosive growth of bariatric surgery has garnered much attention in the media, with much speculation about

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the risks, both short- and long-term, of RYGB. Unfortunately, to date, little information from large series is available concerning the operative mortality of RYGB and those factors that predict mortality. In 2002, Livingston et al.[2] reported an operative mortality of 1.3% in 1,067 patients after open RYGB and found that only age over 55 years correlated with perioperative mortality. More recently, Fernandez et al.[3] analyzed their patient cohort of 1,431 patients having open RYGB and found a 1.9% mortality, which was associated with age, weight, longer limb gastric bypass, and the occurrence of a leak or pulmonary embolism.

This report is a multivariate analysis of preoperative mortality and morbidity in 1,000 consecutive open RYGBs performed over a 5-year period by a single surgeon (LF) in at a single institution.

Materials and Methods

Bariatric Surgery Program The bariatric surgery program at St. Luke's–Roosevelt Hospital Center in New York City was initiated in April 1999 and the first operation performed in June 1999. The basis of this report consists of 1,000 consecutive open RYGBs (primary cases and revisions) performed by a single surgeon, LF, between June 1999 and June 2004.

Clinical Protocol and Surgical Technique All patients were evaluated preoperatively and met generally accepted criteria outlined by the NIH at its Consensus Development Conference on Gastrointestinal Surgery for Severe Obesity.[4] In addition, all patients were routinely evaluated by a registered dietitian experienced in the treatment of obesity. Mental health and other specialty consultations were only obtained if they were felt to be clinically indicated or were required by an insurance carrier. All patients were evaluated by an attending anesthesiologist before surgery.

Routine preoperative studies included: electrocardiogram, chest x-ray, gallbladder ultrasonography, serum electrolytes, glucose, HbA1c, calcium, albumin, lipid profile, liver function tests, complete blood count, platelets, prothrombin time, partial thromboplastin time, INR, and urinalysis. Over time, additional preoperative studies, including serum insulin, iron, ferritin, vitamin B_{12}, 25-OH vitamin D, and thiamine (vitamin B_1) were added.

RYGB was performed in a standard fashion with the following common elements: (1) open technique; (2) 20–30 ml pouch, nondivided stomach, TA 90B (US Surgical, Norwalk, CT, USA) applied twice; (3) hand-sewn two-layer retrocolic, antegastric gastrojejunostomy, 12 mm in length, tested with methylene blue under pressure intraoperatively; (4) side-to-side, functional end-to-end jejunojejunostomy with dispSAble GIA (US Surgical) or LC (Ethicon Endosurgery, Sommerville, NJ, USA) 75 mm staplers, and TA55 (US Surgical) or TX 60 (Ethicon Endosurgery) staplers and routinely oversewn with 3–0 silk Lembert sutures. The biliopancreatic limb-length measured 75 cm along the antimesenteric border for patients with BMI less than 50 and 150 cm for patients with BMI greater than or equal to 50. The Roux or alimentary limb-length was 150 cm in all patients. For the initial 14 cases, the stomach was divided using the GIA-100 stapler. This technique was abandoned and switched to the nondivided stomach after a stapler malfunction led to a leak.

Closed suction drains were placed in all revisions, patients with BMI>55, or if clinically indicated (e.g., identification of an intraoperative leak, technically difficult anastomosis). Drains were removed as clinically indicated. Fascia was closed with a running looped #1 PDS (Ethicon, Sommerville) and infiltrated with 0.25% bupivacaine. The subcutaneous space was drained with a #10 Jackson–Pratt drain and the skin was closed with a running subcuticular stitch.

The gallbladder was removed if gallstones were documented by preoperative ultrasound. Incisional or umbilical hernias were primarily repaired if encountered, oftentimes through a separate periumbilical incision.

Invasive monitoring was not used routinely and Foley catheters were only placed if patients required invasive hemodynamic monitoring or in the case of revisions or when patients had multiple prior abdominal operations. Nasogastric tubes were left in placed as clinically indicated (intraoperative leak identified) or in patients with BMI>55. All patients received perioperative antibiotics for 24 h, cefazolin (2 g intravenously every 8 h for three total doses) or clindamycin (900 mg intravenously every 6 h for four doses). Prophylaxis against deep vein thrombosis consisted of 5,000 units of unfractionated heparin administered subcutaneously every 8 h and pneumatic compression stockings until ambulatory. All patients were given a PCA pump (patient-controlled analgesia) for pain. Patients were routinely cared for on a regular surgical floor, equipped for severely obese patients. Patients with significant SA or documented CAD were usually observed in the recovery room overnight, and only rarely admitted to the intensive care unit. On the morning of postoperative day 1, patients were routinely studied with gastrografin upper-GI studies. If no leak was identified, they were given liquids for lunch and advanced to soft food (yogurt, apple sauce, and cottage cheese) for dinner and switched to oral pain medications. Drains were usually removed before discharge. Patients were discharged on POD #2 or #3 as indicated with the following medications: a codeine-derivative for pain, prenatal vitamins, iron polysaccharide, calcium citrate, ursodeoxycholic acid, if the gallbladder was present.

After hospital discharge, patients were scheduled to be seen at 2 and 8 weeks, 6, 12, 18, 24 months, and yearly thereafter. All routine follow-up appointments included nutritional counseling and those after 2 weeks included laboratory studies [serum electrolytes, glucose, HbA1c, calcium, albumin, lipid profile, liver function tests, complete blood count, platelets, serum insulin, iron, ferritin, vitamin B_{12}, 25-OH vitamin D, and thiamine (vitamin B_1)]. Follow-up was 74% at 1 year, 68% at 2 years, 59% at 3 years, 53% at 4 years, and 48% at 5 years.

Clinical Data and Data Analysis Clinical and laboratory data were PC-based database prospectively maintained since the program's inception in 1999. Data collected included: age, sex, height weight, BMI, race/ethnicity, payer status, obesity-related comorbidities, operative procedure, duration of stay, mortality, major complications, and death. Complications were classified as systemic (prolonged intubation, deep venous thrombosis, pulmonary embolism, and myocardial infarction/fatal arrhythmia) or technical (incisional hernia, intestinal obstruction, leak/perforation, dehiscence, GI bleeding, anastomotic stricture, and anastomotic ulcer). Deaths were analyzed with respect to BMI, demographics, comorbidities, and complications.

Superficial wound infections were not included; the incidence of urinary tract infections was not tracked. Nutritional complications were not evaluated because all patients were routinely maintained on vitamins, iron, and calcium supplements postoperatively; it would be impossible to determine the true incidence of any of these nutritional deficiencies.

Univariate analyses and logistic regression with SPSS 11.0 were used to determine significance.

Results

The population consisted of 854 women and 146 men. Their demographic characteristics are summarized in Table 1. The prevalence of obesity-related comorbid conditions is shown in Table 2.

The most common comorbidites encountered were dyspnea on exertion (94%), joint pain/arthritis (92%), and gastroesophageal reflux disease (59%). The comorbidites typically associated with systemic disease included hypertension (HTN, 39%), obstructive sleep apnea (SA, 24%), dyslipidemia (46%), and asthma (15%). Approximately 23% of the patient population suffered from type II diabetes mellitus (DM). At time of initial evaluation, 13.0% of this diabetic patient subset had a prior history of insulin-dependent DM, 57.6% had noninsulin dependent DM, and 23% had a previous diagnosis of DM intermittently controlled on diet or were newly diagnosed with DM during their preoperative evaluation. Six percent of the patient population had angiographically documented histories of coronary artery disease (CAD) but were deemed suitable risk by their respective specialists.

Procedures and Duration of Hospital Stay There were 966 primary RYGB and 34 revisions of failed bariatric procedures (21—VBG, 5—RYGB, 8—other; all performed at outside institutions) to RYGB. The median length of stay for primary procedures was 2.4 days compared to 3.7 days for revisions. Average (LOS) for all patients having primary RYGB was 3.8 days with 87% of the group leaving in 3 days or less.

Complications Overall, 91% of the procedures were without systemic or technical complications.

The incidence of complications in relation to BMI is summarized in Table 3. Overall, systemic complications occurred rarely, but did not usually correlate with BMI. The most common technical complications were incisional hernia (3.5%), intestinal obstruction (1.9%), and leak/perforation (1.6%).

Thirty-one patients (3.1%) required reoperation within 30 days of the original procedure. The indications for reoperation within 30 days were leak/perforation (11), intestinal obstruction (9), bleeding (4), rule-out leak (2), dehiscence (4), and subphrenic abscess (1).

Indications for late operations (>30 days postoperatively) included incisional hernia repair in 35 patients, intestinal obstruction in 10 patients, and repair of leaks/

Table 1 Demographic Characteristics by Sex and Race

	Women	Men	Total	*p*-Value
Age (years)	38±1.0 (15–73)	40±11.9 (15–65)	38±11.17 (15–73)	0.064
Weight (kg)	134±27 (84–263)	170±43 (81–345)	139±33 (82–345)	<0.01
BMI (kg/m^2)	51±10 (35–1,000)	55±13 (24–116)	51±10 (24–116)	<0.01
Caucasian	(28%) 238/853	(53%) 78/147	32%	<0.01
African–American	(30%) 253/853	(20%) 29/147	28%	0.01
Hispanic	(42%)358/853	(27%)40/147	40%	<0.01
Other	(0.5%) 4/853	(0%) 0/147	0.4%	0.41

Table 2 Prevalence of Obesity-Related Comorbid Conditions by Sex

	Women (*N*=853) (%)	Men (*N*=147) (%)	Total (%)	*p*-Value
Type II diabetes mellitus	177 (21)	54 (37)	23	<0.01
Hypertension	310 (36)	79 (54)	39	<0.01
CAD/CHF	29 (3)	26 (18)	6	<0.01
Dyslipidemia	376 (44)	80 (54)	47	0.02
Sleep apnea	172 (20)	63 (43)	24	<0.01
Asthma	135 (16)	16 (11)	15	0.12
Dyspnea on exertion	811 (95)	127 (86)	48	<0.01
GERD	513 (60)	77 (52)	59	0.08
Osteoarthritis	791 (93)	126 (87)	92	<0.01
Urinary stress incontinence	430/(50)	5 (3)	44	<0.01
Irregular menses	276 (32)	NA	32	NA

CAD/CHF coronary artery disease/congestive heart failure, *GERD* gastroesophageal reflux disease

perforations in five patients who were experiencing ongoing postoperative complications. No patients required reoperation for refractory anastomatic stricture or ulcer. One patient developed a gastrogastric fistula after repair of an early leak, which was treated expectantly since it was clinically insignificant. No late gastrogastric fistulae were identified.

Deaths Thirty-day mortality was 1.2%. Overall mortality attributable to surgery was 1.5%. Patients with late deaths due to unrelated events, such as motor vehicle accidents (*N*=2) or drug overdoses (*N*=1), were excluded and not classified as mortalities in the analysis. Mortality correlated with BMI, with four (0.8%) patients having a BMI<50 dying compared to 11 (2.1%) patients with BMI≥50 (p= 0.03) (Table 3).

Causes of death after RYGB, along with their timing and relationship to BMI are shown in Table 4. Two patients died of fatal arrhythmias on POD #3 and #4. Both were males, ages 48 and 54, with BMIs>50, DM, CAD, HTN, and SA. Autopsies were performed in both instances and no other precipitating factors were identified. One patient, a 43-year-old woman with a BMI 59, died of a pulmonary embolism (identified at autopsy) at home after 2 weeks.

Six patients died from MSOF after postoperative leaks, three from the gastrojejunostomy and three from perforations of the distal small bowel within the common channel. Of these, four occurred and were diagnosed within 48 h of the initial RYGB and all were emergently explored. All four developed MSOF and expired between 14 and 211 days postoperatively. Of the remaining two deaths, one patient, 46-year-old woman with a BMI 79 and a history of chronic ventilator dependence due to a paralyzed left

Table 3 Incidence of Complications after RYGB

Complication	BMI<50 (%) (*N*=481)	BMI>50 (%) (*N*=515)	Total (%)	*p*-Value
Systemic complications				
Prolonged intubation	3 (0.6)	8 (1.5)	1.1	0.16 (NS)
Deep venous thrombosis	0 (0)	2 (0.4)	0.2	NS
Pulmonary embolism	0 (0)	3 (0.6)	0.3	NS
MI/fatal arrhythmia	1 (0.2)	1 (0.2)	0.2	NS
Technical complications				
Incisional hernia	10 (2.1)	25 (4.8)	3.5	0.019
Intestinal obstruction	10 (2.1)	9 (1.7)	1.9	NS
Leak	7 (1.5)	9 (1.9)	1.6	NS
Dehiscence	2 (0.4)	2 (0.4)	0.4	NS
GI bleeding requiring transfusion	3 (0.6)	6 (1.2)	0.9	NS
Anastomotic ulcer	2 (0.4)	0 (0)	0.2	NS
Anastomotic Stricture	6 (1.2)	2 (0.4)	0.8	NS
Death	4 (0.8)	11 (2.1)	1.5	.03

Table 4 Causes of Early and Late Deaths Related to BMI

Cause of death	Early (<30 days) (*N*=11)		Late (>30 days) (*N*=4)	
	BMI< 50	BMI≥ 50	BMI< 50	BMI≥ 50
MI/arrhythmia	0	2	0	0
Pulmonary/PE	0	1	0	0
MSOF 2^0 leak	1	2	1	2
MSOF 2^0 bowel obstruction	0	1	0	0
MSOF cause unknown	1	1	0	0
Bleeding complications	1	2	0	0

PE Pulmonary embolism, *MSOF* multisystem organ failure

hemidiaphragm on chronic steroid therapy developed a late leak and multiple intestinal fistulae and eventually succumbed to MSOF. The other patient, a 43-year-old woman, BMI 43, had undergone a laparoscopic RYGB at another institution that was complicated by a strangulated internal hernia, massive intestinal gangrene, and short-bowel syndrome. She underwent a reversal of her RYGB with reconstruction of her GI tract, but developed multiple small bowel fistulae 2 weeks postoperatively and died of MSOF several months later.

Three patients died from a severe systemic inflammatory response syndrome (SIRS) with MSOF accompanied by extremely high fevers, without any identifiable source. One was a 70-year-old woman with BMI 68 underwent reexploration for an early postoperative small bowel obstruction. The others were a 54-year-old woman with a BMI 47, DM, HTN, and SA and a 37-year-old male with BMI 94 and severe SA and HTN. Each developed SIRS and MSOF with temperatures of 105–107°F and hyperdynamic circulations. No intraabdominal or other sources were identified despite numerous cultures and radiologic studies.

Three patients died of bleeding complications. A 43-year-old woman with a BMI 48 suffered progressive hypotension and tachycardia in the recovery room postoperatively. These symptoms were initially addressed with rehydration allowing the patient's hematocrit to fall to a level where hypovolemic shock and resulting coagulopathy obscured efforts to surgically control or identify a single source. A 31-year-old woman with a BMI 50 was returned to the OR 4 h postoperatively for control of bleeding from the small bowel mesentery. After this second procedure, she developed SIRS, temperatures of 106°F, and MSOF, with no identifiable source of sepsis. A 54-year-old male with a BMI 56 and a history of HTN, CAD, and chronic atrial fibrillation suffered a postoperative myocardial infarction and developed a coagulopathy complicated by a massive intraspenic hematoma after restarting coumadin, which rapidly progressed to anuria and MSOF. Attempts to reverse his anticoagulation and control the bleeding angiographically were unsuccessful.

The necessity for reoperation within 30 days of the original procedure was particularly ominous. Overall, the incidence of death after a second operative procedure within 30 days was 9/31 (29%). Two of the 16 patients with a BMI<50 who required reoperation within 30 days died (12.5%) compared to 7 out of 15 patients with BMI≥ 50 (47% p=0.03). This is similar to the mortality for the entire series where 0.8% for patients with a BMI<50 died compared to 2.1% for patients with BMI≥50 (p=0.03). However, among those 15 patients classified as operative deaths for the entire series, 9 (60%) died after their second operative procedure.

Logistic regression demonstrated that CAD [LR 7.5 p< 0.01 (95% CI 2.2 to 25.3)], and SA [LR 3.3 p=0.03 (95% CI 1.1 to 10.1)], followed by age [LR 1.06 p=0.042 (95% CI 1.00 to 1.12)], were risk factors for death in all patients (Table 5). Although a small sample set, 12.7% of patients with CAD died (7/55) and 29% of patients with BMI>50 and CAD and SA died.

Although the average BMI of males was slightly greater than that of females (55.2 vs 51.2 kg/m^2, p<0.01), the two populations also differed in characteristics other than BMI. The male population had a significantly significant greater prevalence of DM, HTN, CAD, dyslipidemia, and SA. Females had a greater prevalence of pulmonary comorbidities, including asthma and dyspnea on exertion (Table 2).

When logistic regression was performed specific to the subsets of sex, males with angiographically demonstrated CAD were 30 times more likely to die [LR 30.1 p=0.028 (95% CI 1.4 to 631.4)]. Logistic regression did not identify CAD as a significant predictor when the analysis was limited to women. Predictors of death for women include

Table 5 Logistic Regression Evaluation of Patient Comorbidity as Predictors of Mortality

	p-Value	Relative Risk	95% Confidence Interval
Age	0.042	1.059	1.002–1.120
BMI	0.130	1.025	0.993–1.058
Female	0.612	0.729	0.215–2.474
DM	0.852	0.889	0.259–3.054
HTN	0.257	2.085	0.585–7.438
CAD	0.001	7.446	2.195–25.258
Dyslipidemia	0.099	0.359	0.106–1.211
Asthma	0.070	3.065	0.913–10.293
SA	0.033	3.342	1.104–10.115
SOB	0.693	0.644	0.073–5.725

age [LR 1.07 p=0.033 (95 % CI 1.0 to 1.14) and SA [LR 4.1 p=0.040 (95% CI 1.07 to 16.2)].

Logistic regression was repeated specific to race. When limited to Caucasian patients only, Caucasians with CAD were 58 times more likely to die [LR 58.8 p<0.01 (95% CI 4.8 to 716.9)] than those Caucasians without CAD. Increasing BMI was also significant among Caucasians. [LR 1.08 p=0.02 (95% CI 1.01 to 1.16)]. Evaluation of African–American patients demonstrated that only SA was significant [LR 19.1 p=0.03 (95% CI 1.29 to 282.8)]. Regression of the Hispanic population did not identify a specific factor. One-way ANOVA did not demonstrate any significant differences in prevalence of death or CAD between the three racial groups for the entire population or specific to sex.

Hispanic patients had significantly less SA than either the Caucasian or African–American patients (18.1 vs 25.6 and 27.4%, respectively (p=0.01)). When examined specifically in relation to sex, there were no differences among prevalence of SA in the males. African–American women, however, had the greatest prevalence of SA (26.4%) compared to Caucasian (18.9%) and Hispanic (15.7%) women (p<0.01).

Discussion

The tremendous growth of bariatric surgery over the past several years has spawned much interest in its complications and mortality, first in the media, but most recently in the public health arena as well. Health and malpractice insurance carriers as well as governmental agencies and professional societies are evaluating the risks of bariatric surgery and the surgeons that perform it. In several states, insurance companies have stopped covering bariatric surgery at the same time that the Centers for Medicare and Medicaid Services have approved coverage for them. Several malpractice carriers have stopped issuing policies for surgeons performing bariatric procedures while others are categorizing bariatric surgery as a high-risk subspecialty area, similar to obstetrics and neurosurgery, and increasing premiums accordingly. In each of these instances, the overriding fear or consideration appears to be that the risks associated with bariatric surgery are excessively high.

Much of the information being utilized in this regard has come form series utilizing pooled data from multiple smaller series or government databases.[1,5–9] Buchwald et al.[5] performed a metaanalysis of 16,944 patients which included 7,074 patients that underwent gastric bypass (open and laparoscopic) in 44 studies with a 30-day mortality rate of 0.5%. Several authors have reported that complication rates of bariatric surgery were inversely correlated with case loads, reporting mortality rates of in the range of 0.1–0.5% for surgeons more than 100 or 150 cases per year.[6–8] Flum et al.[9] recently reported 30- and 90-day mortality rates of 2.0 and 2.8%, respectively in Medicare beneficiaries having bariatric surgery, with men having higher rates than women and those over 65 years of age having higher rates than those younger than 65. Many of these series lack data concerning BMI and comorbidities, making risk assessment difficult or impossible. In one large series from a single-center, Christou et al.[10] reported a 30-day mortality of 0.4% in 1,035 patients undergoing RYGB, of whom 820 had open RYGB. No details about preexisting comorbidities or perioperative complications were given.

The results of these pooled series differ from those in several large series of open gastric bypasses[2,3,11]. Livingston et al.[2] reported an operative mortality of 1.3% in 1,067 patients after open RYGB. In his series, mean BMI was 53.6 kg/m^2, mean age 42.3 years, and the incidence of comorbidities was diabetes (23%), hypertension (48%), and sleep apnea (39%). Only male sex was predictive of severe life-threatening complications; mortality in patients over 55 years was significantly greater than in patients under 55 (3.5 vs 1.1%, p<0.05). More recently, Fernandez et al.[3] analyzed their patient cohort of 1,431 patients having open RYGB and found a 1.9% mortality, which was associated with age, weight, longer limb gastric bypass, and the occurrence of a leak or pulmonary embolism. In that series, the mean BMI was 53.3, mean age 40.7 years, and incidence of serious comorbidities was diabetes (19.5%), hypertension (51%), and sleep apnea (33%). In both of these series, the BMI was higher, the patients were older and the incidence of serious comorbidities, such as diabetes, hypertension, dyslipidemia, and sleep apnea, higher. Pories et al.[11] reported a 1.5% perioperative mortality rate, with 0.8% dying of sepsis, 0.5% dying of pulmonary embolism, and 0.2% of an unknown cause. Additional information regarding the incidence of leaks, bowel obstructions and other complications was not reported as these were not the focus of the original paper.

Similarly, in the present series, the 30-day mortality rate was 1.2% in 1,000 patients with a mean BMI of 52 kg/m^2. The prevalence of preoperative comorbidities was comparable to the larger series (diabetes—23%, hypertension—39%, dyslipidemia—46%, coronary artery disease/congestive heart failure—5.5%, sleep apnea—23.5%, and asthma—15%) and generally higher than in the pooled series. The incidence of leaks and postoperative small bowel obstruction in our series was comparable to the other series. The incidence of pulmonary embolism was less than those reported, perhaps related to the use of both pneumatic compression stockings and subcutaneous heparin and early ambulation with a shorter length of stay. Although the incidence of incisional hernia in our series was low (3.5%), this may well be affected by our suboptimal follow-up.

Multisystem organ failure accounted for 11 deaths in our series (73%). In six patients, this resulted from leaks or perforations; in one it followed a bowel obstruction, in two it followed postoperative hemorrhage and in two patients, the cause was never determined. In each of these instances, the complication was identified early and appropriate treatment and supportive care instituted. In four of the patients, the clinical course of SIRS and MSOF was characterized by extremely high temperatures (>105°F), with no apparent source ever identified. To our knowledge, this "syndrome" has not been reported, but may be due to the fact that the enormous adipose tissue stores in these patients may act as a "metabolic sink", releasing cytokines and other mediators and perpetuating this extreme systemic inflammatory response. Two of the deaths were due to fatal arrhythmias, both in patients with known CAD, who were extensively evaluated preoperatively. The death due to pulmonary embolism occurred after discharge, even though the patient received prophylaxis with both heparin and pneumatic compression stockings in the hospital. The remaining death due to exsanguination was clearly preventable.

Although males were significantly heavier and had higher BMIs than women, sex was not an independent predictor of morbidity. However, the presence of angiographically documented coronary artery disease was particularly ominous in men. Males with angiographically demonstrated CAD were 30 times more likely to die. In women, predictors of death included age and SA, but not CAD. With respect to race, Caucasian males with BMI>50 and CAD were most likely to die, whereas SA was a predictor in African–American men. There were no predictors in Hispanics. Despite the increased mortality in Caucasian males with CAD, these patients were not candidates for cardiac revascularization and extreme weight loss was the only intervention thought to make a beneficial health impact.

Based upon our data and those of others[2,3,11], it appears that the risk of open RYGB is in the range of 1–2%. Risk appears to be adversely affected by increasing BMI and those factors with which it is often associated namely male sex and coronary artery disease. How this compares with the perioperative mortality after laparoscopic RYGB is still unclear because many series of patients having laparoscopic RYGB do not include patients with the highest BMIs, above 60 or 70 kg/m^2, or patients having revisional surgery.

A perioperative mortality rate of 1.2% after RYGB compares favorably with that after other common surgical procedures. For example, perioperative mortality after elective surgery for abdominal aortic aneurysms has been reported at 3.1–4.7% overall, 1.0–2.7% in patients under 65 years of age, and 3.5–5.2% in patients over 65 years of age.[12] Using Medicare data adjusted for high volume surgeons, Birkmeyer et al.[13] reported perioperative mortality rates of 4.5% for colectomy, 8.6% for gastrectomy, 8.4% for esophagectomy, 3.8% for pancreatic resection, 4.0% for pulmonary lobectomy, and 10.7% for pneumonectomy. While it is true that all of these patients were over 65 years of age, the fact still remains that these perioperative mortality rates are all substantially greater than that after RYGB (even in Medicare recipients, as recently reported[9]) and neither the public, the press, the insurance industry, or various state Departments of Health are appalled or alarmed, or calling for a moratorium on those procedures. This is not meant to suggest that every effort should not be made to lessen the risks of bariatric surgery and to improve operative mortality, but rather to inject some proportionality into the discussion. The importance of such careful analysis of bariatric surgical data, including its limitations, and the need to continue to offer bariatric surgery to those patients for whom it constitutes the best available treatment has recently been emphasized.[14] In his 2004 PERSPECTIVE, Surgery for Severe Obesity, Steinbrook[15] quotes Robert Brolin, MD, cautioning physicians and the public "...to reconcile the fact that the operation has a real mortality and it will continue to have a real mortality under the best of circumstances. Some of these patients are just profound operative risks for any kind of surgical intervention...The sickest ones are the ones who benefit the most, but they are also the highest risk".

Conclusion

RYGB can be performed with acceptable perioperative morbidity in patients over a wide range of BMIs. Patients with BMI≥50 have a higher morality for both initial operations and after reexploration. Age, coronary artery disease, and obstructive sleep apnea correlate with perioperative mortality. These three comorbidities were more prevalent in these patients and may contribute to this finding.

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Intestinal Perforations in Behçet's Disease

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Abstract Behçet's disease accompanied by intestinal involvement is called intestinal Behçet's disease. The intestinal ulcers of Behçet's disease are usually multiple and scattered and tend to perforate easily, so that many patients require emergency operation. The aim of this study is to determine the extent of surgical resection necessary to prevent reperforation and to point out the findings of concurrent oral and genital ulcers and multiple intestinal perforations in all patients of our series. During a 25-year study period, information of 125 Behçet's disease cases was gathered. Among the 82 patients who were diagnosed with intestinal Behçet's disease, 22 cases had intestinal perforations needing emergency laparotomy. We investigated and analyzed these cases according to the patients' demographic characteristics, clinical presentations, laboratory data, and surgical outcome. There were 14 men and 8 women ranging from 22 to 65 years of age. Nine cases were diagnosed preoperatively, and the diagnoses were confirmed in all 22 cases during the surgical intervention. Surgical resection was performed in every patient, with right hemicolectomy and ileocecal resection in 11 cases, partial ileum resection in 8 cases with two reperforations, and ileocecal resection in 3 cases with one reperforation.

Keywords Behçet's disease · Intestinal ulcers · Intestinal perforations

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Introduction

Behçet's syndrome is a systemic process affecting multiple organ systems[1,2]. Surgeons need to be aware of the lethal complication of Behçet's disease with intestinal ulcers, which tend to perforate at multiple sites[3,4]. A review of the literature reveals that involvement of the gastrointestinal tract is not infrequent. Most cases reported in the literature are in the eastern Mediterranean countries and Japan[5–7]. We report here a series of 22 cases of intestinal Behçet's disease with multiple perforations, treated by emergency surgical resections.

Materials and Methods

During the 25 years from July 1979 to June 2004, 125 patients with Behçet's disease were encountered at the Cardinal Tien Hospital and Tri-Service General Hospital, Taipei, Taiwan. Eighty-two patients were diagnosed as having intestinal Behçet's disease, which was based on the Mason–Barnes criteria (Table 1)[1,2]. Among these patients,

Table 1 The Mason–Barnes Criteria

Major Symptoms	Minor Symptoms
Buccal ulcerations	Gastrointestinal lesions
Genital ulcerations	Thrombophlebitis
Ocular lesions	Cardiovascular lesions
Skin lesions	Arthritis
	Neurologic lesions
	Family history

Three major or two major and two minor criteria are required to establish the diagnosis of Behçet's disease

22 had intestinal perforations (see Table 2 for the details of these 22 cases).

In 13 of these 22 cases, the diagnosis was confirmed at surgical resection for multiple perforations. Nine of the 22 cases had Behçet's disease with intestinal involvement, which was confirmed preoperatively, six were confirmed by endoscopic examination; two by radiological examination; and one patient had gastrointestinal symptoms of intermittent abdominal pain, diarrhea, and nausea.

Results

Patient Characteristics

There were 14 men and 8 women in the 22 cases investigated. The ages of the patients with perforated intestinal Behçet's disease ranged from 22 to 65 years, with a mean age of 35.3 years. The age at onset of symptoms of Behçet's disease varied from 18 to 64 years on diagnosis, with a mean age of 33.1 years.

In Table 2, oral ulcers with gastrointestinal symptoms and signs were found concurrently in all 22 cases, genital ulcers in 19 cases, ocular lesions in 12 cases, and skin lesions in 11 cases. The painful oral ulcers (Fig. 1) occurred on oral mucosa, lips and in the larynx. They varied from 2 to 8 mm in size and invariably healed without scarring. The genital ulcers (Fig. 2) resembled the oral ulcers in appearance and course, except that vaginal ulcers were painless. Four patients had anterior uveitis and eight had a mild relapsing conjunctivitis as their sole ocular lesion. The nodular cutaneous lesions resembled those of erythema nodosum and were chronic and multiple. Most lesions

Table 2 Intestinal Perforation in Behçet's Disease Encountered at CTH and TSGH (from 1979 to 2004, n=22)

Case No.	Age (years)	Sex	Oral Ulcer	Genital Ulcer	GI S & S	Ocular Signs	Skin Lesion	Pathergic Reaction	Arthritis or Arthalgia
1	38	M	+	+	+	−	−	+	+
2	45	M	+	+	+	+	+		+
3	26	F	+	−	+	+	−		−
4	47	M	+	+	+	+	+		−
5	28	F	+	−	+	+	−	+	+
6	36	F	+	+	+	+	−		−
7[a]	22	M	+	+	+	−	−	+	
8	42	M	+	+	+	+	−		
9	22	M	+	+	+	−	+	+	+
10	28	F	+	+	+	+	−		−
11	65	M	+	+	+	−	+		−
12[a]	23	M	+	+	+	−	+	−	−
13	32	F	+	−	+	+	+		−
14	24	M	+	+	+	+	−	+	+
15	34	M	+	+	+	−	−		
16	41	F	+	+	+	−	+		
17[b]	38	M	+	+	+	+	+	+	−
18	33	M	+	+	+	−	+	−	−
19	25	M	+	+	+	−	+	+	+
20	48	F	+	+	+	+	−		
21	29	M	+	+	+	−	+	−	−
22	50	F	+	+	+	+	−		+

Plus signs mean that the feature is present; minus signs mean that the feature is not present.
CTH = Cardinal Tien Hospital, TSGH = Tri-Service General Hospital, S & S = symptoms and signs
[a] Reperforations at ileum after partial resection of ileum
[b] Reperforation at ileum after ileocecal resection

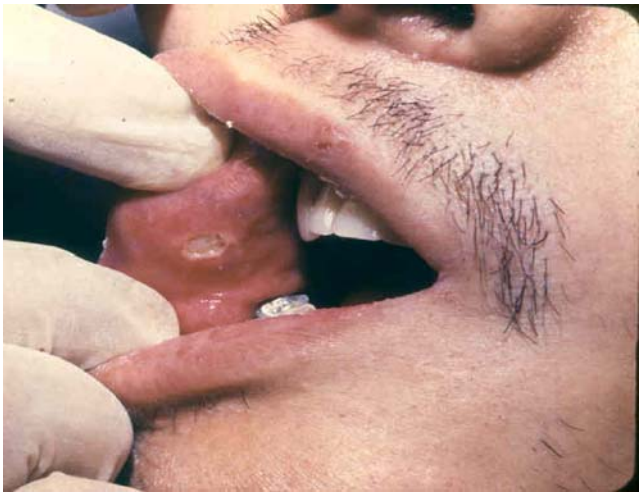

Figure 1 Buccal ulcer.

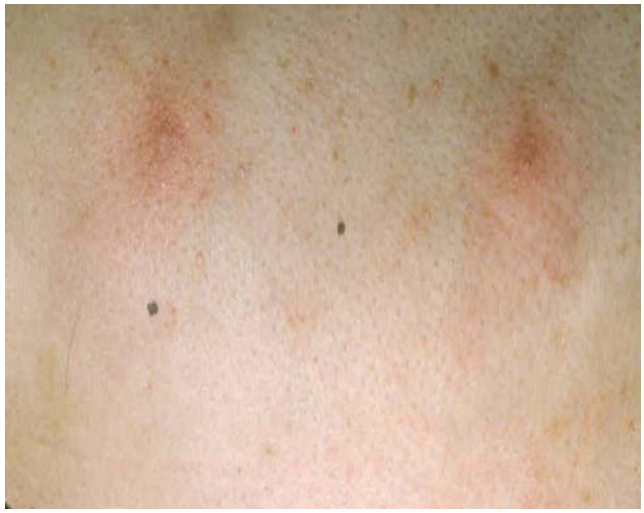

Figure 3 Nodular cutaneous lesion on the back.

occurred on the chest wall, back (Fig. 3), and legs. Biopsy of dermal subcutaneous lesions had been done in 10 cases. In each of them, a nonspecific vasculitis of subcutaneous capillaries and venules was present (Fig. 4). Pathergic reaction was found positive in 7 of 10 patients.

There were no specific immunologic abnormalities in any of the 16 patients tested (Table 3). The levels of immunoglobulin were variable. IgG was increased in 3 of 16 patients, IgA in 5 patients, and IgM in 3 patients. There was a significant decrease of IgG in two patients and of IgA in one patient. The total hemolytic complement was normal in all 16 serum samples. Alpha-2 globulin was increased in 9 of 16 patients, and gamma globulin was increased in seven patients.

Multiple concurrent penetrating ulcers (Fig. 5) were found in all 22 cases, with multiple perforation sites identified from terminal ileum to the ascending colon (Table 4). The size and number of perforated ulcers were variable, ranging from 0.2 to 6 cm in size, and 4 to 16 in number. The perforations were found at the ileocecal region and ascending colon in 10 cases, at the terminal ileum in 8 cases, and at the cecum and ascending colon in 4 cases.

Operative Treatment and Outcome

All 22 perforated intestinal Behçet's disease cases were confirmed at operation, with nine of them correctly diagnosed preoperatively. Surgical resection of the perforated intestinal ulcers was done in all cases, with right hemicolectomy and ileocecal resection in 11 cases, partial ileum resection in 8 cases, and ileocecal resection in 3 cases. No reperforation occurred in the group of patients who underwent right hemicolectomy and ileocecal resection. However, two reperforations ocurred in patients who underwent partial ileum resection alone and one in the ileocecal resection group.

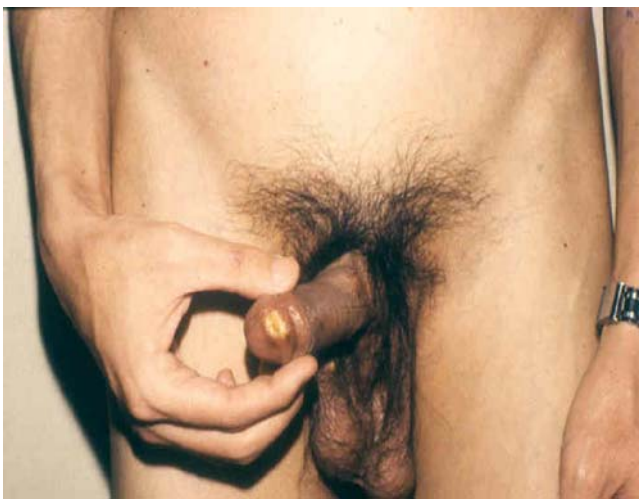

Figure 2 Penile ulcer.

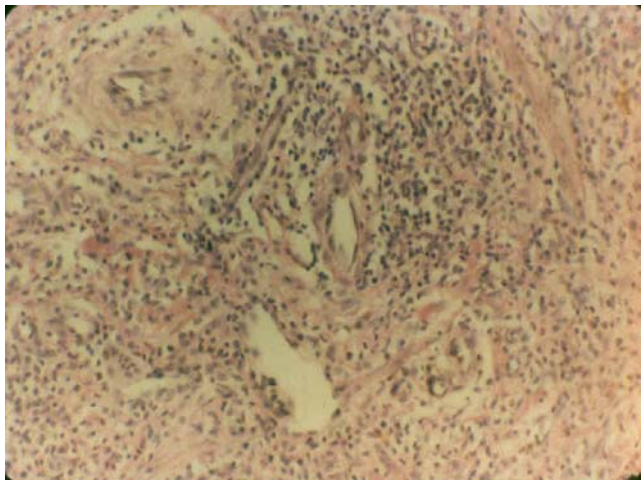

Figure 4 Vasculitis characterized by lymphocytic and plasmacytic infiltration of perivascular tissue (hematoxylin and eosin; 10×40).

Table 3 Laboratory Data

Case No.	Immunoglobulins (mg/dl)			Serum Complement (mg/dl)		Globulin (%)	
	IgG	IgA	IgM	C′3	C′4		
1	1,976	375	250	145	38	13.8	23.8
2	1,726	245	174	92	40	12.0	10.8
4	2,150	400	240	110	45	14.2	24.6
5	1,500	590	300	38	25	10.5	18.0
7[a]	740	185	60	90	38	7.8	14.3
8	1,180	195	140	59	32	6.6	12.2
9	2,270	464	262	127	46	14.0	16.2
11	1,850	380	250	190	50	12.5	23.5
12[a]	1,300	320	235	88	39	9.6	15.0
14	2,350	490	295	180	48	13.3	25.0
16	680	98	56	150	35	13.0	21.8
17[b]	1,650	475	280	76	34	9.4	12.5
18	1,800	290	150	105	45	13.8	23.2
19	2,418	581	209	166	40	14.4	28.0
21	1,880	330	250	180	35	10.5	20.0
22	1,985	386	228	168	38	13.8	24.2
Normal range	950–2,110	170–410	54–262	47–191	27–52	4.8–12.1	8.8–22.8

[a] Reperforations at ileum after partial resection of ileum
[b] Reperforation at ileum after ileocecal resection

The pathologic study of the resected specimens showed nonspecific inflammatory reactions with the infiltration of lymphocytes and plasma cells as the predominant finding (Fig. 6). Histological sections from the ulcer walls showed changes consistent with a nonspecific ulcerative inflammatory process and infiltration containing both plasma cells and chronic inflammatory cells.

After operation on these 22 patients with Behçet's disease and intestinal perforation, four patients died during the postoperative course due to septic shock, which was present prior to the surgical intervention; three died from complications of hypertension and diabetes mellitus; and three were lost to follow-up. Thus, only 12 patients are still under observation, without evidence of gastrointestinal complications up to this date. The remaining 60 cases of intestinal Behçet's disease, without perforations, are still under surveillance.

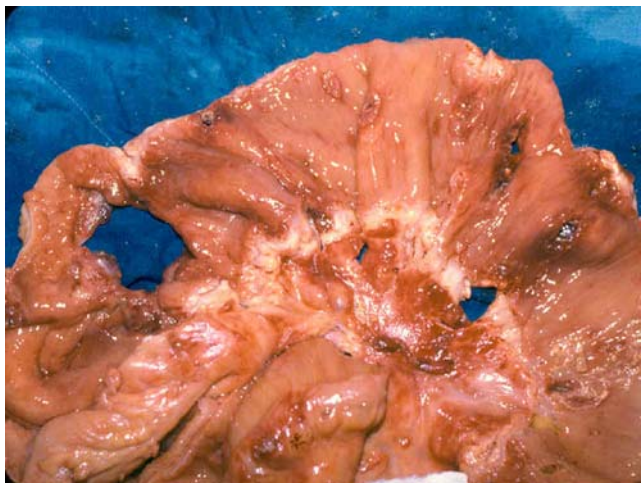

Figure 5 Surgical specimen of ileocecal region showing multiple penetrating ulcers.

Discussion

In 1937, Behçet described a chronic relapsing triple-symptom complex of oral ulceration, genital ulceration, and ocular inflammation[5]. Over the years, it has become apparent that the process is a systemic recurrent inflammatory disease affecting a number of organs consecutively[6]. In 1940, Bechgaard first described intestinal involvement in Behçet's disease. Tsukada et al. proposed the term "intestinal Behçet's disease" in 1964[2,3]. Baba et al.[4]. agreed to this proposal and cited 49 cases of the disease treated from 1975. Since then, the number of operations reported has increased rapidly[3], but perforated intestinal Behçet's disease is still rarely reported.

In a large review series, Oshima and colleagues reported that 40% of patients with Behçet's disease had gastrointestinal complaints, such as nausea, vomiting, and abdominal pain[2–4,8,9]. The age at onset of these symptoms ranges from 16 to 67 years, and the male-to-female ratio ranges from 1.5:1 to 2:1[2,5]. Our cases were in accordance with this reported age range and sex ratio. The third decade is the most commonly reported age of onset for Behçet's disease[6,8,10,30] and the fourth decade for intestinal Behçet's disease[3]. In our study, intestinal Behçet's disease occurred at a mean age of 33.1 years. However, Behçet's disease and intestinal involvement were diagnosed simultaneously in some of these patients, most of whom had already experienced systemic manifestations.

The exact cause of this disease still remains an enigma. Current hypotheses include allergic vasculitis of small vessels, autoimmune disease, and immunologic deficiency[2,4,11,12]. The deposition of immune complexes in the walls of small blood vessels was found by the laboratory results of three of our cases, and this process has been proposed as one of the underlying pathologic mechanisms in intestinal Behçet's disease[12].

Since no clinicopathologic findings are pathognomonic in this disease, the diagnosis is made on the basis of combinations of various clinical symptoms and signs[13]. Mason and Barnes constructed an elaborate set of major and minor criteria for diagnosis[1]. They suggested the triad of buccal ulceration, genital ulceration, and eye lesion and skin lesion as major symptoms. The minor symptoms included gastrointestinal lesions, arthritis, thrombophlebitis,

Table 4 Operative Findings and Operation Performed in 22 Perforated Intestinal Behçet's Disease Patients

Case No.	Location of Perforated Ulcers	No. of Perforations	Oral/genital Ulcer	Operation Performed
1	Terminal ileum	4	+/+	Partial resection of the ileum
2	Terminal ileum	6	+/+	Partial resection of the ileum
3	Ileocecal region and ascending colon	10	+/−	Right hemicolectomy and ileocecal resection
4	Ileocecal region and ascending colon	16	+/+	Right hemicolectomy and ileocecal resection
5	Cecum and ascending colon	5	+/−	Ileocecal resection
6	Terminal ileum	5	+/+	Partial resection of the ileum
7[a]	Terminal ileum	4	+/+	Partial resection of the ileum
8	Cecum and ascending colon	9	+/+	Right hemicolectomy and ilececal resection
9	Terminal ileum	8	+/+	Partial resection of the ileum
10	Ileocecal region and ascending colon	11	+/+	Right hemicolectomy and ileocecal resection
11	Ileocecal region and ascending colon	10	+/+	Right hemicolectomy and ileocecal resection
12[a]	Terminal ileum	5	+/+	Partial resection of the ileum
13	Terminal ileum	7	+/−	Partial resection of the ileum
14	Ileocecal region and ascending colon	11	+/+	Right hemicolectomy and ileocecal resection
15	Ileocecal region and ascending colon	5	+/+	Right hemicolectomy and ileocecal resection
16	Ileocecal region and ascending colon	13	+/+	Right hemicolectomy and ileocecal resection
17[b]	Cecum and ascending colon	4	+/+	Ileocecal resection
18	Ileocecal region and ascending colon	7	+/+	Right hemicolectomy and ileocecal resection
19	Ileocecal region and ascending colon	9	+/+	Right hemicolectomy and ileocecal resection
20	Cecum and ascending colon	6	+/+	Ileocecal resection
21	Terminal ileum	4	+/+	Partial resection of the ileum
22	Ileocecal region and ascending colon	12	+/+	Right hemicolectomy and ileocecal resection

[a] Reperforations at ileum after partial resection of ileum
[b] Reperforation at ileum after ileocecal resection

cardiovascular lesions, neurologic lesions, and family history. Three major criteria or two major criteria and two minor criteria are necessary for diagnosis. These various symptoms are not usually present at the same time. If we hold the original triple-symptom complex as a prerequisite for the diagnosis, cases may be missed. In 1990, the International Study Group for Behçet's Disease[14] introduced a diagnostic criteria requiring the presence of oral ulcerations plus any two of the following: genital ulcerations, typical eye lesions, typical skin lesions, or positive results to a pathergy test. However, some reports have shown that almost 20% of patients with Behçet's disease presented without oral lesions initially[15,16]. Furthermore, 2–5% of patients did not show any oral lesions at all[16,17]. In our series, all patients had manifestations of concurrent oral ulceration. All perforated cases present oral or genital ulcerations at the same time. Because we warned that patients of intestinal Behçet's disease may have abdominal pain and oral or genital ulcerations concurrently, intestinal perforations should always be kept in mind.

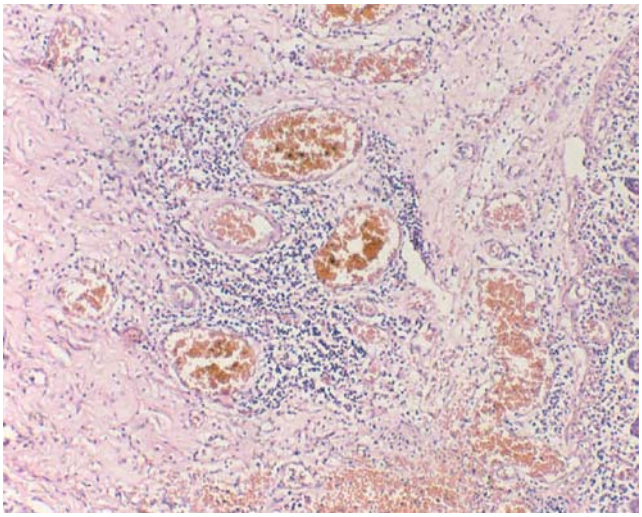

Figure 6 Chronic inflammatory response and perivascular infiltration (hematoxylin and eosin; 10×10).

A phenomenon of pathergy was first described by Blobner in 1937 and was further elaborated by Katzenellenbogen in 1968. It consists of an itradermal test applied to Behçet's disease patients with a sharp needle prick causing skin hypersensitivity, which is characterized by the formation of a sterile pustule 24 to 48 h after the trauma. Biopsy at the intradermal puncture site is taken 48 h after for histopathologic evaluation. In a study conducted by Tuzum et al., this reaction was found to be positive in 84% of 58 patients with the disease, as compared to 3% of 90 healthy controls[1]. A positive pathergic reaction should make us aware of the possibility of the disease in the presence of any of the accepted symptoms of this process. However, the recent

results and interpretations of pathergy tests have varied widely according to the technical aspects of the tests[18,19] and ethnic differences of the patients.

The histological lesions in Behçet's disease are rather uncharacteristic. Nonspecific perivascular infiltrations of plasma cells and lymphocytes are usually found in the cutaneous and mucosal lesions[5,20]. The intestinal ulcers in Behçet's disease are characterized not only by the absence of the granulomatous formation of Crohn's disease, but also by deeper penetration of the ulcers to areas nearer to serosa membrane than the ulcers of ulcerative colitis[3,4,21]. The ulcers tend to be undermined, and the submucosal connective tissues are usually destroyed. The bases of the ulcers are avascular with edema-like swelling and crater-shaped formation around the ulcer margin.[2,22–24] These ulcers are usually found in the terminal ileum and the cecum, but they may be present at any site throughout the digestive system and tend to perforate at multiple sites[25–29]. The gross pathologic characteristics of our intestinal Behçet's disease included perforations at multiple sites concurrently in variable sizes and configurations, extending from the ileocecal region to ascending colon, in accordance with the reported literature[3,4,8,30,31].

The medical treatment of the intestinal Behçet's disease remains unsettled. The beneficial effect of steroid therapy has not been convincing in most series[2,7,30]. It may control the disease initially, but recurrences are common. Topical application of corticosteroids decreases the ocular inflammation, and is also useful in relieving the pain of oral ulcers. Haim and Sherf reported a favorable response to fresh blood and plasma in cases of Behçet's disease, but the nature of the useful component in hematotherapy is unknown[5]. In our two patients with perforations, steroid therapy was given for 2 weeks after surgery with favorable outcomes.

Resection of the ileocecal region or the right half of the colon is the usual operation in the treatment of gastrointestinal complications[3,4]. In our series, perforations at multiple sites were found in all cases; right hemicolectomy and ileocecal resection were performed in 11 cases without reperforation; ileocecal resection in 3 cases with one reperforation; and partial resection of the ileum in 8 cases with two reperforations.

Conclusion

Because concurrent oral and genital ulcers were found in all patients in our series, the presentation of this seemingly innocuous clinical manifestation along with gastroinstestinal symptoms should raise the level of suspicion that intestinal involvement and complications of perforations may have already happened. The other constant finding among our 22 patients is that all the intestinal perforations were located between the terminal ileum and the ascending colon. Therefore, to prevent reperforations, wide excision of the terminal ileum with right hemicolectomy is recommended for perforated intestinal Behçet's disease. We found out that the specimens of the resected bowel of the 19 nonreperforated patients all had more than 60 cm of terminal ileum, but those of the three reperforated cases had less than 60 cm. Furthermore, the perforation sites were all at 10 to 12 cm proximal to the anastomosis. This is the main reason we recommend the resection of up to 80 cm of ileum from the ileocecal valve at the time of right hemicolectomy[4,31].

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Acquiring Tetanus After Hemorrhoid Banding and Other Gastrointestinal Procedures

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Abstract Tetanus after hemorrhoidal banding is an extremely rare but serious complication of the procedure. We describe the second reported case of this complication and review the literature concerning tetanus after different gastrointestinal procedures. Although a rare complication, practicing physicians need to be aware of the clinical presentation of this deadly disease when encountered in at-risk patient populations. Such cases also reemphasize the importance of primary tetanus immunization and follow-up boosters for all vulnerable patients.

Keywords Tetanus · Hemorrhoids · Surgical procedures operative · Postoperative complications · Digestive system surgical procedures

Introduction

Tetanus is currently a rare disease in the United States and other developed countries where active immunization programs provide a considerable degree of immunity to the infection in the general population. The incidence of tetanus has dropped dramatically in the United States and other developed countries due to a successful vaccination program instituted in the 1940s.[1] During the period from 1998 to 2000, the Centers for Disease Control (CDC) reported the average annual incidence of tetanus to be 43 new cases in the United States per year. This is equivalent to 0.16 cases/million people in the US.[2] The worldwide incidence of tetanus, however, is much higher and estimated to be around 500,000 to 1 million per year.[3] In developed countries, tetanus is most commonly seen in immigrant patients who have never received a complete primary immunization series. Another at-risk group is the elderly people who have not received recent booster doses. Such cases in the older, previously vaccinated adult reflects waning immunity if a booster shot is not received every 10 years.

Tetanus is caused by the toxin-producing anaerobic bacterium *Closteridium tetani*. *C. tetani* is a spore-forming bacteria that once inside the body of susceptible host, produces a potent toxin named tetanospasmin. Tetanospasmin binds to the central nervous system causing diffuse muscle spasms and autonomic instability that characterizes tetanus. Tetanus is usually seen in association with soil contamination of a cutaneous wound; however, on rare occasions it may occur after a surgical procedure such as gastrointestinal surgery. In this paper, we describe the second reported case of tetanus after banding ligation of internal hemorrhoids and will review the other reported cases of tetanus after gastrointestinal procedures.

Case Report

A 63-year-old female with no significant past medical history presented with chief complaint of 5 days of anal

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discomfort due to hemorrhoids. Physical exam showed a 1.5 cm soft and inflamed external hemorrhoid. She was initially treated with pramoxine suppositories and a week later was scheduled for elective hemorrhoid banding. At the time of surgery, she was noted to have a small noninflamed external hemorrhoid as well as a grade III internal hemorrhoid at the eight o'clock position; there was no evidence of infection. The patient underwent rubber band ligation of the internal hemorrhoid with no immediate complications. After the procedure, the patient was instructed to take daily Sitz baths and given a prescription for docusate (oral) and psyllium to prevent constipation. Five days after the surgery, the patient returned to the hospital with a 1-day history of sore throat, pain upon swallowing, headache, and inability to open her mouth. She was noted to have a hoarse voice and stated that she had difficulty sticking out her tongue. Initial vital signs showed blood pressure of 150/70 mmHg, pulse of 95, temperature of 37.1°C, and respiratory rate of 18 per minute. Neurological examination was remarkable for inability to completely open the mouth; the rest of the neurological examination showed normal findings including muscle tone, bulk, and strength. A neck x-ray was obtained and it was normal. Patient's inability to open mouth prompted further evaluation and the diagnosis of tetanus was entertained. Further history revealed that patient had never been immunized against tetanus. She was subsequently admitted to the intensive care unit and initially treated with 1,000 units of intervenous (IV) human tetanus immune globulin, 2 g of IV ceftriaxone every 24 h, IV diazepam, and methylprednisolone. On the next day, the patient had severe pain on attempting to open her mouth and diffuse muscular spasms of jaw, neck, abdominal musculature consistent with trismus and generalized tetanus. A rectal exam at the time showed normal postoperative changes; there were no masses, bleeding, signs of infection, or hemmorhoids. She subsequently developed respiratory difficulties due to laryngeal spasms and required intubation and paralysis. In the next days, she developed a number of complications related to hospitalization and the underlying tetanus. The patient had autonomic lability with associated hypertension (systolic blood pressure up to 220 mmHg) and tachycardia (pulse of 110s); she developed an episode of chest paint and was found to have an acute anterior wall ST-elevation myocardial infarction confirmed with EKG abnormalities and elevated troponins. Additional complications included a small pneumothorax after placement of a Swann–Ganz catheter, left lung collapse due to mucous plugging, and nosocomial pneumonia due to *Acinetobacter baumanii*. Attempts to wean her during endotracheal intubation were unsuccessful and the patient required a tracheostomy. After about 2 months of hospitalization, she gradually improved and was weaned from the respirator. She had upper and lower muscle atrophy, global muscle weakness, and ankle contractures bilaterally. She had no obvious sensory, cognitive, or language deficits. She was able to roll herself in bed and feed herself; however, she was unable to stand, walk, or place herself on bedpan. She was subsequently transferred to an inpatient rehabilitation facility for intensive physical and occupational therapy. At the completion of a month-long inpatient rehabilitation program, she showed some improvement but still had some lower extremity weakness (grade 3–4 out of 5 of muscle strength bilaterally) and residual ankle contractures; she could walk with assistance using a forearm crutch. The patient was discharged from the hospital with a continuing outpatient rehabilitation program.

Review of Literature

Methods

We searched the English language articles from 1966 to January 2005 in the MeSH system of PubMed for relevant case reports and articles. MeSH keywords identified included *tetanus*, combined with *digestive system surgical procedures*, *surgery*, *surgical procedures operative*, and *hemorrhoids*. All the relevant articles were reviewed, and their reference list examined for other relevant articles. Other articles were obtained and reviewed from these reference lists. Postoperative tetanus cases after obstetric–gynecology procedures in which the appendix was removed were not included; one such paper is included in the reference list however.[4]

Results

We found 14 case reports of tetanus after gastrointestinal procedures. Findings and case summaries are outlined in the tables below (see Tables 1 and 2).

Table 1 Reported Cases of Gastrointestinal Procedures Complicated by Tetanus

Cases	References
Open cholecystectomy	5–7
Cholecystectomy with exploration of bile duct	8
Resection for a gangrenous perforated small intestine	9,10
Rubber band ligation of hemorrhoids	11
Cryosurgery for internal hemorrhoids	12
Drainage of anorectal abscess	13
Sigmoidoscopic polypectomy	14
Gastrectomy, Billroth II, and transverse colectomy, (for large cell lymphoma)	15
Exploratory laparotomy (for carcinoma in omentum and liver)	5

Table 2 Summary of Presentations for the Reported Cases

Author	Year	Age (Year)	Gender (Male/ Female)	Time to Initial Symptoms. (Days Postprocedure)	Initial Symptoms	Later Symptoms	Onset of Later Symptoms (Days Postprocedure)	Tetanus Immunization	Outcome
Open cholecystectomy: (four cases) [5–7]									
Parker& Mandal [5]	1984	47	Female	10	No mention	Trismus	10	uncertain	Alive
Parker& Mandal [5]	1984	59	Female	17	Spastic gait	No mention	22	No mention	Dead
O'Riordain, Buckley, & Kirwan [6]	1991	46	Male	11	Abdominal spasm, pain, fever, mild trisumus	Trismus	12	No	Dead
Crokaert, Glupczynski, Fastrez, Alle, & Yourassowsky [7]	1984	44	No mention	6	Neck and face pain, stiffness	Opisthotonus	6	No mention	No mention
Cholecystectomy with exploration of bile duct: (two cases) [8]									
Lennard, Gunn, Sellers, & Stoddart [8]	1984	49	Female	12	Sub-costal pain, abdominal distention	Opisthotonus	No mention	No	Alive
Lennard et al. [8]	1984	66	Female	16	Abdominal pain	Trismus	19	No	Alive
Resection for a gangrenous perforated small intestine: (two cases) [9,10]									
Furui et al. [9]	1998	75	Male	1	Jerking, limb rigidity	Opisthotonus	1	No	Alive
Clay & Bolton [10]	1964	61	Male	2	Jerking	Opisthotonus	4	No mention	Alive
Rubber band ligation of hemorrhoids: (two cases) [11]									
Murphy [11]	1978	33	Female	7	Dysphagia, neck pain	Trismus	9	No	Alive
Present case	1997	63	Female	4	Dysphagia	Trismus	6	No	Alive
Cryosurgery for internal hemorrhoids: (one case) [12]									
Singh, Chhina, & Kaul [12]	1992	42	Male	14	Fever, Dysphagia	Trismus	19	No	Alive
Drainage of anorectal abscess: (one case) [13]									
Myers et al. [13]	1984	62	Male	10	Restlessness, limb rigidity	Trismus	12	No	Alive
Sigmoidoscopic polypectomy: (one case) [14]									
Segel & Shaff [14]	1969	55	Female	10	Fatigue, weakness	Trismus	19	No	Alive
Gstrecotmy, Billroth II, and transverse colectomy, for "large cell lymphoma": (one case) [15]									
Fleshner, Hunter, & Rudick [15]	1988	48	Male	21	Fever, abdomen, back pain, dysphagia	Trismus and opisthotonus	26	No	Alive
Exploratory laporatomy (for carcinoma in omentum and liver): (one case) [5]									
Parker & Mandal [5]	1984	65	Female	12	No mention	No mention	12	No	Dead

Discussion

This is the second case of tetanus after hemorrhoid banding that we were able to find in the literature. As noted in Table 1, tetanus can occur after a wide variety of gastrointestinal surgical procedures including major intra-abdominal surgery (e.g., cholecystectomy for cholecystitis; exploratory laparotomy for intestinal perforation), as well as relatively "trivial" procedures such as hemorrhoid surgery and sigmoidoscopic polypectomy. Tetanus occurs after germination of the spores and subsequent production of toxin by the organism. *Clostridium tetani* will not grow in healthy tissue, therefore a number of factors need to be present for germination to occur including ischemia, devitalized tissue, coinfection, and injury from penetration or foreign body.[1] In gastrointestinal surgical procedures, presence of ischemic or devitalized tissues permits proliferation of *C. tetani* and subsequent toxin production. In our case, the devitalized tissue from banded hemorrhoid was the likely entry point for the organism with subclinical *C. tetani* infection occurring at the site. *C. tetani* may be isolated from stool flora in asymptomatic individuals; in farming regions where individuals are in constant contact with soilor domestic animals (e.g., horses, cattle), up to 1/3 of individuals may have *C. tetani* in their stools.[16] Given standard sterilization procedures, tetanus associated with infected surgical instruments is extremely uncommon in industrialized countries—our patient most likely developed the condition after contamination of the wound with organisms from the stool or external environment. In our experience with patients from Latin America, it has come to our attention that some of them use herbal products such as out-door plants known as aloe vera ("buena herba" in Spanish) for treatment of local wounds. Although we are not aware of any documented case report of this practice causing transmission of tetanus, we wonder if application of contaminated outdoor plants might play a role in some of the postoperative cases. Our patient did not provide history of such practice and the exact mode of contamination will not change the clinical presentation or management. Once suspicion arises for presence of tetanus, identification depends upon recognition of the characteristic clinical syndrome. Although isolation of *C. tetani* from a wound is supportive of the diagnosis, many patients have negative wound cultures and presence of the characteristic clinical syndrome is adequate evidence to support the diagnosis.[1]

Although rare, it is prudent for practitioners to be mindful of signs that suggest the possibility of postoperative tetanus. Patients with tetanus usually have painful spasms and contractions of their skeletal muscles; this can present as stiff neck, trismus, or opisthotonus. Lockjaw, also known as trismus, leads to inability to open the mouth and the characteristic sardonic smile (risus sardonicus)—it is a sign of spasm of muscles of mastication. Trismus, along with back pain and diffuse muscle spasms, is one of the most frequent findings in tetanus.[17] Opisthotonus is a sign of generalized tetanus and is characterized by painful involuntary bending of spine and extremities. It leads to forward convexity of the body, with patient's torso arching upward and body supported on head and heels. There can also be periods of apnea due to thoracic, glottal, pharyngeal muscle contractions often requiring intubation and respiratory support. Irritability, restlessness, sweating, labile vitals signs, or even a myocardial infarction can occur due to autonomic instability. Presence of these signs or symptoms could be due to underlying tetanus and should alert the practitioner of possibility of the condition. Despite the case reports in Table 1, it should be emphasized that tetanus is a highly unusual complication of gastrointestinal surgical procedures. Given the extremely rare incidence of this complication, it does not appear to be practical to require evidence of full tetanus immunization before a procedure. Nevertheless, our case reemphasizes the importance of routine tetanus immunization, especially in patient populations that were not immunized in childhood or failed to receive a complete series of vaccinations. As part of their general health maintenance, adults should continue to receive periodic booster shots every 10 years as recommended by public health authorities.[18] Furthermore, despite its rarity, practitioners need to be aware of the clinical presentation of tetanus and consider the diagnosis in at-risk patients who present with characteristic symptoms such as trismus and muscle rigidity.

Conclusion

Postoperative cases of tetanus have been reported after a number of different gastrointestinal procedures. Tetanus can occur after relatively minor procedures such as hemorrhoidal banding. Practicing physicians need to be aware of the clinical presentation of this deadly disease when encountered in vulnerable patient populations.

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Bromodeoxyuridine Labeling Index as an Indicator of Early Tumor Response to Preoperative Radiotherapy in Patients with Rectal Cancer

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Abstract
Purpose Assessment of tumor proliferation rate using Bromodeoxyuridine labeling index (BrdUrdLI) as a possible predictor of rectal cancer response to preoperative radiotherapy (RT).
Methods and material Ninety-two patients were qualified either to short RT (5 Gy/fraction/5 days) and surgery about 1 week after RT (schedule I), or to short RT and 4–5 weeks interval before surgery (schedule II). Tumor samples were taken twice from each patient: before RT and at the time of surgery. The samples were incubated with BrdUrd for 1 h at 37°C, and the BrdUrdLI was calculated as a percentage of BrdUrd-labeled cells.
Results Thirty-eight patients were treated according to schedule I and 54 patients according to schedule II. Mean BrdUrdLI before RT was 8.5% and its value did not differ between the patients in the two compared groups. After RT tumors showed statistically significant growth inhibition (reduction of BrdUrdLI). As the pretreatment BrdUrd LI was not predictive for early clinical and pathologic tumor response, prognostic role of the ratio of BrdUrdLI after to BrdUrdLI before RT was considered. The ratios were calculated separately for fast (BrdUrd LI>8.5%) and slowly (BrdUrd LI≤8.5%) proliferating tumors and correlated with overall treatment time (OTT, i.e., time from the first day of RT to surgery). One month after RT, accelerated proliferation was observed only in slowly proliferating tumors.
Conclusions Pretreatment BrdUrdLI was not predictive for early clinical and pathologic tumor response. The ratio after/before RT BrdUrdLI was correlated to inhibition of proliferation in responsive tumors.

Keywords BrdUrdLI · Proliferation rate · Early tumor response · Rectal cancer · Radiotherapy

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Introduction

In specialized centers, a refined surgical technique has resulted in high local control figures in rectal cancer. However, local recurrence rates after "standard" surgery are generally high, with figures ranging between 20 and 40%[1,2], although after adopting the total mesorectal excision (TME) concept they fell down to 10–12%[3,4]. Radiotherapy in addition to surgery significantly diminishes the risk of local failure by more than half, from 8 to 2% after 2 years[3]. Therefore, combined treatment: radiotherapy (RT) and surgery in the treatment of patients with resectable rectal cancer has been proposed in many trials using either preoperative[5,6] or postoperative irradiation[7,8]. Better results of preoperative RT for 5 days (25 Gy in five fractions) in comparison with postoperative 60 Gy in 30 fractions were achieved by a Swedish group[4,9,10], with respect to the local recurrence rate[11] and overall survival[11,12].

A corresponding improvement in overall survival has not been demonstrated after postoperative radiotherapy alone[13]. Graf's[12] study provided a clinically significant biologic effect of a short preoperative course of radiotherapy on the tumor size and on the incidence of nodal metastases; however, this effect was minimized if surgery was performed immediately after radiotherapy. The effect is most likely caused by death of tumor cells in the primary tumor and in the involved nodes. A short treatment course of radiotherapy, i.e., 5×5 Gy is desirable, and this regimen is currently considered as the gold standard in many centers. However, using this schedule it is difficult to observe a down-staging and/or downsizing of the tumor, which is of importance for the selection of patients for sphincter-preserving surgery (anterior resection).

In clinical practice there are no certain methods able to predict tumor response to preoperative radiotherapy (RT). The optimal timing of surgery after preoperative radiotherapy in rectal cancer is unknown. However, it was shown that a long interval (6–8 weeks) between preoperative radiotherapy (39 Gy in 13 fractions) and surgery was associated with a significantly greater clinical tumor volume reduction than a short interval (2 weeks)[14]. On the other hand, it was shown that subclinical pelvic deposits of rectal cancer could grow rapidly during preoperative radiation therapy and during the radiotherapy–surgery interval, with an adverse influence on the rate of pelvic tumor control from protracting the overall treatment time[15]. Graf et al[12] showed that low doses in short RT only offer clinically relevant reduction in the risk of pelvic relapses if the overall radiation treatment time is short. Thus, the rate of cancer cell proliferation seems to be a very important prognostic factor.

The aim of this study is to evaluate BrdUrd LI and S-phase fraction (SPF) as the possible indicators of tumor proliferation rate and predictors of the tumor response to neoadjuvant RT in patients with rectal cancer, and to suggest an optimal interval between short RT course and surgery.

Methods and Materials

Patients

Between November 2003 and January 2006 we recruited 92 patients with resectable rectal carcinoma for whom curative surgery was planned. Patients were eligible for the trial if they were less than 75 years old, had a histopathologically proved adenocarcinoma (T2/T3)[16] situated less than 12 cm from the verge of the anus, and gave informed consent for their participation. The protocol was approved by the Ethical Committee of the Center of Oncology, and each patient gave written consent.

The criteria for exclusion were: locally nonresectable tumor; plan to perform only local tumor excision; known metastatic disease; previous radiotherapy of pelvis region; other malignant disease; and patient's refusal.

Preoperative Radiotherapy

The patients assigned to preoperative radiotherapy received a total tumor dose of 25 Gy. The treatment was given in five fractions over 5 days, one posterior and two lateral wedged fields were irradiated with photons of maximum 6 MV energy. According to the random selection surgery was performed the following week (schedule I) or after longer interval of 4–5 weeks (schedule II).

Surgery

Anterior resection of rectum or abdominoperineal excision was performed within a week or a month after the completion of RT. Type of surgery was resection of the rectum and lower sigmoid with involved adjacent tissue and regional lymph nodes up to or above the origin of inferior mesenteric artery. A minimal touch technique was used with high tight ligation of the inferior mesenteric artery. The decision whether the patient should have an abdominoperineal resection or a sphincter-preserving surgery was made by the surgeon during the operation.

An abdominoperineal resection of rectum was performed in 41 (44.6%) of the patients, and sphincter preserving surgery was performed in 51 (55.4%).

Biological Assessment of Tumor Response

Tumor samples were taken twice: before radiotherapy (through a rectoscope) and during surgery from the same

place, i.e., at the lowest edge of the tumor mass. Each biopsy was divided into two parts: one was used for BrdUrd LI assessment, and the second was used for immunohistochemical analysis (these results will be the subject of a separate study).

Bromodeoxyuridine Labeling Index

Incorporation of BrdUrd in tumor samples from a biopsy (0.3–0.5 cm^3) was carried out *in vitro* according to the high-pressure oxygen method. The BrdUrd staining procedure and flow cytometry have been described in detail elsewhere[17]. The stained preparations were analyzed with a FACS Calibur flow cytometer (Becton Dickinson Immunocytometry Systems, Sunnyvale, CA, USA) by one coauthor (AG) and 20×10^3 events were collected in each histogram. The BrdUrdLI was calculated as a percentage of BrdUrd-labeled cells in a sample, which incorporated BrdUrd during 1 h of incubation at 37°C (with discrimination of diploid subpopulation in aneuploid tumors). The tumor ploidy and SPF were calculated from the DNA profile with ModFit software running on a MacIntosh computer. Apoptotic cells were identified as objects with a fractional DNA content not less than 20% of the 2n DNA content. Cell death was calculated as the sum of apoptosis and debris. The tumor ploidy was estimated by evaluating the DNA index, i.e., the ratio of the modal DNA fluorescence of abnormal to normal $G_{1/0}$ cells. Aneuploidy was assessed in cases in which the normal and neoplastic cell populations gave two separate peaks. Human lymphocytes were used for the reference peak. Tumors with BrdUrdLI >8.5% (median value) were considered as fast, and those with BrdUrdLI ≤8.5% were considered as slowly proliferating tumors.

Clinical Assessment of Tumor Response

Tumor size before RT was assessed basing on measures taken during rectoscopy, and endorectal sonography. Tumor regression after RT was assessed at the time of operation by surgeons according to the following Response Evaluation Criteria in Solid Tumors (RECIST)[18]:

Complete response (CR): 100% disappearance; partial response (PR): 30–99% decrease; stable disease (SD): neither CR, PR or PD criteria met; progression of disease (PD): 20% increase in sums of tumor longest diameters.

Pathological Assessment of Tumor Response

Tumor regression after RT was evaluated by a pathologist on the excised tumor mass. The following criteria of tumor regression assessed by Dworak et al.[19] were applied:

D0—no regression; D1—dominant tumor mass with obvious fibrosis and/or vasculopathy; D2—dominantly fibrotic changes with few tumor cells or groups; D3—very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; D4—no tumor cells, only fibrotic mass (total regression or response).

Statistical Methods

Statistical analysis was performed with STATISTICA vs.5. Intergroup differences in the ordinal data were tested with ANOVA test or Student's *t* test. *P* values of less than 0.05 were considered to indicate statistical significance. Linear regression was applied for assessing differences between fast and slowly proliferating tumors in relation with OTT, and its significance was determined by testing the difference between two correlation coefficients. Stratification by BrdUrd LI level was introduced and tested by the inclusion of dummy variable in the regression model.

Results

Patients

A total of 92 patients were included in the study. Twenty-eight (23.3%) out of 120 patients initially qualified for this study were excluded from the analysis because of discontinuation of treatment, metastatic tumor noticed at operation, or no tumor samples taken for biological assessment during surgery. Mean age for the entire group of patients was 61.6 years (range 30–75). There were 68 men and 24 women. There were no statistical differences between the two groups at the time of recruitment for prognostic factors such as: sex, age, histologic grade, or tumor stage (Table 1).

In our series of patients, there were 27 stage 1 (29.3%), 55 were T2 (59.8%), and 10 were T3 (10.9%). In 26 patients, tumor cells well differentiated (G1), 63 moderately differentiated (G2), and three poorly differentiated (G3) (Table 1). Thirty-eight patients were treated according to schedule I, in which time interval between end of irradiation and surgery averaged 8.8 days (range 2–14; Table 1). In 54 patients, schedule II was applied, in which mean break was 32.9 days (range 17–45). Because the interval between RT and surgery appeared to be longer than planned, overall treatment time (OTT), e.g., time from the beginning of RT to surgery, was calculated and it appeared to be 7–50 days (Table 1).

Biologic, Pathologic, and Clinical Assessment of Tumor Response

Mean BrdUrd LI before RT was 8.5% (range 1.0–24.2%) and SPF was 22.0% (range 3.8–49.9%) and the mean values did not differ between the two schedules (Table 2).

Table 1 Selected Characteristics of Patients and Treatment Parameters

Characteristics	Schedule I	Schedule II	Total
Age mean (±SD) years	(38)[a] 61.2± 12.0	(54) 61.9± 9.5	(92) 61.6± 10.6
Sex			
Male	30	38	68
Female	8	16	24
Histological grade			
G1	6	20	26
G2	29	34	63
G3	3	0	3
Tumor stage			
T1	8	19	27
T2	25	30	55
T3	5	5	10
PTNM			
1	16	25	41
2	8	6	14
3	13	17	30
4	1	2	3
Interval between RT and surgery			
Mean (range) days	(38)[a] 8.8 (2–14)	(54) 32.9 (17–45)	(92) 22.9 (2–45)
OTT mean (range) days	(38) 13.8 (7–19)	(54) 37.9 (22–50)	(92) 27.9 (7–50)
Surgery			
Sphincter-preserving	20 (52.6 %)	31(57.4 %)	51
Abdominoperineal resection	18	23	41

[a] Number of patients

Poorly differentiated tumors showed statistically significant higher BrdUrd LI than grades 1 and 2 tumors (P=0.015; Table 3). After RT, tumors treated according to both schedules showed statistically significant growth inhibition (reduction of BrdUrd LI and percentage of SPF cells) in comparison with the values obtained before RT (Table 2). Radiation induced inhibition of tumor proliferation was expressed as a percentage of the after RT to before RT BrdUrd LI, and SPF as after/before RT percentage. This ratio ranged from 2.5 to 514% for BrdUrd LI (Fig. 1) and from 5.8 to 522.2% for SPF. When we stratified patients into two groups according to their biological RT response, those radioresponsive with reduction of pretreatment values after radiotherapy above 50% and those less responsive with reduction below 50%, it appeared that the mean values (of the after/before RT ratios of BrdUrd LI and SPF) for the more radioresponsive tumors were significantly higher than for the less responsive ones. Therefore, these ratios were presented separately for fast (BrdUrd LI >8.5%, SPF >22.0%) and slowly (BrdUrd LI ≤8.5%, SPF ≤22.0%) proliferating tumors. Mean BrdUrd LI value after RT for fast proliferating tumors (41 cases) showed statistically significant (P=0.027) reduced pretreatment percentage (46.8%) in comparison with slowly proliferating tumors (85.3%, 51 cases). The same was true for SPF of fast (56.4%, 55 cases) and slowly (113.8%, 37) proliferating tumors (P=0.006).

Next, the after/before RT ratios for BrdUrd LI and SPF were correlated with OTT. For SPF, statistical difference between linear regression coefficients for fast and slowly proliferating tumors was not obtained (P=0.446), therefore the data for BrdUrd LI only are shown (Fig. 1). Insert on Fig. 1 shows a significant (P=0.033) difference in proliferation rate between fast and slowly proliferating tumors treated within OTT >30 days. At that time slowly proliferating tumors, contrary to fast proliferating ones, show no inhibition but accelerated proliferation of tumor cells. This phenomenon was also confirmed by increased fraction of S-phase cells in tumors treated with longer RT schedule (Table 2). The influence of BrdUrdLI level has been also tested by the extended regression model between OTT and the percentage of after/before RT BrdUrd LI. BrdUrd LI level higher than 8.5% has been coded as dummy variable. It appeared to be significant (P=0.025) in the relation between OTT and the percentage of after/before RT BrdUrd LI. The partial regression coefficient indicates that the average decrease of the percentage after/before RT BrdUrdLI for fast proliferating tumors (BrdUrd LI >8.5%) equals 39%.

All 92 irradiated rectal tumors were reviewed by the same pathologist (KN). The tumors were classified according to the World Health Organization classification of

Table 2 Status of Biological Parameters Before and After RT

Group	BrdUrd LI (%) Mean (range)	S-phase fraction (%) Mean (range)	Apoptosis (%) Mean (range)
All patients			
Before RT	8.5 (1.0–24.2)	22.0 (3.8–49.9)	5.9 (0–52.8)
After RT	4.1* (0.4–18.3)	16.8** (1.5–101.0)	9.8*** (0–45.9)
RT schedule I			
Before RT	8.4 (1.1–24.2)	21.5 (6.1–49.2)	6.6 (0–32.4)
After RT	3.8*(0.8–12.6)	14.1**** (1.5–47.9)	10.5 (0–43.3)
RT schedule II			
Before RT	8.6 (1.0–20.0)	22.3 (3.8–49.9)	5.4 (0–52.8)
After RT	4.5* (0.4–18.3)	17.2 (2.6–101.0)	9.5***** (0–45.9)

*P=0.000
**P=0.015
***P=0.010
****P=0.002

Table 3 The Relationship Between Tumor Biological Parameters and Histological Grade

Histological grade	*N*	BrdUrd LI (%) Mean (range)	S-phase fraction (%) Mean (range)	Apoptosis (%) Mean (range)
G1	26	8.5 (1.1–17.1)	23.7 (5.8–49.9)	3.4 (0–32.4)
G2	61	8.2 (1.0–20.0)	21.0 (3.8–45.6)	7.2 (0–52.8)
G3	3	16.2*, ** (9.5–24.2)	27.7 (18.9–34.7)	2.1 (0.4–4.8)

*P=0.015, difference between G1 and G3
**P=0.013, difference between G2 and G3

intestinal carcinoma[16] and staged according to the TNM classification[20]. Of the 92 rectal tumors four had no pTNM classification, 41 were pT1 (46.6%), 14 were pT2 (15.9%), 30 were pT3 (34.1%), and three were pT4 (3.4%). Regional lymph node metastases were found in 27 (30.7%) patients, and 27 (30.7%) patients had their tumor down-staged.

Pathologic assessment of tumor regression after RT according to classification described by Dworak[19] was performed in 90 out of 92 patients (for two patients the assessment was impossible). The analysis showed no tumor regression (D0) in 18 (20.0%) tumors, dominant tumor mass (D1) in 46 (51.1%) tumors, a few tumor cells in fibrotic mass (D2) in 18 (20.0%) tumors, single tumor cells (D3) in four (4.4%), and no tumor cells were observed in four (4.4%) of the examined tumors (Fig. 2a). In 25 (27.8%) out of 90 patients marked pathologic down-staging (no residual tumor confined to the rectal wall) was visible. Pretreatment BrdUrdLI and SPF were not correlated with early clinical and pathologic tumor response. However, patients having tumors with LI >8.5% were more radio-responsive (showed significant reduction in proliferative rate after radiotherapy) than patients with BrdUrdLI ≤8.5% tumors, although statistically significant difference between the two tumor subgroups was seen only for D0–D1 grade (Fig. 2b).

In the clinical assessment of tumor mass resected during surgery, 34 (36.9%) tumors showed stable disease, 12 (13.0%) showed progressive disease, 41 (44.6%) showed partial response, and four (4.3%) showed complete response (Fig. 3a). And again, in fast proliferating tumors, greater inhibition in tumor proliferation rate (reduction of pretreatment BrdUrd LI value >50%) was observed in fast than in slowly proliferating tumors; however, this difference was not statistically significant (Fig. 3b). As the observed correlation between clinical assessment and SPF was weaker than for BrdUrd LI, the data were not shown. Partial and total tumor regression was observed in 45 (48.9%) tumors. However, tumor proliferation status was not in agreement with the kind of surgery. Sphincter-preserving surgery was performed in 51 out of 92 patients: in

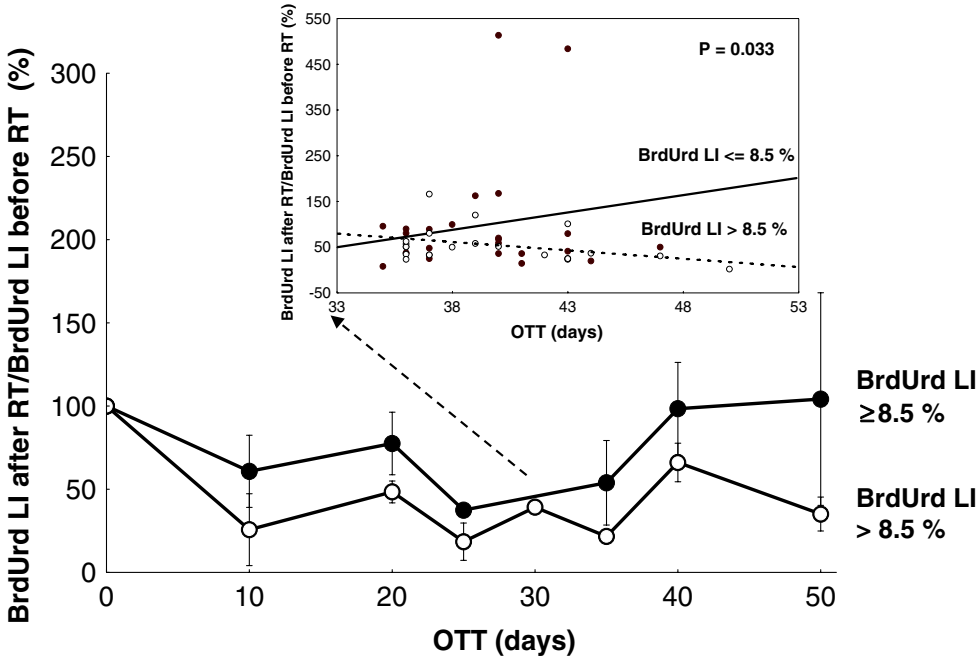

Figure 1 The association between biological tumor response for slowly (BrdUrd LI≤8.5%; closed symbol) and faster proliferating tumors (BrdUrd LI>8.5%; open symbol) and overall treatment time. Insert shows linear regression performed separately for each of the tumor subgroups for OTT>30 days. *P* value shows difference between two correlation coefficients.

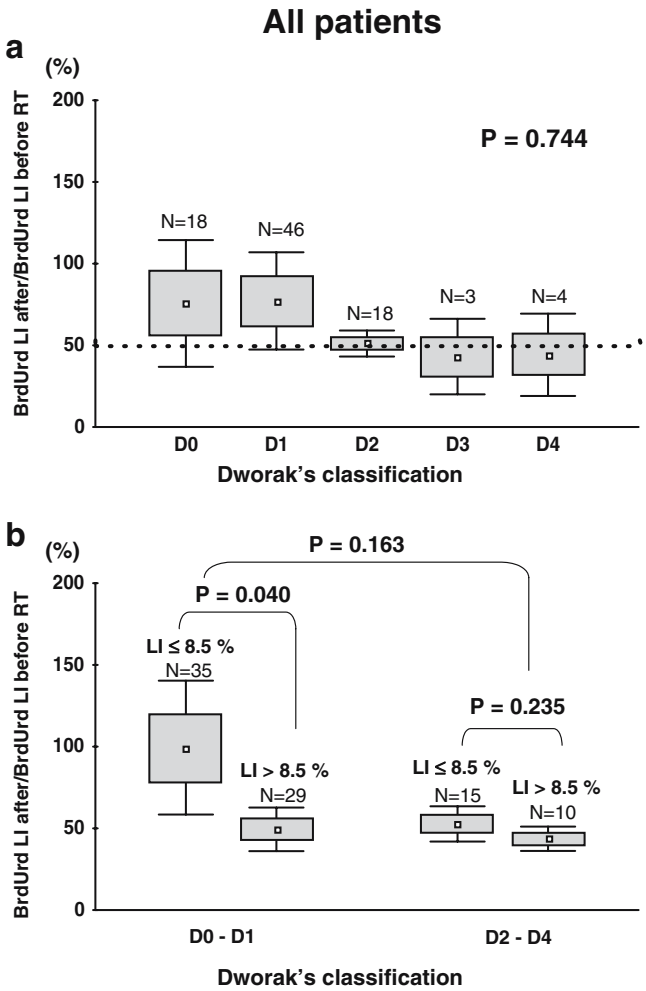

Figure 2 Association between biological and pathological assessment (Dworak classification) of early tumor regression for (a) total group of patients and (b) for slowly (BrdUrdLI≤8.5%) and fast proliferating (BrdUrdLI>8.5%) tumors. Mean values±SE are shown. For stages D0–D1, statistically significant lower inhibition of tumor cell proliferation after RT was observed for slowly than fast proliferating tumors.

22 (23.9%) fast proliferating and in 29 (31.5%) slowly proliferating tumors.

Discussion

This study provides evidence of a clinically significant biological effect of a short preoperative course of RT on tumor proliferation rate. The impact of irradiation on biological tumor response was assessed by BrdUrd LI, SPF, and the degree of subsequent pathologic and clinical down-staging of the tumors after surgery. The study showed differences in the pretreatment proliferation rate of the tumor. Mean BrdUrd LI before RT was equal to 8.5% and ranged from 1 to 24.2%. Mean SPF was 22.0% and ranged from 3.8 to 49.9%. The proportion of cells in S-phase as estimated by the DNA content overestimates the labeling index determined by the uptake of BrdUrd. This may be so because the exposure time is quite short and there may be subpopulations in the tumors that are synthesizing DNA at a very slow rate, or there may indeed be cells with an S-phase DNA content that are not synthesizing DNA (as a result of nutrient or oxygen supply, lack of growth factors, inadequate vascularity).

Mean value of the BrdUrd LI obtained in this study was lower than the one estimated by Bergstrom et al.[21], Palmqvist et al.[22], and Terry et al.[23], and can be explained by a different method used by these authors: in vivo incorporation of iodouridine/bromodeoxyuridine, which can cause longer exposure of the tracers to S-phase cells. The differences in the LI value might be caused also by heterogeneity in proliferation within the tumor. It was shown by Bergstrom et al.[21] that rectal tumors are polarized, having the superficial surface toward the lumen of the gut and the other toward deep structures facing

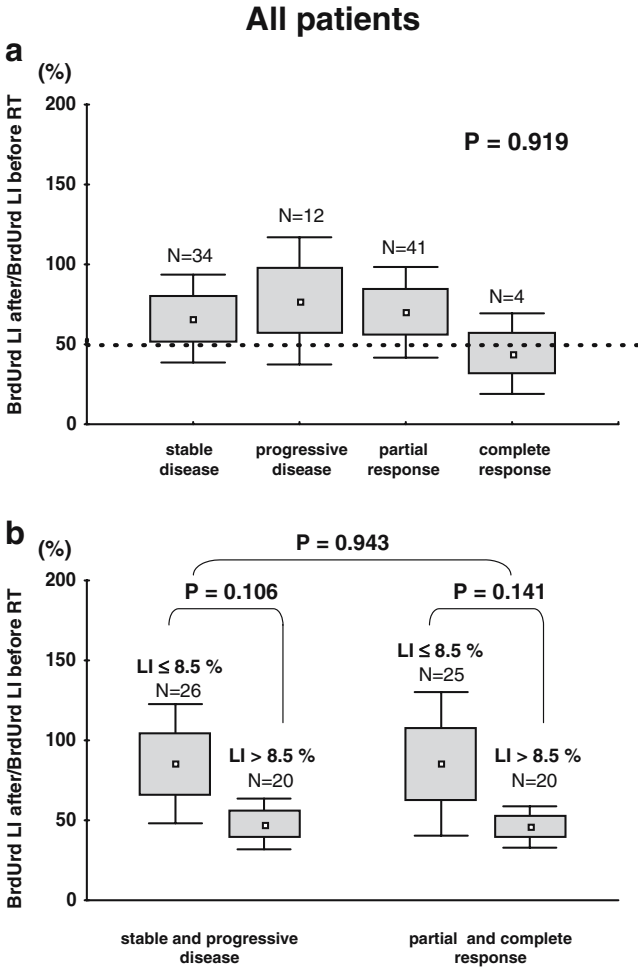

Figure 3 Association between biological and clinical assessment of early tumor regression after RT for all tumors (a) and separately for slowly and fast proliferating tumors (b). Mean value±SE are shown.

totally different environments. Apart from Bergstrom et al., none of the above-mentioned authors gave account of site from where the tumor samples were taken. In each tumor analyzed by us, all the samples were taken from the same region, i.e., the bottom part of the mass.

In our study, pretreatment BrdUrd LI or SPF was not predictive for early clinical and pathologicl tumor response, probably because of different tumor microenvironment. However, BrdUrd LI after/before RT ratio gave information on the different significant biological processes that take place after irradiation, and have impact on cell death like redistribution, repopulation, and reoxygenation.

BrdUrd LI after RT decreased to mean 4.1% independently of the time interval between RT and surgery. Magnitude of LI reduction after RT was correlated with tumor proliferation rate. Greater reduction of BrdUrd LI value was observed in fast proliferating (LI >8.5%) tumors (to mean 46% of the pretreatment value) than in slowly (LI ≤8.5%) proliferating tumors (to mean 85.3% of pretreatment value). What then is the justification for better RT response of fast proliferating tumor cells? According to current knowledge on tumor proliferation, radiation therapy should preferentially inactivate rapidly dividing cells, leaving behind a population biased toward slow proliferation. However, recruitment is a known effect of cytotoxic treatment, and new cells from quiescent cell populations are recruited into active proliferation after irradiation. Probably, slowly proliferating tumors might have greater propensity to recruit cells into rapid cycle in response to treatment than fast proliferating tumors, which might have little reserve capacity for further accelerating their cell cycle[24]. That might be why we observed acceleration of proliferation rate in slowly proliferating tumors from 5 weeks after RT (basing on after/before RT BrdUrd LI ratio), which followed temporary reduction of the number of DNA-synthesizing cells, 4–5 weeks after the start of RT. Accelerated proliferation was confirmed by increased S-phase fraction. However, better biological tumor responsiveness of fast proliferating tumors on cellular level did not find confirmation on tissue level that is in surgery because a fewer number of sphincter saving resections were performed in patients with fast (22) than those with slowly proliferating tumors (29).

Regression of rectal carcinoma after preoperative irradiation varies, likely reflecting differences in the physical and biologic properties of these tumors. Apart from biological characteristics discussed here, tumor down-staging depends on the total irradiation dose, the fractionation, and the interval between irradiation and surgery[25]. We showed association of tumor proliferation rate after RT with tumor response basing on BrdUrd LI. SPF, considered as a less sensitive method of tumor proliferation, did not show such a correlation. The after/before radiotherapy BrdUrd LI ratios correlated, however nonsignificantly, with the degree of pathologic and clinical down-staging, which indicates that more radiation-induced cell death occurred in tumors that expressed high levels of BrUrd LI, or that an increased rate of tumor clearance occurred in more rapidly proliferating tumors. This effect was reflected by significantly higher incidence of apoptosis observed after RT only in fast proliferating tumors (4.1% vs 11.1%; P=0.000). However, patients having tumors with LI >8.5% did not show higher rate (11.2%) of tumor pathological down-staging (D2–D4) than patients with BrdUrd LI ≤8.5% (16.8%) tumors, which may be suggestive of significant impact on tumor response also by biological processes other than proliferation. In the Spanish study[26], high proliferative activity of rectal cancer, as determined by PCNA immunostaining, was predictive of response to preoperative chemoradiotherapy. Willett et al.[27], in the same tumor type treated with higher RT dose (47–52 Gy) and 5 FU, showed that patients having tumors with extensive Ki-67 staining had also a higher rate of tumor down-staging (36%) 4–6 weeks after treatment than patients with minimal to moderate Ki-67 staining tumors (22–23%). These authors show that elevated postirradiation tumor proliferative activity correlated strongly with improved survival[28]. These authors, in contrast to our study, did not consider the proliferation profile of pre- and postirradiation for individual patients. The correlation of down-staging and higher survival rates was also found by other authors[29,30].

In our study, even in totally regressed tumors (D4), the percentage of the after/before radiotherapy BrdUrd LI was about 50%, which may not indicate tumor but normal cell proliferation, mainly a fraction of activated fibroblasts or cycling endothelial cells in capillaries high in colorectal carcinoma[31]. Our study showed complete pathologic response (D4) similar to that in a Norwegian study (4.5%)[32,] where histological tumor slides were analyzed after treatment with a dose of 31.5 Gy in 18 fractions and 2–3 weeks interval between RT and surgery. However, it should be stressed that in this study, a high incidence (31.3%) of recurrences was observed at late follow-up. Our analysis showed that patients having fast proliferating tumors, as assessed by BrdUrdLI, experienced higher rates of regression than patients with slowly proliferating tumors, which could suggest a more frequent possibility of performing sphincter-preserving procedures in these tumors. However, this was not confirmed in surgical procedures. Therefore, we do not know yet if pretreatment BrdUrd LI assessment will be a good predictor for a locoregional failure. Berger et al.[25], analyzing tumor sterilization after preoperative RT for rectal cancer, did not find a predictive factor for complete pathological response among such factors as age, sex, tumor stage, and pathologic grade. However, they found favorable influence of higher doses (>44 Gy) on pathologic stage.

There is no known optimal time for the interval between RT and surgery. The Swedish group keeps the interval at about a week; however, in other institutions, using longer RT treatments and higher total dose, longer intervals—4 to 6 weeks were adopted[14,25]. The main reason for a longer interval is tumor regression, which makes sphincter preservation possible. Similar to Francois et al[14], we observed higher clinical and pathologic response rate after longer interval between RT and surgery. However, these authors[14] showed nonsignificantly better overall survival for patients treated with shorter interval. Withers and Haustermans[33] estimated the interval between long course of fractionated RT (40–54 Gy) and surgery and stated that the interval is not critical to either local recurrence or distant metastases. The authors offered the following arguments: the tumor cells do not disseminate until the primary tumor is large enough to be clinically detectable (probably 80% of patients whose rectal tumors have not metastasized to lymph nodes will be free of metastases). Irradiation with a dose of 40 Gy in 2 Gy fractions (equivalent to 25 Gy in five fractions) reduces tumor cell survival by about six decades, e.g., from 10^{10} to 10^{4} cells. However, we have to remember that although the short overall treatment duration in the 25 Gy in five-fraction regimen provides a radiobiological advantage, this is a relatively low dose[34], which causes about a 66% reduction in the rate of local recurrence[11]. A retrospective analysis of published results of preoperative radiation therapy for rectal cancer showed that local control probability curves were displaced toward higher doses as the overall duration of preoperative radiation therapy was increased[15]. Therefore, longer intervals between short RT schedule (25 Gy) and surgery may be inappropriate in case of patients with incomplete resection (cut-through) of primary tumor, in whom the average subclinical cancer cell burden increases during long interval. Also, subclinical disease beyond the future surgical margins, may be a potential target for future recurrences. Longer intervals after short RT can be dangerous because of potential subclinical tumor, which may grow more quickly than primary tumor[15,33], the and risk of developing distant metastases. If we imply that moderately differentiated adenocarcinoma cells have different metastatic and proliferative activities from poorly differentiated cancer cells, which was shown by Taniyama et al[35], then we could have an indication to adjuvant chemotherapy for patients with differentiated tumors. The authors[35] indicated that moderately differentiated cancer cells are associated with hematogenous metastases to the liver, and the loss of tubular formation of cancer cells in poorly differentiated tumors may be fundamentally related to lymph node metastases and infiltrative growth. Therefore, particularly in patients with moderately differentiated and slowly proliferating tumors, adjuvant chemotherapy could be suggested after OTT shorter than 4 weeks, to prevent developing metastases to the liver.

In conclusion, our study shows that pretreatment BrdUrd LI or SPF were not predictive for early clinical and pathologic tumor response. After/before BrdUrd LI ratios showed inhibition of proliferation in responsive tumors, but this was not reflected in the number of sphincter preserving procedures performed. As 1 month after RT, accelerated proliferation of tumor cells is observed only in slowly proliferating tumors, we think that longer interval between RT and surgery is inadvisable.

If late tumor response confirms that patients having tumors with increased proliferative activity have statistically significantly less recurrences and improved survival rates compared with patients with less proliferative tumors, then we will be able to suggest a prognostic factor for individual rectal cancer patient, and a basis for selection to postoperative adjuvant chemotherapy.

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Conflicts of Interest None.

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Risk of Fecal Diversion in Complicated Perianal Crohn's Disease

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Abstract The purpose of the study was to determine the overall risk of a permanent stoma in patients with complicated perianal Crohn's disease, and to identify risk factors predicting stoma carriage. A total of 102 consecutive patients presented with the first manifestation of complicated perianal Crohn's disease in our outpatient department between 1992 and 1995. Ninety-seven patients (95%) could be followed up at a median of 16 years after first diagnosis of Crohn's disease. Patients were sent a standardized questionnaire and patient charts were reviewed with respect to the recurrence of perianal abscesses or fistulas and surgical treatment, including fecal diversion. Factors predictive of permanent stoma carriage were determined by univariate and multivariate analysis. Thirty of 97 patients (31%) with complicated perianal Crohn's disease eventually required a permanent stoma. The median time from first diagnosis of Crohn's disease to permanent fecal diversion was 8.5 years (range 0–23 years). Temporary fecal diversion became necessary in 51 of 97 patients (53%), but could be successfully removed in 24 of 51 patients (47%). Increased rates of permanent fecal diversion were observed in 54% of patients with complex perianal fistulas and in 54% of patients with rectovaginal fistulas, as well as in patients that had undergone subtotal colon resection (60%), left-sided colon resection (83%), or rectal resection (92%). An increased risk for permanent stoma carriage was identified by multivariate analysis for complex perianal fistulas (odds ratio [OR] 5; 95% confidence interval [CI] 2–18), temporary fecal diversion (OR 8; 95% CI 2–35), fecal incontinence (OR 21, 95% CI 3–165), or rectal resection (OR 30; 95% CI 3–179). Local drainage, setons, and temporary stoma for deep and complicated fistulas in Crohn's disease, followed by a rectal advancement flap, may result in closing of the stoma in 47% of the time. The risk of permanent fecal diversion was substantial in patients with complicated perianal Crohn's disease, with patients requiring a colorectal resection or suffering from fecal incontinence carrying a particularly high risk for permanent fecal diversion. In contrast, patients with perianal Crohn's disease who required surgery for small bowel disease or a segmental colon resection carried no risk of a permanent stoma.

Keywords Fecal diversion · Crohn's disease · Perianal abscesses · Fistulas

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Introduction

Crohn's disease was initially described as a nonspecific inflammatory bowel disease, affecting mainly the terminal ileum and characterized by a subacute or chronic necrotizing and cicatrizing inflammation.[1] Eventually, gastrointestinal Crohn's disease became recognized as a full-thickness disease of the gastrointestinal wall that may affect the entire gastrointestinal tract, including the perianal region.[2–6]

Perianal lesions are common in patients with Crohn's disease.[7–13] Clinical manifestations vary from asymptomatic skin tags to severe, debilitating perianal destruction and sepsis. Asymptomatic perianal lesions require no treatment, but

because they become painful and disabling, they may require surgical treatment. Surgical management needs to be conservative and should focus on the drainage of septic sites, preserving sphincter function and palliating symptoms.[10–13] Medical management has had some success in improving symptoms, but as yet, it has not been able to eliminate most perianal complaints permanently.[14,15]

Fecal diversion was successfully used to achieve remission in colonic Crohn's disease. Moreover, it was utilized to allow severe perianal disease to settle, thereby avoiding proctectomy.[16–19] However, restoring the intestinal passage carries the risk of recurrent perianal disease activity, possibly resulting in a decreased quality of life compared to the situation with fecal diversion.

We investigated the overall risk of a permanent stoma in patients with severe perianal Crohn's disease and tried to identify risk factors predicting permanent stoma carriage.

Methods

Patients

A total of 102 consecutive patients with Crohn's disease presented with the first manifestation of a perianal fistula or a perianal abscess in our outpatient department between 1992 and 1995. Patients were investigated in Trendelenburg's position by perianal inspection, proctoscopy, rectoscopy, and rigid sigmoidoscopy. Endoanal ultrasound was performed in case of suspected perianal abscess formation, and MRI was conducted of the pelvic floor in case of complicated fistulizing disease or intrapelvic abscess formation. All patients were documented prospectively. Follow-up data of 97 patients (95%) were available by a standardized questionnaire mailed to the patients and by a standardized chart review. There were 50 female and 47 male patients (ratio 1.06:1) with a median age of 23 years (range 8–51 years). Patients were evaluated with respect to the recurrence of perianal abscesses, fistulas, or surgical treatment of Crohn's disease over the years. The median interval between the first diagnosis of Crohn's disease and last follow-up was 16 years (range 8–37 years). Four patients had isolated small intestinal disease, 11 patients had isolated colonic disease, and 82 patients had small intestinal and colonic disease.

The abscess location was categorized as subcutaneous, intersphincteric, deep perianal, ischiorectal, and above the pelvic floor. Abscess formations were categorized into simple (subcutaneous, intersphincteric, deep perianal, and ischiorectal, circular extension less than 90°, pelvic floor not involved) and complicated (circular extension more than 90° [horse shoe abscess] or pelvic floor involved).

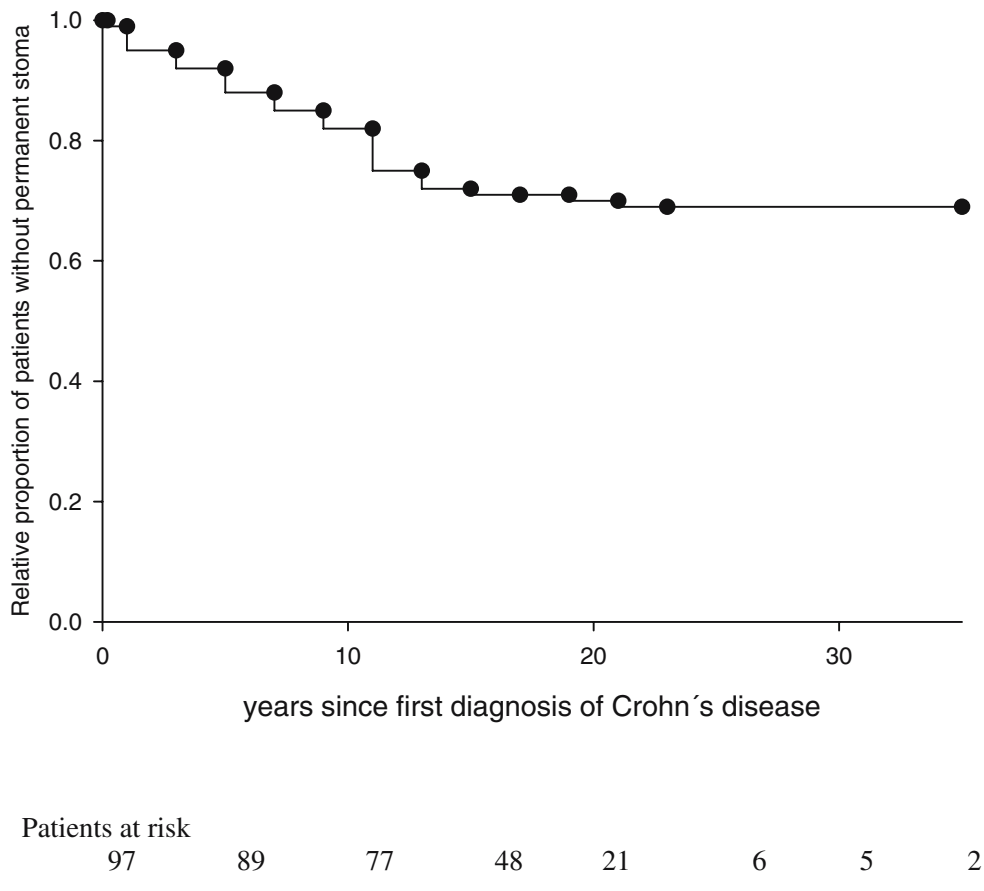

Figure 1 Relative proportion of patients without permanent stoma in complicated perianal Crohn's disease (n=97) during follow-up.

Table 1 Patients with First Manifestation of Complicated Perianal Crohn's Disease (n=97) and the Rate of Fecal Diversion During Follow-up

	Patients	Temporary Stoma	Permanent Stoma
Overall	97	51 (53%)	30 (31%)
Abscess formation	75	32 (43%)	21 (28%)
Simple abscess formation	33 (44%)	13 (39%)	7 (21%)
Complex abscess formation	42 (56%)	23 (55%)	15 (36%)
Fistulas	88	51 (58%)	26 (30%)
Simple perianal fistulas	42 (48%)	17 (40%)	8 (19%)
Complex perianal fistulas	46 (52%)	34 (74%)	23 (50%)
Rectovaginal fistulas	26 (54% of ♀)	18 (69% of 26)	14 (54% of 26)

Overlap between abscess formation and presence of fistulas exists, and abscesses led to fecal diversion in combination with fistulas only.

Fistulas were classified according to Parks et al.[20] into subcutaneous, intersphincteric, extrasphincteric, transsphincteric, rectovaginal, and suprasphincteric, as described previously.[21] We divided fistulas into simple fistulas (no more than two perianal openings) and complex fistulas (rectovaginal, three or more perianal openings).

A variety of factors, such as sex of the patient, perianal fistula, rectovaginal fistula, abscess formation, anal stricture, fecal incontinence, or abdominal surgery were evaluated with regard to their predictive character for permanent stoma carriage by univariate and multivariate analysis.

Statistical Analysis

Kaplan–Meier analysis using a log-rank test was used for comparing risk rates over time. Factors that might influence permanent fecal diversion were analyzed using the chi-square test. Fisher's exact test was used for univariate analysis and multiple logistic regression and Wald's test for multivariate analysis. Subgroup analysis was performed for rectovaginal fistulas, as present in female patients only. Data are given as numbers of cases and percentages or median and interquartile ranges. A $P<0.05$ was considered as significant.

Results

Overall Risk of Permanent Fecal Diversion

Thirty of 97 patients (31%) with perianal Crohn's disease eventually required a permanent stoma. Nineteen patients were female and 11 male (ratio 1.73:1). The median time from first diagnosis of Crohn's disease to permanent fecal diversion was 8.5 years (range 0–23 years; Fig. 1). Increased rates of permanent fecal diversion were observed in 53% of patients with previous temporary fecal diversion, in 54% of patients with complex perianal fistulas, in 54% of female patients with rectovaginal fistulas, and in 83% of patients with fecal incontinence (Table 1). Patients who required subtotal colon resection (60%), left-sided colon resection (83%), or rectal resection (93%) needed a permanent stoma at high rates (Table 2).

Abscess Formation

Seventy-five of 97 patients (77%) had at least one perianal abscess at first presentation or during follow-up. Surgical therapy for abscesses consisted of seton drainage, mushroom catheter drainage, or incision and drainage, as described previously.[21] A permanent fecal diversion because of recurrent abscess formations, always in combination with fistula problems and perianal sepsis, became necessary in 21 of 75 cases (28%). Simple abscess formations occurred in 33 patients, and 7 of those patients

Table 2 Abdominal Procedures and the Rate of Fecal Diversion During Follow-up in Patients with Complicated Perianal Crohn's Disease (n=97)

Small Bowel Procedures	Patient Number	Permanent Stoma (% of Patients)
Stricturplasty	7	0
Small bowel resection because of stenosis	23	0
Small bowel resection because of enteroenteric fistula	7	0
Anastomosis resection because of inflammatory stenosis	30	0
Stoma revision	4	0
Large bowel procedures		
Segmental colon resection	14	0
Right-sided colon resection	20	4 (20)
Ileocecal resection	68	24 (35)
Subtotal colon resection	35	21 (60)
Left-sided colon resection	6	5 (83)
Rectal resection	13	12 (92)

Patients that required small bowel resections carried no risk of fecal diversion, whereas patients with colon resections carried an increased risk of fecal diversion.

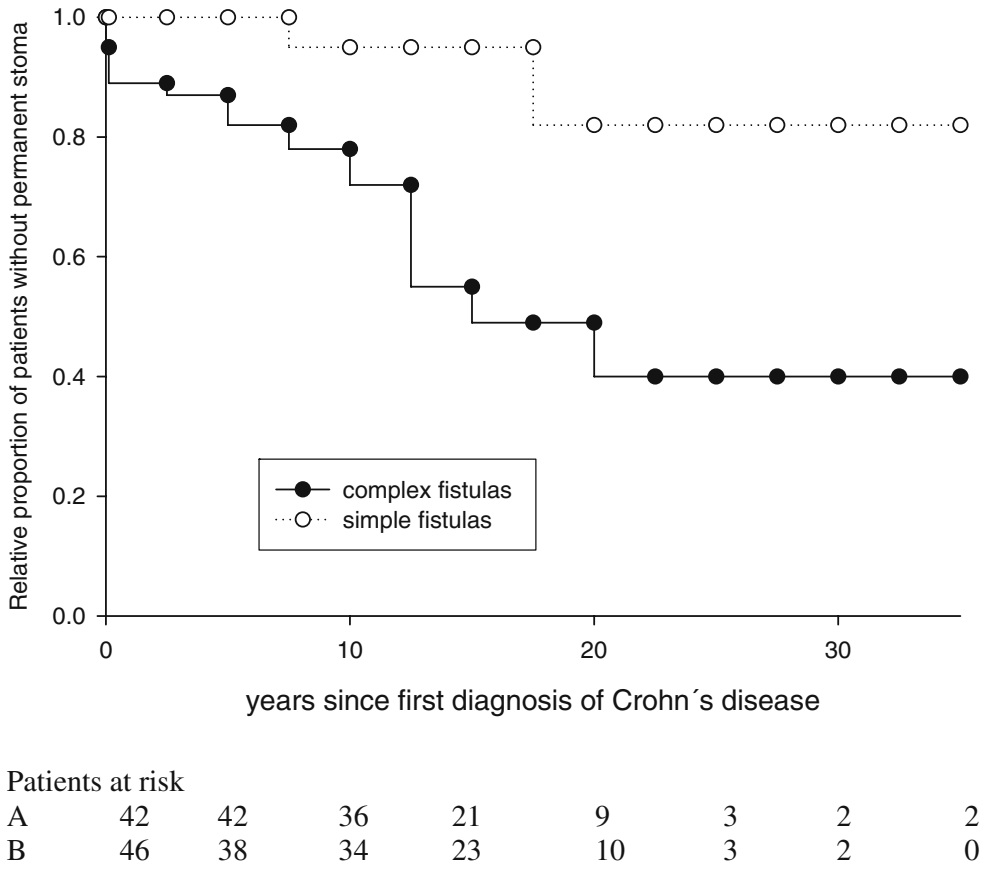

Figure 2 Relative proportion of patients without permanent stoma in complicated perianal Crohn's disease with simple (n=42) and complex (n=46) fistulas during follow-up. The presence of a complex fistula significantly increased the risk of permanent fecal diversion (P<0.001).

Table 3 Abdominal Procedures per Patient and Percentage of Patients with Abdominal Surgery

Abdominal Procedures	Median	(25–75%)	Patients with Abdominal Surgery (%)	*P* Value
Permanent fecal diversion	3	(2–4)	100	P<0.05
Without permanent fecal diversion	1	(1–3)		
Temporary fecal diversion	3	(2–4.25)	80	P<0.05
Without temporary fecal diversion	1	(0–2.5)		
Anal stricture	2	(1–4)	60	n.s.
Without anal stricture	2	(1–3)		
Incontinence	2	(2–4.5)	10	n.s.
Without incontinence	2	(1–3)		

Patients with Crohn's disease and complicated perianal fistulas who required temporary or permanent stoma had more abdominal procedures than patients who did not need a stoma, whereas patients with anal stricture or fecal incontinence had no increased abdominal procedure rate (the number of abdominal procedures per patient is given as median with interquartile ranges). Abdominal surgery and fecal diversion correlated on univariate analysis (P<0.05).

(21%) required permanent fecal diversion (Fig. 2). Complex abscess formations were present in 42 patients, with permanent fecal diversion being necessary in 14 cases (33%; Table 1).

Perianal and Rectovaginal Fistulas

Perianal fistulas affected 88 of 97 patients (91%), including 26 female patients with rectovaginal fistulas. Symptomatic fistulas with abscess formation were treated by simple drainage procedures and provided with a seton. Azathioprine therapy was tried if purulent secretion persisted. Infliximab was rarely used in recent years at the discretion of the referring gastroenterologist. Overall, permanent fecal diversion became necessary in 26 of 88 patients (30%). Forty-two patients (48%) had simple fistulas, whereas 46 patients (52%) had complex fistulas. Of these, permanent fecal diversion was documented in 14 patients (54%), whereas simple fistulas eventually required a permanent stoma in only 8 cases (16%). Twenty-six of 48 female patients had rectovaginal fistulas, of which 14 (54%) eventually required permanent fecal diversion (Table 1).

Thirty-four of 97 patients (35%) developed anal strictures, whereas fecal incontinence was documented in 12 patients (12%) during the follow-up. In 14 of 34 patients (41%) with anal stricture, a permanent fecal diversion became necessary,

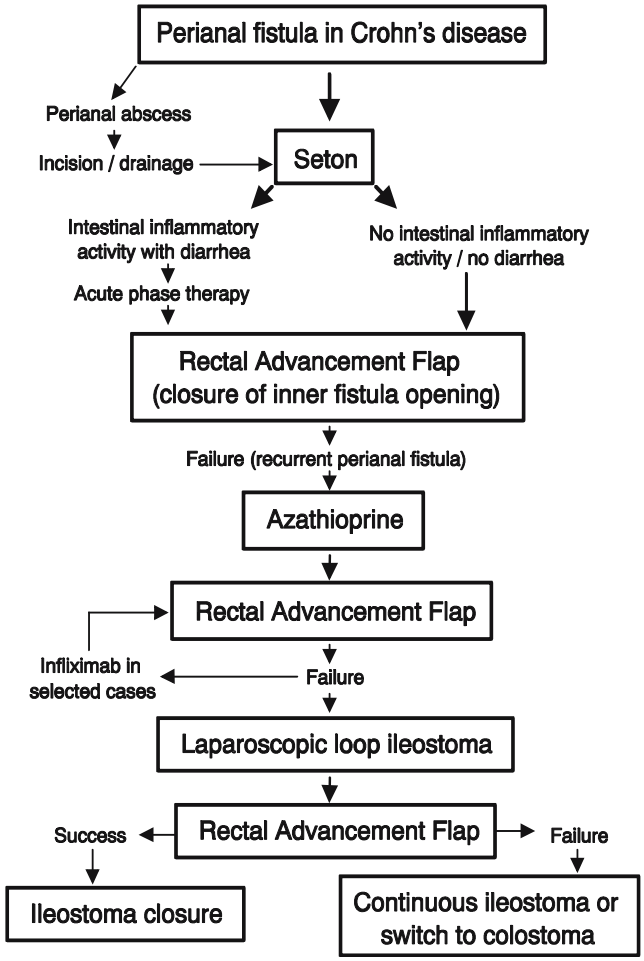

Figure 3 Treatment algorithm for patients with complicated perianal Crohn's disease.

whereas 10 of 12 patients (83%) suffering from fecal incontinence required a permanent stoma.

Abdominal Surgery

Eighty-three of 97 patients with perianal Crohn's disease (86%) underwent abdominal surgery at least once during follow-up because of Crohn's disease activity, with a total of 227 abdominal procedures being performed. In 68 of 227 operations (29%), intestinal stenosis required surgery. Segmental colon resection was performed 108 times (46%), whereas subtotal colectomy for fulminant colitis was performed 35 times (15%). One patient required surgery because of a fistula carcinoma. Patients with complicated perianal Crohn's disease who required a small bowel resection carried no risk of permanent fecal diversion, whereas the majority of patients with left-sided colon resection, subtotal colon resection, or rectal resection needed permanent fecal diversion (Table 2). Patients that needed abdominal surgery repeatedly carried an increased risk for a permanent stoma (permanent stoma rate: three or more abdominal operations, n=20, 50%; less than two abdominal operations, n=20, 15%; P<0.043). Patients with permanent fecal diversion had undergone previous abdominal surgery three times as often as those patients without (P<0.05; Table 3). Eventually, 17 patients (18%) needed proctectomy, of which 13 were female patients with rectovaginal fistulas. In 14 patients with a permanent stoma, a rectal stump remained in place and was controlled at yearly intervals. Patients with complicated perianal Crohn's disease and large bowel resection carried a significantly increased risk of permanent fecal diversion compared to patients with complicated perianal Crohn's disease and small bowel resection (48 vs 0%, P<0.001) (Fig. 3).

Temporary Fecal Diversion

Temporary fecal diversion, done mostly by loop ileostomy, became necessary in 51 of 97 patients (53%). Increased rates of temporary fecal diversion were observed in 55% of patients with complex abscess formations, including those with severe perianal sepsis, in 77% of patients with complex perianal fistulas, and in 69% of female patients with rectovaginal fistulas. In 24 of 51 patients (47%) the temporary stoma could be removed after perianal disease had subsided. Fistulas were closed in these patients by rectal advancement flaps,[23] whereas cutting setons, fistulectomy, or infliximab infusions were not employed in these patients.

Risk Factors Predictive of a Permanent Fecal Diversion

Univariate Analysis

Complex perianal fistulas (P<0.04), fecal incontinence (P< 0.001), and rectovaginal fistulas in female patients (P<0.001)

Table 4 Risk Factors for Permanent Fecal Diversion by Univariate and Multivariate Analysis in Patients with Complicated Perianal Crohn's Disease

Risk Factors	Univariate Analysis		Multivariate Analysis		
	Permanent Fecal Diversion (%)	*P* Value	OR	95% CI	*P* Value
Rectal resection	92	P<0.001	30	5–179	P<0.002
Fecal incontinence	83	P<0.001	21	3–165	P<0.02
Subtotal colectomy	60	P<0.001			
Rectovaginal fistulas	54	P<0.001			
Temporary fecal diversion	51	p=0.001	8	2–35	P<0.02
Complex perianal fistulas	54	P<0.04	5	2–18	P<0.03

carried an increased risk for a permanent stoma. Patients with high rates of abdominal surgery had a significantly increased risk for fecal diversion, whereas the frequency of abdominal surgery was not influenced by the presence of anal stricture or fecal incontinence (Table 3). The need for subtotal colon resection ($P<0.001$), rectal resection ($P<0.001$), or temporary fecal diversion ($P=0.001$) also resulted in an increased risk of permanent fecal diversion. A variety of factors did not increase the risk of a permanent stoma, such as sex of the patient, anal stenosis, perianal abscesses, and abdominal surgery, excluding subtotal colon and rectal resection (Table 4).

Multivariate Analysis

According to multivariate analysis, complex perianal fistulas ($P<0.03$), fecal incontinence ($P<0.02$), temporary fecal diversion ($P<0.02$), or rectal resection ($P<0.002$) still carried a significantly increased risk for permanent fecal diversion (Table 4).

Discussion

Perianal disease is a feature of Crohn's disease that afflicts approximately one third of patients, but prevalence rates vary between 8 and 90%.[19] Patients with colonic involvement will have perianal disease in more than 50% of cases, whereas patients with small bowel disease are affected in less than 20%.[24] Perianal Crohn's disease can present as minor lesions, such as skin tags, skin excoriations, and fissures, which rarely need surgical treatment. In contrast, perianal fistulas often result in abscesses or perianal sepsis, requiring urgent surgery, and fistulas and abscesses are considered as suppurative complications of perianal Crohn's disease.[25] We conducted surgery as conservatively as possible because sphincter function should be preserved as much as possible.[19,22,23] Throughout the study period, 77% of patients developed abscess formations, which is considerably more than the 48% rate reported previously with a shorter mean follow-up of 32 months.[22]

The incidence of perianal fistulas in Crohn's disease is somewhat lower, affecting 10–34% of patients.[26] Healing rates of 60–70% in patients with Crohn's disease and perianal fistulas were reported in earlier series.[21,26–28] However, these series contained a large proportion of simple fistulas, whereas most of our patients had complex transsphincteric or rectovaginal fistulas and fistulas that did not heal through conservative treatment. Perianal fistulas that resulted in abscess formation were drained surgically, and in case of massive purulent secretion or perianal sepsis, oral antibiotics were used additionally. Setons were put into place to prevent recurrent abscess formation, a treatment that is well known as a possible means for controlling perianal sepsis and preventing recurrent abscess formation.[19,21–23,29] We did not use cutting setons nor fistulotomy for transsphincteric fistulas, as fecal incontinence may succeed.[19,22,23] Infliximab was successfully shown to reduce fistula secretion, and outer fistula openings may heal.[30] However, fistula tracks persist with varying degrees of residual inflammation, which may cause recurrent fistulas and perianal abscesses.[31]

Rectal advancement flaps can be used to close the inner opening of transsphincteric or rectovaginal fistulas when perianal disease has abated and the rectal mucosa is not inflamed. However, fistulas eventually recurred in about one third of patients after a mean follow-up of 19 months, and some patients developed new fistulas.[23] Hyman[32] reported an initial 79% healing rate in a series of 14 patients with Crohn's disease and perianal fistulas, but observed longer term success in only 50% of patients. Our current approach is to use rectal advancement flaps for transsphincteric fistulas while delaying surgery if there is an acute flare of Crohn's disease, in particular, if proctitis is present.[23,33] Perianal fistulas in Crohn's disease closed by a rectal advancement flap have a recurrence rate of 50–60%, but can be attempted repeatedly.[23,34] If a second rectal advancement flap fails, the failure rate increases up to 75%,[34] and a temporary stoma is suggested to the patient before a third attempt is made. By this approach, we were able to heal perianal fistulas in 24 out of 51 patients (47%) who required a temporary stoma. In a previous study, diversion was the most powerful factor influencing healing according to multiple regression analysis.[23] The chances of a symptomatic fistula recurrence were increased without a stoma (52% vs 14%, 21), and patients with Crohn's colitis carried an increased risk of fistula recurrence.[23]

A particular problem is rectovaginal fistulas, which almost always open at the dentate line.[19] They occur in 3–10% of patients with Crohn's disease.[19] In our series, 54% of female patients had rectovaginal fistulas, indicating that a large patient proportion had complex perianal fistulas; referral bias might have contributed to this high proportion of rectovaginal fistulas, as our outpatient clinic for Crohn's disease is well known regionally. Rectovaginal fistulas carry a poor prognosis,[18] and a 70% recurrence rate was observed 24 months after a rectal advancement flap was performed.[23] In the experience of Keighley et al.[35], 11 of 13 patients with rectovaginal fistulas required proctectomy with a permanent stoma. In our series, 8 out of 26 rectovaginal fistulas healed by a rectal advancement flap. Eighteen patients required a temporary stoma, of which four could be removed after a rectal advancement flap was tried again successfully (overall healing rate 12 of 26, 46%), resulting in a permanent stoma rate of 14 of 26 patients (54%). Healing rates of rectovaginal fistulas

associated with Crohn's disease vary widely, and low patient numbers are usually reported.[18] In the Cleveland clinic, 16 of 37 rectovaginal fistulas (43%) healed using an endorectal advancement flap, but patients not having Crohn's disease were included in the study.[36] In low anovaginal fistulas, higher healing rates of up to 68% were reported in patients with Crohn's disease.[37] Recurrent rectovaginal fistulas were shown to heal after repeated rectal advancement flap procedures were conducted at about the same rate even in Crohn's disease, but surgery should be delayed for at least 3 months after a previous repair,[38] which is standard policy at our clinic. It is interesting to note that Halverson et al.[38] reported that the presence of a diverting stoma significantly increased the fistula recurrence rate (67 vs 50%).

After years of perianal or transvaginal pus secretion and recurrent abscess formations, patients are often tired of the suffering involved. Antibiotics, azathioprine, or 6-mercaptopurine may be used successfully in suppurative perianal Crohn's disease.[15,18,38,39] In our department, this is routinely tried if perianal disease does not settle after surgical drainage is provided. However, azathioprine or 6-mercaptopurine are not tolerated by all patients and may also fail to relieve perianal Crohn's disease. In these cases, fecal diversion can be offered as a relatively minor procedure with low morbidity,[18] and might be performed laparoscopically in selected cases.[40] However, overall healing rates of perianal disease are only around 40%, with 87% of those being diverted eventually retaining their stoma.[18] We diverted 51 patients, of which 27 retained there stoma (53%), which compares favorably, but indicates a considerable risk for a permanent stoma if diversion is tried, and being a significant risk factor according to multivariate analysis in our series.

Perianal disease in combination with fecal incontinence might necessitate fecal diversion as well. Factors that may contribute to fecal incontinence in patients with Crohn's disease are reduced stool consistency, sphincter injuries after abscess incisions, and keyhole deformities after laying open perianal fistulas. The latter was reported to result in fecal incontinence in 5 of 27 patients with perianal fistulas in Crohn's disease,[41] which is why we did not use this technique or cutting setons in transsphincteric fistulas. We always incise perianal abscesses along a circular perianal line, meticulously preserving sphincter integrity. Nevertheless, fecal incontinence became prevalent in 12% of our patients during follow-up and was a significant predictor of permanent fecal diversion by multivariate analysis. Rectal advancement flap procedures may influence continence,[22] and a 9% rate of worsened continence was reported thereafter.[33] In particular, the risk of fecal incontinence was increased after flap repairs in patients with previous surgical fistula repairs,[33] but only 2 out of 12 patients with fecal incontinence had a previous rectal advancement flap repair in our study. A high rate of abdominal procedures was associated with an increased risk for a temporary or a permanent stoma, possibly reflecting high intestinal disease activity of Crohn's disease in these patients. All 30 patients that ended with a permanent stoma had frequently undergone abdominal procedures (median of three procedures).

Because of the suffering involved and unsuccessful previous attempts to heal perianal fistulas, about half of our patients eventually opted for temporary ileostomy, being brought into contact with a stoma nurse and stoma carriers with Crohn's disease before, and 31% of all patients remained with a permanent stoma. In general, the need for a stoma was reduced during recent decades in Crohn's disease,[43] but the overall long-term risk for a stoma in patients with Crohn's disease who require abdominal surgery was reported between 30 and 40%.[44,45] Fecal diversion remains an option to subside perianal disease activity, with an early response rate of about 70–80%.[46–48] Unfortunately, 75% of those patients eventually experienced a relapse, and the restoration of intestinal continuity was achieved in 10% only.[48] In 130 patients with surgically treated perianal Crohn's disease, a permanent stoma became necessary in 24%, and this rate increased to 53% in patients with Crohn's colitis.[45] In this light, considering that all of our patients had complicated perianal disease and almost all (93 of 97 patients, 96%) had colonic involvement, we judge a 31% permanent stoma rate as a success in a subset of patients carrying a particularly high risk for a stoma. Local drainage, setons, and, if not successful, a temporary stoma after a rectal advancement flap, resulted in closure of the stoma in 47% of the time, which is an improvement compared to previous studies where restoration of intestinal continuity was reported in only 10–40% of patients, with most studies providing the lower end percentages.[44,46–48] If perianal Crohn's disease was the indication for creating a stoma, stoma closure was successful in 2 out of 15 patients only (13%).[47]

Eventually, proctectomy became necessary in 18% of patients, which is in the range others have reported.[24,44,49,50] However, if the presence of colonic disease was considered separately, seven out of eight patients with complicated perianal Crohn's disease needed proctectomy, again indicating that an 18% proctectomy rate in our high-risk population is rather low. All of our patients who needed proctectomy had colonic disease, and 13 of 17 had a rectovaginal fistula.

In a recent study investigating the quality of life in patients with Crohn's proctocolitis, patients in remission had a health-related quality of life similar to controls. Patients with active disease had a reduced quality of life, and only the symptom index negatively predicted a reduced quality of life, whereas neither previous colonic surgery nor the presence of a stoma did.[51] Accordingly, carrying a stoma

does not necessarily mean a reduced quality of life, although a slight reduction in two out of eight domains (physical and emotional role) was detected.[51] However, in patients with perianal disease, the cumulative abscess rate during 3 years of follow-up and the symptomatic fistula recurrence rate with a mean follow-up of 22 months were both greatly reduced with a stoma (76 vs 13% and 52 vs 14%), indicating reduced suffering and need for surgery.[21,22]

In summary, patients with complicated perianal Crohn's disease, colonic involvement, and a high rate of abdominal procedures carried a significant risk for a permanent stoma. However, if the risk factors identified were taken into account, the rate of patients eventually requiring a permanent stoma seemed low and showed a decrease compared to previous studies, indicating that multiple treatment episodes and complex surgery, including temporary fecal diversion, might eventually heal at least some patients in this high-risk population, as was also observed by others.[50]

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Successful Internalization of a Chronic Biliary Cutaneous Fistula After Liver Transplantation: Deepithelializing the Fistula Tract

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Abstract Biliary cutaneous fistulas are uncommon sequelae after biliary surgery and can be a source of significant morbidity. We describe a liver recipient who developed a biliary cutaneous fistula secondary to hepatic artery thrombosis; this subsequently drained for over 7 years. Through a novel approach, using the transabdominal fistula tract as a conduit, the fistula skin opening was deepithelialized and anastomosed to a jejunal loop, internally draining the tract. For over 7 years postoperatively, this internal drainage procedure has continued to function effectively. This approach may have value in internalizing longstanding biliary cutaneous fistulas in well-selected patients in whom there is no existing biliary ductal system or the existing system anatomically does not lend itself to restoration of functional internal drainage through conventional approaches.

Keywords Biliary fistula · Liver transplantation

Introduction

Biliary cutaneous fistulas are uncommon sequelae after biliary surgery and hepatic trauma. Persistent biliary fistulas can be associated with local skin morbidity, malabsorption of fat soluble vitamins, steatorrhea, impaired wound healing, and sepsis as a result of fistula tract obstruction.[1] We describe a rare scenario in which a liver transplant recipient developed a biliary cutaneous fistula secondary to hepatic artery thrombosis. Through a novel approach, the fistula skin opening was deepithelialized and, using this transabdominal fistula tract as a conduit, anastomosed to a jejunal loop, thereby internally draining the fistula. This operative procedure, which has provided a successful long-term result, is discussed.

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Materials and Methods

Case Report

A 60-year-old man of Chaldean descent underwent orthotopic liver transplant for cirrhosis secondary to chronic alcohol use. His early postoperative course was complicated by hepatic artery thrombosis with necrosis of the extrahepatic biliary system. Because of sepsis and family issues, retransplantation was not a realistic option. Surprisingly, his graft remained viable with good metabolic function despite the absence of normal extrahepatic drainage. For 7 years subsequent to transplantation, his biliary drainage was managed with a U-tube connected to a bulb drain exiting the skin in the right subcostal region (Fig. 1). As a result, he suffered from severe malnutrition, pain, and skin breakdown. The persistent external drainage markedly affected his lifestyle, as the continuously draining bile required dressing changes over the exit site two to four times per day. The U-tube, frequently becoming obstructed with biliary sludge, required bimonthly replacement. Preoperative fistulogram (Fig. 2)

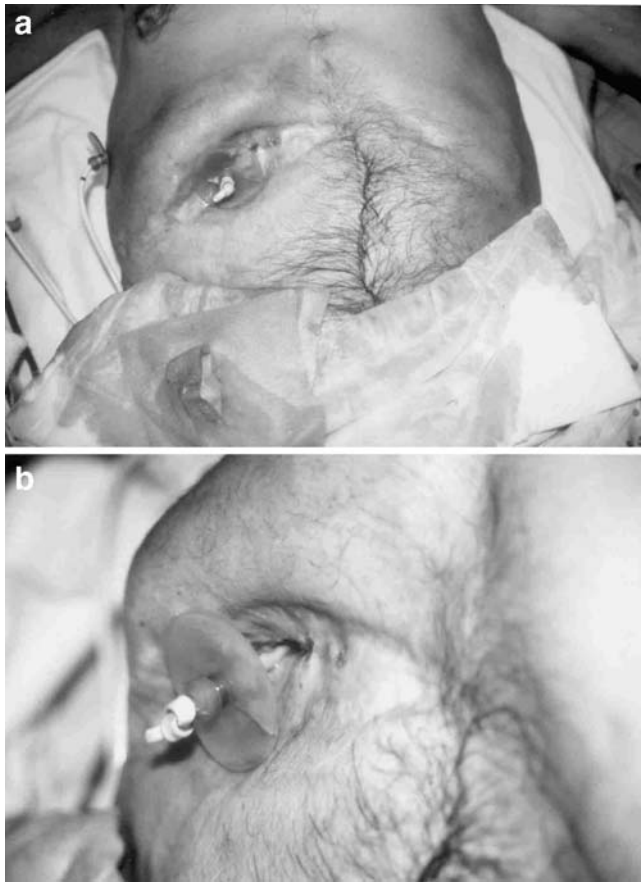

Figure 1 (**a**) Longstanding (7-year-old) biliary cutaneous fistula draining through right upper quadrant scar. Functional U-tube in place with copious biliary drainage. (**b**) Close-up of U-tube exit site.

demonstrated the continuity of the cutaneous opening with a large channel through the mid portion of the liver, but with no evidence of a true ductal system.

Surgical Procedure

With the patient under general anesthesia, the abdominal cavity was entered through a right subcostal incision along the scar of the previous transplant incision. The incision was fashioned so as to preserve a 1" diameter button of full-thickness skin surrounding the opening to the fistula tract (Fig. 3). Extensive adhesions between the fascia, liver surface, and small intestine were carefully lysed. The fistula tract was dissected retrogradely from surrounding subcutaneous tissue and muscle, preserving a rectus fascial ring. This created a conduit that could be anastomosed to small intestine. Dissection of the tract was stopped proximally at the level of the liver surface to preserve its integrity and vascularity. The fistula opening was lowered into the abdominal cavity. A 60-cm long Roux-en-Y jejunal limb was constructed 50 cm distal to the ligament of Treitz using stapled technique.

A 4-mm-wide skin edge was sharply deepithelialized circumferentially around the dissected fistula opening. This conduit was then anastomosed to the Roux limb using two layers of running 4-0 Prolene suture (Fig. 4). The inner layer approximated the deepithelialized skin edge of the fistula tract to full-thickness jejunum. The outer layer approximated the conduit's scar tissue and the preserved rectus fascial ring to seromuscular jejunum. An omental wrap was fashioned around the anastomosis. The anastomosis was performed over an 8-French feeding tube, which was exteriorized through a previous U-tube exit site and connected to a bile bag.

The abdominal cavity was irrigated and closed in the standard fashion. The patient tolerated the 3-h procedure well. Blood loss was minimal. He was discharged on postoperative day 8.

Result

This patient has now been followed for 7 years since the described procedure and is doing well without external drainage of bile. The condition of his periincisional skin improved dramatically shortly after the procedure. At this time his liver function tests and nutritional parameters are normal and his graft function remains adequate on a low dose immunosuppressive regimen.

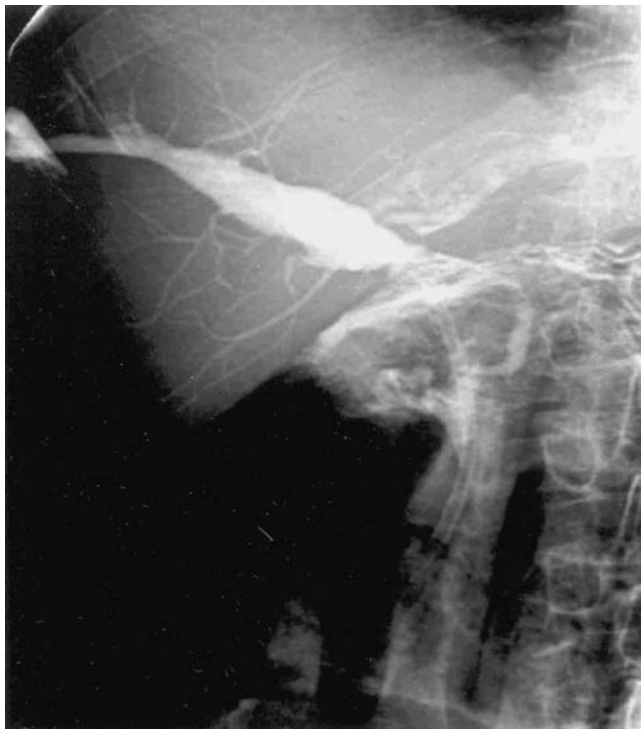

Figure 2 Preoperative fistulogram in which contrast was injected through the existing U-tube. The cutaneous opening at the upper left side of the frame is in continuity with the large contrast-filled channel that enters the substance of the liver. Note the complete absence of an extrahepatic biliary system.

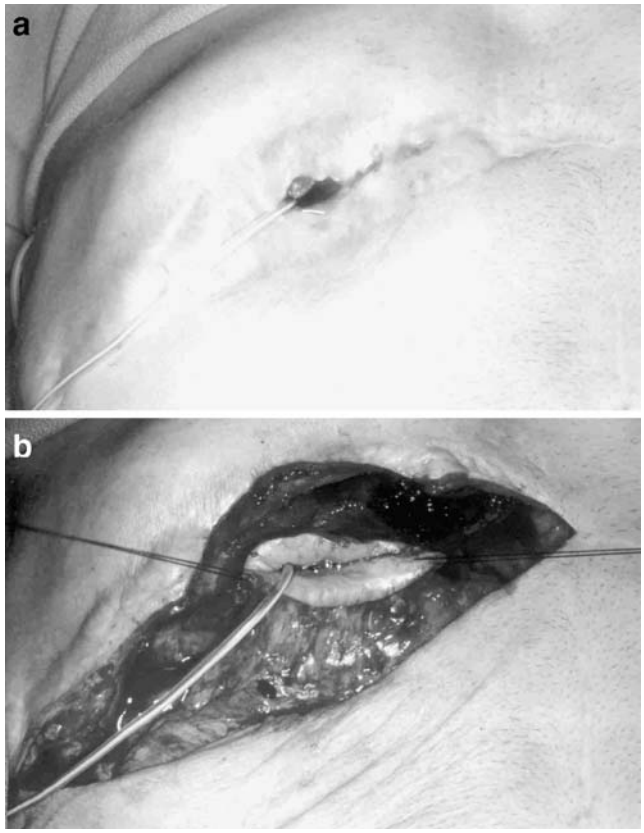

Figure 3 (**a**) At operation, the U-tube was prepped into the surgical field. (**b**) Dissection of the epithelialized chronic biliary cutaneous fistula tract. In entering the abdomen through the previous right subcostal incision, a 1" diameter button of full-thickness skin containing the fistula tract was preserved.

Discussion

Chronic biliary cutaneous fistulas are challenging to manage from many standpoints: metabolic, nutritional, hygienic, and quality of life. The patient's being a liver transplant recipient, added further complexity. First, malignant change was reported in chronic biliary cutaneous fistulas[2]; this possibility is of real concern in light of this patient's immunosuppressed state. Second, this patient had severe malabsorption and resulting difficulty in maintaining acceptable cyclosporin blood levels. Finally, the ongoing presence of his U-tube poses the threats of ascending cholangitis, hemobilia, intrahepatic biloma, and biliary-venous fistula, which are all well-documented complications that have been associated with U-tubes.[3] The decision for operative intervention was made out of these concerns and for progressive difficulty in maintaining adequate external biliary drainage. Late retransplantation was considered; however, the patient's graft function had been excellent over the 7 years subsequent to his transplant, and the patient and his family refused to consider it.

In both the posttraumatic and postbiliary surgery settings, existing literature advocates initial nonsurgical management of biliary cutaneous fistulas, as a significant number will close either spontaneously or with nonsurgical intervention.[1,4,5] In the series by Zer, four of seven biliary fistulas sealed spontaneously.[5] Endoscopic approaches to reducing intrabiliary pressure and thereby encouraging drainage along a path of least resistance include endobiliary stenting, sphincterotomy, and nasobiliary drainage.[1,4] Finally, selective biliary embolization, percutaneous transhepatic catheter drainage, sclerosis with tetracycline, and oral nitrates were also described to promote closure.[4,6–9]

Operative procedures for refractory biliary cutaneous fistula were dictated by the anatomic site of biliary tract disruption. Roux-en-Y hepaticojejunostomy, in which a jejunal loop is sutured directly to the liver capsule, was employed in the context of intrahepatic biliary injury after trauma.[4,10,11] Reports in which an actual fistula tract is used as a conduit and sutured to a loop of small bowel, however, are rare. Smith described the anastomosis of a jejunal loop

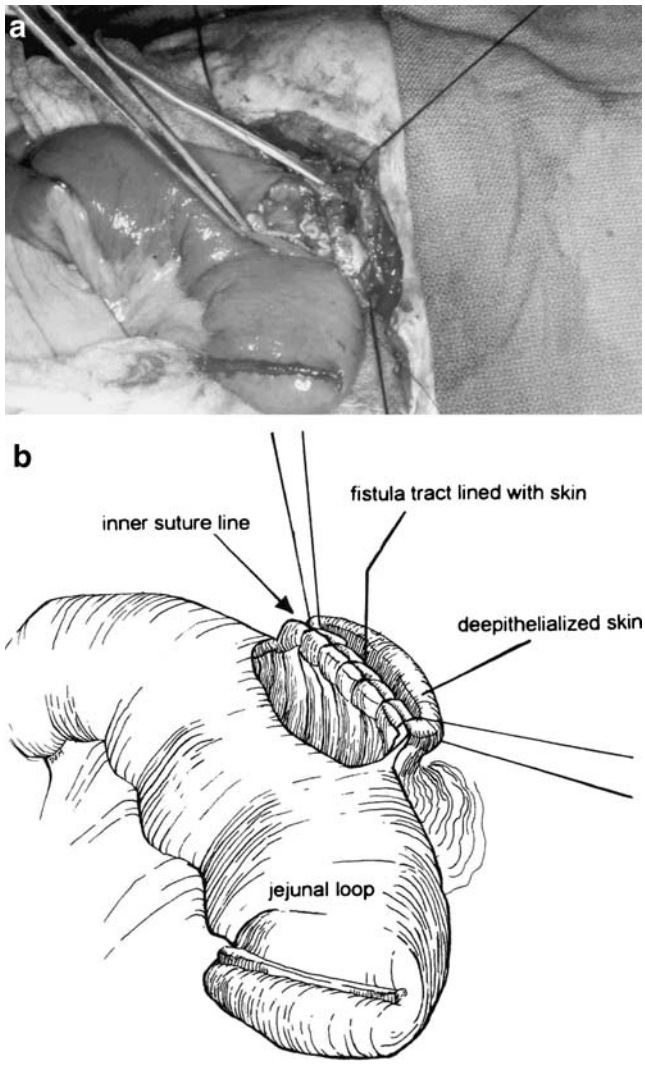

Figure 4 (**a**) Anastomosis of Roux-en-Y jejunal limb to deepithelialized fistula tract. (**b**) Illustration depicting the anastomosis.

to a divided fistulous tract arising from the lateral surface of the liver in a patient with a penetrating injury to the upper abdomen.[12] That same author described the internal drainage of a biliary cutaneous fistula secondary to blunt liver trauma into the gallbladder.[12] In both cases the fistula tract was divided and then the proximal end of the divided tract was anastamosed to an intestinal loop over a tube.

Deepithelialization of the skin opening and its direct usage in an anastomosis has not, to our knowledge, been previously described. Furthermore, this procedure is unique in that the internalization was done in the case of a functioning liver after hepatic artery thrombosis. The existing anatomy that had been established over 7 years of fistulous drainage dictated the type of procedure that was performed. In contrast to fistulas that arise after biliary tract surgery (for example, after cholecystectomy with common bile duct exploration), there was no remnant of a previous biliary ductal system. The preoperative fistulogram revealed flow of contrast from the skin directly to the liver surface with no evidence of an extrahepatic ductal system. The fistula therefore provided the only source of biliary drainage for the entire liver.

An alternative surgical option would have been hepatico-jejunostomy, in which the jejunum would have been sutured to a fibrous ring at the origin of the fistula tract from the liver surface. This, however, would have required more extensive dissection with possible disruption of collateral vasculature to the previously ischemic liver and to the tract itself, as well as dissection of the transverse colon, which in part bordered the tract. At operation, the superficial portion of the fistula tract was well established and appeared well vascularized. The potentially harmful deep dissection necessary for a hepatico-jejunostomy was therefore avoided.

We emphasize the decision to have fashioned a tongue of omentum over the anastomosis. By nature, the tissue comprising a fistula tract is probably somewhat tenuous. This patient's immunosuppressed and malnourished state compound the risk of anastomotic breakdown. We feel that the well-vascularized, adherent omental tongue was an important aspect of the operation in reinforcing the anastomosis.

As of 7 years of follow-up, the patient has not developed signs of biliary obstruction. His immunosuppressant levels are easier to maintain and he does not have evidence of malabsorption. It is unlikely that he will develop cicatricial narrowing of the tract, as it had remained well epithelialized for the 7 years before this operation. There is a theoretical concern about formation of squamous cell carcinoma at the anastomotic site, which we continue to keep in mind during long-term follow-up.

Conclusion

In summary, through a novel approach this patient's biliary cutaneous fistula was internalized, which has eliminated his associated skin morbidity and malabsorption. Furthermore, his well-functioning graft was salvaged, thus saving the cost of retransplantation and sparing an additional liver for another patient. Internalization of a long-standing biliary cutaneous fistula through deepithelializing the skin opening and using the tract as a conduit is technically feasible. We believe it to be a valid approach in the patient in whom there is no existing biliary ductal system or the existing system anatomically does not lend itself to restoration of functional internal biliary drainage by conventional approaches.

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Controversies in the Surgical Management of Sigmoid Diverticulitis

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Abstract The timing and appropriateness of surgical treatment of sigmoid diverticular disease remain a topic of controversy. We have reviewed the current literature on this topic, focusing on issues related to the indications and types of surgery. Current evidence would suggest that elective surgery for diverticulitis can be avoided in patients with uncomplicated disease, regardless of the number of recurrent episodes. Furthermore, the need for elective surgey should not be influenced by the age of the patient. Operation should be undertaken in patients with severe attacks, as determined by their clinical and radiological evaluation.

Keywords Sigmoid diverticulitis · Surgical management · Diagnosis · Elective surgery

Magnitude of the Problem

Diverticular disease, either diverticulosis or diverticulitis, was regarded as a surgical curiosity in the 19th surgery, but over the past 100 years, its prevalence in Western countries has increased dramatically. In the US, an individual's risk for developing diverticular disease approaches 50% by age 60.[1] Diverticulitis, defined as inflammation and infection related to diverticula, occurs in 20 to 30% of patients with diverticulosis and is one of the most common indications for gastrointestinal tract-related hospitalizations. One in four of these patients presenting with diverticulitis will require an emergency operation because of perforation, peritonitis, or systemic complications. At present, diverticulitis is the associated diagnosis for one third of all colostomies and/or colon resections.[2] As such, diverticulitis is one of the five most costly gastrointestinal disorders affecting the US population.[3]

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Etiology

Colonic diverticula tend to develop in the areas of weakness in the colonic wall, most frequently at the sites of penetration of the wall by blood vessels.[4] These outpouchings of mucosa and peritoneum are of the pulsion type and are thought to be caused by an increase in the intraluminal pressure within the colonic wall in affected individuals (Fig. 1).

It is thought that a low intake of dietary fiber and resultant decrease in stool bulk predisposes those in Western societies to an elevation in colonic pressure. Some authors attribute the high rate of diverticular disease to the development of the roller mills during the last half of the 19th century, causing the grains to be crushed so effectively as to nearly eliminate all of the cellulose from the Western diet.[5] Despite significant supporting evidence for fiber and its role in the development of diverticulosis, no study to date has demonstrated that a high fiber diet can reverse this process or reduce the incidence of complications in cases of established diverticulosis.[6]

In addition to dietary intake, other factors have been implicated in the development of diverticular disease. Most studies report that diverticular disease is more common in the elderly, especially elderly women, and in patients who smoke cigarettes or drink alcohol.[7] Sigmoid colon specimens from patients with diverticulosis have been found to have increased in vitro sensitivity to acetylcholine, as well as reduced smooth muscle choline acetyltransferase activity and upregulation of

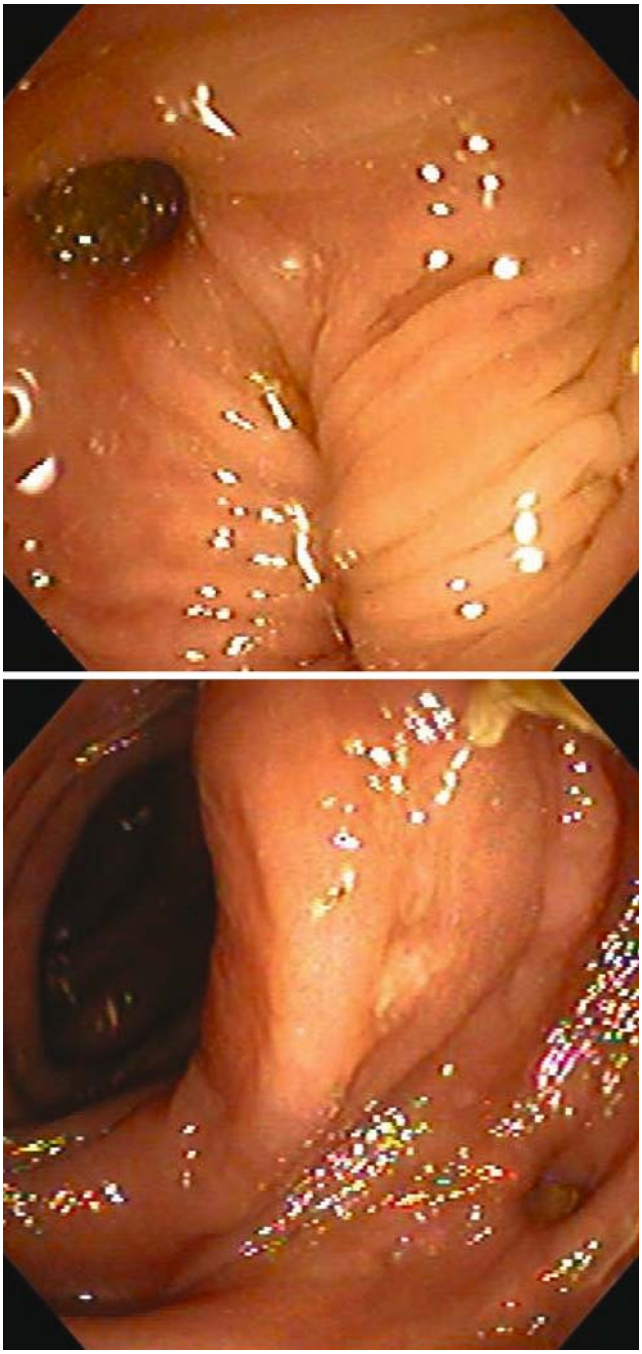

Figure 1 Endoscopic images of diverticuli. Colonoscopy can be rather difficult when several diverticula are encountered because of increased colonic tortuosity and lack of distensibility.

smooth muscle muscarinic M3 receptors.[8] The significance of these biochemical characteristics still needs to be elucidated, but the differences suggest that there are underlying physiological abnormalities that may predispose to the development and progression of diverticular disease.

Clinical Presentation and Evaluation

The clinical presentations of diverticular disease range from asymptomatic diverticulosis, diverticulosis with periodic spasmodic abdominal pain and bloating, diverticulosis with hemorrhage, and finally, diverticulitis. Although diverticula can occur in any portion of the colon, this review will only focus on sigmoid diverticulitis, by far, the most common site for this disease process.

Most patients with diverticulitis present with symptoms of left lower quadrant abdominal pain, fever, and leukocytosis (Table 1). Additional symptoms of acute sigmoid diverticulitis may include nausea, vomiting, change in bowel habits, urinary frequency, and/or dysuria.[1] In cases of clear-cut diverticulitis based upon the clinical picture, one can manage the patient without any imaging studies. In many cases, especially in those with severe symptoms and potential complicated diverticulitis, computed tomography (CT) scanning should probably be performed. The value of CT scanning is the ability to confirm the diagnosis and confidently stratify the severity of the disease process, differentiating mild, localized inflammation from advanced inflammation with abscess formation and/or distant extension.

Before the advent of CT, the contrast enema was the primary tool in the evaluation of colonic diverticular disease. However, CT scans have largely replaced barium enema as the preferred imaging modality to evaluate patients with suspected diverticulitis. The use of CT scanning has been justified by several studies from the radiological literature, demonstrating a high sensitivity (97%) and specificity (100%) for diverticulitis (Fig. 2). Contrast enema, on the other hand, has a sensitivity of only 82% and a specificity of 81% for diverticulitis.[9]

Classification

There are two commonly utilized classifications of diverticulitis. The European Association for Endoscopic Surgeons developed a classification scheme based upon the

Table 1 Clinical Symptoms of Diverticulitis

Symptoms	Frequency (%)
Left lower quadrant pain	93–100
Leucocytosis	69–83
Fever	57–100
Nausea	10–30
Vomiting	15–25
Constipation	10–30
Diarrhea	5–15
Dysuria	5–20
Urinary frequency	6–25

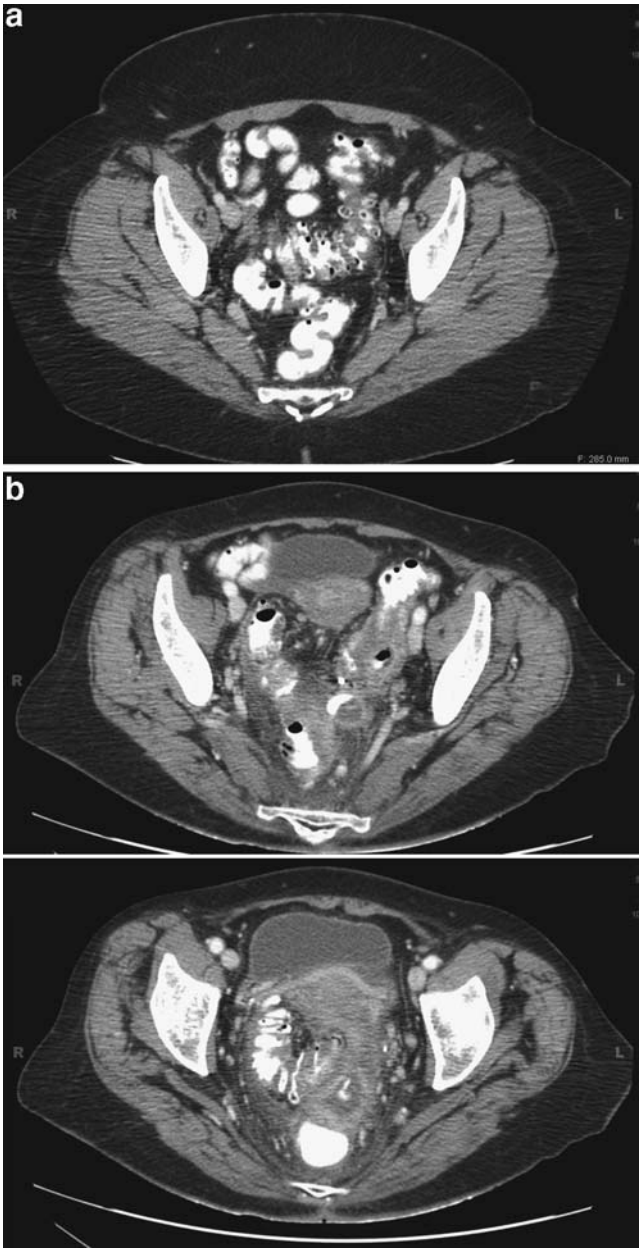

Figure 2 **a** Computed tomography scan images of a patient who presented with uncomplicated diverticulitis that was subsequently treated successfully with antibiotics. Note the thickening of the sigmoid colon, yet the lack of any extraluminal fluid or air. **b** Computed tomography scan images of a patient who presented with complicated diverticulitis and an extraluminal fluid collection that did not resolve with attempted CT-guided drainage an required an eventual sigmoid colectomy.

severity of its clinical presentation.[10] In this system, diverticulitis is divided into symptomatic uncomplicated disease, recurrent symptomatic disease, and complicated disease (Table 2).

Another classification system was developed by Hinchey et al.[11] and is used to describe the stages of complicated diverticulitis (Table 3). This scheme allows for good communication among surgeons when it comes to describing the various degrees of diverticular perforation, ranging from a localized perforation with a small abscess to generalized fecal peritonitis. Clearly, the proper surgical approach will vary depending upon the Hinchey stage.

We will refer to both of these classifications when discussing the appropriate management of this disease. Yet another classification, developed by Ambrosetti et al.[12], is based upon the CT findings. The criteria of Ambrosetti et al. are being increasingly utilized to stratify patients into optimal pathways for management (Table 4). Thus, patients with mild disease are likely to be successfully managed with intravenous antibiotics, whereas percutaneous drainage and surgery is generally indicated for cases of complicated diverticulitis.

Management of Complicated Diverticulitis

Surgical intervention is rarely indicated in cases of acute diverticulitis because most of these cases will resolve with appropriate antibiotic management. Operations are reserved for cases of complicated diverticulitis, i.e., patients with perforation and peritonitis, abscess formation, fistula, or obstruction. Although this may seem clear-cut, decisions regarding if and when to operate patients with diverticulitis remain a topic of significant debate.

Operation is clearly indicated when the patient presents with perforation and diffuse peritonitis, whether it is purulent or feculent (Hinchey stages III and IV). However, the ideal surgical procedure in such cases of perforation remains a matter of debate. The possible operations advocated range from a simple washout of the abdomen with drainage, as described in a few case reports from Scotland and France, to primary resection with a Hartmann pouch, primary resection with anastomosis, diverting ileostomy, and finally, a primary resection with anastomosis and no temporary stoma. Of these,[1,13,14] American surgeons are most likely to perform the Hartmann procedure, which has been advocated as the standard of care for perforated diverticulitis.[1] The Hartmann's resection has proven to be a safe and effective approach, and is based upon the idea that an anastomosis in the setting of acute infection/inflammation is dangerous and associated with a high rate of suture line breakdown.

A simple washout without resection would not be considered an appropriate approach because ongoing infection/inflammation of the involved bowel is likely to occur. There is a paucity of data to support a minimalist, simple washout approach; there are only 18 case reports in the literature describing the technique and its results.[13,14] On the other hand, the practice of routine stomas in operations for acute diverticulitis may not be justified. Belmonte et al.[15] looked at 277 consecutive patients treated

Table 2 Clinical Classification of Diverticulitis (Adapted from Kohler et al.[10])

Grade	Clinical Description	Symptoms
I	Symptomatic uncomplicated disease	Fever, crampy abdominal pain, CT evidence of diverticulitis
II	Recurrent symptomatic disease	Recurrence of above
III	Complicated disease	Hemorrhage Abscess Phlegmon Perforation Purulent and fecal peritonitis Stricture Fistula Obstruction

for acute diverticular disease at the University of Minnesota, both urgently and electively. Of these, 88% had a primary anastomosis, most of them without diversion. They found that primary anastomosis was quite safe, with an overall 4% leak rate. Interestingly, none of these leaks were in their subset of patients with Hinchey stage IV diverticulitis, a group that comprised 9% of their total study population.

A systematic literature review of 50 studies comparing a Hartmann's procedure to a primary resection with anastomosis for perforated diverticulitis found 569 reported cases of primary anastomoses. The reported mortality and morbidity in the patients with an anastomosis was the same as in the patients who underwent the Hartmann's procedure.[16] These data suggest that in a select group of patients undergoing surgery in the acute stage of diverticulitis, an anastomosis is probably safe, even in the milieu of feculent peritonitis.

These data are intriguing, but must be viewed with caution, especially in the case of a very sick or toxic patient with multiorgan system failure and/or shock. In the absence of randomized controlled studies, we still recommend the Hartmann's procedure in patients with significant purulent or feculent peritonitis, and those patients with any instability related to the systemic effects of sepsis. However, in a patient who is clinically stable, a primary anastomosis at the first operation can be performed even in the setting of perforation (Fig. 3).

Mention should be made of the meticulous surgical technique that must be used in this situation. The splenic flexure of the colon may need to be mobilized to ensure a tension-free anastomosis. One should imagine the rectum collapsing back into the pelvis with the patient standing upright when deciding on whether the bowel ends are truly free of tension. The margins of resection must be clearly viable with regard to vascularity. Finally, it may be best to avoid the crossed staple lines inherent to the double-stapled technique. Either a double pursestring technique with a stapled end-to-end anastomosis or a standard hand-sewn anastomosis are preferred when operating in an inflamed milieu.

Table 3 Hinchey Classification of Complicated Diverticulitis (Adapted from Hinchey et al.[11])

Stage	Description
I	Pericolic or mesenteric abscess
II	Walled off pelvic abscess
III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis

Preventive Surgery

The question of when to recommend elective, preventive surgery for patients with diverticulitis remains very controversial. Current American Society of Colon and Rectal Surgeons (ASCRS) guidelines suggest preemptive surgery for any patient who has had two attacks of acute diverticulitis, with the intention of preventing another attack that could present with perforation and would necessitate a stoma.[1] This recommendation for surgery after the second episode of diverticulitis is based on the data published in 1969 by Parks[17] showing that the mortality rate for each subsequent attack of diverticulitis increases from 4.7% during the first admission to 7.8% during each subsequent admission. Parks is also widely quoted for stating that each subsequent episode of diverticulitis is less likely to respond to medical therapy, with a 70% response after the first episode vs 6% response after the third episode.[1] However, there are little data to support this concept of poor response to medical treatment in subsequent attacks of diverticulitis. Furthermore, the advent of CT scanning and better antibiotics has improved nonoperative management of these patients. In a modern series of 673 patients with diverticular disease, only 3% of patients required emergency operations during a follow up of 10 years.[18] Another 10-year study of 366 patients showed that recurrence was not associated with

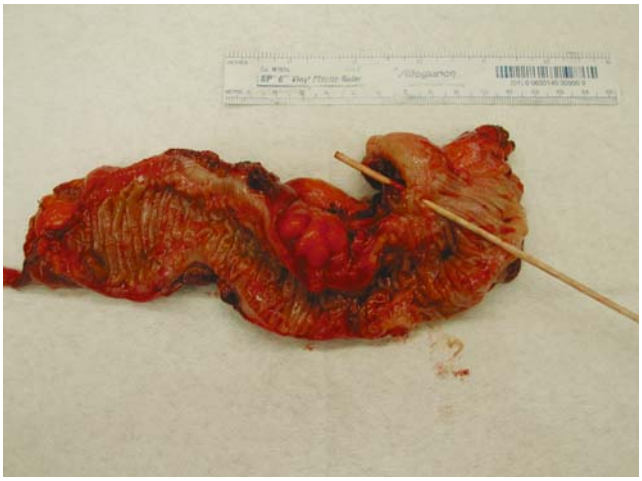

Figure 3 Gross specimen of the sigmoid colon that was resected from a patient who presented with freely perforated diverticulitis (Hinchey III). Proximal margin extends to the area where the diverticuli end, and the distal margin is at the rectum.

an increased rate of either complications or less successful medical management.[19]

Looking at the issue from another angle, Somasekar et al.[20] reviewed 108 patients admitted with complicated diverticulitis. Almost all of them (104) required emergency surgery. Interestingly, only 26% of these patients were previously diagnosed with diverticular disease and only three patients had been admitted in the past with a prior episode of acute diverticulitis. In other words, only 2.7% of patients in this group would have benefited from an elective resection. Complications would still have occurred in 92.6% of patients in whom these attacks happened de novo.

Thus, it appears that elective resection might have little impact on the incidence of patients requiring emergency procedures because most of these occur with the first attack of diverticulitis. Subsequent attacks of diverticulitis in the same patient seem to be akin to their previous ones, suggesting that specific patients are predisposed to a set pattern of diverticulitis, and once settled into this pattern they stay within it. The threat of the colostomy bag to a patient who has been successfully managed medically during two previous attacks may be unwarranted and misleading.

In addition, it is important to recognize that elective surgery for diverticulitis is not without complications. Bookey et al.[21] demonstrated that elective diverticular disease resection is associated with higher rates of morbidity and mortality than elective colorectal carcinoma resection, with the mortality rate increasing from 0 to 15% with advancing age. Furthermore, colectomy is not a guaranteed cure for diverticulitis, with recurrence rates varying from 3 to 13%. These rates have improved, however, with the recognition that the chances of recurrence are fourfold higher if a colosigmoid anastomosis is performed, emphasizing the importance of resecting the entire sigmoid colon in an operation for diverticulitis.[22]

With these conflicting data in mind, we maintain that the patients with uncomplicated diverticulitis can be managed nonoperatively regardless of the number of recurrent episodes. Patients who develop complications, such as fistulas, obstruction, or nonresolving smoldering disease, are best managed with surgical resection. Elective surgery may also be offered to patients who have had two or more episodes of *severe* diverticulitis, as determined by their clinical presentation and CT grade. In addition, elective surgery may be justified in patients with limited access to medical care or in those who are concerned about the negative impact of repeated illnesses with regard to work productivity and/or psychosocial issues.

In elective or semielective circumstances, both open and laparoscopic sigmoid resection with a primary anastomosis have been considered as acceptable methods of treatment.[23] Laparoscopy has been shown to be associated with an approximate 10% rate of conversion to open surgery. Interestingly, no direct relationship has been found between the number of attacks of diverticulitis or the timing after an acute attack with regard to complications or conversion rates with laparoscopic colectomy.[24]

Diverticulitis in Young Men

Many authors believe that diverticulitis is a more virulent disease in younger patients. As such, it has been argued that all patients younger than 50 should undergo elective colon resection after an initial attack of diverticulitis.[1,25] This argument arose from studies in the pre-CT era, which were replete with data, indicating a high risk of surgical intervention in young patients eventually diagnosed with diverticulitis. Subsequent authors have argued that these earlier studies were flawed because of a significant rate of unnecessary laparotomies in the younger patients because of erroneous preoperative diagnoses of appendicitis.[26] Vignati et al.[27] were among the first to challenge the concept that diverticulitis in the young is a more virulent disease. These authors surveyed 40 patients under the age of 50 that where treated with intravenous antibiotics and

Table 4 Ambrosetti's CT Staging of Diverticulitis (Adapted from Ambrosetti et al.[12])

Mild Diverticulitis	Severe Diverticulitis
Localized sigmoid wall thickening (<5 mm)	Abscess
Inflammation of pericolic fat	Extraluminal air
	Extraluminal contrast

bowel rest and found that at a 5- to 9-year follow-up, none of these patients required colostomies. One third of them did undergo surgery, but most of these procedures where either elective or, if urgent, still conducive to a successful primary anastomosis.

Guzzo et al.[26] performed a retrospective review of 762 patients with diverticulitis treated at their institution from 1990–2000 and found that 76% of the patients under age 50 improved with antibiotics and did not require surgery during their first attack. These rates did not differ from the rates of surgery in the elderly patients. Of the patients treated nonoperatively, only four patients had a recurrence requiring surgery at a later time and only one needed a colostomy. Thirty-eight additional patients underwent preemptive elective surgery based upon their surgeon's recommendation. One hundred fifty-five patients, 60% of the entire group, did not require surgery at all.[26]

A prospective study from Switzerland followed 118 patients who had their first attack of diverticulitis and found that recurrence rates in the younger patients were similar to those seen in the older patients, once stratified by their CT severity.[28]

Based upon these studies, we believe that young patients should generally be treated using the same criteria as older patients, and that the there is no justification for the routine recommendation for surgery after a single attack of diverticulitis in young patients. Elective preemptive surgery should be reserved for those who had at least two episodes of severe diverticulitis, and this decision should be supported by CT scan documentation of prior complicated disease.

Fistulas

As we succeed with the nonoperative treatment of acute diverticulitis, the incidence of fistulas appears to be increasing, reported to occur in approximately 12% of patients.[29] Colovesical fistulas account for two thirds of the cases, followed by colovaginal, colocutaneous, and enterocolic cases.[30] These patients can present a significant challenge to the surgeon. Some fistulas will close spontaneously as the inflammatory process resolves. Therefore, a selective approach should be used, in which operation is offered to those patients with persistent symptoms after 5–6 months after an acute attack. The most commonly reported symptoms in this group of patients include abdominal pain (43%), pneumaturia (43%), cystitis (40%), fecaluria (38%), diarrhea (15%), and hematuria (5%).[31]

In the operating room, the surgeon should expect a significant desmoplastic reaction and a contained abscess cavity in the area of fistulization. It may be prudent to place ureteral stents before the procedure, although most fistulas to the bladder will be at the dome and away from the trigone region, allowing relatively safe access for identification, dissection, and closure. Most of these cases should be amenable to resection with primary anastomosis, avoiding the need for a temporary stoma.[32]

In expert hands, a colectomy can be accomplished by either an open or laparoscopic approach.[33] Some authors suggest that these procedures are best performed by surgeons whose main interest focuses on colon and rectal surgery. A study from McGill University comparing outcomes of surgery for diverticulitis-induced fistulas found that colorectal surgeons performed less diverting Hartmann's and colostomies (5 vs 27%), and had a lower rate of complications, including wound infections and anastomotic leaks.[31] It is not clear, however, whether the data from this small study of 121 patients are applicable to all surgeons in all centers.

Diverticulitis in the Immunocompromised Patient

Diverticulitis in immunocompromised patients can be virulent because there is an increased likelihood of free perforation and fecal peritonitis. In addition, the clinical presentation of these patients often underestimates the severity of their disease.[34] Marked differences have also been noted in the response of these patients to medical treatment. In the nonimmunocompromised group one should expect that 75% of patients will respond to antibiotics. In contrast, a very large percentage of immunocompromised patients will fail standard, nonoperative treatment.[35] As such, most of these patients require urgent surgical intervention, and this is associated with a significantly higher mortality rate: 39 vs 2% in noncompromised patients.[35] Given these data, most authors and the ASCRS recommend elective sigmoid resection after the first episode of diverticulitis in immunocompromised patients.[1,34–36]

Conclusion

The management of patients with sigmoid diverticulitis is still evolving. We should continue to constantly reassess the surgical dogma regarding the appropriate treatment of this common disease entity. Clearly, a randomized controlled study comparing the Hartmann's procedure to primary anastomosis in the setting of perforated diverticulitis would be worthwhile. It is becoming increasingly clear that mandatory operations may not be warranted in young patients or those with two episodes of diverticulitis. As in other areas of clinical surgery, we must tailor our treatment to the specific situation for each individual patient.

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Hemangiopericytoma of the Greater Omentum

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Abstract A 41-year-old Chinese woman was admitted to our hospital with epigastric pain. Computed tomography detected a heterogeneous enhancement tumor fed by the left gastroepiploic artery in the left lower quadrant and cholelithiasis. Excision of the tumor in the greater omentum and cholecystectomy were performed laparoscopically. Histological findings confirmed a diagnosis of hemangiopericytoma with low-grade malignancy. To our knowledge, hemangiopericytoma of the greater omentum is very rare, and only 12 cases were reported in English literature. We report a case of hemangiopericytoma arising in the greater omentum and review the literature.

Keywords Hemangiopericytoma · Greater omentum · Laparoscopic surgery

Introduction

Hemangiopericytoma is a rare tumor of the Zimmermann's pericyte, which was first described by Murray and Stout[1] in 1942. Pericytes are rudimentary cells that have contractile properties and regulate the blood flow through capillaries. Although hemangiopericytoma may arise anywhere, the musculature of the lower extremities, the pelvic fossa, and the retroperitoneum are the predominant sites of origin[2]. The development of hemangiopericytoma in the greater omentum is rare; to our knowledge, only 12 cases were reported in the English literature until the end of 2003[3–11]. We report a patient with hemangiopericytoma originating in the greater omentum.

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Case Report

A 41-year-old Chinese woman was admitted to our hospital with epigastric pain of 6-months in duration. On physical examination, the abdomen was flat and no tumor was palpable. Enhanced computed tomography detected a well-defined tumor with heterogeneous contrast enhancement and no calcifications in the left lower quadrant whose arterial blood supply came from the left gastroepiploic artery (Fig. 1). Cholecystolithiasis was an incidental finding. With a preoperative diagnosis of abdominal stromal tumor of the greater omentum, laparoscopic surgery was performed; a solitary tumor arose with a vascular pedicle originating from the greater omentum, which was free from adjacent organs and structures (Fig. 2). There was no evidence of peritoneal or liver metastases. The tumor was excised with 10 cm of the vascular pedicle to secure sufficient surgical margin, and cholecystectomy was also performed. The resected tumor was a solid tumor with the largest diameter of 55 mm, measured 55×45×40 mm, weighed 68.5 g, and was encapsulated without central necrosis or hemorrhage (Fig. 3). On histological examination, hematoxylin–eosin staining demonstrated that spindle cells grew around the vascular endothelial cells, and no mitoses were found in high power fields. Immunohistochemical examination exhibited that the tumor was positive for CD34, factor-XIIIa, and HLA-DR. These findings confirmed a diagnosis of hemangiopericytoma with low-grade malignancy, and the resection

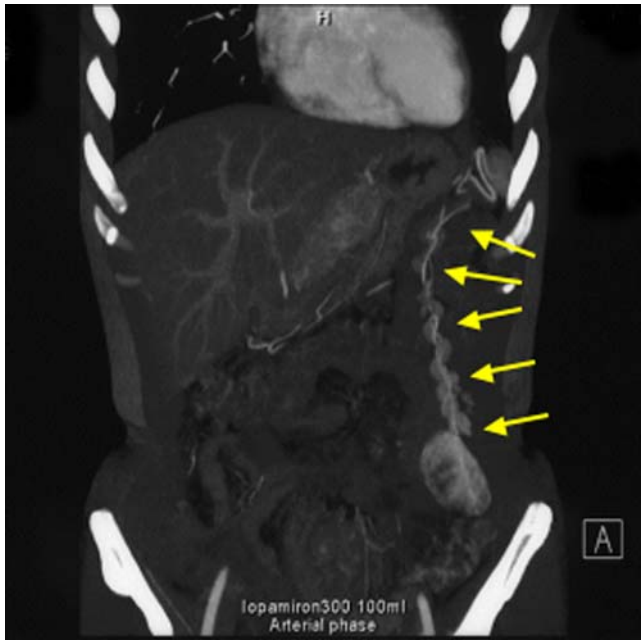

Figure 1 Enhanced computed tomography exhibited a well-defined heterogeneous tumor with contrast enhancement in the left lower quadrant of the abdomen, and demonstrated that the left gastroepiploic artery (arrow) was feeding the tumor.

margin was clear. The resected gallbladder demonstrated chronic cholecystitis with gallstones. The patient made a satisfactory recovery and was discharged on the fifth postoperative day. Histological findings and absence of mitoses suggests hemangiopericytoma with low-grade malignancy. Therefore, adjuvant chemotherapy was not given. She remains well with no evidence of tumor recurrence 6 months after resection.

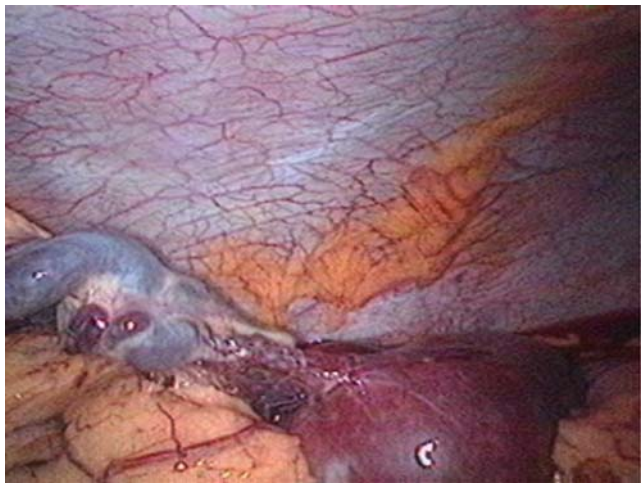

Figure 2 A solitary tumor arose in the greater omentum and was connected with the greater omentum by a vascular pedicle.

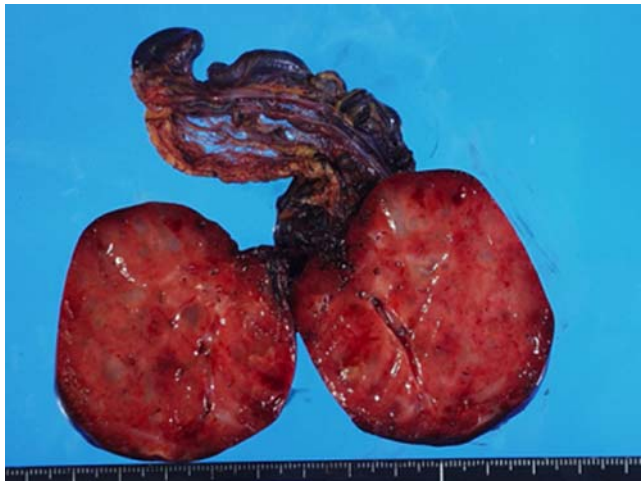

Figure 3 The resected tumor measured 55×45×40 mm, weighed 68.5 g, and was solid and encapsulated without central necrosis or hemorrhage.

Discussion

Hemangiopericytoma arising in the greater omentum is extremely rare and only 12 cases were reported in the English literature[3–11]. A review of the reported cases revealed that three patients died of recurrence. Therefore, evaluation of the malignant potential seems important. Recent reports proposed that malignant hemangiopericytoma is suspected for tumor size of more than 5 cm, a high mitotic index with more than four mitoses per ten high power fields, and necrosis and hemorrhage within the tumor[12]. According to the 13 reported cases[3–11], tumor size and mitotic index related to tumor recurrence after resection.

Because most recurrences developed at distant sites, i.e., the liver, lung, and peritoneum, systemic chemotherapy may be an additional treatment for hemangiopericytoma with high malignant potential after resection and for recurrence. However, effective chemotherapeutic regimens and molecular targeting therapy have not been established to date. Because three of the four patients who underwent omentectomy in the literature had peritoneal recurrences, the significance of omentectomy is questionable, especially for these with low-grade malignancy like in our patient. Therefore, surgical resection provides the only opportunity of cure for patients with hemangiopericytoma arising in the greater omentum. For pedunculated tumors like in our patient, laparoscopic excision is feasible.

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Consensus Statement on Mandatory Registration of Clinical Trials

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The member journals of the Surgery Journal Editors Group (SJEG), in keeping with their commitment to high ethical standards and integrity in surgical publishing and surgical science, agree to adopt the position of the International Committee of Medical Journal Editors (ICMJE)[1,2] requiring mandatory registration of all clinical trials, whether publicly funded or commercially sponsored, as a condition of consideration for publication. In addition, the SJEG will require registration of phase I and phase II trials.

Specifically, the SJEG supports the idea of promoting a publicly accessible clinical trial database as suggested by the World Health Organization (WHO) International Clinical Trials Registry Platform established in August 2005, which specifies 20 key study data reporting requirements[2]. The goal of the WHO initiative and this SJEG requirement, based on the ICMJE statement, is to promote transparency and honesty in reporting prospective clinical trial conduct and results (including negative results), to foster public trust, and to ensure that researchers behave in an ethically responsible manner toward patients and study participants[3].

The SJEG member journals will require all clinical trials that prospectively assign human subjects to medical interventions, comparison groups, or control groups for the purpose of examining the potential health effects of such interventions, to be registered in one of several free, publicly accessible, nonprofit electronically searchable databases such as the one administered by the National Library of Medicine (NLM), which is located at http://www.clinicaltrials.gov. The ICMJE defines medical interventions as those that include, among other things, drugs, surgical procedures, devices, behavioral treatments, and process-of-care changes[2].

The required minimal registration data set includes a unique trial number established by the registry, funding source(s), primary researcher and public contact person, ethics committee approval, trial recruitment information, interventions and research hypotheses, and basic methodology[2,4].

The SJEG member journals will require registration of all prospective clinical trials as of July 1, 2007. Trials that begin after July 1, 2007 must register before enrollment of the first study subject, and trials that began before the deadline must register before editorial review. Submitted manuscripts must include the unique registration number in the abstract as evidence of registration.

Authors submitting manuscripts reporting on unregistered clinical trials may request consideration of their papers if they can provide sufficient evidence of merit, although we anticipate that all clinical trials will be registered after July 1, 2007.

This statement is being simultaneously published in the respective journals of the members of the Surgery Journal Editors Group, as follows:

American Journal of Surgery	Kirby I. Bland, MD
Annals of Surgery	Layton F. Rikkers, MD, Keith D. Lillemoe, MD
Annals of Surgical Oncology	Charles M. Balch. MD
Annals of Thoracic Surgery	L. Henry Edmunds, Jr., MD
British Journal of Surgery	John Murie, MD
Canadian Journal of Surgery	Garth L. Warnock, MD, James P. Waddell, MD
Digestive Surgery	Markus W. Büchler, MD, John P. Neoptolemos, MD
Diseases of the Colon and Rectum	Robert D. Madoff, MD
Journal of the American College of Surgeons	Timothy J. Eberlein, MD
Journal of Burn Care and Research	Richard Gamelli, MD
Journal of Gastrointestinal Surgery	John Cameron, MD, Keith Kelly, MD
Journal of Laparoendoscopic & Advanced Surgical Techniques	Mark Talamini, MD
Journal of Pediatric Surgery	Jay L. Grosfeld, MD
Journal of Pelvic Medicine and Surgery	Alfred E. Bent, MD
Journal of Plastic & Reconstructive Surgery	Rod J. Rohrich, MD
Journal of Surgical Education	John A. Weigelt, MD
Journal of Surgical Research	David McFadden, MD, Wiley W. Souba, MD
Journal of Thoracic & Cardiovascular Surgery	Andrew S. Wechsler, MD
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Journal of Vascular Surgery	Jack L. Cronenwett, MD, James M. Seeger, MD
Pediatric Surgery International	Arnold G. Coran, MD, Prem Puri, MD
Surgery	Andrew L. Warshaw, MD, Michael Sarr, MD
Surgery for Obesity & Related Diseases	Harvey J. Sugerman, MD
Surgical Endoscopy	Bruce V. MacFadyen, Jr, MD, Alfred Cuschieri, MD
Surgical Innovation	Adrian Park, MD, Lee Swanstrom, MD
Surgical Laparoscopy, Endoscopy & Percutaneous Techniques	Maurice E. Arregui, MD, Carol Scott-Conner, MD
World Journal of Surgery	John G. Hunter, MD
Zentralblatt für Chirurgie	Hans Lippert, MD, Ulrich Hopt, MD

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