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Quality of Life in Pancreatic Cancer: Analysis by Stage and Treatment

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Abstract In pancreatic cancer patients, survival and palliation of symptoms should be balanced with social and functional impairment, and for this reason, health-related quality of life measurements could play an important role in the decision-making process. The aim of this work was to evaluate the quality of life and survival in 92 patients with different stages of pancreatic adenocarcinoma who underwent surgical and/or medical interventions. Patients were evaluated with the Functional Assessment of Cancer Therapy questionnaires at diagnosis and follow-up (3 and 6 months). At diagnosis, 28 patients (30.5%) had localized disease (group 1) and underwent surgical resection, 34 (37%) had locally advanced (group 2), and 30 (32.5%) metastatic disease (Group 3). Improvement in quality of life was found in group 1, while in group 3, it decreased at follow-up ($p = 0.03$). No changes in quality of life in group 2 were found. Chemotherapy/chemoradiation seems not to significantly modify quality of life in groups 2 and 3. Median survival time for the entire cohort was 9.8 months (range, 1–24). One-year survival was 74%, 30%, and 16% for groups 1, 2, and 3 respectively ($p = 0.001$). Pancreatic cancer prognosis is still dismal. In addition to long-term survival benefits, surgery impacts favorably quality of life.

Keywords Pancreatic cancer · Quality of life · Meaningful important difference · Palliation · Survival

Introduction

Pancreatic cancer remains the fourth leading cause of cancer-related death in the USA. Of the 32,180 patients diagnosed with pancreatic adenocarcinoma in 2006, the great majority will die within 2 years from initial diagnosis.[1] Less than 20% of the patients are candidates for surgical resection, which remains the only treatment offering the possibility of long-term survival, even if this is only 10% to 25%.[2–4] The remaining patients present with locally advanced or metastatic disease, and for them, chemotherapy or chemoradiation represent the current standard of care with the aim of improving survival.[5–7]

During the course of disease, 70% to 80% of patients with pancreatic head tumors develop obstructive jaundice, and 10% to 20% duodenal obstruction.[8–10] Many also will manifest pain, which is probably the most disturbing and incapacitating symptom in advanced pancreatic cancer.[11] Adequate palliation of biliary and duodenal obstruction, as well as of pain, is one of the goals in the treatment of these patients. However, optimal methods of palliation remain controversial in terms of patient benefit perception and

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durability.[12–15] Many studies have compared different treatments and palliative procedures in different stages of the disease, but few have considered these issues among the entire spectrum of pancreatic cancer patients.[4,16]

To assess the value of a treatment, physicians routinely use "physician-centered" objective outcomes, such as disease recurrence, complications, treatment toxicity, or survival, but infrequently consider patients' perception and quality of life.[17] Health-related quality of life (HQOL) seeks to measure the impact of disease process on physical, psychological, and social aspects of the person's life and feeling of well-being,[18–20] and recently, has become an important subject in pancreatic cancer care, with the aim of measuring the impact of different interventions on patients' health and life.[18,21–24] It has become clear that in a disease-like pancreatic cancer, in which patients have a short life expectancy, improvements in survival and treatment-related complications must be carefully balanced against HQOL outcomes to define better approaches while considering patients' personal needs.

The aim of this prospective study is to analyze the effects of therapeutic and palliative treatments on health outcomes and HQOL in a contemporary cohort of patients with pancreatic cancer.

Patients and Methods

After obtaining Institutional Review Board approval, 105 patients with histologically proven ductal adenocarcinoma of the pancreas, treated at Massachusetts General Hospital between September 2004 and January 2006, were enrolled in this study after obtaining informed consent. Demographics, clinical presentation, laboratory and radiologic findings, type of surgery, postoperative morbidity and mortality, pathology, neoadjuvant or adjuvant treatments, type of palliation, disease recurrence, and number of readmissions were recorded. Patients with adenocarcinoma arising in intraductal papillary mucinous neoplasm of the pancreas were excluded.

Patients were classified in three clinical stages: apparently localized cancer (group 1), locally advanced (group 2), and metastatic (group 3). Localized cancer permitted resection. Locally advanced cancer was defined as extension of the neoplasm outside the pancreas with major vascular encasement or other features precluding potentially curative resection. Local recurrence was defined as recurrent retroperitoneal mass or regional lymph nodes in patients who had undergone pancreatic resection with curative intent. Metastases were defined as a relapse of disease in the peritoneal cavity or at any distant site.

Follow-up data was obtained through direct contact with patients' oncologists, primary care physicians, and families.

Quality of Life Assessment

To assess health-related quality of life, the fourth version of the Functional Assessment of Cancer Therapy (FACT-G) and the hepatobiliary and pancreatic specific module (FACT-Hep) were used. The FACT-G is a 27-item self-report instrument that assesses four different dimensions of quality of life: physical (seven items), social (seven items), emotional (six items), and functional (seven items). The specific subscale for hepatobiliary and pancreatic diseases (FACT-Hep) has 18 additional items. Patients responded to HQOL questions on a five-point Liker-type scale ranging from 0 (not at all) to 4 (very much). FACT-G and FACT-Hep have been previously validated in cancer populations.[25–27]

From these two questionnaires, three scores were obtained: the FACT-G score, which is the sum of the four subscales; the FACT-Hep, which is the sum of the FACT-G and the disease-specific module (FACT-Hep), and the Trial Outcome Index (TOI), which is the sum of the physical, functional and disease-specific module. The TOI has been demonstrated to be a sensitive indicator of clinical outcome.[27]

Each questionnaire was applied at diagnosis (baseline) and sent by mail after 3 and 6 months from the initial diagnosis.

Data Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. We performed paired and unpaired t student and χ^2 tests when comparing nominal and categorical variables, respectively. In the case of a nonparametric distribution, a Mann–Whitney U was done. One-way ANOVA with post hoc analysis was performed for multiple comparisons with normal distribution, and the probability was adjusted by Tukey's correction. A 5% of significance was accepted. Survival curves were constructed with the Kaplan–Meier method.

HQOL scores were analyzed from a statistical and clinical significance viewpoint. For the statistical analysis, due to a lack of complete sets of questionnaires in some patients, a cross-sectional analysis was done, and all patients who provided HQOL questionnaires at baseline were compared with all those provided follow-up HQOL data. Thus, scores available at 3- and 6-month follow-up were grouped together as "follow-up scores." For the purpose of the clinical analysis, scores available at 3- and 6-month were considered separately. HQOL scores were compared among the three groups at baseline and follow-up and within each group (baseline versus follow-up scores). Moreover, HQOL scores were compared in the entire cohort (n = 92) or in groups 2 and 3 patients (n = 64) to

evaluate differences in the following independent variables: age, resection, CA 19.9 level, adjuvant/neoadjuvant treatment in the entire cohort, and need for stents, chemotherapy/chemoradiation, and celiac block in groups 2 and 3.

Clinical significance was determined using the meaningful important difference (MID). MID is defined as "the smallest difference in score in the outcome of interest that informed patients perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management".[27,28] MIDs measure the clinical relevant changes in HQOL perception derived from a treatment or the disease itself. To estimate MID, the mean of all HQOL scores (FACT-G, FACT-Hep, TOI) were first assessed, and subsequently, differences between mean HQOL scores at baseline and at 3- and 6-months were evaluated. Differences in mean HQOL scores considered clinically significant (MIDs) were as follows: 8–9 for FACT-Hep, 7–8 for FTOI and 6–7 for FACT G.[27]

Results

Of the 102 patients initially enrolled, ten with no complete HQOL questionnaires at baseline were excluded, and therefore, final analysis was performed in 92 patients (46 women and 46 men; mean age ± SD of 66±10 years; range, 42–88).

At diagnosis, 28 patients (30.5%) had localized disease (group 1), 34 (37%) had locally advanced disease (group 2), and 30 (32.5%) had metastatic disease (group 3).

Demographics

Demographic characteristics of the three groups are shown in Table 1. There were no differences among the three groups with regard to age, sex, and tumor location. Jaundice was the most common presenting symptom in group 1 (86% of patients), while its frequency was lower in groups 2 and 3 (21% and 14%, respectively; $P = 0.0001$). Abdominal pain and weight loss were more likely to be associated with locally advanced or metastatic disease. As expected, median CA 19.9 was significantly higher in patients with metastatic disease.

Diagnostic and Palliative Procedures

Table 2 shows diagnostic and palliative procedures as well as data regarding hospital stay and readmissions. All the patients underwent at least one computed tomography (CT) scan. The mean number of CTs performed per patient was significantly greater in those with localized disease. The number of endoscopic ultrasounds (EUS), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopically placed biliary stents was greater in group 2 patients, but the difference was significant only when comparing EUS between groups 2 and 3 (83% versus 53%, $P = 0.01$). Only three patients (10%) in groups 3 and two (6%) in group 2 required a percutaneous transhepatic biliary drainage during their clinical course. No patient in group 1 underwent percutaneous or intraoperative celiac block compared to 14 patients (41%) in group 2 and 6 (20%) in group 3. Enteral stents were used to palliate malignant duodenal obstruction in six patients (18%) in group 2 and in two patients (7%) in group 3. Four patients in group 2 and one in group 3 had both enteral and biliary stents.

The overall mean hospital stay and the number of readmissions were significantly shorter in patients with metastatic disease. Fifty-six percent of patients with locally advanced disease required two or more readmissions, compared to 36% in group 1 and 27% in group 3. There were no differences between groups 2 and 3 in the number

Table 1 Demographics, Presenting Symptoms, and Tumor Site in 92 Patients with Pancreatic Cancer Classified According to the Clinical Stage (Group1, Localized Disease; Group 2, Locally Advanced Disease; Group 3, Metastatic Disease)

	Group 1 (28 Patients), *n* (%)	Group 2 (34 Patients), *n* (%)	Group 3 (30 Patients), *n* (%)	1 vs. 2 (*P* value)	2 vs. 3 (*P* value)	1 vs. 3 (*P* value)
Age (years), mean ± SD	65±10	66±11	65±11	1	1	1
Sex						
Male	14 (50)	16 (47)	16 (53)	0.5	0.4	0.5
Female	14 (50)	18 (53)	14 (47)			
Presenting symptoms						
Jaundice	24 (86)	7 (21)	4 (14)	0.0001	0.3	0.0001
Abdominal pain	3 (11)	13 (38)	9 (30)	0.1	0.6	0.2
Weight loss	1 (3)	14 (41)	17 (56)	0.0001	0.1	0.0001
Tumor site						
Proximal	21 (75)	25 (73.5)	19 (63)	0.5	0.2	0.3
Distal	7 (25)	9 (26.5)	11 (37)			
Median CA 19.9 (U/L)	60.5	264	1536	0.2	0.02	0.003

Table 2 Diagnostic and Palliative Procedures in 92 Patients with Pancreatic Cancer Classified According to the Clinical Stage (Group1, Localized Disease; Group 2, Locally Advanced Disease; Group 3, Metastatic Disease)

	Group 1 (28 Patients)	Group 2 (34 Patients)	Group 3 (30 Patients)	1 vs. 2 *P* Value	1 vs. 3 *P* Value	2 vs. 3 *P* Value
Abdominal CT						
Overall number	117	122	77			
Number of patients[a] (%)	28 (100)	34 (100)	30 (100)	–	–	–
Mean number/pt	4±2.6	3.6±2.7	2.6±2	0.9	0.03	0.3
EUS						
Overall number	18	31	19			
Number of patients[a] (%)	17 (61)	28 (83)	16 (53)	0.5	0.6	0.01
Mean number/pt	1±0.2	1±0.1	1.2±0.4	0.6	0.2	0.4
ERCP						
Overall number	23	38	22			
Number of patients[a] (%)	14 (50)	23 (68)	16 (53)	0.1	0.8	0.2
Mean number/pt	1.64±0.7	1.65±0.7	1.3±0.6	0.9	0.2	0.1
Diagnostic laparoscopy (%)	4 (14)	10 (30)	6 (20)	0.1	0.4	0.3
Biliary stents						
Overall number	20	33	19			
Number of patients[a] (%)	14 (50)	20 (62.5)	14 (47)	0.2	0.8	0.2
Mean number/pt	1.4±0.5	1.65±0.7	1.3±0.6	0.4	0.5	0.2
Hospital stay						
Two or more admissions (%)	10 (36)	19 (56)	8 (27)	0.1	0.4	0.01
Overall mean hospital stay ± SD	15±12	14±11.5	8±7	0.5	0.001	0.03
Celiac block (%)	0	14 (41)	6 (20)	–	–	0.6
Enteral stent (%)	0	6 (18)	2 (7)	–	–	0.1
Palliative surgery (%)	0	6 (17.5)	4 (13)	–	–	0.4

Palliative surgery consisted of gastrojejunostomy ($n = 5$) and gastrojejunostomy plus a hepaticojejunostomy ($n = 1$) in group 2; gastrojejunostomy and hepaticojejunostomy (n = 2), gastrojejunostomy (n = 1), hepaticogastrostomy (n = 1) in group 3.
[a] Overall number of patients who underwent at least one examination/procedure in each group

of surgical palliative procedures. Five patients with locally advanced disease received intraoperative radiation therapy (IORT) in association with palliative surgery.

Treatment

Twenty-nine patients underwent pancreatic resection with curative intent. Of these, 28 patients had localized disease at diagnosis, and one patient had locally advanced disease and underwent resection after chemoradiation. Table 3 shows the intraoperative, postoperative, and pathologic features of these patients. Overall morbidity was 24%, mortality was nil, and no patient required surgical re-exploration.

Of the 29 resected patients, four underwent neoadjuvant chemoradiation (three patients of group 1 and one of group 2), and 21 underwent adjuvant chemoradiation. Of these patients, ten received gemcitabine, and the remaining, 5-fluorouracil. Four patients declined further treatment.

With regard to the 34 patients in group 2, 18 (53%) underwent chemoradiation (including the five who received also IORT), 11 (32%) chemotherapy alone, and five (15%) refused any treatment or were considered unsuitable for chemotherapy or chemoradiation because of major comorbidities. In group 3 ($n = 30$), 24 patients (80%) underwent chemotherapy, three (10%) chemoradiation, and three (10%) refused treatment. In patients who underwent chemotherapy alone, gemcitabine was administrated as single agent in 14 cases, and in association with new agents, as part of clinical trials in the remaining ten patients.

Survival

All but two patients were followed until death or at least 12 months. The median survival for the entire cohort was 9.8 months (mean ± SD, 9.5±6; range, 1–24). Figure 1a shows survival of the entire cohort, and Fig. 1b the survival of the three different groups. One- and 2-year survival for the entire cohort was 39% and 23%. One-year survival was 74%, 30%, and 16% for groups 1, 2, and 3, respectively ($P = 0.001$). The median survival for group 3 was 5.8 months, for group 2 8.6 months, and for group 1, it has not been reached. With regard to the 29 patients who underwent surgical resection, 12 of them developed tumor recurrence at a median time of 7 months from operation. Sites of recurrence were distant metastases in eight patients

Table 3 Perioperative Findings and Postoperative Complications in 29 Patients Who Underwent Pancreatic Resection for Ductal Adenocarcinoma

	Number of Patients (%)
Type of resection	
Pancreaticoduodenectomy[a]	21 (73%)
Distal pancreatectomy and splenectomy	7 (24%)
Total pancreatectomy	1 (3%)
Mean blood loss (ml)	670±430
Mean operative time (min)	286±78
Patients requiring blood transfusions	3 (10)
Postoperative complications	
Overall morbidity	7 (24)
Pancreatic fistula	2 (7)
Abscess	2 (7)
Mean postoperative length of stay (days)	8±2
Surgical-related mortality[b]	0
Neoadjuvant chemoradiation[c]	4 (13)
Adjuvant chemoradiation	21 (73)
Mean pathologic tumor size	30±12
Positive lymph nodes	17 (58)
Positive resection margins	3 (10)
Tumor grading	
G1	1 (3)
G2	14 (48.5)
G3	14 (48.5)
Presence of perineural infiltration	23 (79)
Presence of microvascular infiltration	18 (62)

They include 28 patients with localized neoplasm (group 1) and one patient with a locally advanced neoplasm (group 2) who underwent neoadjuvant chemoradiation.

[a] Whipple procedure with pancreatojejunostomy was performed in all the cases.

[b] Surgical-related mortality was defined as in-hospital or 30-day postoperative mortality.

[c] Neoadjuvant chemoradiation was performed in one patient affected by a locally advanced neoplasm with clear evidence of vascular infiltration (group 2) and in three patients with localized disease (group).

and locoregional in four. Ten patients died of disease while two remain alive with disease. The remaining 17 patients are alive with no evidence of disease at a median of 14 months (range, 12–23).

The mean survival for the five patients who underwent IORT was 10.6±6.2 months. Two of these patients died for tumor progression after 8.8 and 8.6 months, while the remaining patients are alive with stable disease.

Quality of Life

Baseline questionnaires were completed in 92 patients (100%). The rate of completed questionnaires decreased to 56% at 3 months and to 48% at 6 months. Excluding dead patients, the rate of completed questionnaires was 63% at 3 months and 59% at 6 months.

Table 4 shows HQOL scores at baseline and during follow-up. At baseline, no statistical differences were found in the HQOL scores among the three groups, while during follow-up, patients in group 1 had higher HQOL scores compared to groups 2 and 3. Comparisons within each group showed an improvement of HQOL scores from baseline to follow-up in groups 1 and 2, and a worsening of all scores in group 3.

Clinically meaningful changes (MIDs) from baseline to 3- and 6-months were found in groups 1 and 3 but not in group 2 (Fig. 2). The MIDs in group 1 were toward improvement and in group 3 toward deterioration.

Since HQOL scores at baseline were homogeneous among the three groups, we performed statistical analysis of HQOL scores considering different variables in the entire cohort (n = 92; Table 5). Patients who underwent resection

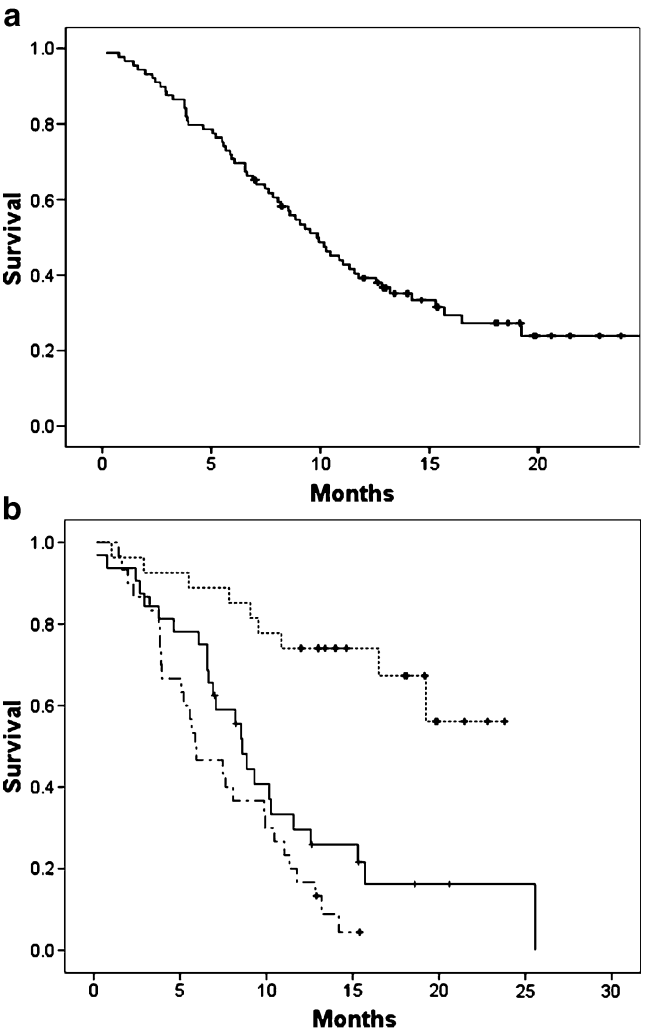

Figure 1 **a** Kaplan–Meier overall survival curve in 92 patients with pancreatic cancer. One- and 2-year survival was 39 and 23 months. **b** Kaplan–Meier survival curves in patients with localized (group 1, n = 28), locally advanced (group 2, n = 34), and metastatic pancreatic cancer (group 3, n = 30) at initial presentation. One-year survival was 74%, 30%, and 16% for groups 1, 2, and 3, respectively (P = 0.001).

Table 4 Health Related Quality of Life Scores (FACT G, FACT Hep, FTOI) in the Different Groups

HQOL Scores	Group 1 (28 Patients), Mean ± SD	Group 2 (34 Patients), Mean ± SD	Group 3 (30 Patients), Mean ± SD	1 vs. 2, *P* Value	2 vs. 3, *P* Value	1 vs. 3, *P* Value
Baseline						
FACT Hep	124.7±21.6	122.6±23.7	122.7±20.2	0.9	0.9	0.9
FTOI	83.7±19.4	82.5±19.1	83.2±16.8	0.9	0.9	0.9
FACT G	76.3±14.4	72.5±17.5	69.5±19.3	0.7	0.7	0.3
Follow-up						
FACT Hep	134±17.9	125±21.4	113.3±34.7	0.4	0.3	0.03
FTOI	93.5±16	84.2±17	74.7±14	0.2	0.3	0.02
FACT G	78.8±11.6	74.7±14	68.7±20	0.6	0.4	0.1
P value[a]						
FACT Hep	0.1	0.6	0.2			
FTOI	0.06	0.7	0.09			
FACT G	0.5	0.6	0.8			

[a] Comparison between baseline and follow up scores within each group

(n = 29) had significantly higher HQOL scores at follow-up compared to nonresected ones (n = 63; P = 0.001). Patients with CA 19–9 values above 200 U/l (n = 46) had lower HQOL scores both at baseline (P = 0.01) and during follow-up (P = 0.04). There were no statistically significant differences in HQOL scores regarding age (cut-off, 60 years) and chemotherapy/chemoradiation both at baseline and during follow-up.

Patients in groups 2 and 3 who required biliary or enteral stents, celiac block, and chemoradiation/chemotherapy alone were analyzed from a clinical viewpoint (Figs. 3, 4, and 5). Patients with locally advanced or metastatic disease who underwent stent placement had a decrease in HQOL scores at 3 months but a clinically significant recovery at 6 months, whereas patients without stents did not have significant changes in HQOL mean scores at 3 and 6 months (Fig. 3). Patients who underwent chemoradiation showed no significant differences in HQOL scores at 3 and 6 months, whereas those who received chemotherapy alone presented a significant decrease in HQOL score at 3 months with a nonsignificant improvement at 6 months (Fig. 4). Patients who underwent celiac block had a decrease in HQOL score at 3 months and a significant recovery at 6 months. No changes in quality of life were found in patients without celiac block from baseline to follow-up (Fig. 5).

The statistical analysis of these variables in groups 2 and 3 patients was not significant.

Discussion

"The outlook in carcinoma of the pancreas continues to be grim." With this peremptory sentence, Morrow and colleagues summarized the 1975–1980 experience of Memorial Sloan–Kettering Cancer Center in treating 231 patients with ductal adenocarcinoma of the pancreas.[29] They reported a resecability rate of 16.9% and a median survival of 18 months for patients who underwent resection, and of only 4 months for those who had surgical bypass. Over the last 25 years, many efforts have focused on improving outcomes in pancreatic cancer patients. Morbidity and mortality after pancreatic surgery have decreased markedly,

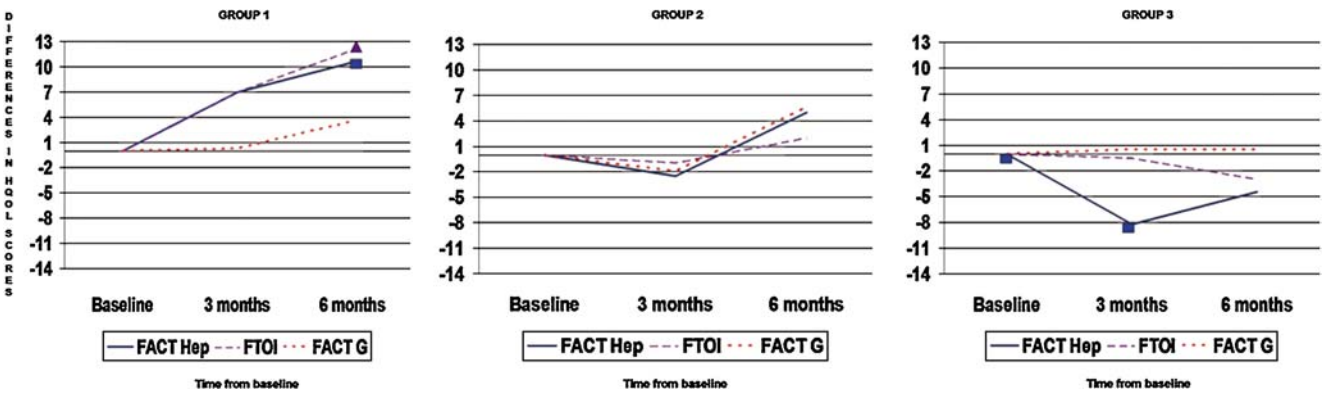

Figure 2 Clinical changes in health-related quality of life (*HQOL*) of patients with local (group 1), locally advanced (group 2), and metastatic (group 3) pancreatic cancer. *Square and triangle* Meaningful important differences (MID).

Table 5 Health-Related Quality of Life Scores at Baseline and Follow-up in the Whole Cohort (n = 92) Considering the Following Variables: Pancreatic Resection, CA 19.9 (cut-off, 200 U/l), Age (cut-off, 60 years), Chemotherapy Versus Chemoradiation During the Disease Course

Variable	Baseline				Follow-up			
	FACT-Hep	FTOI	FACT-G	p	FACT-Hep	FTOI	FACT-G	p
Resected	125.7±21.6	84.5±19.5	77±14.5	NS	134.6±17.6	93.6±15	79.6±12	0.001
Nonresected	122.2±22	82.5±18	70.8±18.2		119.8±27.5	80.4±22	71.8±16.5	
CA 19–9>200	118.3±22.5	78.4±18.6	69.8±19	0.01[a]	119±26.4	80±20.5	71.5±15.7	0.04[a]
CA 19–9<200	128.8±19.7	88.4±16.5	75.6±15		131.8±22.5	90.8±19	78±14.4	
Age>60	126.2±19.5	84.3±18	74.4±16.8	NS	127.2±26.2	86.5±21	76.4±15	NS
Age<60	116.4±25.3	80±19	68±18.1		121.4±23.4	82.8±19	71.3±14	
Chemotherapy	123.6±20	83.3±17	72±15	NS	118.6±32.5	79±25.2	72.5±19	NS
Chemoradiation	122.8±20.5	82.2±17.6	74.7±14.4		127.6±17.4	87.6±15	74.8±12	

Statistically significant mean differences in FACT-Hep, FTOI and FACT-G scores. No statistically significant differences were found when comparing baseline versus follow-up scores for all the variables.
[a] Statistically significant mean differences in FACT-Hep and FTOI scores

chemotherapy and chemoradiation regimens have been developed, and 5-year survival rates of up to 25% have been reported in resected patients.[2,16,30–35]

While many studies have evaluated specific stages of pancreatic cancer, few have reported data on the entire spectrum of disease, considering treatments, palliative procedures, and outcomes.[16] The present study specifically addresses this point to give the reader a "snapshot" of pancreatic cancer treatment at the beginning of the twenty-first century. Unfortunately, the picture that emerges continues to be as grim as that described by Morrow 25 years ago. Our data shows that, despite chemotherapy and chemoradiation, the median survival is only 5.8 months for patients with metastatic disease and 8.6 months for those with locally advanced cancers, these two groups together constituting two thirds of the pancreatic cancer population seen in a cancer center. The one-year survival rate for the entire cohort was only 39%, and 58% of these are patients who underwent resection. Our survival rates did not significantly differ from those generally reported in the literature.[4–7,30–35] Moreover, we considered a consecutive series of patients newly diagnosed with pancreatic cancer, not a selected population with favorable prognostic factors in which better survival rates can be achieved.[16,24,33]

Surgery remains the only possibility of long-term survival for patients with pancreatic cancer, but the great majority of them are not amenable to resection even after neoadjuvant treatments.[16,36] In this series, 53% of group 2 patients underwent chemoradiation, but only in one case was sufficient "downstaging" obtained to allow subsequent surgical resection. These data underscore that palliation rather than curative treatment still remains the most relevant goal in the great majority of patients with pancreatic cancer.

In addition to evaluating treatment and survival, our study assessed longitudinal changes in HQOL, using validated instruments administrated at diagnosis and during follow-up. Physicians aiming to keep patients comfortable and free of symptoms must evaluate the impact of these

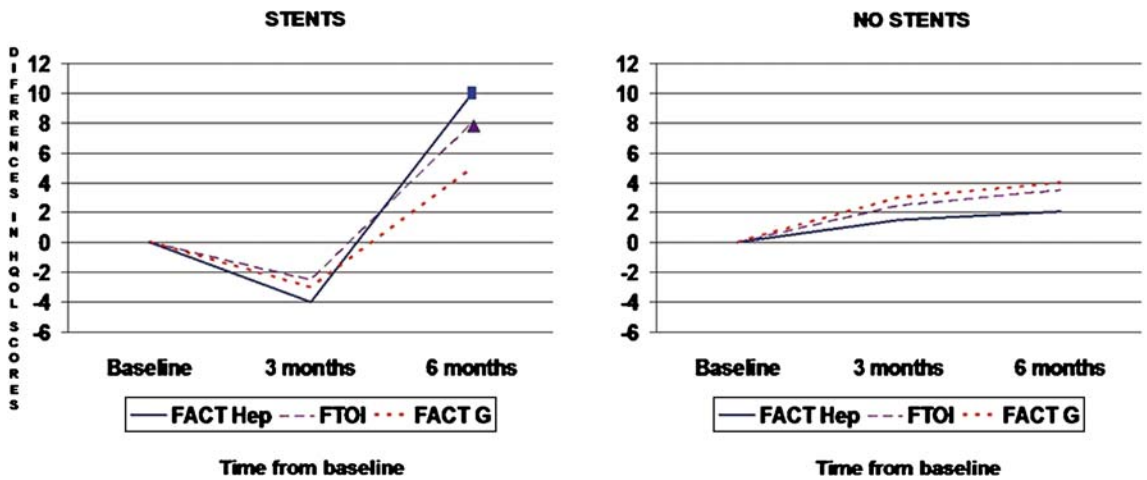

Figure 3 Clinical changes in HQOL in patients affected by locally advanced and metastatic pancreatic cancer with or without biliary/enteral stents. *Square and triangle* Meaningful important differences (MID).

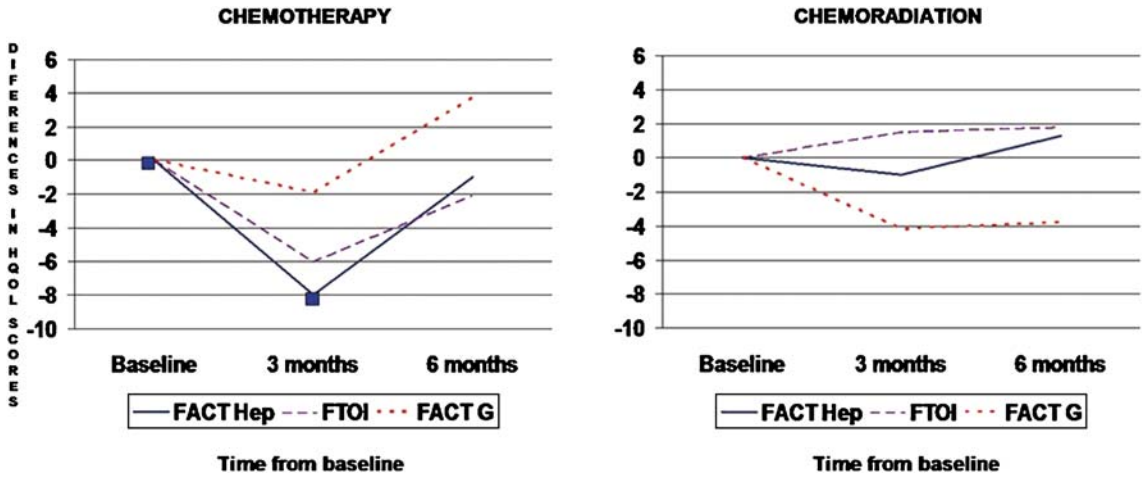

Figure 4 Clinical changes in HQOL of patients with locally advanced and metastatic pancreatic cancer who underwent chemotherapy or chemoradiation. *Square* Meaningful important differences (MID).

interventions on patients' quality of life.[17] To the best of our knowledge, this is the first prospective study that considers HQOL in patients with the full spectrum of localized, locally advanced, and metastatic pancreatic cancer.

The instruments used for HQOL evaluation in pancreatobiliary diseases range from visual analogue scales to generic HQOL (FACT-G or EORTC QLQ-C30) or disease-specific (FACT-Hep) questionnaires.[18,23,24,37] We used both the FACT-G and FACT-Hep questionnaires, which have an excellent test–retest reliability, and high internal consistency are easy to complete and have been validated for patients with pancreatobiliary cancers.[23–26] In addition to the general and disease-specific scores we also evaluated the F-TOI, a functional index that is a sensitive indicator of clinical outcome.[27]

In the present study, data were analyzed to look for both statistical and clinical significance, which account for two different perspectives in HQOL interpretation.[28,38] The purpose of statistical analysis is to quantify the importance of differences in a cohort of patients (population), and the sample sizes inevitably affect statistical power. However, statistically significant changes in a general population setting may not be meaningful in the context of single or few individuals. Clinical significance focuses upon detecting changes that are important in the patient's perspective and therefore relevant in the management of individual patients. MIDs were used to define clinical significance in this study.[27]

Interestingly, our data shows no statistical or clinical significant differences in HQOL scores at baseline among the three groups, which were also homogeneous for age, sex, and site of tumor. Only patients with localized disease who underwent surgical resection (group 1) had a subsequent improvement in quality of life: Scores on almost all HQOL scales improved during follow-up after surgical resection. In contrast, a decrease of all the scores was evident in group 3, while a slight increase was found in group 2 (Table 4).

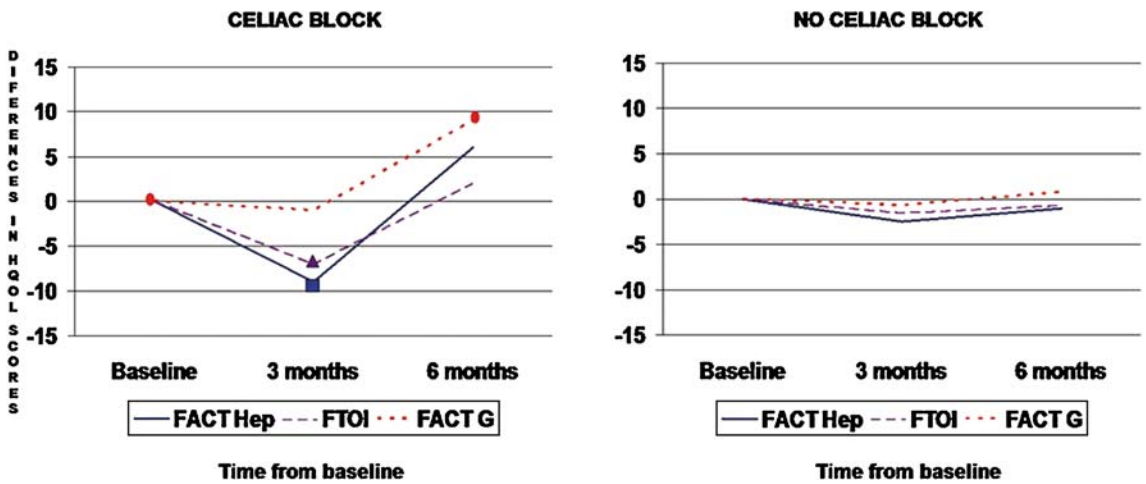

Figure 5 Clinical changes in HQOL of patients with locally advanced and metastatic pancreatic cancer who underwent celiac block or did not. *Square, triangle; and circle* Meaningful Important Differences (MID).

It is difficult to compare HQOL results among different studies because of differences in instruments, methodology, and patient population.[37,39] In some, various periampullary tumors or pancreatic diseases were considered,[18,21] or HQOL was not assessed longitudinally but only after the therapeutic intervention.[23] Not surprising therefore, our results differ from those previously reported in the literature. Schniewind et al.[37] in a prospective study evaluating HQOL in a group of 91 patients who underwent pancreaticoduodenectomy for pancreatic cancer, showed a large decrease in most HQOL scales after surgery, followed by a slow recovery to preoperative levels. A similar trend was found by Nieveen van Dijkum et al.[21] who compared pancreaticoduodenectomy versus biliary and duodenal bypass for pancreatic and periampullary carcinomas. Farnell et al.[24] comparing pancreaticoduodenectomy with or without extended lymphadenectomy in pancreatic cancer, found a decrease in most of HQOL scores from baseline to 4 months after surgery in both groups.

In contrast, we found an improvement of HQOL scores from baseline to follow-up only after surgical resection. This difference was clinically but not statistically significant despite pancreatic surgical resections being extensive procedures associated with potential major complications. The difference between group 1 versus groups 2 and 3 certainly depend upon the differences in cancer stage and are influenced by the curative potential of surgical resection and the rapid evolution of the disease in unresected patients. It is nonetheless remarkable that HQOL scores improved during follow-up in group 1 patients, even though 73% of them underwent adjuvant chemoradiation.

A common methodological problem of HQOL studies is missing data, which may lead to bias.[21,23,37] Specifically, missing data can result in overestimation of HQOL since very sick or dying patients are less likely to complete the questionnaires. In our study, this defect might be more prevalent in groups 2 and 3, but it is unlikely that overestimation affected group 1 because the majority of patients were alive with no recurrent disease 3 and 6 months after surgery.

In patients with advanced disease, we evaluated the impact of different palliative procedures and treatment on HQOL. In patients who develop jaundice and/or gastrointestinal obstruction but who are judged to be unresectable, endoscopic procedures are our first choice for palliation, while surgical bypass is generally performed for tumors found to be unresectable at laparotomy. Several studies in assessing the feasibility and efficacy of endoscopic biliary and enteral stenting as an alternative to surgical bypasses have shown that stenting is associated with lower costs and better quality of life when compared to surgical bypass.[10,12,13] In our cohort, patients who underwent stent placement had a decrease in HQOL at 3 months but a clinically significant improvement at 6 months, while there were no significant changes in patients who did not require or receive stents (Fig. 3).

Pain control is a major issue in patients with advanced pancreatic cancer.[11,15] Recently, Yan et al. and Wong et al. showed that,[14,40] compared with standard analgesia, celiac block is associated with a significant but limited reduction of pain but does not improve either quality of life or survival. They concluded that celiac block should not replace standard pain control measures but should be used selectively as an adjunct. Pain relief based on systemic analgesics was successfully obtained in 59% of group 2 and 80% of group 3 patients. Patients who underwent celiac block had a decrease in HQOL at 3 months but a clinical significant improvement at 6 months, while no changes in HQOL were detected in the remaining patients (Fig. 5).

Chemotherapy and chemoradiation did not seem to impact HQOL differently in patients with locally advanced and metastatic disease. At 3 months, worse scores were found in the chemotherapy group, although this can be explained by the fact that chemotherapy was preferentially performed in patients with metastatic pancreatic cancer (Fig. 4).

Conclusion

In conclusion, because the rate of cure for pancreatic cancer continues to be very low, palliation of symptoms remains the more attainable goal for most cases. This study shows that there is a good overall impact of surgical and medical interventions on the quality of life in patients with pancreatic cancer. Despite potential perioperative and long-term complications, pancreatic resection improves quality of life of those with localized disease. Chemoradiation and chemotherapy do not negatively impact the quality of life in patients with locally advanced disease, but chemotherapy in patients with metastatic disease is associated with a significant decrease in quality of life during follow-up, due either to chemotherapy, the progression of the cancer, or both.

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Discussion

Thomas J. Howard, MD (Indianapolis, IN): This study is unique and what is unique about it is that they classified patients into three clinically relevant stages: Stage I is patients with localized cancer, stage II is patients with locally advanced cancer, and stage III is patients with metastatic cancer. They used a validated instrument to prospectively measure health-related quality of life, and they have an acceptable 59% response rate at 6 months. Their survival rates were as expected with a median survival of 9.8 months in the entire cohort and significant improvement in survival and health-related quality of life in those patients able to be resected. In contrast, patients with metastatic disease showed significant overall decline in health-related quality of life over time. These data fail to show the benefit of the use of chemotherapy or chemoradiotherapy in these patients, and I have several questions regarding this.

Question number one is, bias, in particular in studies with limited accrual, is a constant nemesis. I assume these patients represent a nonselected sampling of patients who were seen over this 16-month period at the MGH. Besides the 102 patients that were enrolled in your study, how many other patients with pancreatic adenocarcinoma were treated at your institution who declined to be part of this enrollment?

My second question is that the FACT-G questionnaire, as you know, covers multiple health dimensions expressed by four subscale measurements: physical, social, emotional, and functional well-being. Did you find any differences either within or between groups in these subscales rather than just the overall scale to explain the findings that you report?

And my last question is could you speculate to the reasons, e.g., perhaps lack of a control group, underpowered, or the use of combination therapy, that you failed to identify any clinical benefit response to the use of systemic chemotherapy in your cohort of patients with pancreatic cancer?

Stefano Crippa, MD (Boston, MA): Thank you for reviewing our manuscript in advance and for these excellent questions. The first question is whether our patients represent no selected sampling of patients seen at Mass General Hospital during the study period. Well, every year, approximately 250 patients are referred to our hospital with the diagnosis of pancreatic cancer, and of these, 15% will undergo surgical resection. They come through different routes. Some are referred to the department of surgery, basically patients with localized disease, but many others with advanced pancreatic cancer and metastatic pancreatic cancer are referred to the department of oncology just for a second opinion or to the department of gastroenterology to have a stent placed. Many patients with advanced pancreatic cancer after the workup at Mass General will be followed out in other hospitals outside MGH. Therefore, we first tried to enroll in this study those patients who were actually treated at our institution to have more specific and detailed data regarding their treatment, the need for readmission, stents, and so on. And I have to say that a few patients declined to participate in the study.

The second question regards differences in subscale analysis among the three groups. Actually, we did not perform a subscale analysis. We analyzed only the FACT-G and the FACT-Hep models and the TOI, the trial outcome index, which is the sum of the functional, physical, and disease-specific models. Basically, the TOI gives you a better idea on the functional and physiological status of these patients, and we found an improvement of the TOI in patients with localized disease who underwent surgery, and this was a surprise for us. As expected, a decrease of the physiological and functional status in patients with advanced and, in particular, metastatic pancreatic cancer was found.

Finally, why our study failed to show a clinical benefit in patients with metastatic cancer. I agree with you that our study is certainly underpowered and we have a small sample size for each group. However, when we talk about patients with metastatic cancer and we look at the studies reported in the literature, we have to consider that, in many cases, the clinical benefit is measured in terms of a few weeks of improved survival, and I am not sure that this data is perceived as important, meaningful, or whether relevant by the single patient. Therefore, I think that, in this subset of patients, probably more detailed quality of life studies are needed.

Jennifer F. Tseng, MD (Boston, MA): This is a very nicely presented work from a great center. I have a comment and a question. It is a truism in those people who study quality of life that all quality of life is relative

and that, in fact, when they have done studies of people that have either (a) won the lottery or (b) had an amputation, 12 months later, those people's quality of life is equivalent. Therefore, my question to you is about the arbitrary nature of time points at 0, 3, and 6 months, et cetera. Did resection occur at 0 months, and so then, the first data point was three months after presumably any complications?

Dr. Crippa: Yes.

Dr. Tseng: Can you stratify by people that actually had surgical complications and people that did not have surgical complications?

Dr. Crippa: We did not do that because we had only 29 patients who had surgical resection, 28 with localized disease and one with locally advanced. Sorry, I cannot answer.

Dr. Tseng: And then if you follow those patients out, it will be interesting if you can present this in a year or two and see actually if those patients who underwent resections quality of life also diminishes, as one would expect, to the same level as those who did not undergo resection.

Dr. Crippa: For this study, we decided to evaluate quality of life at 3 and 6 months because this study was not focused only on patients with localized pancreatic cancer who had resection but also on patients with locally advanced or metastatic pancreatic cancer. Therefore, we scheduled the questionnaire time at 3 and 6 months because the median survival of metastatic patients is only 6 months. This is why we chose also this particular time.

O. Joe Hines, M.D. (Los Angeles, CA): I enjoyed your talk. Although pancreatic cancer is a grim disease, there are some lights of hope, so I don't absolutely agree with your comparison to data that is from the 1970s and 1980s. There are some groups of patients that are having significantly improved survivals over the past 5 years, upwards of 35% to 40% 5-year survivals. My question for you really relates to the way you grouped your patients. You chose to group them by a staging system that is something that you developed for your study, and so, when someone looks at your paper and reads your data, it is going to be difficult for them to compare it to their own experience. I wonder why it is that you used this grouping. And secondly, have you had the chance to use something like the AJCC staging system to compare the groups so that others can understand the information in your paper a little better?

Dr. Crippa: We did not use the AJCC system. We basically decided to classify the patients according to their status at presentation. Therefore, these patients had a CT scan, endoscopic ultrasound, a detailed imaging workup, and they were classified in localized disease and locally advanced if there was an encasement of the vessel or an infiltration of the retroperitoneum without evidence of metastatic disease, and finally, patients with metastatic disease. We decided to do that because that was the presentation of our patients, and we did not do a stratification according to the AJCC system, which is a pathological and not a clinical classification.

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Treatment of Hemorrhoids in Day Surgery: Stapled Hemorrhoidopexy vs Milligan–Morgan Hemorrhoidectomy

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Abstract
Background Recently, it has been demonstrated that surgical treatment of hemorrhoids in a day-care basis is possible and safe. The aim of this study was to compare the Longo stapled hemorrhoidopexy (SH) and the Milligan–Morgan hemorrhoidectomy (MMH).
Methods One hundred seventy one patients (95 cases in SH group and 76 cases in MMH group) entered the study: 83 cases were III degree hemorrhoids, 88 IV degree. A priori and a post hoc power analysis were performed. Results, prospectively collected, were compared using chi squared test and student *t* test. Visual analog scale was used for pain evaluation. Postoperative pain, duration of pain, wound secretion, bleeding, resumption of a normal lifestyle, and postoperative complication were evaluated.
Results Surgical time was 28.41±10.78 for MMH and 28.30±13.28 min in SH (P=0.94). Postoperative pain was not different between MMH and SH during the first two postoperative days (4.73±2.91 vs 5.1±3.048; P=0.4), during the following 6 days, patients treated with SH had less pain (4.63±2.04 in MMH vs 3.60±2.35 in SH; P=0.006). In the SH group, seven patients needed further hospital stay for complicated course. SH showed higher incidence of anal fissure compared with MMH (6.3% vs 0%; P=0.025) but no differences in urinary retention, anal stricture, urgency, or anal hemorrhage.
Conclusions This study confirms that SH is associated with less postoperative pain and shorter postoperative symptoms, compared with MMH. SH may be a viable addition to the therapy for hemorrhoids with some advantages in early postoperative pain and some disadvantages in postoperative complications and costs.

Keywords Hemorrhoids · Day surgery · Milligan–Morgan hemorrhoidectomy · Longo stapled hemorrhoidopexy

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Introduction

Hemorrhoids are one of the most common anorectal disorders. The Milligan–Morgan open hemorrhoidectomy (MMH) is the most common surgical technique used for the treatment of hemorrhoids. Circular stapled hemorrhoidopexy (SH) was described by Longo in 1998 as an alternative surgical technique for grade III and IV hemorrhoids. Early small studies comparing SH with standard hemorrhoidectomy have shown that SH is less painful and associated with quicker recovery.[1–4] Driven by this early success, SH has achieved rapid popularity as an alternative to excisional surgery in many centers. Later on, several authors reported severe complications, such as pelvic sepsis, rectal obstruction, rectal perforation, and stapled

line dehiscence following SH.[5–7] Doubts about the adequacy of SH in managing concomitant external hemorrhoids were raised together with the fact that this technique carries a postoperative bleeding rate higher than that of excisional hemorrhoidectomy and has an early reoperation rate of more then 5%.[5] A severe postdefecation pain syndrome and fecal urgency have also been reported.[6] Moreover, in the past 2 years, a few randomized clinical trials comparing SH with Milligan–Morgan have been published with a higher number of cases and a longer follow-up.[8–10] Conclusions from these studies are that SH may be at least as safe as the Milligan–Morgan technique. SH in most studies causes significantly less postoperative pain and earlier resumption of normal activities than MMH. Despite this evidence in support of SH, controversy still exists due to rare but occasionally life-threatening complications, and also due to significant chronic pain experienced by a small subset of patients. More recently, a large meta-analysis study on the safety and efficacy of SH compared to MMH in the treatment of hemorrhoids has concluded that SH may be at least as safe as MMH. However, the efficacy of SH compared with MMH could not be determined absolutely, and the conclusion was that further, more rigorous studies with longer follow-up periods and larger sample sizes need to be conducted.[11] In the past few years, some studies have demonstrated that surgical treatment of hemorrhoids on a day-care basis is possible and safe. The aim of this study was to compare two surgical techniques, the SH and the MMH, in day surgery.

Materials and Methods

Between January 2002 and June 2006, 200 consecutive patients were enrolled in this study to be treated on a day-care basis in our University Hospital. Two groups were created: a SH group (100 patients) operated on using the PPH-01 kit (Ethicon Endo-Surgery) with the technique described by Longo,[12] and a MMH group (100 patients) operated on using a standard open hemorrhoidectomy technique.[13] Patients were enrolled in the study after an office visit and a rigid proctoscopy. All patients over 40 years old underwent colonoscopy. After the patients had given their written consent, they were informed of the result of the randomization. Seven patients rejected the result of the randomization and six others refused surgery thereafter. Inclusion criteria were third- and fourth-degree symptomatic hemorrhoids that could be treated by either surgical technique. A further criterion was that the patients had to be classified ASA I or ASA II to fulfill the day-care anesthesiology standard. Exclusion criteria were acute thrombosis, concomitant anal fissure, previous surgical treatment of hemorrhoids, Crohn's disease, and ASA classification over II. All patients were operated on in the lithotomy position under local anesthesia by local injection of 20 ml of naropine 0.75% in the anal verge and submucosa of the anal canal, 1 mg of i.v. Midazolam was administered in all patients, and general anesthesia was provided when required. All patients were operated on by two certified colorectal surgeons with a previous experience of over 100 SH procedures and hundreds of MMH procedures. The protocol was approved by an ethics committee. In the comparison of the two groups, we considered the following parameters: postoperative pain, relevant pain duration (in days), duration of wound secretion, bleeding duration, and resumption of a normal lifestyle. Postoperative pain was assessed using a visual analog scale (VAS) in which zero corresponds to no pain and ten to maximum experienced pain. The VAS score was recorded by the patient daily for 8 days starting the day of surgery. The analgesic regimen included Ketorolac 30 mg 1 h after surgery and at the moment of discharge from the day care. At home, the patients were given oral Ketorolac 20 mg up to three times a day. All patients were given daily postoperative laxative (lactulose 30 ml q.d.) for 1 week. Antibiotic prophylaxis was administered using Ciprofloxacine 400 mg i.v. intraoperatively and 250 mg p.o. bid for 3 days. Starting January 2003, antibiotic profilaxis was revised using intravenous cephalosporin (1 g) and Metronidazole (500 mg). A high-fiber diet was recommended together with adequate oral fluid intake. Patients were encouraged to take sit baths two or thee times a day. Patient follow up was 8 days after surgery, 1 month, 3 months, and then every 6 months. Mean follow up was 34.8± 15.6 months. Patients were asked at follow up to fill out a questionnaire about symptoms, continence, defecation, and quality of life. Patients were also asked to express a score on the quality of care and assistance received. Randomization was stratified at the moment of the first diagnosis. Two different groups were compared with the following assumptions: independent samples from normal population having equal variances. Then, we compared the results with a chi-squared test for qualitative variables and a parametric T test to compare means for quantitative variables. Statistical test was carried out, choosing a bilateral test and a first type α-error risk of 0.05 (α=5%). A priori power analysis was performed as a component of the design experiment to estimate required total sample size as a function of power 1-β (at least 0.80) with medium effect size ($\mu_1-\mu_2/\sigma=0.5$),[14] and $\alpha=0.05$ (Fig. 1). We also considered a post hoc power analysis to decide how likely it would be that our statistical test would detect the specified effect with the observed samples. Power analysis was carried out both for the two independents means under investigation and for the difference between two independents proportions (Table 1). With regard to the chi square test

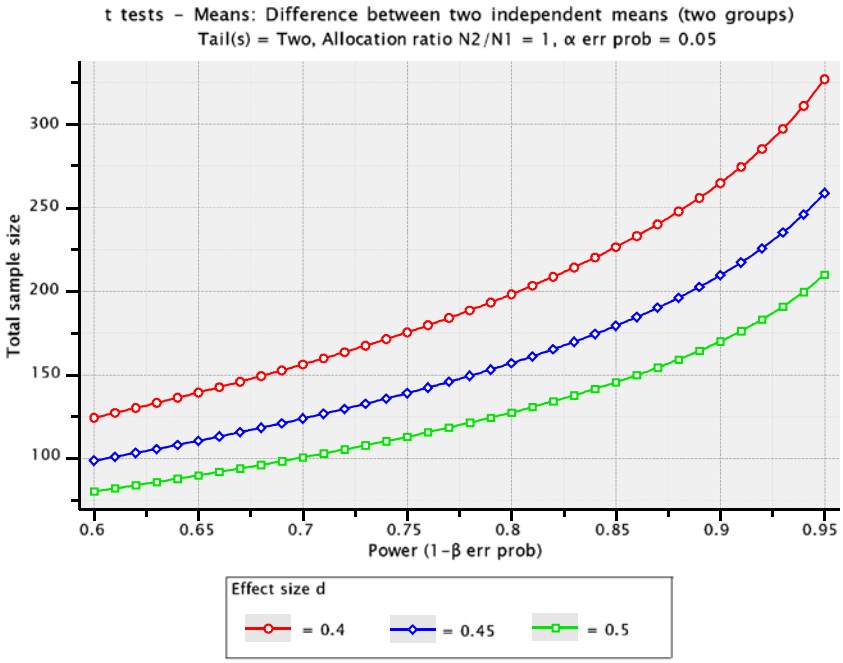

Figure 1 Total sample as function of power with effective size from 0.4 through 0.5 (two tails); allocation ratio=1.

between two independent proportions, power analysis performed a priori required a sample size of 82 patients (pts) equal for the two groups to detect a difference of 0.2 in the proportion of the two population with a power of 0.80 ($\alpha = 0.05$). Although one of the two samples was slightly less (MMH=76 pts) the achieved power was 0.81. Some of the results are expressed as a mean ± standard deviation (sd). The software used was SPSS version 11.0 for Windows. The power calculation was computed using G*Power 3.[15]

Results

A total of 200 patients, 109 males and 91 females, all affected by III- and IV-degree hemorrhoids, were included and randomized for SH (100 patients) and MMH (100 patients) in the study, and there were no significant differences with respect to mean age, weight, history, or risk factors. Thirteen patients refused randomization or did not undergo surgery and 16 were lost at follow up; therefore, 171 patients were considered in the results of the study, 102 male and 69 female. Among these patients, 95 underwent SH and 76 MMH. Eighty three patients had III-degree hemorrhoids, while 88 had IV-degree hemorrhoids.

Clinical data were comparable in both groups; the most common problems reported from the patients before the operation were the impression of a mass at the anus (85%), rectal bleeding (77%), pain (65%), itching (32%), and discharge and soiling (20%). The same anesthesia protocol was used in all patients, and no intraoperative complications were observed. Surgical time was not significantly

Table 1 Achieved Power—Given α=0.05, Sample Size and Effect Size d=0.5

Test: difference between two independent means	Sample size		Power (1-b error)	Noncentrality parameter $\delta = d\sqrt{\frac{n_1 n_2}{n_1+n_2}}$	Critical t (n_1+n_2-2 df)
	MMH	SH			
Surgical time (min)	41	64	0.697	2.499	1.983
First 2 days postop pain	73	93	0.888	3.197	1.974
Days 3 to 8 postop pain	73	82	0.870	3.107	1.975
8 Days postop pain	73	82	0.870	3.107	1.975
Pain duration (days)	59	78	0.820	2.897	1.977
Secretion duration (days)	58	79	0.818	2.891	1.977
Hitching duration (days)	56	73	0.797	2.814	1.978
Bleeding duration (days)	59	80	0.824	2.913	1.977
Return to work (days)	62	75	0.824	2.912	1.977

different: 28.41±10.78 min for MMH and 28.30±13.28 min for SH (P=0.94). In the Longo prolassectomy group, 88 patients (92.6%) were managed in a day-care setting, 4 (4.2%) were in 1-day surgery (they were discharged the day after) and three required further admission for complicated course (3.2%). All of the 76 patients operated on with MMH were treated in day care. The necessity of prolonged hospital stay was significantly higher in SH than MMH (P=0.014): in the SH group, four patients required observation overnight for pain or urinary retention and three patients required admission for 2 to 4 days for postoperative complication, vs none of the patients treated by MMH. The mean follow up period was 34.8±15.6 months; a total of 16 patients (12 MMH and 4 SH) failed to come back for follow up.

There were no significant differences between MMH and SH related to postoperative pain in the first 2 days (5.13±2.98 vs 5.10±3.04; P=0.959), but during the following 6 days, patients treated with Longo technique had significantly less pain (4.71±21.94 vs 3.60±2.35; P=0.002) (Fig. 2, Table 2). The statistical evaluation among the whole period considered (8 days) was significantly less in SH compared to MMH (P=0.016). The duration of postoperative pain, (in days) secretion, and bleeding are significantly less in the Longo group then in the Milligan–Morgan group, as is shown in Table 2.

Among postoperative complications, SH showed a significantly higher incidence of anal fissure compared with MMH (6.3% vs 0%; P=0.025). In both groups, few cases of urinary retention (3 pts in SH vs none in MMH), anal stricture (2 pts in each group), urgency (5 pts in SH group vs 2 pts in MMH group), or anal hemorrhage (3 pts in SH group vs 1 pts in MMH group) were observed, but there was no significant difference (Table 3). Despite the difference in pain, bleeding, and soiling duration, the resumption of a normal lifestyle was not different between the two techniques (17.28±11.32 days in SH group vs 18.37±9.65 days in MMH group; P=0.550) (Tables 2 and 3). Recurrence was based on the physical examination of the surgeon 1 and 2 years after the procedure. In SH, recurrence of prolapse was 7.4% (7 cases) and 2.6% in MMH (2 cases); the difference was not significant (P=0.17). All patients were either satisfied or very satisfied and considered themselves cured by both surgical techniques.

Discussion

Hemorrhoids are one of the most common afflictions in the populations of industrialized countries, probably promoted by bipedal ambulation (gravity), lack of fiber in the diet, and the habit of squatting on a commode for relatively long periods of time. All these factors combine to increase pressure in the submucosal venous plexus in the anal canal, leading to venous and capillary distension and breakdown of the supporting submucosal connective tissue. Many surgical operations have been advocated for hemorrhoids over the centuries, with some from as far back as the time of Hippocrates (500 B.C.). During the past few decades, the favored operation has been the MMH and the Ferguson hemorrhoidectomy because of the relatively simple technique and reliable outcome observed. Complication rates are relatively low in experienced hands and are simple to manage.[16] In 1998, Longo proposed a technique of SH for

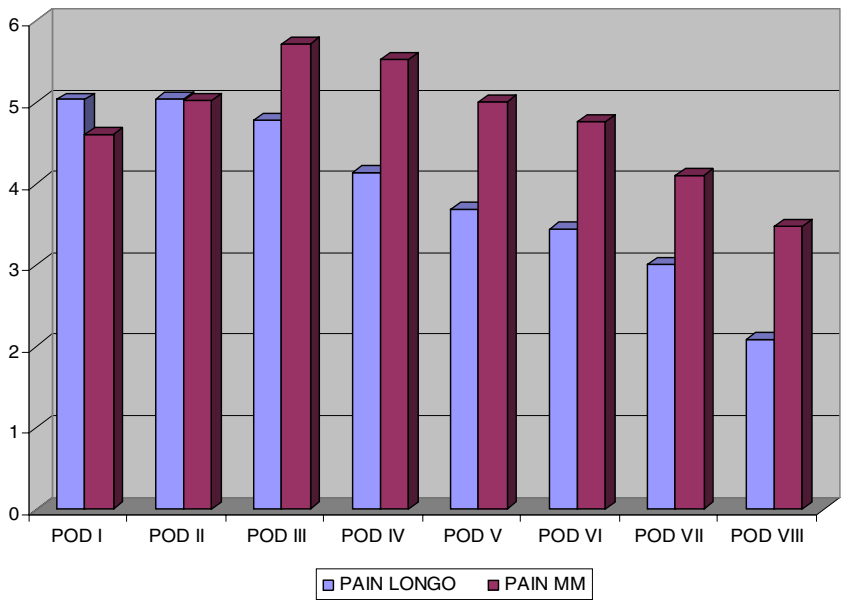

Figure 2 Evaluation of pain in the first eight postoperative days for SH and MMH.

Table 2 Evaluation of Postoperative Symptoms in SH and MMH

	SH 95 pts	MMH 76 pts	*P* (two tails)	95% confidence interval
Surgical time (min)	28.3+/−8.7	28.4+/−10	*P*=0.949	−3.544, 3.909
First 2 days po pain	5.106+/−3.048	5.13+/−2.987	*P*=0.959	−0.9086, 0.9573
Days 3–8 po pain	3.606+/−2.352	4.719+/−1.946	*P*=0.002	0.4233, 1.8034
8 Days po pain	3.978+/−2.391	4.822+/−1.870	*P*=0.016	0.1464, 1.5306
Pain duration	12.63+/−9.011	19.90+/−12.261	*P*=0.000	3.677, 10.864
Secretion duration	5.668+/−8.636	19.22+/−12.015	*P*=0.000	10.078, 17.054
Itching	5.96+/−11.288	9.45+/−14.08	*P*=0.121	−0.933, 7.909
Bleeding duration	6.08+/−7.417	19.08+/−13.089	*P*=0.000	9.545, 16.475
Return to work	17.49+/−11.9	17.18+/−9.9	*P*=0.550	−2.508, 4.69

po = Postoperative

the treatment of hemorrhoids whereby a cylinder strip of mucosa and submucosa at the top of the hemorrhoids is removed by a 33-mm circular stapler, which creates an anastomosis between the proximal and distal mucosa and submucosa.[12] The staple line is created approximately 4 cm above the dentate line. The procedure does not excise hemorrhoids. The purpose of the procedure is to pexy the anal canal in a more cranial position and to divide the terminal branches of the superior hemorrhoidal arteries, decreasing the blood supply to the hemorrhoidal venous plexus. Several prospective randomized controlled trials have been published comparing SH with MMH, diathermy excision, Ferguson hemorrhoidectomy, etc.,[8–10] and few meta-analyses.[4,11] The results of these studies suggested that SH may be at least as safe as standard open or closed hemorrhoidectomy including the MMH, but the efficacy could not be determined absolutely. The results of the published studies tend to show reasonable evidence in favor of SH for operating time, length of hospital stay, pain, anal discharge, and patient satisfaction. Skin tags and relapse of prolapse were more frequent after SH. Moreover, hemorrhoidopexy was not superior to MMH with regard to postoperative bleeding, urinary retention, difficulty in defecating, anal fissure, anal stenosis, sphincter damage, resumption of normal activity, incontinence, itching, anal resting, and squeezing pressures and analgesia. Recurrence rates are controversial; in some studies, they seem to be higher in SH than MMH;[17] in other studies, there is no significant difference.[9] Longo SH remains somewhat controversial despite the popularity that it has gained largely to the highly publicized "decreased pain" compared to traditional hemorrhoidectomy, although not all studies report this advantage. The reason for the controversy is due to many serious, and sometimes devastating, complications after the use of the PPH instrument including retroperineal sepsis,[7] rectovaginal fistula, life-threatening stapled line hemorrhage, and severe and long-lasting pain reported in a small subset of patients.[6,18,19] This catastrophic report of devastating and life-threatening complications, including a few deaths, has led to a consensus conference in which indications, contraindications, and even the surgical training necessary to be proficient in the technique are thoroughly addressed.[20] The results of our study confirm that SH, when performed by trained specialists, is at least as safe as MMH. We had no life-threatening complications in this study, and the difference in postoperative complications such as anal stricture, urgency, urinary retention, postoperative hemorrhage, and the persistence of skin tags, was not significant. The occurrence of postoperative anal fissure, not present preoperatively, was significantly more frequent after SH than after MMH (6.3% vs 0%, *P*=0.025) (Tables 2 and 3). This may be partially due to the technique itself, with the anal insertion of the large bore operating anoscope CAD used in SH. With regard to operating time, we did not find significant differences between the two techniques. Both surgeons who participated to the study are certified colorectal surgeons with a long learning curve on PPH use of more than 100 procedures done before the beginning of this study. The meticulous attention paid to surgical technique combined with a long learning curve probably contributed to minimizing complications both in SH and in MMH. In our study, the overall assessment of pain during the first eight postoperative days, considered as a whole,

Table 3 Complications, Side Effects and Recurrence

Complications	SH 95 pts	MMH 76 pts	*P*
Anal fissure	6 (6.3%)	0 (0%)	*P*=0.025
Anal stricture	2 (2.1%)	2 (2.6%)	*P*=0.82
Urgency	5 (5.3%)	2 (2.6%)	*P*=0.14
Urinary retention	3 (3.1%)	0 (0%)	*P*=0.11
Skin tags	12 (14.8%)	16 (21%)	*P*=0.14
Hemorrhage	3 (3.1%)	1(2.6%)	*P*=0.43
Recurrence	7 (7.4%)	2 (2.6%)	*P*=0.17
Prolonged hospital stay	7 (7.4%)	0 (0%)	*P*=0.014

showed significantly less pain in SH compared to MMH (P=0.016). In contrast to what other investigators have shown,[1,2,21–24] we detected little difference in pain between the two groups on days 1 and 2 (Fig. 2); although, if we consider the period between the third and the eight postoperative days, the group of patients treated by SH experienced significantly less pain than the group treated with MMH (P=0.002). In a prospective randomized study, a similar phenomenon was observed, with no difference in pain between the two groups on day 1.[9] In most centers, hemorrhoids are not treated in a day-care setting. In our hospital, since 2002, a choice has been made to treat hemorrhoids in day care, and the population of our hospital district has been educated over the years to accept the method so well that, nowadays, most people would refuse to undergo hemorrhoidectomy with a regular hospital admittance and a hospital stay of 2 or 3 days, as most patients are subjected to in other hospitals in our town. Also, to our surprise, the great majority of patients treated for hemorrhoids regardless of the technique did not require further hospital stay; in fact, in the SH group, four patients required observation overnight for pain or urinary retention and three patients required admission for 2 to 4 days for postoperative complication, vs none of the patients treated by MMH. Postoperative symptoms such as pain, soiling, and anal bleeding lasted significantly less in SH than in MMH, as reported in several studies.[1,9,21,22] It was interesting to observe that, regardless of the longer duration of postoperative symptoms related to surgery, there was no significant difference in resumption of normal activities between the two groups, although MMH patients complained about the length of time it took for anal wounds to heal. Both types of treatment were equally effective in curing the symptoms, with no patient declaring him\herself less than satisfied of the cure received. Among early postoperative complications, such as urgency of defecation, urinary retention, and postoperative hemorrhage, there is no difference between the two groups (Table 3) as shown in other studies,[9] while postoperative anal fissure not present preoperatively was significantly more frequent after SH (P=0.025) and usually persisted for several weeks or months, being a major complaint for the patients affected. Late complications such as skin tags and anal stricture did not show differences in the two groups, contrary to several other studies.[1,2,9,21–23,25] There was a low rate of recurrence 2 years after surgery that was not different in the two groups (P=0.17). Recurrence was assessed by the surgeon at physical examination and anoscopy and generally was asymptomatic. With regard to costs, in our experience, SH surgery is more expensive than MMH because of the cost of the stapler device, which is not offset by other costs such as operation time, shorter hospital stay, and earlier resumption of normal activities.

Conclusions

This prospective randomized study with a 3-year medium follow up confirms that SH is associated with less postoperative pain and shorter postoperative symptoms, compared with MMH. The technical component of the operation is straightforward and is feasible with local anesthesia, with very little sedation in a day care setting, the same as the MMH. Long-term outcome is good, and long- and short-term complications are low and comparable to those of MMH. SH in our study was not superior to MMH with regard to postoperative bleeding, urinary retention, anal stenosis, sphincter damage, and resumption of normal activities. Longo SH may be a viable addition to the therapy options available for hemorrhoids with advantages in early postoperative pain and some disadvantages in postoperative complications and costs.

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Surgical Outcomes in Esophageal Cancer Patients with Tumor Recurrence After Curative Esophagectomy

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Abstract This study aimed to identify predictive factors and to evaluate appropriate treatments for recurrence of esophageal cancer after curative esophagectomy. About 166 consecutive patients, who underwent curative esophagectomy, were enrolled between April 1994 and March 2003. Recurrence was classified as loco-regional or distant. Logistic regression analysis was used to identify predictive factors for recurrence. Prognostic factors were evaluated by Log-rank test and Cox proportional hazard regression analysis. The disease-specific 5-year survival was 56.8%. Recurrence was observed in 72 patients (43.4%), with 64 of these occurring within 3 years. The number of metastatic lymph nodes and lymphatic invasion independently predicted recurrence. There were significant differences in time to recurrence and survival time between loco-regional, distant recurrence, and combined recurrence. The 5-year survival time in patients with recurrence was 11.9%, and median survival time was 24 months. There was also a significant difference in survival after recurrence between treatment methods (no treatment vs chemo-radiotherapy, $p=0.0063$; chemotherapy, $p=0.0247$; and radiotherapy, $p<0.0001$). Meticulous, long-term follow-up is particularly necessary in patients with four or more metastatic lymph nodes to achieve early detection of recurrence. Randomized controlled trials should be used to develop effective modalities for each recurrence pattern to improve therapeutic outcomes.

Keywords Esophageal cancer · Lymph node dissection · Metastasis · Tumor recurrence

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Introduction

Many esophageal carcinomas are found to be at the far advanced stage at the time of initial diagnosis[1,2] and cannot be treated curatively. Survival time in patients with advanced esophageal cancer is therefore unsatisfactory in spite of the development of operative procedures and perioperative managements.[3,4] Super-extended (three-field) or extended lymph node (two-field) dissection for esophageal cancer, however, offers favorable surgical outcomes,[5,6] whereas the significance of metastatic lymph nodes has been suggested as an independent prognostic factor in many reports.[7–9]

Some reports did not find preoperative chemoradiotherapy or chemotherapy to be efficacious,[10,11] and others suggested no survival benefits for adjuvant chemotherapy after curative surgery.[12,13] The recurrence rate after curative esophagectomy varies from 25 to 80%,[14–16] which is higher

than many other types of cancer, and patients can recur within only a few years after surgery. Therefore, it is important to understand the predictive factors and to assess the pattern and timing of recurrence after curative esophagectomy to improve therapeutic outcomes. This can also assist in the administration of appropriate treatment according to recurrence pattern. A previous report suggested that treatment response depends on type of recurrence, history of perioperative adjuvant therapy, time of recurrence, and laboratory data.[17] In this study, therapeutic outcomes in patients with recurrent esophageal cancer were retrospectively evaluated according to the pattern of recurrence to evaluate therapeutic strategies after curative esophagectomy.

Materials and Methods

Between April 1994 and March 2003, 166 patients with histologically proven squamous cell carcinoma or adenocarcinoma were enrolled in the study. The patient population was composed of 136 men and 30 women aged 30 to 85 years [mean age±standard deviation (SD)=63.7± 8.4 years]. Exclusion criteria included previous gastric resection, preoperative chemoradiotherapy and postoperative radiotherapy for esophageal cancer. The patients underwent transthoracic esophagectomy followed by esophagogastric anastomosis using the gastric conduit at the Department of Gastroenterological Surgery and the Department of Surgery, Gastroenterological Center, Yokohama City University, Japan. Preoperative diagnosis involving a barium-meal study, endoscopic examination with biopsy, and computed tomography (CT) was routinely carried out on all patients. Some patients underwent endoscopic ultrasonography to evaluate the depth of invasion.

Staging was principally based on the International Union Against Cancer (UICC)/TNM Classification of Malignant Tumors.[18] The quality of pathological diagnosis was controlled by experienced pathologists in each institution. About 72 patients had tumors located in the lower thoracic of the esophagus, 75 in the middle thoracic, and 19 in the upper thoracic. Pathological stage I of the disease was present in 30 patients, stage IIA in 27 patients, stage IIB in 47 patients, and stage III in 62 patients.

Well-defined tumors were macroscopically observed in 68 patients, ill-defined tumors in 64 patients, and superficial type (flat, slightly elevated, or slightly depressed) tumors were seen in the remaining 34 patients. The mean pathologic tumor diameter (±SD) was 56.2±19.6 mm. Two-field (thoraco-abdominal) lymph node dissection was performed in 123 patients and three-field (cervico-thoraco-abdominal) lymph node dissection in 43. Three-field lymph node dissection was selected for patients with a tumor in the upper or middle third near the upper third of the esophagus. Lymph node metastasis was observed in 102 patients (61.4%). All lymph nodes were defined in accordance with the TNM Classification of Malignant Tumors.

Adjuvant Chemotherapy

Adjuvant chemotherapy was performed in 59 (35.5%) patients with pathologically identified lymph node metastasis, good performance status, and who gave informed consent. About 600 mg/m^2 5-fluorouracil and 6 mg/m^2 cisplatin were intravenously administered for 2 weeks at 2-day intervals. The protocol was continued twice a year for 2 years.

Follow-up Protocol

All patients underwent a blood examination every 3 months, a CT scan every 6 months, and an annual endoscopic examination. If gastrointestinal symptoms were reported, an additional examination was carried out. After the fifth year, patients received an annual check-up at an outpatient clinic. The mean follow-up time was 44.9+31.3 months.

Definition of Recurrence

Loco-regional recurrence was defined as tumors occurring at lymph nodes in the neck, mediastinum including anastomotic site, or upper abdomen at the site of initial esophagectomy and lymph node dissection. Distant recurrence was defined as hematogenous metastasis within the solid organ, lymph nodes at the abdominal para-aorta, or peritoneal metastasis. Diagnosis of recurrence was made histologically, cytologically, and radiologically. Combined recurrence was defined as that both loco-regional and distant recurrence were detected simultaneously or within 30 days.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program version 10.0 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. The chi-square test was used to evaluate the difference in proportions and the Student's t test was used to evaluate the continuous variables. All data were expressed as means±SD. The predictive factors of recurrence was evaluated by univariate analysis using the following 13 variables (age, gender, location of tumor, macroscopic appearance, tumor diameter, histologic type, depth of invasion, lymph node metastasis, number of metastatic lymph nodes, lymphatic invasion, venous invasion, type of lymph node dissection, and adju-

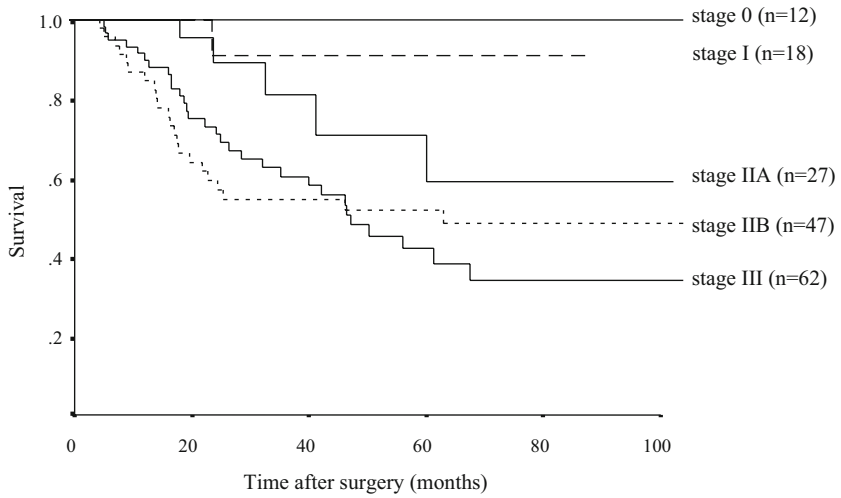

Figure 1 Disease-specific survival according to UICC/TNM classification.

vant chemotherapy). Of these 13 covariates, location of tumor, histological type, depth of invasion, and lymph node metastasis were employed based on UICC/TNM classification. Macroscopic appearance, lymphatic invasion, and venous invasion were principally according to the Japanese guidelines for clinical and pathological studies on carcinoma of the esophagus.[19] Number of metastatic lymph nodes,[8] type of lymph node dissection,[15] and adjuvant chemotherapy[20] were selected according to the previous studies. The logistic regression model was used for independent predictive factors of recurrence by using the variables selected as significant on univariate analysis. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Cox proportional regression analysis for disease-specific survival was applied using the following 12 variables (age, gender, location of tumor, macroscopic appearance, tumor diameter, histological type, depth of invasion, lymph node metastasis, number of metastatic lymph nodes, lymphatic invasion, venous invasion, and adjuvant chemotherapy). A p value of <0.05 was regarded as significant.

Treatments were selected after all possible alternative procedures had been explained to the patient and their informed consent had been obtained. Of the 166 patients, 89 patients gave informed consent who were alive when this retrospective study was conducted. The institutional review board approved this study.

Results

Pattern and Timing of Recurrence

Of the 166 patients registered, recurrence was observed in 72 (43.4%). A total of 38 patients (52.8%) recurred within the first year, 60 (83.3%) within 2 years, and 64 (88.9%)

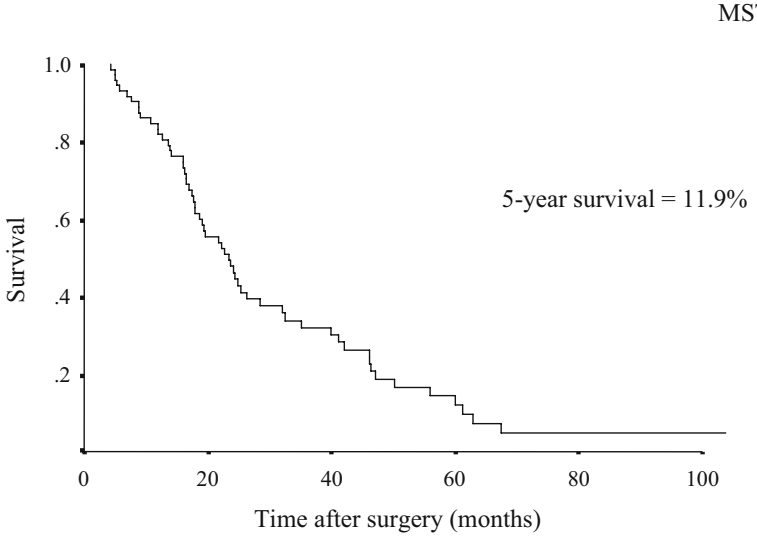

Figure 2 Disease-specific survival in patients with recurrence. *MST* Median survival time.

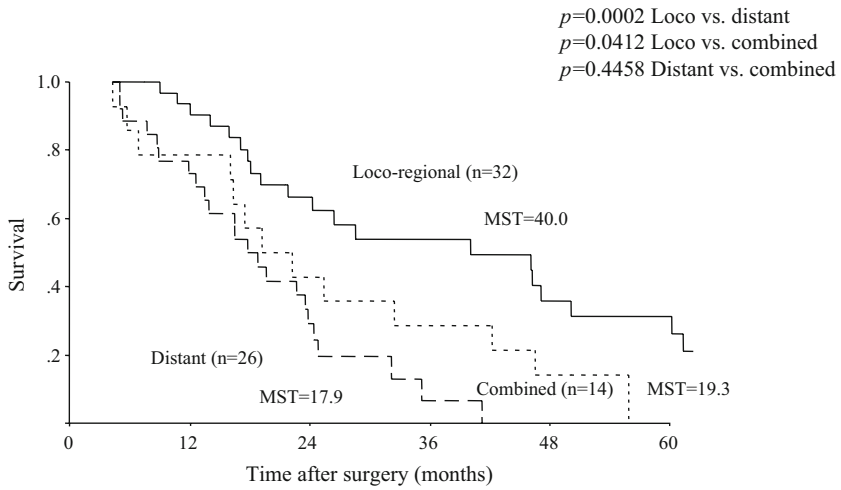

Figure 3 Disease-specific survival according to recurrence pattern. *MST* Median survival time.

within 3 years. Loco-regional recurrence was observed in 32 patients, distant recurrence in 26, and combined (loco-regional and distant) in 14. About 48 patients had a single site of recurrence, 21 had two recurrence sites, and 3 patients had three recurrence sites. There was no local recurrence amenable to re-resection. There was no significant difference in the 13 clinicopathological factors between patients with each pattern of recurrence. Time to recurrence in patients with loco-regional recurrence was 21.6± 16.3 months, that in patients with distant recurrence was 9.7±5.1 months, and that in patients with combined recurrence was 11.9±8.1 months. There were significant differences in time to recurrence between loco-regional and distant recurrence (p=0.0007) and combined recurrence (p=0.0409). Of 46 patients with loco-regional recurrence, 15 had cervical lymph nodes recurrence. Of 32 patients with only loco-regional recurrence, 9 had cervical lymph node recurrence. Moreover, only cervical lymph node recurrence was initially detected in 3 patients (9.4%) among 32. There was no significant difference in the incidence of cervical lymph node recurrence between patients receiving three-field and two-field lymph node dissection (5/11 vs 10/20) in 46 patients with loco-regional recurrence. Of the 32 patients who developed a loco-regional recurrence, 26 who developed distant recurrence and 14 with combined recurrence, 14, 6, and 6 had received adjuvant chemotherapy, respectively.

Survival

The 5-year disease-specific survival rate of the 166 patients was 56.8%. According to UICC/TNM classification, there were significant differences in survival between stage 0 and stages IIA and IIB, between stage I and stages IIB and III, and between stage IIA and stage III (Fig. 1). Of 72 patients with recurrence, 60 died of esophageal cancer during the

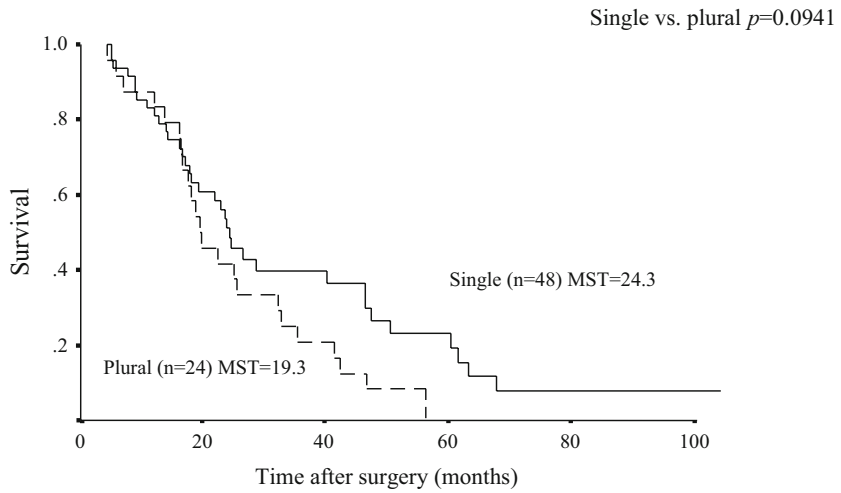

Figure 4 Disease-specific survival according to number of recurrence sites. *MST* Median survival time.

follow-up period. The remaining 12 patients who survived had only loco-regional recurrence (lymph node metastasis).

The 5-year survival time in patients with recurrence was 11.9%, and median survival time was 24 months (Fig. 2). Survival time according to the pattern of recurrence was calculated: median survival time in patients with loco-regional recurrence (n=32), distant recurrence (n=26), and combined recurrence (n=14) were 40.0, 17.9, and 19.3 months, respectively. There was a significant difference in survival between loco-regional recurrence and distant (p=0.0002) or combined recurrence (p=0.0412; Fig. 3). Survival time according to the number of recurrence sites was calculated, but the difference was shown to be non-significant (Fig. 4): Median survival time in patients with a single recurrence site was 24.3 months and that in patients with plural sites was 19.3 months.

Predictive Factors for Recurrence

Clinicopathological determinants were compared between patients with and without recurrence. A macroscopically ill-defined tumor type, deeply invading tumor, greater lymph node metastasis, presence of lymphatic invasion, and presence of venous invasion significantly predicted recurrence (Table 1). Of 13 clinicopathological factors used in univariate analysis, 6 factors (macroscopic appearance, depth of invasion, lymph node metastasis, number of metastatic lymph nodes, lymphatic invasion, and venous invasion) selected as significant were inserted into the logistic regression analysis. According to the logistic regression model, the number of metastatic lymph nodes and lymphatic invasion independently predicted recurrence. Similarly, presence of lymph node metastasis (UICC/TNM, N1) and lymphatic invasion

Table 1 Univariate Analysis of Recurrence After Curative Esohagectomy

Clinical variables	Recurrence (+)(72)	Recurrence (−)(94)	p value
Age (year)			0.7719
<70/≥70	58/14	74/20	
Gender			0.2202
Female/Male	10/62	20/74	
Location of tumor[a]			0.2390
Lower thoracic	26	46	
Middle thoracic	36	39	
Upper thoracic	10	9	
Macroscopic appearance[b]			0.0031
Superficial	6	28	
Well-defined	34	34	
Ill-defined	32	32	
Tumor diameter (mm)			0.1163
<50	32	57	
≥50 to <100	39	36	
≥100	1	1	
Histological type[a]			0.0516
Well diff. squamous	16	22	
Moderately diff. squamous	8	52	
Poorly diff. squamous	17	15	
Adenocarcinoma	11	5	
Depth of invasion[a]			0.0002
T1/T2/T3/T4	8/23/39/2	35/20/30/9	
Lymph node metastasis			<0.0001
N1	59	43	
Number of metastatic lymph nodes			<0.0001
0/≤3/≥4	13/37/22	51/5/8	
Lymphatic invasion[b]			<0.0001
Presence	56	38	
Venous invasion[b]			<0.0001
Presence	49	46	
Type of lymph node dissection			0.1200
Two-field	49	74	
Three-field	23	20	
Adjuvant chemotherapy			0.8934
Presence	26	33	

[a] TNM/UICC classification
[b] Japanese guidelines for clinical and pathological studies on carcinoma of the esophagus

Table 2 Logistic Regression Analysis of Recurrence After Curative Esophagectomy

Variable	χ^2	Odds ratio (95% CI[a])	p value
Number of metastatic lymph nodes	11.263		0.004
≤3/0		2.568 (1.109–5.947)	
≥4/0		6.249 (2.116–18.455)	
Lymphatic invasion	7.889		0.005
Presence/absence		3.038 (1.399–6.598)	
Lymph node metastasis[b]	8.199		0.004
N1/N0		3.226 (1.447–7.193)	
Lymphatic invasion	8.641		0.003
Presence/absence		3.155 (1.466–6.787)	

[a] 95% Confidence interval
[b] TNM/UICC classification

significantly predicted recurrence in another analysis using lymph node metastasis (UICC/TNM, N1) instead of the number of metastatic lymph nodes (Table 2).

Treatments for Recurrence

Chemoradiotherapy was employed in 29 patients, chemotherapy in 28, radiotherapy in 5, and no treatment was performed in 10 patients. Chemo-radiotherapy was performed in 24 patients with loco-regional recurrence and 9 patients with distant recurrence. Chemotherapy was performed in 22 patients with distant recurrence and 14 patients with loco-regional recurrence. Radiation alone was employed in five patients with loco-regional recurrence and one patient with distant recurrence. No treatment was performed in eight with distant recurrence and three with loco-regional recurrence. There was a significant difference in the correlation of recurrence site and treatments (p=0.0043).

Survival After Recurrence

The 5-year survival time after recurrence in 72 patients with recurrence was 14.3 months and median survival time was 10 months (Fig. 5).

Prognostic Factors for Disease-specific Survival After Recurrence

Cox proportional regression hazard model was used to evaluate prognostic factors after recurrence using 12 clinicopathological factors (age, gender, location of tumor, macroscopic appearance, tumor diameter, depth of invasion, lymph node metastasis, histological type, lymphatic invasion, venous invasion, pattern of recurrence, and treatment for recurrence). The treatment for recurrence was selected as an independent prognostic factor after recurrence. Each treatment significantly affected survival after recurrence (chemotherapy, hazard ratio=0.340 (0.158–0.733); radia-

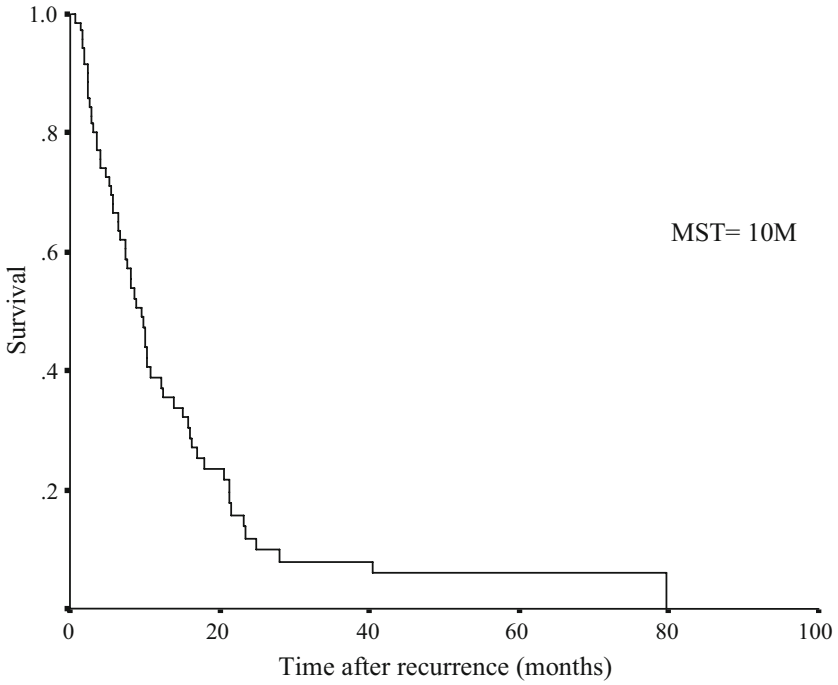

Figure 5 Disease-specific survival after recurrence. *MST* Median survival time.

tion, hazard ratio=0.180 (0.047–0.684); chemotherapy, hazard ratio=0.166 (0.073–0.375), $p<0.0001$).

Survival After Recurrence in Each Treatment

Median survival times in patients with chemoradiotherapy, chemotherapy, radiotherapy, and no treatment were 11, 8, 16, and 3 months, respectively. There were significant differences in survival between no treatment and chemoradiotherapy, chemotherapy, or radiotherapy ($p=0.0063$, $p=0.0247$, $p<0.0001$, respectively). Moreover, there was a significant difference in survival between chemoradiotherapy and chemotherapy ($p=0.0217$; Fig. 6).

Discussion

The current study shows that patients with four or more metastatic lymph nodes are likely to experience tumor recurrence after curative esophagectomy for esophageal cancer. It is therefore necessary to perform meticulous follow-up appointments for such patients. Patients with loco-regional recurrence may be treated effectively with chemoradiotherapy or radiotherapy, whereas new effective modalities for distant recurrence should be established.

Surgical resection with lymph node dissection is one of the most effective modalities for treatment of esophageal cancer.[5,6] In Japan, cervical lymph node dissection in addition to conventional thoraco-abdominal lymph node dissection, i.e., three-field lymph node dissection, has been advocated for the improvement of surgical outcomes at many institutions.[21,22] However, the efficacy of this operative procedure has not been widely accepted. As shown in the current study, the number of retrieved lymph nodes did not affect tumor recurrence after curative surgery. Moreover, the incidence of cervical lymph node recurrence was equal after both three-field and two-field lymph node dissection.

A previous study found that the incidence of cervical lymph node recurrence was 15% even after three-field lymph node dissection,[20] which is a similar value to that reported after two-field lymph node dissection.[23] Two-field lymph node dissection may therefore offer equal therapeutic outcomes to those achieved by three-field lymph node dissection when radiotherapy is performed for cervical lymph node recurrence.

As shown in the current study, the number of metastatic lymph nodes is an independent predictive factor of recurrence. Therefore, even super-extended lymph node dissections are limited in their improvement of survival for patients with multiple metastatic lymph nodes. Consequently, the oncological behavior of the tumor rather than the extension of lymph node dissection may affect survival outcomes.

More than 50% of tumor recurrences occurred within 12 months of curative esophagectomy in the present study. Moreover, occurrences were earlier and therapeutic outcomes worse in patients with distant recurrences compared with loco-regional recurrences. These findings contrast with previous reports that observed early distant recurrence after curative esophagectomy.[23,24]

A previous prospective study showed a high incidence of micrometastasis in the rib or the iliac bone.[25] Neither micrometastasis nor macrometastasis can be identified by current imaging tools and may already occur at the time of operation, after which they grow rapidly. Therefore, it is important to establish the usefulness of adjuvant chemotherapy, particularly as its significance has been questioned by the

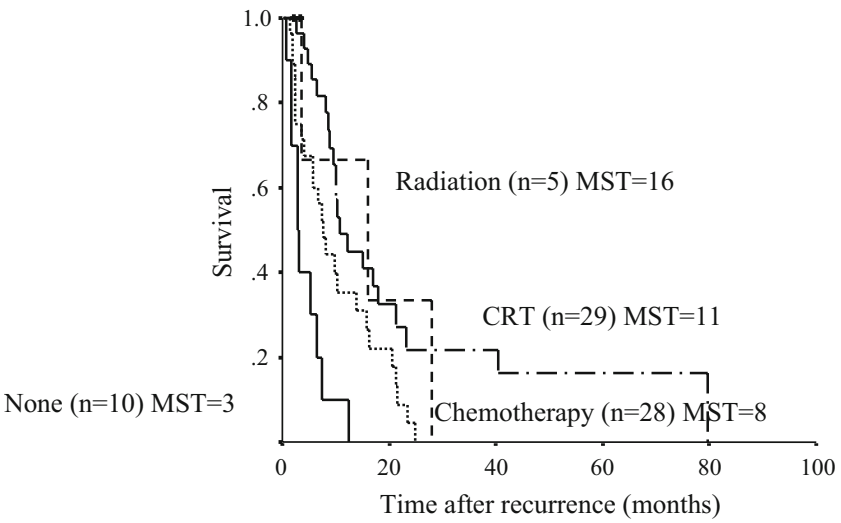

Figure 6 Disease-specific survival after recurrence in each treatment. *MST* Median survival time.

findings of some randomized controlled trials.[12] One study, however, revealed the therapeutic effect of adjuvant chemotherapy in patients with pN1 esophageal cancer,[13] whereas the NCCN esophageal cancer guidelines of 2007 suggested that adjuvant therapy has only category 2B level evidence.[26] In the current study, we also found that adjuvant chemotherapy did not influence tumor recurrence, but its usefulness should be examined in a larger volume study of patients with a high number of metastatic lymph nodes. Moreover, it is important to establish a detection method for the site of recurrence at the earliest opportunity and to develop effective chemotherapeutic agents to improve therapeutic results.

In the current study, many loco-regional recurrences were detected in the mediastinum, where lymph nodes had been dissected at the initial operation. Preoperative diagnosis by positron emission tomography/CT[27,28] or concept of sentinel node navigation surgery[29,30] may decrease the number of residual metastatic lymph nodes and improve surgical outcomes. In our study, chemoradiotherapy or radiotherapy were used for the treatment of loco-regional recurrence and offered favorable therapeutic outcomes. As blood flow to the remaining lymph nodes may be reduced after surgical lymph node dissection, chemotherapy alone may not be sufficient to deliver chemotherapeutic agents to the tumors. Chemoradiotherapy or radiotherapy, therefore, may be more effective for treatment of localized tumors. As loco-regional recurrence often occurs long after initial surgery, compared with distant recurrence, meticulous long-term follow-up of patients is necessary to achieve early detection.

In the current study, each treatment was selected as an independent prognostic factor after recurrence and resulted in a more favorable therapeutic outcome compared with no treatment. However, this study is retrospective and statistical bias may affect the outcomes. Patients who did not receive treatment had a poor performance status, were older, or gave no informed consent. Moreover, chemotherapy was frequently performed in patients with distant metastasis, whereas chemoradiotherapy was mainly employed in patients with loco-regional recurrence. Radiotherapy alone was chiefly advocated in patients with loco-regional lesions who had already been administered adjuvant chemotherapy. As the selection criteria for treatment were controlled by the physician, future work should focus on a randomized controlled trial conducted in patients who do and do not receive treatment.

Conclusion

Meticulous and long-time follow-ups are necessary, particularly for those patients with four or more metastatic lymph nodes, to achieve early detection of recurrence. It is also important to develop effective modalities for each recurrence pattern using randomized controlled trials to improve therapeutic outcomes.

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Long-term Outcome of Cruroplasty Reinforcement with Human Acellular Dermal Matrix in Large Paraesophageal Hiatal Hernia

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Abstract
Background Laparoscopic repair of a large hiatal hernia using simple sutures only for the cruroplasty is associated with a high recurrence rate. The solution was to place synthetic mesh over the cruroplasty thereby decreasing recurrence rates in exchange for complications, such as gastric and esophageal erosions. Our initial report investigated the use of human acellular dermal matrix (AlloDerm) as a more suitable alternative. This study highlights our long-term results > 1 year of cruroplasty reinforcement with AlloDerm in the repair of large hiatal hernias.
Methods and Material This is a retrospective study performed at our university. Between 2005 and 2006, 52 consecutive patients with large hiatal hernias had the cruroplasty site reinforced with AlloDerm. The variables analyzed were age, sex, weight, height, hiatal hernia size, operative time, length of hospital stay, follow-up, and postoperative complications.
Results The mean for age was 56.7 years, for weight was 87.9 kg, for height 117 cm, for hernia size was 5.75 cm, operative time was 121 min, and for hospital stay was 1.36 days. Complication included pneumothorax, 3 (5.5%); atelectasis, 1 (1.9%); urinary retention, 1 (1.9%); and recurrence, 2 (3.8%).
Conclusion Laparoscopic hiatal hernia repair with reinforcement using human acellular dermal matrix can be performed safely with a short hospital stay and low rate of complications, especially a low rate of recurrence.

Keywords Large hiatal hernias · Cruroplasty · Mesh · Human acellular dermal matrix · Hernia recurrence

Introduction

Laparoscopic repair of large hernias has been shown to be safe with similar benefits to most minimally invasive surgical procedures, including less pain, shorter hospital stay, and a quicker recovery. However, a number of studies have questioned whether the repair done with suture approximation of the crura alone is effective and durable. Many believe that the reason a laparoscopic repair fails to maintain a durable and lasting closure of the hiatus is related to increased intra-abdominal pressure weakening the repair, leading to prolapse of the stomach and fundoplication through the crus.

The initial laparoscopic technique of cruroplasty place interrupted, nonabsorbable sutures. However, some reports have shown that patients with a laparoscopic repair of a hiatal hernia had a higher recurrence rate compared to those with thoracotomy or laparotomy repair.[1,2] In addition, this laparoscopic primary repair has been complicated with high rates intrathoracic wrap migration.[3,4]

Several studies have addressed this issue by looking at synthetic mesh for a nontension or tension-free repair of large hiatal hernias.[4,5] Granderath et al. published in 2005 a prospective randomized study, which demonstrated a significant reduction in recurrence rates by using synthetic mesh in large hiatal hernia repairs.[5] However, other studies reported erosion of the synthetic prosthesis into the esophagus and stomach resulting in infections and strictures.[6–9] Even pediatric surgeons were having similar problems with the synthetic mesh hiatoplasty. Dutta reported on a 12-year-old boy that presented with esoph-

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ageal obstruction from the erosion of a synthetic mesh used to buttress a hiatal hernia repair 9 years prior.[10] It is a delicate balance in the younger patient population to find a material that does not have these complications as they will have to live a lifetime with the prosthetic.

Therefore, in 2006, several authors published papers, including our own paper, as well as the randomized prospective trials published by Oelschlager et al. looking at the use of biological material for the repair of large hiatal hernia.[11] In the study by Oelschlager et al., patients with biological material for hiatal repair had a decrease in recurrent hiatal hernia over a 6-month period compared to a control group who had just cruroplasty repair. Ringley et al. demonstrated a similar decrease in recurrence rates compared to historical controls, during the 6 months in our trial study.[12]

It appears that the ideal material for a cruroplasty would provide the reinforcement needed to diminish recurrent herniation whereas being recalcitrant to visceral erosions and postoperative dysphagia. An optimal biodegradable material would provide the scaffolding for significant growth of tissue, continued reinforcement, and absence of a permanent foreign body at the gastroesophageal junction. Alloderm is a biologic that does not dissolve, but is incorporated into the host tissue and should do so by 9 months. It would be imperative to know what the long-term data reports beyond the 1-year mark. Therefore, we reviewed our long-term outcomes and are presenting the data on the use of acellular dermal matrix to augment the repair of large hiatal hernias at our institution.

Materials and Methods

Patients

Adult patients undergoing laparoscopic large hiatal hernia (Fig. 1) repair combined with Nissen fundoplication procedures in a single academic institution between March 2005 and March 2006 were entered into the study prospectively.

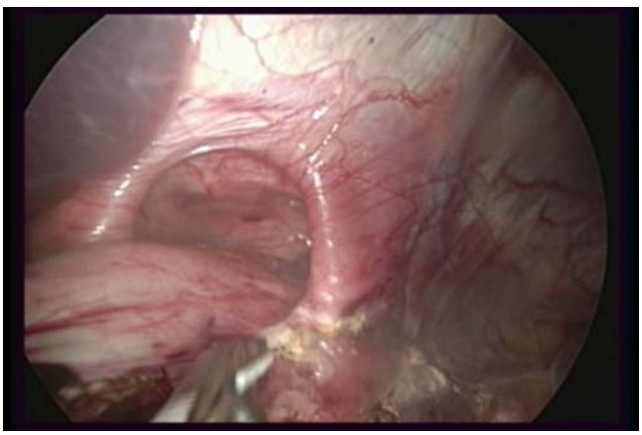

Figure 1 Laparoscopic view of hiatal hernia.

This study was IRB approve #042-05. There were 52 patients (24 male, 28 female). A large hiatal hernia was defined as a defect >5 cm, by a radiologist during the upper gastrointestinal (UGI) study. Variables collected were age, gender, weight, height, follow-up, size of the hiatal hernia, preoperative and postoperative symptom scores, pH studies, operative times, complications, length of hospital stay, and hiatal hernia recurrence. All patients had cruroplasty reinforced with an onlay AlloDerm patch.

Patients were seen in postoperative follow-up at 2 weeks, 6 months, and then yearly thereafter. Upper gastrointestinal swallow studies were obtained postoperatively at day 1, 6 months, and then yearly.

Preoperative Evaluation

All subjects underwent preoperative barium upper gastrointestinal radiological studies to define their esophageal anatomy and to screen for evidence of hiatal herniation. Routine preoperative esophageal gastroduodenoscopies (EGD) were completed on all patients to confirm hiatal herniation and screen for sequela of gastroesophageal reflux disease (GERD). This evaluation was performed with all patients off prokinetic and gastrointestinal antisecretory agents. The pH study data was obtained by a dual-probe catheter placed transnasally with a distal probe located 5 cm proximal to the upper border of the distal high-pressure zone. A portable digital data logger (Synetics Medical, Shoreview, MN, USA) was used to record pH fluctuations whereas the patient recorded symptoms in an event diary.

Esophageal manometry was performed using water perfused capillary system along with an 8-port, radial manometry catheter (Medtronic, Shoreview, MN, USA). Patients were examined in the supine position. The catheters were perfused with distilled water at a constant rate of 0.06 ml/s. The lower esophageal sphincter (LES) was measured using a station pull-through technique, averaging the pressure from four radially placed channels over three to five respiratory cycles. With a linear arrangement of four channels, the esophageal body was evaluated with ten wet swallows of five milliliters of water. Motility studies were performed in all 52 patients preoperatively.

All subjects scored symptoms of regurgitation, chest pain/discomfort, dysphagia, heartburn, and hoarseness preoperatively in the following manner: 0=never, 1=once a month, 2=once a week, 3=once a day, 4=several times a day. Any reported frequency that fell between two parameters was assigned to the subsequent higher parameter. Symptom scores were repeated 6 months after surgery for comparison to preoperative values.

Surgical Procedure

Patients were placed in the supine position with both arms tucked. Four ports were introduced, and a liver retractor

placed through the epigastrium. The standard left crus approach was used to expose the hiatus and esophagus. Extended transhiatal mediastinal esophageal dissection (Fig. 2) was undertaken until at least 3 cm of intra-abdominal esophagus was achieved without tension, and the hernia sac was completely excised.[12]

The hiatoplasty (Fig. 3) was performed by reapproximation until tension was judged excessive and an onlay patch was then used. A 4×7-cm piece of AlloDerm was soaked in saline for 10 min and a U-shaped section was cut from the center of the mesh to accommodate the esophagus (Fig. 4). The patch was then positioned posterior to the esophagus such that the midportion of the mesh covered the crural sutures. The AlloDerm was then sutured to the diaphragm with four to six 2-0 silk stitches, one at each corner of the patch. Upon completion of crural closure with mesh reinforcement, Nissen fundoplication was performed in the standard fashion followed by an intraoperative upper endoscopy.[13] All trocars were removed under direct visualization. In addition, a barium swallow was performed on postoperative day 1, 6 months, and yearly thereafter.

Results

There were 52 patients with symptomatic large hiatal hernias included in this study (24 male, 28 female). No patient withdrew from the study during follow-up. Regarding follow-up, the median was 16 months (range 12–24). All of the original 20 patients that began with this study including the additional ones have all followed-up at their 2-year mark. The following variables were collected: age, gender, weight, height, follow-up, and size of hernia and listed in Table 1. A large percentage of preoperative patients had GERD symptoms as illustrated in Table 2. There were no conversions to an open procedure, and no major intraoperative or postoperative complications.

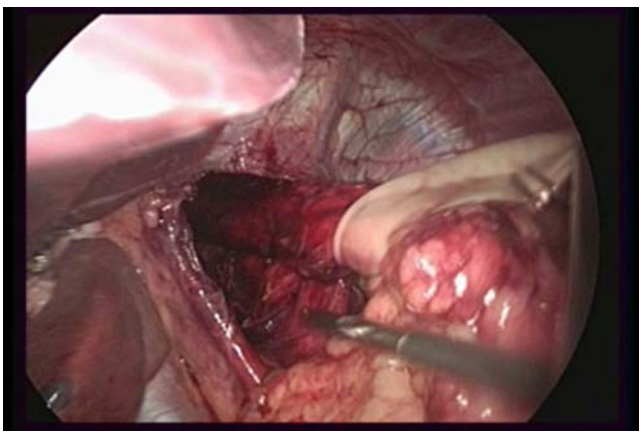

Figure 2 Laparoscopic view of hiatal hernia after transhiatal mediastinal esophageal disection.

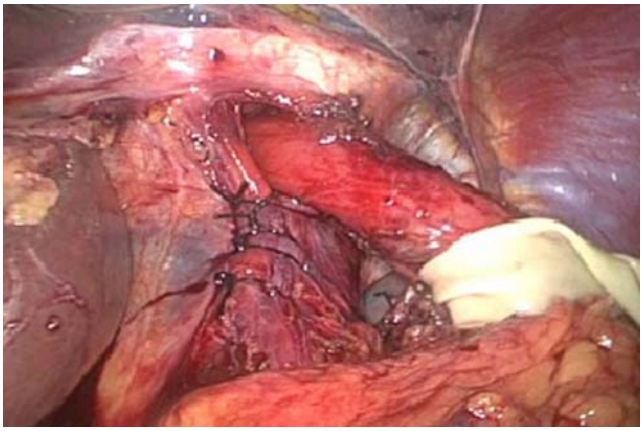

Figure 3 Suture repair of large hiatal hernia.

Minor complications (Table 3) were as follows: pneumothorax, 3 (5.5%), which resolved spontaneously; atelectasis, 1 (1.9%); urinary retention, 1 (1.9%); and finally, recurrence, 2 (3.8%). An EGD diagnosed the first patient's recurrence at 6 months postoperatively. This was followed by a UGI; both studies documented a migration of the wrap, and the patient was rescheduled for surgery. At the time of surgery, the AlloDerm onlay mesh was still intact but the hernia reoccurred above the mesh, the Nissen fundoplication was redone, and the patient has done well. The second patient was diagnosed at her 12-month routine UGI study with a small wrap herniation. The follow-up studies included an EGD and a Bravo pH study confirming the small herniation and the minimal symptoms. This patient was treated conservatively with diet and PPIs and has done well. The two patients with the recurrences had no differences from patients without recurrences.

Discussion

Large hiatal hernia is an acquired diaphragmatic defect with the migration of the gastroesophageal junction or variable

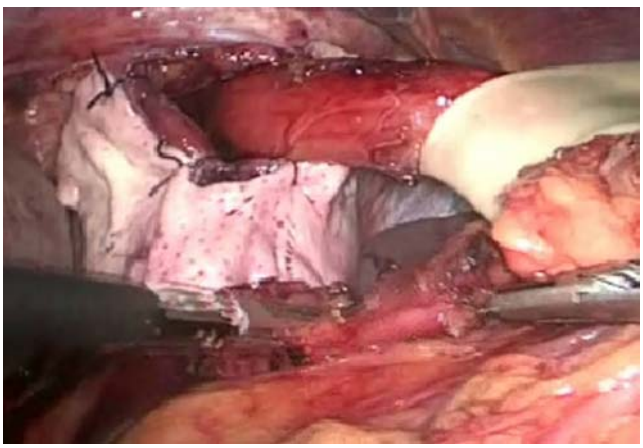

Figure 4 A U-shaped mesh placed over hiatal hernia repair.

Table 1 Patient Demographics

Mean age (years)	56.7 (34–74)
Female number (%)	28 (54)
Male number (%)	24 (46)
Mean weight (kg)	87.9 (63–114)
Mean height (cm)	173 (156–185)
Mean hiatal hernia size (range; cm)	5.75 (5–10)
Median follow up (range; months)	16 (12–24)

In the table above, we have shown the demographics of the patients that took part in our study. There were 52 patients with symptomatic paraesophageal hiatal hernias included in this study (24 male, 28 female).

amounts of the stomach with or without other intra-abdominal organs. The etiology is uncertain, but probably results from a combination of predisposed weakness in the tissues and stress over time. Presentation can occur at any age. These hernias have a risk for serious complications, such as strangulation, necrosis, or gastric perforation.[13] Once a patient has developed a symptomatic paraesophageal hiatal hernia, surgical intervention should be considered.

Reliable hiatal hernia repair remains to be a challenge, secondary to high recurrence rates between 7% and 42%.[1,5,14] Many technical alterations have been proposed to diminish this rate, such as gastropexy, hernia sac resection, and extended esophageal mobilization via a thoracotomy.[14] However, these alterations have not alleviated the problem of intrathoracic wrap migration. Based on data gained from tension-free inguinal and ventral hernia repair, there has been heightened interest in applying these principles to hiatal closure in an attempt to reduce the associated high recurrence rates.[15–18]

Currently, many surgeons choose to perform a laparoscopic approach in large hernia repair for a better anatomical approach to the surgical area and good visualization. Moreover, the benefit of smaller incisions, less postoperative pain, shorter hospital stay, and a more rapid return to normal daily function are desired advantages over open surgery. Using primarily interrupted sutures leads to a high recurrence rate. This can be because of previous thinning and laxity of the muscles, which are devoid of any fascial envelope or significant tendonous tissue. The larger the hiatal hernia defect, the greater the resulting tension on the native tissue during approximation. These characteristics combined with intermittent increases in intraabdominal pressure associated with lifting, coughing, and Valsalva maneuvers experienced throughout a typical day lay the foundation for recurrent herniation.[14] The technical difficulty and morbidity associated with reoperations on hiatal herniation has led many to explore the possibility of adding a prosthetic mesh to buttress the hiatal repair.[14] Multiple publications have revealed a reduction in recurrent herniation with the addition of mesh.[5,9,11,12,19]

However, utilization of a synthetic mesh was reported to have major complications because of ongoing friction at the mesh–esophageal and stomach interface.[20,21] This has resulted in mesh erosion into the esophagus and migration into the stomach. This phenomenon has also been seen with the use of pledgets to augment suture cruroplasty.[22] This permanent foreign body reaction could also explain an increased dysphagia rate and esophageal strictures reported by some with the use of synthetic mesh at the esophageal hiatus.

All of these factors have led to the use of biologic mesh, as an effective alternative, in reducing the recurrence rate as well as avoiding the above mesh-related complications. One type of biologic material is AlloDerm made by LifeCell in Branchburg, New Jersey,USA. It is an acellular dermal matrix derived from donated human skin tissue. The matrix consists of proteins with structurally intact basement membranes, collagen fibers and bundles to support tissue ingrowth, elastin filaments for biomechanical integrity, hyaluronan, and proteoglycans. Experimental evidence suggest that this matrix supports rapid revascularization, and the proteins allow for precipitous migration and binding of host stem cells to promote total integration and transition of the material into surrounding tissue. Animal studies suggest that there is a reduction in adhesions to intraabdominal contents with AlloDerm use. These characteristics appear very advantageous for use in hiatal hernia repair by avoiding the prolonged foreign body phenomenon at the gastroesophageal junction whereas adding strength to the crural closure.

Table 2 Preoperative Symptoms

Symptom	Patients, *n*	Percentage
Regurgitation	48	93
Dysphasia	23	44
Chest Pain	21	41
Hoarseness	27	52
Heartburn	41	79

As shown above, a high percentage of patients had GERD symptoms preoperatively.

Table 3 Operative Statistics and Complications

Mean operative time (range; min)	121 (75–235)
Mean hospital stay (range; days)	1.36 (1–3)
Minor postoperative complications, *n* (%)	
Pneumothorax	3 (5.5)
Atelectasis	1 (1.9),
Urinary retention	1 (1.9)
Recurrences	2 (3.8)

This table shows the average statistical ranges for operative time and hospital stay of the 52 patients that participated in our study at UNMC. No patient withdrew from the study during follow-up. There were no conversions to an open procedure, and no major intraoperative or postoperative complications. The minor complications that were encountered by the patients during their follow-up care are also shown above.

Oelschlager et al. studied this premise, and in 2006, they published a prospective, randomized multicenter study with biologic prosthetic mesh in the repair of hiatal hernias with a recurrence rate of 9%.[11] Our 2 years of experience supports the benefits of AlloDerm when used for cruroplasty reinforcement. The most important finding in this publication is that AlloDerm used as an onlay mesh to buttress cruroplasty is not associated with significant complications including erosions, strictures, obstructions, or high recurrence rates.

In this study, the AlloDerm mesh was used as an onlay and not a bridging method. Meticulous dissection was done to free up both the left and right crus to get a relatively tension-free primary cruroplasty, and then overlaid the mesh on the abdominal side of the repair. We know from studies on ventral hernia by Stoppa and others that when the mesh faces the surface of greatest pressure known as an underlay technique, the result is greater mesh longevity and lower recurrence rates. An integral part to our surgical technique was the combination of suture approximation and mesh onlay. We suggest that this would become the ideal surgical repair for any hiatal hernia of 5 cm or more. We would also propose that similar repairs of smaller hiatal hernias would have the same benefits, although we did not have this data in our study. Finally, if the defect is so large that the biologic mesh has to be used as a bridge, we feel that this may be less suited, as we saw a slightly higher rate of recurrence when we could not achieve primary cruroplasty.

Conclusion

Laparoscopic repairs of large hiatal hernia with reinforcement of human acellular dermal matrix can be performed safely with a short hospital stay and low rate of complications, especially a low rate of recurrence. This procedure provides a more durable and effective method of repairing a large paraesophageal hiatal hernia with low morbidity and mortality in spite of one patient requiring a reoperation. The use of this application in smaller hiatal hernia repairs warrants further investigation, as well as increasing the thickness of the graft when used as a bridging mesh. We will continue to monitor these patients, and further our prospective data collection, whereas including additional patients in this study group.

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Efficacy of Laparoscopic Mesh-Augmented Hiatoplasty in GERD and Symptomatic Hiatal Hernia. Study Using Combined Impedance-pH Monitoring

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Abstract
Background Laparoscopic fundoplication is the standard antireflux procedure. However, side effects such as gas bloating indicate that the procedure is not unproblematic. Laparoscopic mesh-augmented hiatoplasty (LMAH) might be an alternative operation aimed at restoring the intra-abdominal part of the esophagus and reducing the size of the diaphragmatic hiatus.
Aim The aim of this study was to prospectively evaluate gastroesophageal reflux disease symptoms and gastroesophageal reflux before and after LMAH using 24 h impedance-pH monitoring (MII-pH).
Materials and Methods Twenty patients underwent MII-pH monitoring pre- and 3 months post-LMAH. Symptoms were assessed using the Gastrointestinal Symptom Rating Scale questionnaire.
Results LMAH reduced the mean (SD) reflux syndrome score [pre-op 4.5 (1.7) vs post-op 1.4 (0.9); $p<0.001$], median (25th–75th percentile) distal %time pH<4 [4.9 (3.4–10.3) vs 1.0 (0.3–2.5) %; $p=0.001$) and total number of liquid reflux episodes [27.5 (17.5–38.3) vs 18 (7.3–29.3); $p<0.05$] without changing the number of gas reflux episodes [12 (6–34.3) vs 13.5 (6–20); $p=0.346$). All patients reported no limitation of their ability to belch.
Conclusion LMAH significantly reduces reflux symptoms and esophageal acid exposure without interfering with the ability to vent gas from the stomach documented by an unchanged number of gas reflux episodes before and after LMAH.

Keywords Antireflux surgery · Gastroesophageal reflux disease · Laparoscopic mesh-augmented hiatoplasty · Gas bloat syndrome · Multichannel intraluminal impedance and pH monitoring

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Introduction

Laparoscopic fundoplication (LF) is the operative standard procedure in the treatment of gastroesophageal reflux disease (GERD) and symptomatic hiatal hernias (HH) with paraesophageal involvement.[1,2] However, persisting side-effects such as gas bloating or dysphagia occur in about 20% of the patients and are seen in up to 60%.[3–6] Recently, we described the laparoscopic mesh-augmented hiatoplasty (LMAH) as a potential treatment option for both GERD and symptomatic HH.[7] The procedure combines the modern technique of mesh reinforcement at the hiatus[8–10] and the traditional method of gastropexy[11–13] in fixing the

esophagogastric junction below the diaphragm. Stretching the esophagus and reconstructing an acute angle of His as described by Allison, Hill, and Narbona an efficient reflux control with minor side effects was achieved initially. Still, given the recurrence rates up to 60% after gastropexy without mesh reinforcement, the method was eventually abandoned.[11–13] A consecutive study evaluating symptoms before and 12 months after LMAH in 22 patients reported reflux symptom control of about 80% with hardly any side effects such as gas bloating.[7]

Because of the limited predictive power of symptoms such as reflux or the ability to belch,[14–16] objective evidence should be obtained.

Recently, ambulatory 24 h multichannel intraluminal impedance and pH monitoring[17] (MII-pH) has been validated for the detection of bolus movement in the esophagus and is able to characterize physical (liquid, gas, or mixed) or chemical (acid and non-acid) gastroesophageal refluxates. So far, MII-pH monitoring has been applied in healthy volunteers,[18] patients with GERD[19] and after LF.[20] The aim of this prospective study was to compare the number and chemical and physical content of reflux episodes and symptoms with the focus on gas bloating and the ability to belch before and after LMAH using MII-pH monitoring. A secondary aim of the study was to report MII-pH values after LMAH.

Materials and Methods

From 2004 to 2006, the LMAH was prospectively evaluated at the Surgical Department of the Kantonsspital St. Gallen (tertiary care hospital) in a consecutive, non-selected group of all patients who agreed to undergo this technique. Indications for operation were either objectively proven GERD or symptomatic HH. Informed consent was obtained from every patient.

The surgical technique of LMAH was performed as described in detail previously.[7] Upon incision of the lesser omentum and the peritoneum over the hiatus, the hernia sac, if existent, was reduced completely. After circular dissection of the esophagogastric junction, the hiatus was narrowed by non-absorbable sutures. The specially fashioned polypropylene mesh (Surgipro™ Mesh, Autosuture™, Tyco Healthcare, Wollerau, Switzerland) was applied from behind around the esophagus and fixed towards the diaphragm with staples (Multifier Endo Hernia™ stapler, Autosuture™, Tyco Healthcare, Wollerau, Switzerland). Finally, an anterior cardiopexy was added with non-absorbable sutures (Fig. 1).

HH were intraoperatively classified into type I (sliding), type II (pure paraesophageal), type III (mixed), and type IV (mixed with other than only gastric hernial sac content)

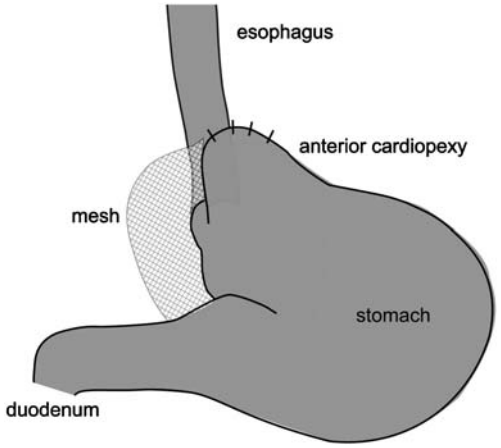

Figure 1 Laparoscopic mesh-augmented hiatoplasty after anterior cardiopexy.

HH. Esophagitis was graded during preoperative upper gastrointestinal endocopy by either Savary-Miller or Los Angeles classification. For the purpose of the present study, we matched Savary-Miller classes I through IV to Los Angeles classes A through D.

Symptoms were assessed preoperatively and 3 months postoperatively by a modified Gastrointestinal Symptom Rating Scale questionnaire[21] including additional questions for gas bloating, vomiting, and dysphagia. Each item was rated on a seven-point Likert scale from no discomfort to very severe discomfort.

Ambulatory MII-pH monitoring was performed using a 6-impedance 1-pH catheter (Sandhill Scientific, Littleton, Colorado, USA). The configuration of the catheter allowed monitoring of changes in intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter (LES) and pH data 5 cm above the LES with a frequency of 50 Hz. Acid suppressive therapy was discontinued for at least 1 week before the recording period. After an overnight fasting period, the combined MII-pH catheter was passed transnasally into the esophagus and stomach and the pH electrode positioned 5 cm above the proximal border of the LES located by stationary pull-through manometry. After a 24-h period of data acquisition, tracings were edited and initially analyzed using a software program (BioView Analysis™, Sandhill Scientific, Highlands Ranch, Colorado, USA). Subsequently, MII-pH data were reviewed by an experienced investigator for artifacts and accuracy of reflux events. The following variables were assessed: esophageal acid exposure calculated as percentage time with esophageal pH<4; number of liquid, gas and mixed reflux episodes (Fig. 2); and acidity of reflux episodes as described by Mainie et al.[22] (acid reflux as MII-detected reflux event with esophageal pH<4; non-acid reflux as MII-detected event during which the pH stays above 4). The Symptom Index (SI) was calculated as the percentage of symptoms preceded by a reflux episode within a 5-min

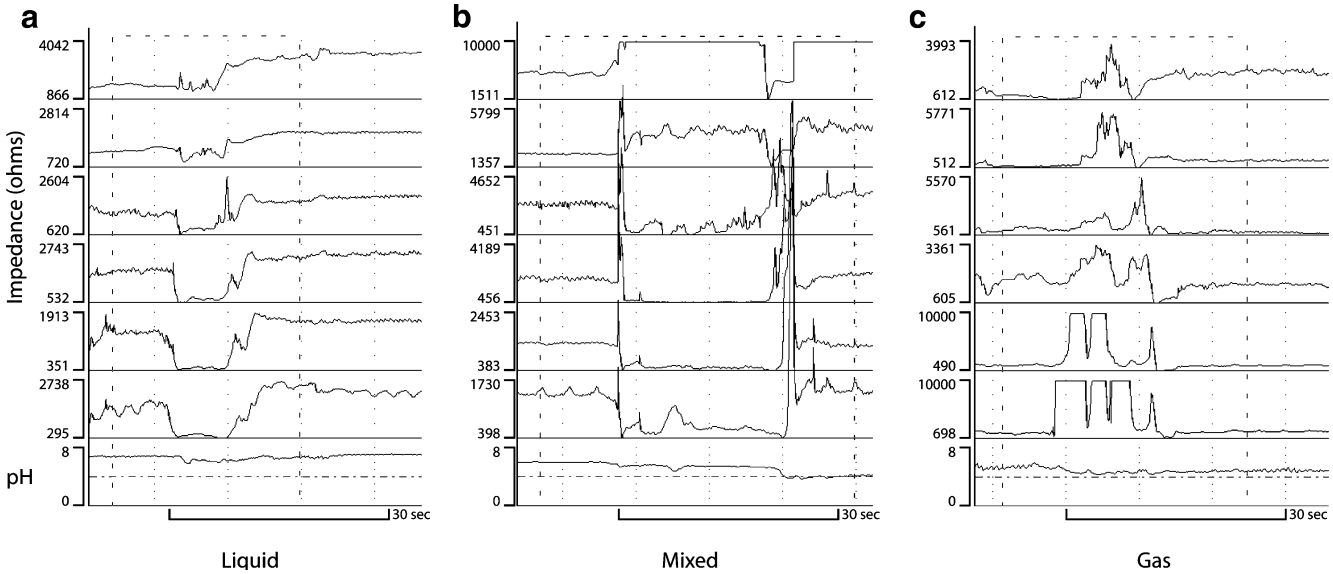

Figure 2 Examples of impedance-pH recordings of liquid, mixed and gas reflux episodes. Impedance measuring segments are located 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter (*LES*) and the pH sensor 5 cm above the LES. Liquid gastroesophageal reflux episodes (**a**) are identified by impedance as rapid decline in impedance starting in the distal esophagus and advancing over time to the proximal esophagus. Gas reflux episodes (**c**) are identified by a rapid orally progressing rise in impedance to high values. Mixed reflux episodes (**b**) have features of both liquid (i.e., decline in impedance) and gas (i.e., rise in impedance) presence in the esophagus.

time window divided by the total number of symptoms. The symptom index was considered positive if SI>50% (i.e., at least half of the symptoms being temporally associated with reflux). Previously published normal value data were used to assess if patients had a normal or abnormal number of reflux episodes.[18]

Patients available for pre- and postoperative MII-pH monitoring were included in this study.

Symptom scores are expressed as mean (SD), and measured variables are presented as median (25th–75th percentile). The normality of data distribution was assessed by Kolmogorov–Smirnov analysis. Statistical analysis was performed using the paired *t* test, Wilcoxon signed rank test, chi-square test, and Mann–Whitney *U* test as dictated by data distribution. A two-sided error probability of $p<0.05$ was considered statistically significant.

In determining the sample size for the present study, we considered a 30% reduction in the total number of reflux episodes a clinical meaningful improvement after LMAH. Based on previously published data in healthy volunteers[18] (mean number of reflux episodes of 42 with SD of 20), we calculated that paired data from 20 patients would be a sufficient large sample size to detect the 30% difference with a power of 80%, whereas the criterion for significance (alpha) was set at 0.05.

Results

In the study period, 48 patients underwent LMAH for GERD or symptomatic HH. Preoperatively and 3 months postoperatively, MII-pH monitoring data were available in 20 patients [8 female; mean age, 51 (range, 27–79) years]. Patient characteristics are shown in Table 1. Nine additional patients had only 3 months postoperative data, as preoperative evaluation included conventional pH monitoring performed at an outside institution. Data from these nine patients were used only to determine normal values post-LMAH.

Pre- and postoperative symptom scores are shown in Table 2. Reflux syndrome score and indigestion syndrome score improved significantly after LMAH. Patients reported less discomfort due to eructation, vomiting, and gas bloating. Dysphagia improved postoperatively even if not statistically significant. Three months after surgery, all patients were able to belch. Vomiting was impossible for three (15%) patients.

The MII-pH monitoring results are shown in Table 3. The median esophageal acid exposure decreased significantly from pathologic to normal values after surgery. The impedance analysis documented decrease in the number of acid reflux episodes from 48.5 to 24.5 ($p<0.05$), whereas the number of non-acid reflux episodes remained the same before and after LMAH. Regarding the physical characteristics of content of the refluxate, liquid and mixed reflux episodes were less frequent ($p<0.05$) after LMAH, whereas the number of gas reflux episodes remained unchanged. The median bolus clearance time was 14 s preoperatively and differed not significantly after LMAH. Subsuming the total of 29 postoperatively tested patients, the number of liquid, mixed, and gas reflux episodes was 15 (7–28.5), 21 (10.5–28), and 18 (7–37.5), respectively.

Table 1 Patient Characteristics

	Patients available for pre-and postoperative MII-pH (n=20)	Patients not available for pre-and postoperative MII-pH (n=28)	p value
Hiatal hernia, *n* (%)			
Type I	10 (50)	11 (39)	0.345
Type II	4 (20)	5 (18)	
Type III	6 (30)	11 (39)	
Type IV	0 (0)	1 (4)	
Esophagitis, *n* (%)			
Negative	5 (25)	12 (43)	0.819
LAA/SM I	7 (35)	3 (11)	
LAB/SM II	6 (30)	9 (32)	
LAC/SM III	2 (10)	1 (4)	
LAD/SM IV	0 (0)	3 (11)	
Indication for surgery, *n* (%)			
GERD (HH type I)	10 (50)	11 (39)	0.782
GERD (HH type II/III/IV)	8 (40)	12 (43)	
Symptomatic HH	2 (10)	5 (18)	

HH Hiatal hernia; *LA* Los Angeles classification; *SM* Savary Miller classification; *GERD* gastroesophageal reflux disease

Preoperatively, 13 patients had abnormal distal esophageal acid exposure and 5 patients had normal distal esophageal acid exposure but positive SI. Abnormal distal esophageal exposure was noted in only three patients post-LMAH. Four out of five patients with positive SI improved postoperatively.

Discussion

The present study confirms previously reported observations by our group indicating that LMAH reduces reflux symptoms with little postoperative side effects such as gas bloating.[7] Combined impedance-pH monitoring allowed us to document the selectivity of LMAH in decreasing liquid-containing reflux episodes while allowing gas-only reflux episodes to occur and hereby vent swallowed air from the stomach. The clinical relevance of this observation is supported by the improved eructation and gas bloating scores after LMAH. Last but not least, our study provides a first set of MII-pH values in patients undergoing LMAH.

Recognizing the importance of air swallowing and gas reflux in the pathogenesis of gas bloating, other investigators reported on the frequency of gas reflux after antireflux surgery. Johnsson et al.[23] studied 14 patients before and 3–15 months after total (360°) fundoplication. Evaluating the frequency of manometrically detected gastroesophageal common cavities after gas insufflation into the stomach as surrogate marker for gas reflux episodes, the authors noted a profound decline in the number of transient LES relaxations and gas reflux episodes after 360° fundoplication. Based on these findings, the authors concluded that fundoplication-induced decline in transient LES relaxations contributes to the side effects of the operation, namely, increased flatulence and decreased ability to belch.

More recently, Roman et al.[20] used combined MII-pH monitoring to characterize reflux episodes in 36 patients after LF. Comparing the results with previously collected data in healthy volunteers, the authors noticed a lower number of gastroesophageal reflux in operated patients (11 in operated patients compared to 44 in healthy volunteers; $p<0.001$). Fundoplication affected all types of reflux episodes, including gas reflux episodes. Operated patients had a median of one gas reflux episode per 24 h compared to ten gas reflux episodes per 24 h in healthy volunteers.[18,20] These data underscore the concept that a 360° fundoplication overcorrects the mechanical deficiencies in the gastroesophageal junction[24,25] held responsible for the restriction to belch and increased frequency of gas bloat-

Table 2 Symptoms Preoperative and 3 Months after Laparoscopic Mesh-Augmented Hiatoplasty

	Preoperative (n=20)	3 months postoperative (n=20)	p value
Reflux syndrome	4.5 (1.7)	1.4 (0.9)	<0.001
Indigestion syndrome	3.6 (1.3)	2.6 (1.3)	<0.05
Eructation	3.8 (2.0)	2.4 (1.6)	<0.05
Vomiting	3.1 (2.3)	1.5 (1.1)	<0.05
Gas bloating	3.7 (1.8)	2 (1.3)	<0.05
Dysphagia	2.9 (2.0)	1.9 (1.3)	0.057

Values are mean (SD). Reflux syndrome score and indigestion syndrome score were assessed using the GSRS questionnaire.

Table 3 Results of Combined Impedance-pH Monitoring in Patients before and after Laparoscopic Mesh-Augmented Hiatoplasty

	Preoperative (n=20)	Postoperative (n=20)	p value
Acid esophageal exposure (%)	4.9 (3.4–10.3)	1.0 (0.3–2.5)	0.001
Abnormal pH-metry [n(%)]	13 (65)	3 (15)	0.001
Reflux episodes based on pH			
Acid	48.5 (25.5–68.3)	24.5 (9–31)	<0.05
Non-acid	28 (17.5–51.8)	25.5 (12.3–37)	0.192
Reflux episodes based on physical content			
Liquid	27.5 (17.5–38.3)	18 (7.3–29.3)	<0.05
Mixed	34.5 (16.3–53.3)	20 (9.8–28)	<0.05
Total liquid and mixed	56 (45–87.3)	37 (22–61)	<0.05
Gas	12 (6–34.3)	13.5 (6–20)	0.346
Positive SI [n(%)]	18 (90)	6 (30)	<0.001
Bolus clearance time (s)	14.5 (12–16)	9 (7–13)	0.178

Values are median (25th–75th percentile).
SI Symptom index

ing[3,5] after fundoplication. Noticing that all our patients were able to belch, had lower eructation, and gas bloating scores, our study suggests that LMAH might be a more physiologic intervention than full 360° fundoplication.

Whereas there is no single mechanism explaining the effect of antireflux surgery, the post-surgical augmentation of the antireflux barrier has been explained by changes in the esophageal junction pressure, its incomplete relaxation, and the rate of transient LES relaxations.[23,26] The reduction of the total number of liquid-containing reflux episodes after LMAH noticed in the present study resulted primarily by decreasing in the number of acid reflux episodes, whereas the number of non-acid reflux episodes remained unchanged after the operation. This observation is concordant with the results of Roman et al.[20] documenting a preferential decrease in acid reflux episodes after LF. Whether or not the selectivity of antireflux surgery for acid reflux episodes occurs through the same or different mechanism in patients undergoing LMAH and those undergoing 360° fundoplication warrants further mechanistic evaluations. Although postprandial transient LES relaxations are commonly associated with acid reflux episodes[19] in GERD patients, recent data suggest that, in off acid suppressive therapy, the majority of gastroesophageal reflux episodes occurring primarily in the first postprandial hour are non-acid.[27] A possible explanation for the patterns seen in the present study (reduction of acid but not non-acid reflux episodes) would be that LMAH does not control immediate postprandial reflux episodes, when the stomach is most distended allowing non-acid liquid and gas content to be vent.

Rydberg et al.[28] investigated the impact of total or posterior partial fundoplication on the function of the LES. They found no difference in the frequency of transient LES relaxations between both groups. However, a frequent observation was that the nadir pressure during transient LES relaxation was higher in patients who had a total fundoplication, presumably by mechanical compression of the LES segment. As a probable consequence, gas reflux during transient LES relaxation was noted more often in patients after partial than total fundoplication. These observations may confirm the mechanism of action of LMAH. The fact that acid and liquid reflux episodes are reduced but gas reflux is not influenced by LMAH could be due to restoring the LES by fixing the esophagogastric junction below the diaphragm without compressing the LES segment as in the case of fundoplication. Further studies using esophageal manometry should be done to confirm the effect of LMAH on the LES and thereby to prove the mechanism of action.

In contrast to LF, LMAH involves applying a mesh in the hiatus. Appropriate concerns have been raised on potential mesh-related complications such as stenosis, erosions, and migrations. Still, there are limited data on the prevalence of mesh complications at the hiatus, most reports being in the form of sporadic case reports. In our experience, no such complications occurred until a follow-up of 12 months.[7] Certainly, a follow-up of 12 months might be too short to make conclusion regarding potential mesh complications. In a recent review, Targarona et al.[29] discussed that mesh reinforcement of the hiatus is safe, and the fears expressed have not been confirmed so far.

The present study has certain limitations. First, the relative short postoperative follow-up period does not allow us to evaluate the durability and potential long-term complications of LMAH. Still, the good early postoperative progress in our patients is encouraging. Second, despite the improved ability to characterize the chemical and physical content of gastroesophageal refluxates, combined MII-pH monitoring provides limited data on the mechanism of gastroesophageal reflux. Prolonged (high resolution) manometry and impedance-pH monitoring would have allowed a better evaluation of the reposition of the LES below the diaphragm, appreciation of the LES resting and residual pressure, and frequency of transient LES relaxations associated or not with reflux before and after LMAH.

Third, the study would have been strengthened by the availability of a control group. Still, comparing pre- and postoperative data in our consecutive non-selected patient collective provides adequate information to evaluate the efficacy of LMAH as prerequisite for a randomized trial.

Conclusion

In conclusion, LMAH significantly reduces reflux symptoms and liquid-containing gastroesophageal reflux episodes without interfering with the ability to vent gas from the stomach documented by an unchanged number of gas reflux episodes before and after LMAH. A randomized clinical trial comparing LMAH to LF is currently underway.

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Risk Factors of Postoperative Anastomotic Stricture After Excision of Choledochal Cysts with Hepaticojejunostomy

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Abstract The aim of this study was to investigate the risk factors of postoperative anastomotic stricture after excision of choledochal cysts and hepaticojejunostomy. Among 65 patients who underwent surgery for choledochal cyst between March 1995 and June 2005, we selected 34 adult patients who were diagnosed as having choledochal cyst. We divided patients into two groups, depending on postoperative anastomotic stricture developed or not. Medical records and radiological findings of each patient were reviewed retrospectively. H&E stain and Masson–Trichrome stain of each specimen of the resected cyst were performed, and thickness of cyst wall, the grade of fibrosis, loss of smooth muscle layer, loss of mucosa, and infiltration of inflammatory cells were measured. Of the 34 patients, excision of choledochal cyst and hepaticojejunostomy were done in 33 patients, and 1 patient with chronic pancreatitis underwent pylorus-preserving pancreaticoduodenectomy. Anastomotic stricture and intrahepatic duct stones postoperatively developed in eight patients; one patient of 19 type I cyst and seven patients of 15 type IVa, developing significantly more in the type IVa choledochal cyst ($P<0.05$). The size of choledochal cyst in the stricture group was 7.0 cm, and that of the non-stricture group, 4.2 cm, showing significant difference between the two groups ($P<0.05$). The stricture group presented shorter duration of symptoms (27.63±61.72 days; ranged, 1~180 days) than the non-stricture group (483.33±916.41 days; ranged, 1~3,560 days), and it was statistically significant ($P<0.05$). Pathologically, significant difference was found between anastomotic stricture and infiltration of inflammatory cells ($P<0.05$). The results indicate that anastomotic stricture is influenced by the type IVa choledochal cyst, size of cyst, duration of symptoms, and the grade of infiltration of inflammatory cells. Therefore, closed careful follow-up is important in patients who underwent cyst excision with hepaticojejunostomy for type IVa choledochal cyst. If the anastomotic stricture develops, nonoperative management should be recommended, rather than operation, as much as possible.

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Introduction

Choledochal cyst is a relatively rare disease, characterized by dilatation of the intra- and/or extrahepatic part of the biliary tree. Total cyst excision with hepaticoenterostomy is the treatment of choice for choledochal cyst.[1,2] Cystoenterostomy, which is used as a drainage procedure, has been associated with high morbidity rates and has a potential for malignant change in the biliary tree.[3–5] Furthermore, excision has also the advantage of stopping reflux of pancreatic juice through pancreaticobiliary maljunction, which is often associated with choledochal cysts.[6]

Table 1 Clinical Characteristics

Characteristic	Stricture group (n=8)	Non-stricture group (n=26)	P value
Age (years)	29.25 (19~41)	35.50 (17~55)	>0.05
Gender (male/female)	2/6	3/23	>0.05
Type of choledochal cyst			0.011
Type I	1	18	
Type IVa	7	8	
Type of APBDU			>0.05
C-P type	4	17	
P-C type	1	6	
Unknown	3	3	
Size of cyst(cm)	7.050 (1.4~15.0)	4.212 (1.7~10.0)	0.025
Symptom			>0.05
None	0	2	
Pain	7	20	
Pain & Jaundice	0	3	
Others	1	1	
Duration of symptom (days)	27.63 (1~180)	483.33 (1~3,560)	0.024
Laboratory values (preop.)			>0.05
Total bilirubin	1.075	1.416	
AST	113.13	98.53	
ALT	85.38	128.28	

APBDU Anomalous pancreatico-biliary ductal union, *P-C type* pancreatico-choledochal type, *C-P type* choledocho-pancreatic type

Various aspects of epidemiology, presentation, and management of choledochal cysts have been described in literature.[7–9] In the long-term follow-up of patients with choledochal cyst, however, postoperative intrahepatic stone and cholangitis present serious complications. These complications are likely to develop secondary to a postoperative anastomotic stricture in the intrahepatic duct dilatation, and they occur more commonly in patients with type IVa than in patients with type I choledochal cyst.[10–13] Therefore, a question arises why postoperative anastomotic stricture is more common in the type IVa than type I choledochal cyst. The aim of this study was to investigate clinical features of the anastomotic stricture and to elucidate the clinicopathological factors associated with anastomotic stricture after excision of choledochal cysts.

Patients and Methods

Sixty-five patients, who presented with choledochal cyst, were surgically treated between March 1995 and June 2005. Among the 65 patients, we selected 34 patients who were diagnosed as choledochal cyst in adult. Five patients were male, and 29 patients were female, whose age ranged from 17 to 55 years. We also divided the patients into two groups, depending on postoperative anastomotic stricture developed or not. The stricture group was defined as patients who had intrahepatic duct dilatation with obstructive jaundice and stone formation after surgery. Choledochal cyst was classified according to Todani's classification,[14] type IVa was defined as cystic dilatation of both the intrahepatic and extrahepatic parts of the biliary tree, and anomalous pancreatico-biliary ductal union (APBDU) was classified into two types according to Kimura classification[15]; pancreatico-choledochal type (P-C type) and choledocho-pancreatic type (C-P type). Choledochal cyst and APBDU were diagnosed by computed tomography (CT), endoscopic

Table 2 Case Summary of Stricture Group

Number	Gender/age	Type of choledochal cyst	Complication period* (months)	Complication	Management
1	F/21	I	21.2	Stricture (+) IHD stone (+)	PTCS/ stone removal Balloon dilatation
2	F/41	IVa	27.5	Stricture (+) IHD stone (+)	PTCS/stone removal Balloon dilatation
3	F/41	IVa	7.8	Stricture (+) IHD stone (+)	PTCS/stone removal Balloon dilatation
4	F/29	IVa	41.3	Stricture (+) IHD stone (+)	PTCS/stone removal Balloon dilatation
5	F/19	IVa	89.7	Stricture (+) IHD stone (+)	PTCS/stone removal Balloon dilatation
6	M/34	IVa	34.1	Stricture (+) IHD stone (+)	Conservative management
7	F/23	IVa	23.2	Stricture (+) IHD stone (+)	PTCS/stone removal Balloon dilatation
8	M/26	IVa	50.0	Stricture (+) IHD stone (+)	PTCS/stone removal Balloon dilatation

[a] Complication period: Interval from surgery to diagnosis of stricture

IHD Intrahepatic duct, *PTCS* percutaneous transhepatic cholangioscopy

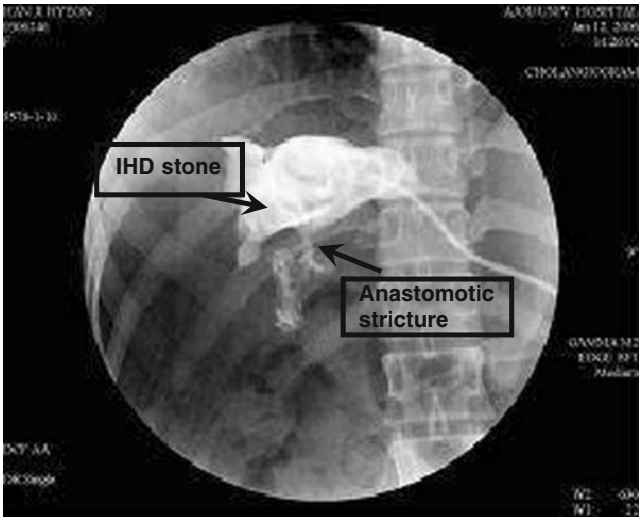

Figure 1 Radiologic figures of postoperative anastomotic stricture. (case no. 5 in Table 2). It showed postoperative percutaneous transhepatic biliary drainage (PTBD) findings. Anastomotic stricture and intrahepatic duct dilatation with stones developed after 7 years. Pig-tail catheter was inserted into the intrahepatic duct.

retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP) and were confirmed by radiologists.

Clinically, we reviewed medical records of each patient and analyzed the gender, type of choledochal cyst, size of cyst, duration of symptoms onset, and laboratory findings. The patients had symptoms such as abdominal pain, jaundice, and fever, but the symptoms improved after operation. Pathologically, we choose a representative section from each case and reviewed Hematoxylin–eosin stain and Masson–Trichrome stain with regard to the following histologic parameters: (1) loss of mucosa, (2) inflammatory activity, (3) degree of fibrosis, (4) loss of muscle layer, (5) thickness of cyst wall. We classified the grade of inflammation of 34 patients from normal to 3, which is considered as infiltration of inflammatory cells and surface erosion in histopathologic findings; infiltration of small number of lymphocyte to grade 1, infiltration of moderate number of lymphocytes with multifocal aggregates to grade 2, and extensive infiltration of lymphocytes with erosion of epithelium to grade 3. We classified the grade of fibrosis, loss of mucosa, and loss of smooth muscle from 1 to 3, which is considered as fractional area of fibrosis, loss of mucosa and smooth muscle from normal layer; less than one-third to grade 1, more than one-third but less than two-thirds to grade 2, and more than two-thirds to grade 3.

Statistical analysis was performed with Fisher's exact test, independent *t* test, and Spearman's correlation. *P* value <0.05 was considered statistically significant.

Results

Clinical Findings

The type of choledochal cyst of the 34 patients: 19 patients presented type I choledochal cyst (56%), and 15 patients had type IVa (44%). Of the 28 patients presented with APBDU, 21 patients were C-P type APBDU (61.8%), and 7 patients were P-C type APBDU (20.6%). APBDU could not be determined in six patients who had markedly dilated choledochal cyst. There was no significant difference in age, gender, type of APBDU and laboratory findings between the two groups (Table 1). The size (transverse diameter) of choledochal cyst in the stricture group was 7.0 cm, ranging from 1.4 to 15.0 cm, and that of the non-stricture group, 4.2 cm (1.7~10.0 cm), showing significant difference between the two groups ($P<0.05$): The size of cyst was estimated by radiological findings. The stricture group presented more short duration of symptoms (27.63± 61.72 days; ranged, 1~180 days) than the non-stricture group (483.33±916.41 days; ranged, 1~3560 days), and it was statistically significant ($P<0.05$).

Of the 34 patients, 33 patients underwent excision of choledochal cyst and hepaticojejunostomy, and 1 patient with chronic pancreatitis underwent pylorus-preserving pancreaticoduodenectomy. One patient had undergone cholecystectomy for gallbladder stone 6 years ago. At the time of initial operation, gallbladder and common bile duct stones were present in eight (23.5%) and nine (26.5%) patients, respectively. Moreover, two (5.9%) patients was

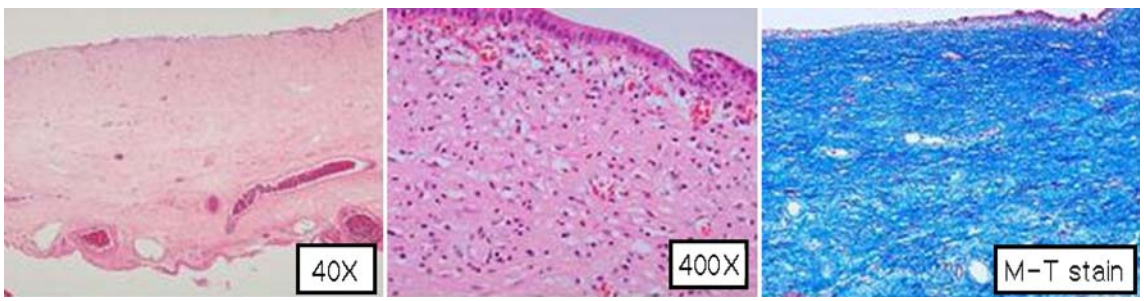

Figure 2 Pathologic figures of a 19-year-old female patient. (Case #5 in Table 2). Thickness of cyst wall was 5 mm. Grade of Infiltration of inflammatory cells was 1, grade of fibrosis and loss of mucosa was 2, and grade of loss of smooth muscle was 3.

Table 3 Pathologic Characteristics

Characteristic	Stricture group (n=8)	Non-stricture group (n=26)	Correlation coefficient	P value
Thickness of cyst wall (mm)			0.250	0.161
0~1	1	7		
1.1~2	3	12		
2.1~3	3	5		
>3	1	1		
Fibrosis			−0.324	0.062
1	2	5		
2	5	15		
3	1	6		
Loss of smooth muscle			0.000	1.000
1	2	9		
2	3	10		
3	4	7		
Loss of mucosa			0.039	0.828
1	3	2		
2	4	10		
3	1	7		
Infiltration of inflammatory cells			0.352	0.045
0	0	1		
1	2	15		
2	4	7		
3	2	2		

incidentally diagnosed with gallbladder cancer; one patient is a 42-year-old man, the other is a 44-year-old woman. Their pathological findings showed early stage (T1b, N0), and they survived without tumor recurrence; follow-up period was 72 and 87 months in each patient.

Anastomotic stricture and intrahepatic duct stones developed postoperatively in eight patients; one patient of 19 type I cyst and seven patients of 15 type IVa, developing more significantly in the type IVa choledochal cyst (P<0.05) (Table 2). The mean period from surgery to diagnosis of anastomotic stricture was 36.83 months (7.8~89.7 months). For the treatment of stricture, one patient was managed conservatively, and seven patients underwent percutaneous transhepatic cholangioscopy (PTCS) with intrahepatic duct stone removal and balloon dilatation. Revision of hepaticojejunostomy was not performed in any of the stricture patients. On the other hand, 29 pediatric patients who underwent cyst excision with hepaticojejunostomy did not complicate by anastomotic stricture. There are illustrations of the anastomotic stricture in a 19-year-old female (case no. 5) who underwent excision for type IVa cyst and hepaticojejunostomy (Fig. 1 and 2).

Pathological Findings

To evaluate pathologic differences between the two groups, we analyzed the thickness of cyst wall, grade of fibrosis, loss of smooth muscle, loss of mucosa, and infiltration of inflammatory cells. There were no significant differences in anastomotic stricture, thickness of cyst wall, fibrosis, loss of smooth muscle, and loss of mucosa between the two groups (P>0.05; Table 3). On the other hand, significant difference was found in anastomotic stricture and the grade of infiltration of inflammatory cells between the two groups (Rsq=0.12, P<0.05; Fig. 3). There was a highly significant correlation between the grade of infiltration of inflammatory cells and size of cyst (Rsq=0.412, P<0.05; Fig. 3). There was significant correlation between inflammation grade and cyst wall thickening (Rsq=0.189, P<0.05), and loss of mucosa (Rsq=0.244, P<0.05; Fig. 4). However, there was no correlation among inflammation grade, type of cyst, and grade of fibrosis (P>0.05; Table 4).

Discussion

For the treatment of choledochal cyst, cystoenterostomy as a drainage procedure has been associated in the past with high morbidity rates and a potential for malignant change in

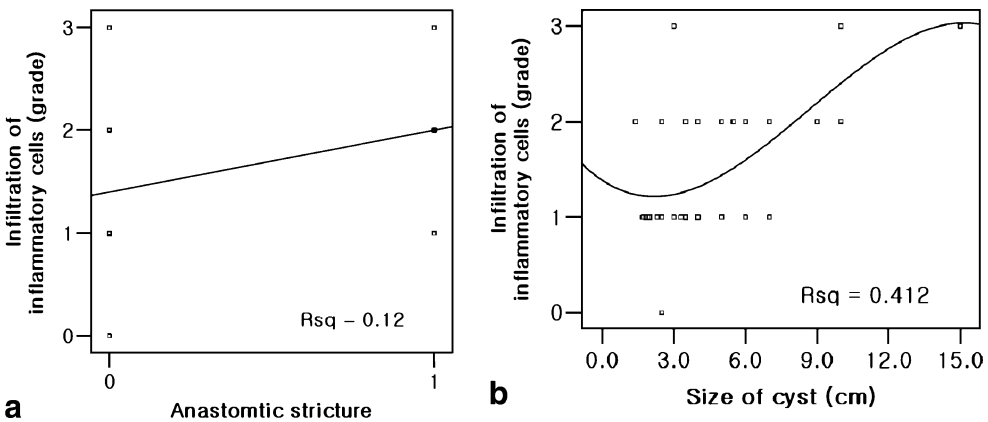

Figure 3 Correlations between the grade of inflammation and clinical parameters. **a** There was significant correlation between the grade of inflammation and anastomotic stricture. As the grade of inflammation was raised, anastomotic stricture increased (r=0.352, P<0.05). **b** There was highly significant correlation between the grade of inflammation and size of cyst; that is, the more severe the grade of inflammation, the bigger the size of cyst (r=0.536, P<0.05).

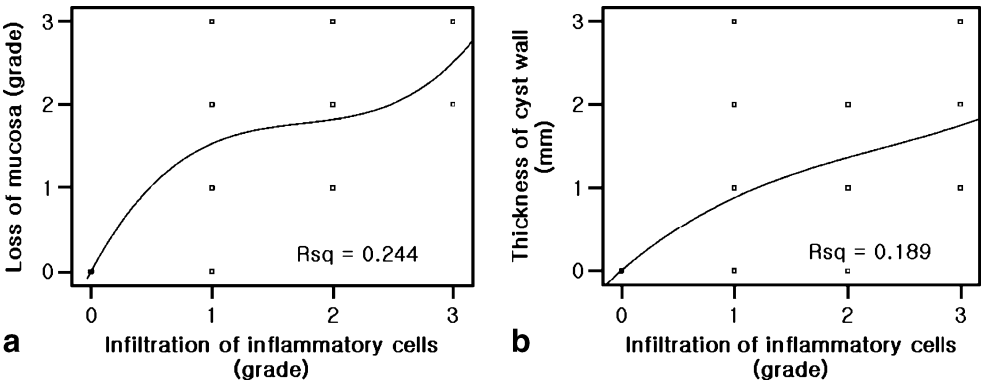

Figure 4 Correlations between the grade of inflammation and other pathologic parameters. **a** There was significant correlation between inflammation grade and mucosal loss (r=0.416, P< 0.05). **b** There was significant correlation between inflammation grade and cyst wall thickness (r=0.439, P<0.05).

the biliary tree.[4–6] Total cyst excision with hepaticoenterostomy is the treatment of choice for choledochal cyst.[2,3] Excision has also the advantage of stopping reflux of pancreatic juice through pancreaticobiliary maljunction, which has so often been associated with choledochal cysts.[7] In the long-term follow-up of patients with choledochal cyst, however, postoperative stone formation and/or cholangitis have presented a serious problem. These complications are likely to develop secondary to a postoperative anastomotic stricture or biliary stasis in the intrahepatic ductal dilatation.[16]

Tsuchida et al. studied 103 patients with a mean follow-up of 12.5 years and found that four patients (40%) out of ten patients with dilated intrahepatic ducts and downstream stenosis developed strictures, and almost all of them had cholangitis.[11] Todani et al. reported that 9 of 22 patients treated with hepaticoenterostomy distal to the hilum required reoperation several years after surgery because of recurrent cholangitis with intrahepatic duct stone secondary to anastomotic stricture formation.[9] Six patients of the nine patients who underwent reoperation were type IVa. These aforementioned studies indicate that the complications involving anastomotic stricture, cholangitis, and intrahepatic duct stones are more common in the type IVa cysts.

In our study, anastomotic stricture and intrahepatic stones postoperatively developed in 8 out of 34 patients (23.5%); 1 patient of 19 type I cyst, and 7 patients of 15 type IVa. The type of choledochal cyst, especially type IVa, was closely related with anastomotic stricture. Our results also support the notion that anastomotic stricture is more common in type IVa choledochal cysts. For the treatment of stricture, seven patients underwent percutaneous transhepatic cholangioscopy (PTCS) with intrahepatic duct stone removal and balloon dilatation by endoscopic specialists. One patient who showed left intrahepatic duct stones and dilatation was managed conservatively without PTCS because his laboratory data and symptoms got better after admission. Revision of the hepaticojejunostomy was not needed in any of the stricture patients. After the intervention, no stricture recurred.

Table 4 Correlations Among Clinicopathologic Parameters

Parameter	Infiltration of inflammatory cells	
	Correlation Coefficient	P value
Type of cyst	0.106	0.556
Anastomotic stricture	0.352	0.045
Size of cyst	0.536	0.001
Thickness of cyst wall	0.439	0.011
Fibrosis	−0.076	0.676
Loss of smooth muscle	0.290	0.101
Loss of mucosa	0.415	0.016

In our recent study, we observed significant correlation between the grade of inflammation and the size of cyst; more severe inflammation in the group with cyst bigger than 4 cm.[17] In our present study, as the size of choledochal cyst increased, the grade of inflammation was raised and anastomotic stricture increased. The high grade of inflammation was related with cyst wall thickening, but no relation with fibrosis grade. On the other hand, there was no correlation between anastomotic stricture and cyst wall thickening and fibrosis grade. The results indicate that the thickness of cyst wall and fibrosis grade may not be risk factors of anastomotic stricture. Also, our results showed that short duration of symptoms was related with anastomotic stricture, but there was no significant difference in age and anastomotic stricture, although the age of stricture group was younger. There was no significant difference between anastomotic stricture and laboratory data; however, the total bilirubin of the non-stricture group was higher than that of the stricture group. It was the reason that three patients of the non-stricture group had jaundice in admission, and laboratory data was obtained preoperatively.

We excluded pediatric patients from the study because of their immature exocrine pancreatic function. In children, there are different levels of biliary amylase,[17–19] and postoperative complications are less common than in adults.[5,6,8–10,16,20,21] Yamataka et al.[20] studied anastomotic stricture that developed in four patients who underwent operation under 19 years of age, respectively, and found that increase of age had increased incidence because there

were no anastomotic strictures in 145 children who underwent operation at 5 years or younger. Furthermore, inflammation of the cyst wall was found to be mild in children under 10 years of age and more severe in older children, indicating that histological damage to the common hepatic duct used for bilioenteric anastomosis is more severe in older children and adults.[21]

We performed total cyst excision and hepaticojejunostomy distal to the hilum in patients with choledochal cyst; nevertheless, the rate of anastomotic stricture was similar or lower than other results.[9,11] In fact, the treatment of type IVa still remains controversial. Some authors suggested that the hilar anastomosis in all patients is necessary to prevent cholangitis and stone formation,[9,22] On the other hand, there was a report that founded no problems in 171 patients who underwent hepaticoenterostomy distal to hilum.[14] The intrahepatic duct dilatation in some patients tends to decrease in size after excision of cyst. Todani et al.[23] suggest that secondary dilatation of the intrahepatic duct should be excluded from type IVa cyst and that detection of ductal stricture is more important than classifying the cyst as type Ic or type IVa. Only one patient in non-stricture group presented with normalized intrahepatic duct after operation, in our cases.

Conclusion

Anastomotic stricture after surgery for choledechal cyst is the most risky complication of the early and late complications. Clinically, anastomotic stricture is closely related with the type of choledochal cyst, especially type IVa, and anastomotic stricture tends to increase with the increase of cyst size and short symptom duration. Pathologically, only the infiltration of inflammatory cells among many parameters was found to be related with anastomotic stricture. Therefore, the type IVa choledochal cyst, bigger cyst size, short symptom duration, and high grade infiltration of inflammatory cells are suggested as risk factors of anastomotic stricture after excision of choledochal cysts with hepaticojejunostomy.

To minimize complications secondary to an anastomotic stricture such as IHD stones and cholangitis, we should detect early the anastomotic stricture after surgery. Therefore, closed careful follow-up is important in patients who underwent cyst excision with hepaticojejunostomy for type IVa choledochal cyst. Moreover, these patients has a need for long-term follow-up over 8 years. If the anastomotic stricture develops, nonoperative management should be recommended, rather than operation, as much as possible.

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Surgical Outcomes of Laparoscopic Cholecystectomy for Severe Acute Cholecystitis

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Abstract The aim of this study was to evaluate the surgical outcomes of laparoscopic cholecystectomy (LC) in patients who were diagnosed with severe acute cholecystitis (SAC) and to clarify the useful treatment modalities of SAC. Of 112 patients who presented SAC, we selected 99 patients and divided them into 3 groups: 37 patients who underwent preoperative percutaneous transhepatic gallbladder drainage (PTGBD; group 1), 62 patients with SAC but not indicated for PTGBD (group 2), and 59 patients with acute and chronic cholecystitis (group 3). The conversion rate was 2.7% (1/37) in group 1, 6.5% (4/62) in group 2, and 1.7% (1/59) in group 3. In groups 1 and 2, the postoperative stay and operative time were longer than those in group 3 with significant difference, respectively ($P<0.05$). In group 2, there was correlation not only between postoperative stay and age but also between postoperative stay and ASA class ($P<0.05$). In group 2, there was no correlation between time to operation and operative time and also between time to operation and postoperative stay, however, there was surprisingly significant correlation between time to operation and conversion rate in SAC ($P=0.018$). In conclusion, PTGBD should selectively be performed in patients with severe comorbidities rather than improving surgical outcomes of LC for severe acute cholecystitis. If patients are not indicated for PTGBD, an early laparoscopic cholecystectomy is recommended because it can decrease conversion rate, although it cannot decrease operative time and postoperative stay.

Keywords Severe acute cholecystitis · Laparoscopic cholecystectomy

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Introduction

Acute cholecystitis (AC) is the most commonly encountered disease, caused by obstruction of the cystic duct with or without gallstones. For the treatment of AC, there has been controversy over the advantages of early laparoscopic cholecystectomy (LC) versus delayed surgical treatment after gallbladder drainage such as PTGBD.[1–3] Recently, early LC is recommended on the basis of randomized studies,[4–6] as failure of initial conservative treatments has been reported in up to 32% of cases and early cholecystectomy has been proved to reduce total hospital stay.

AC can also be complicated by empyema, gangrene, or perforation. Both gangrenous and empyematous acute cholecystitis can be defined as severe acute cholecystitis (SAC), and it is present in up to 30% of patients admitted to hospital with acute cholecystitis.[7] Furthermore, SAC has been reported to be associated with increased mortality (15–50%), especially in the elderly or critically ill patients.[8] Higher conversion and morbidity rates have been reported

when gangrenous cholecystitis or empyema of the gallbladder were approached by laparoscopy.[9,10] Moreover, treatment modalities other than LC, such as cholecystectomy or subtotal cholecystectomy have been considered,[3,11–13] however, the treatment of SAC has not exactly been specified in most literature.

The aim of this study was to evaluate the surgical outcomes of LC in patients who were diagnosed with SAC and to clarify the useful treatment modalities of SAC.

Patients and Method

From January 2003 to September 2006, a total of 1,330 LC was performed at Ajou University Medical Center. Of 427 patients who were admitted with a clinical diagnosis of AC, 26.2% of patients (112/427) who presented SAC were surgically treated during the study. Among the 112 patients, we selected 99 patients excluding 2 patients who underwent other biliary drainage (percutaneous transhepatic biliary drainage), 2 patients who developed cholecystitis during the evaluation of other problems, and 9 patients who underwent initial open cholecystectomy. Forty-five patients were male and 54 patients were female, whose age ranged from 31 to 94 years. We also divided the patients into two groups, depending on whether preoperative gallbladder drainage was performed (group 1) or not (group 2). To compare the length of hospital stay and outcomes of surgery of the SAC with that of other cholecystitis, patients who were diagnosed with acute and chronic cholecystitis (group 3) were also reviewed in a retrograde order.

We collected consecutive identification of patients who underwent LC for SAC or who underwent LC after PTGBD for SAC. We retrospectively reviewed the medical records of all patients and analyzed data including demographic information, clinical presentation, results of laboratory studies, operative records, postoperative complications, and pre/postoperative hospital stay. On preoperative assessment, patients were classified into the American Society of Anesthesiologists (ASA) score. The time to operation was defined as the interval between admission and operation.

The diagnosis of AC was based on clinical signs (fever, right upper quadrant abdominal pain, or right-sided abdominal tenderness) and computed tomography findings (thickening of gallbladder wall and pericholecystic fluid collections). Both gangrenous and empyematous acute cholecystitis were defined as severe acute cholecystitis. SAC was confirmed by operative findings, inspection of gallbladder change of wall color to dark green or gray, and infected bile or pus contained. Finally, SAC was confirmed by postoperative pathologic findings.

Abdominal computed tomography was the initial imaging modality of choice in all patients. Patients with CT findings of severe cholecystitis (a hypoechogenic band in the gallbladder wall and/or a pericholecystic fluid collection and/or thickening of the gallbladder wall to 8 mm or more), with critically ill combined medical disease (diabetes mellitus, cardiovascular disease, old CVA), and/or with septic condition who were suspected of severe cholecystitis were treated with emergency PTGBD. After the resolution of acute attack and medical treatment of any diseases associated with cholecystitis, patients were considered for cholecystectomy. Patients with preoperative hyperbilirubinemia [serum bilirubin higher than twice the normal value and/or dilated common bile duct (>8 mm)] underwent endoscopic retrograde cholangiopancreatography (ERCP). Laparoscopic cholecystectomy was performed using the standard four-trocar technique.

Statistical analysis was performed with Fisher's exact test, independent t test, and Spearman's correlation. P value <0.05 was considered statistically significant.

Results

Clinical Findings

Thirty-seven patients had preoperative gallbladder drainage. PTGBD was performed successfully in all patients, and complication of PTGBD did not occur. The demographic and preoperative laboratory data for each group are compared in Table 1. Patients in group 1 were significantly older than the other groups ($P<0.05$). On the other hand, there was no significant difference in gender and laboratory findings between groups 1 and 2 ($P>0.05$). In group 3, white blood cell count was significantly lower than that of other groups ($P<0.05$). Preoperative CT findings and hyperbilirubinemia yielded a diagnosis of common bile duct stones in 19 patients; and preoperative endoscopic sphincterotomy and stone extraction were performed completely.

Hypertension ($n=56$) and diabetes mellitus ($n=35$) were present in most patients of the three groups. There were other associated diseases such as ischemic heart disease ($n=8$), cerebrovascular disease ($n=10$), liver cirrhosis ($n=1$), and bronchial asthma ($n=4$). Diabetes mellitus was present in 15 patients in group 1 (37.5%), 12 patients in group 2 (17.9%), and 8 patients in group 3 (13.6%); it was statistically significant in the three groups ($P<0.05$), respectively (data not shown).

Severity of illness in the three groups of patients was assessed preoperatively by comparing their ASA classification. The mean ASA score was 1.27±0.6 in group 1, 0.89±0.54 in group 2, and 0.59±0.69 in group 3. There was significant difference in ASA class between the three groups ($P<0.05$): The number of ASA I patients increased (3, 13, and 30 patients in groups 1, 2, and 3, respectively), whereas

Table 1 Clinical Characteristics of the Three Groups on Admission

	Group 1 (n=37)	Group 2 (n=62)	Group 3 (n=59)
Age*	66.8±11.7	60.5±13.4	50.2±14.4
Sex (M/F)	13/24	32/30	32/27
Symptom duration (days)	2.8±1.7	5.2±5.8	3.6±3.3
Fever (°C)	37.6±0.8	37.2±0.8	36.8±0.5
Laboratory findings			
WBC count (/mm^3)	15,551.3±6,485.6	13,281.4±4,930.4	9,743±4,157.0
Total bilirubin (mg/dl)	2.4±2.4	1.7±1.5	1.8±1.9
AST (IU/l)	89.6±132.0	56.5±107.4	59.9±85.9
ALT (IU/l)	109.3±176.6	60.4±101.1	84.5±104.6
Associated disease*	7	4	12
CBD stone, n (%)	4 (10.8)	4 (6.5)	11 (18.6)
Sepsis, n (%)	3 (8.1)		
Acute cholangitis, n (%)	1 (2.7)		1 (1.7)

Group 1 patients underwent PTGBD for severe cholecystitis, *Group 2* patients with severe acute cholecystitis, *Group 3* patients with acute and chronic cholecystitis
*P<0.05

the number of ASA III patients decreased (13, 6, and 5 patients in groups 1, 2, and 3, respectively). Comorbid conditions were significantly more common in the PTGBD group (Fig. 1).

Conversion and Complications

Of 112 patients, LC was the initial surgical approach in 99 patients, and was successfully completed in 94 patients (94.9%), whereas conversion to open procedure was necessary in 5 patients (5.1%). The conversion rate to open cholecystectomy was 2.7% (1/37) in group 1, 6.5% (4/62) in group 2, and 1.7% (1/59) in group 3. Eight patients underwent open cholecystectomy (OC). Moderate to severe adhesion around the gallbladder was observed in all cases; however, the adhesion could be dissected with careful manipulation. One patient (2.7%) of group 1 and two patients of group 2 were converted to open cholecystectomy because of a severe adhesion around the gallbladder. One patient each of groups 2 and 3 was converted to open cholecystectomy because of a super intense Calot's triangle.

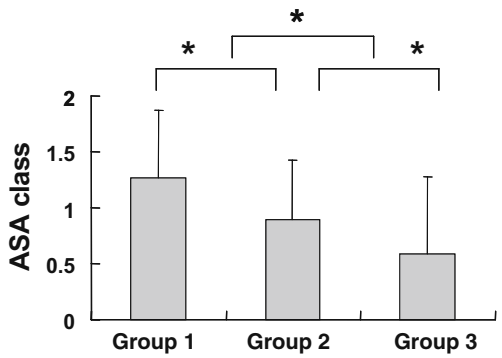

Figure 1 Comparison of severity of illness between the three groups. The mean ASA was 1.27±0.6 in group 1, 0.89±0.54 in group 2, and 0.59±0.69 in group 3.There was significant difference between the three groups (P<0.05). Comorbid conditions were significantly more common in the PTGBD group (*P<0.05).

One other patient of group 2 was converted to open cholecystectomy because of injury of small bowel: Perforated small bowel was primarily repaired immediately by 3-0 black silk, and this patient was discharged at postoperative day 8 after wound seroma was managed.

The complication rates after LC was 8.1% (3/37) in group 1, 11.3% (7/62) in group 2, and 5.1% (3/59) in group 3. Intraoperative uncontrolled bleeding did not occur in any patient of the three groups. Postoperative wound infection occurred in three patients in group 2 and one patient in group 3. A transient biliary leakage occurred in one patient each of groups 2 and 3, and it was managed by endoscopic therapy. One patient in group 1 showed bile leakage at the puncture site of PTGBD after LC. This patient underwent emergency operation, as general condition was then aggravated, however, finally died by multiple organ failure. The mortality rate was 1.7% (2/112) in SAC.

Operative Time

The operative time for LC was 74.86±35.42 min in group 1, 82.18±26.69 min in group 2, and 61.27±22.60 min in group 3. In group 3, the operative time was shorter than in groups 1 and 2 with significant difference (P<0.05). It is interesting to note, however, that the operative time of group 1 was shorter than that of group 2 with no significant difference (P>0.05) (Fig. 2).

Pre/Postoperative Hospital Stay

The total hospital stay was 12.5±4.3 days in group 1, 7.6±4.0 days in group 2, and 4.6±3.7 days in group 3. The average preoperative stay was 8.3±3.1 days in group 1 and 3.2±2.6 days in group 2. In group 3, the preoperative stay was shorter than the other two groups (2.6±2.8 days) (data not shown). The mean hospital stay after LC was 3.9±2.6 days in group 1, 3.7±2.8 days in group 2, and 2.1±

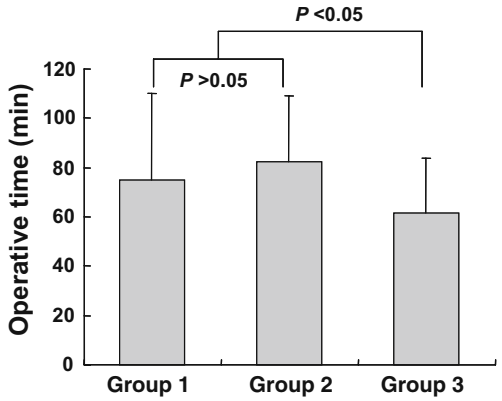

Figure 2 Comparison of operative times between the three groups. There was no significant difference between groups 1 and 2 ($P>0.05$). The operative time of both PTGBD group and severe cholecystitis group was significant longer than acute and chronic cholecystitis ($P<0.05$).

1.8 days in group 3. In groups 1 and 2, the mean postoperative stay was significantly longer than that in group 3 ($P<0.05$). However, there was no difference between groups 1 and 2 ($P>0.05$) (Fig. 3). In group 2, there were significant correlations between postoperative stay and age ($r=0.254$, $P<0.05$), between postoperative stay and ASA class ($r=0.311$, $P<0.05$), and between operative time and postoperative stay ($r=0.322$, $P=0.011$) (Table 2, Fig. 4).

Time to Operation

After PTGBD, the mean duration of drainage was 7.1± 3.5 days. The catheter was removed in all patients at the time of cholecystectomy. There was no correlation between time to operation after drainage and conversion ($P>0.05$) (data not shown).

In group 2, there were no correlations between time to operation and operative time and also between time to operation and postoperative stay. The old-aged patients with high ASA class spent more time before operation. It is surprising to note that there was a significant correlation between time to operation and conversion rate in group 2 ($r=0.299$, $P=0.018$) (Fig. 5): The longer the interval between admission and operation, the higher the conversion rate.

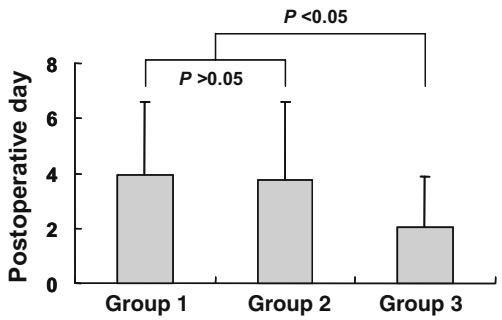

Figure 3 Comparison of postoperative hospital stay between the three groups. The postoperative stay of both PTGBD group and severe cholecystitis group was significant longer than acute and chronic cholecystitis ($P<0.05$). However, there was no significant difference between groups 1 and 2 ($P>0.05$).

Table 2 Correlations Between Postoperative Stay and Other Factors in Group 2

	Postoperative stay in group 2	
	Correlation coefficient	*P* value
Age	0.254	0.046
Symptom duration	0.168	NS
ASA class	0.311	0.014
Time to operation	0.043	NS
Operative time	0.322	0.011
Conversion to open	0.417	0.001

Discussion

The etiology of gallbladder gangrene is related mainly to vascular compromise secondary to continuing obstruction of the cystic duct, which causes the intraluminal pressure within the gallbladder to activate and increase an immediate inflammatory reaction.[14] Gangrenous cholecystitis, the last stage of gallbladder inflammation, is a severe form of acute cholecystitis and is associated with significantly greater morbidity and mortality relative to other forms of acute cholecystitis, especially in elderly, immunocompromised or diabetic patients.[7,8] In our cases, patients in group 2 were older than the other cholecystitis group (60.5 vs. 50.2 years). Moreover, the rate of diabetes mellitus in group 1 was higher than that of group 2. However, there was no significant difference in gender between the three groups.

The rate of conversion to open surgery in cases of severe cholecystitis has been reported to be between 8.7% and 75%.[15–17] In many studies, the rate of complications in cases of severe cholecystitis, including severe complications such as bile duct injury or bleeding, is between 0% and 40%,[7,9,12,16,18] and early consideration of conversion to open cholecystectomy has been advocated by Cox et al.,[19] although Merriam et al.[7] reported a 65% success rate with the laparoscopic approach: They contended that a swift conversion to an open cholecystectomy may be warranted if gangrenous cholecystitis is found.

In the present study, the rate of conversion to open surgery in group 2 was 6.5%, being lower than that of other reports. Moreover, although there was one case of bile leakage at the cystic duct stump, the rate of complications was 11.3% without severe complications. Noticeably, there was no significant difference in the rate of conversion and complications between the three groups.

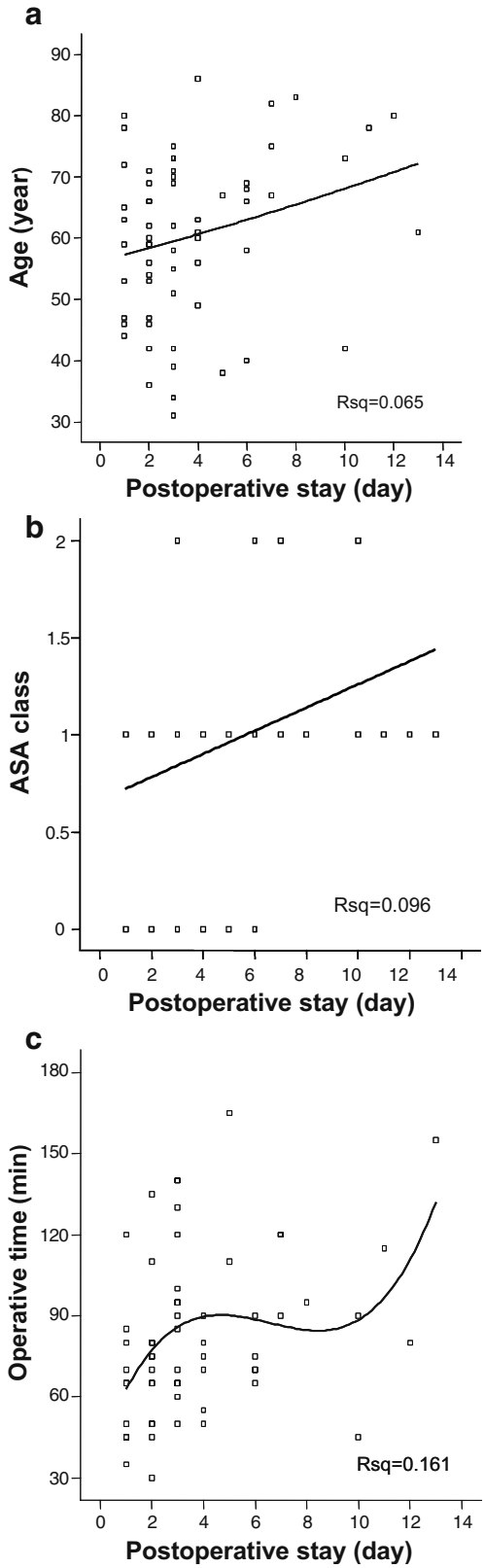

Figure 4 Correlations among postoperative stay, age, and ASA class in severe cholecystitis. **a** There was correlation between postoperative stay and age (r=0.254, P<0.05). **b** There was significant correlation between postoperative stay and ASA class (r=0.311, P<0.05). **c** There was significant correlation between postoperative stay and operative time (r=0.322, P<0.05).

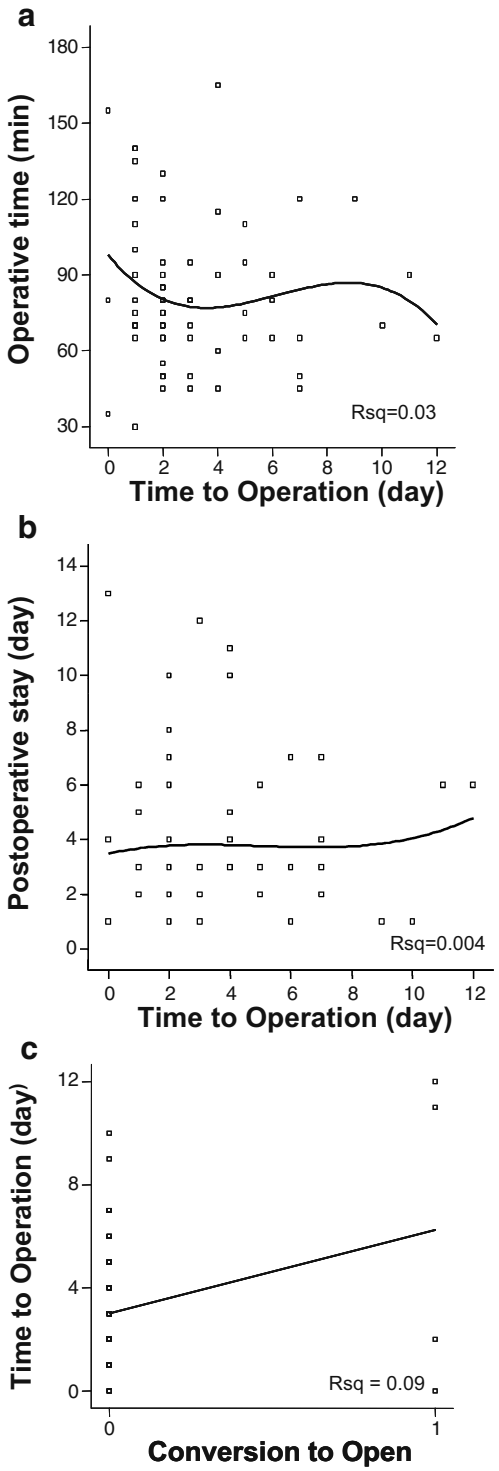

Figure 5 Correlation between time to operation and surgical outcomes in severe cholecystitis. **a** There was no correlation between time to operation and operative time (r=−0.070, P>0.05). **b** There was no correlation between time to operation and postoperative stay (r=0.043, P>0.05). **c** There was significant correlation between times to operation and conversion rate in severe acute cholecystitis (r=0.299, P=0.018). As time to operation is delayed, conversion to open cholecystectomy increased.

According to some literature, LC after PTGBD as another treatment modality for severe cholecystitis may decrease the conversion and complication rates. Chikamori et al.[13] reported that early scheduled LC after PTGBD is a safe and effective therapeutic option for patients with acute complicated cholecystitis, especially in elderly patients and patients with poor general condition. Tseng et al.[20] reported that the complications related to PTGBD were noted in two patients (1.4%). However, the conversion rate to open cholecystectomy in LC was 27% (32/117) with a mean of 4 days after PTGBD. On the other hand, zero conversion rate was reported in 34 days of interval to operation after PTGBD.[3]

In our study, patients with PTGBD were significantly older and comorbid conditions were significantly more common than the other groups. There was one complication related to PTGBD: bile leakage at the puncture site after LC. The rate of complications was 8.1% and lower than other studies. In addition, there was no correlation between time to operation after drainage and conversion, although there was one case of conversion to open.

The results from recent randomized trials have shown that early cholecystectomy is superior to delayed surgery because of shorter hospital stay and economic benefits.[4,21] For patients with severe acute cholecystitis, delayed surgery after initial conservative therapy or open cholecystectomy has been selected because of difficulties associated with early laparoscopic treatment. However, technical advances and increased experience have gradually led surgeons to attempt laparoscopic surgery in cases of acute gangrenous cholecystitis.[7,15,16] Tsushimi et al.[22] reported that there were no postoperative complications. Thus, early laparoscopic cholecystectomy seems to be appropriate for acute gangrenous cholecystitis. Wang et al.[23] reported that the timing of urgent laparoscopic cholecystectomy had no impact on the conversion rate. In the present study, there was significant correlation between the time to operation and conversion rate in group 2. Indeed, early LC for severe cholecystitis decreased the conversion to open cholecystectomy.

There are many reports that the operative time was longer in patients with SAC because of dense adhesion to Calot's triangle. Tsumura et al.[12] reported that surgical duration was 124 min in PTGBD group and 107 min in non-PTGBD group with significant difference. On the other hand, Chikamori et al.[13] found that the duration of surgery was shortened when LC was performed as soon as possible after PTGBD.

In our study, the operative time of group 1 was shorter than that of group 2; however, it was not significant. This might have been because of the fact that much operative time was spent in group 2 because of edematous, tense, and hypervascular tissue. Another reason for the short operative time of the PTGBD group was laparoscopic subtotal cholecystectomy; nine patients in group 1 and five patients in group 2. Beldi et al.[24] observed that laparoscopic subtotal cholecystectomy for AC offers a simple and safe solution that prevents bile duct injuries and decreases the rate of conversion in anatomically difficult situations.

According to some studies, postoperative stay after LC for severe cholecystitis ranges from 3.2 to 8.6 days.[7,13,16,22] In our present cases, postoperative stay was similar or shorter than other reports; 3.7 days in group 2. In group 2, there was significant correlation among postoperative stay, age, and ASA class. Elderly patients with high ASA class stayed in hospital longer postoperatively.

Conclusion

In SAC not indicated for PTGBD, there were no correlations between time to operation and operative time, and between time to operation and postoperative stay. However, there was a significant correlation between time to operation and conversion rate. Moreover, the old-aged patients with high ASA class took longer time to operation and stayed in the hospital longer postoperatively.

In conclusion, PTGBD should selectively be performed in patients with severe comorbidities rather than to improve surgical outcomes of LC for severe acute cholecystitis. If the patient was not indicated for PTGBD, we recommend early laparoscopic cholecystectomy because it can decrease the conversion rate, although it cannot decrease the operative time and postoperative stay.

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Xanthogranulomatous Inflammatory Strictures of Extrahepatic Biliary Tract: Presentation and Surgical Management

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Abstract
Background Xanthogranulomatous cholecystitis (XGC) is a benign, invasive variant of chronic cholecystitis. Invasion of common bile duct (CBD), termed as xanthogranulomatous choledochitis, may mimic malignancy. We describe clinico-pathological features and management of xanthogranulomatous inflammatory biliary strictures.
Methods A review of a prospectively maintained database for XGC was performed.
Results Out of 6,150 cholecystectomies performed, 620 patients had XGC (10% incidence). Four patients had biliary strictures with xanthogranulomatous choledochitis on final histology. All four patients presented with jaundice and history of cholangitis. Ultrasonography revealed gallstones and thick-walled gallbladder in all. Two patients had hilar strictures: one had mid-CBD stricture and one had a lower-CBD stricture with a dilated pancreatic duct. In all four patients, preoperative diagnosis of malignancy was entertained. Three patients underwent resection—CBD excision for mid-CBD stricture, pancreaticoduodenectomy for lower-end stricture, and right hepatectomy for hilar stricture with atrophy-hypertrophy complex. One patient with unresectable hilar stricture underwent hepaticojejunostomy.
Conclusion Xanthogranulomatous choledochitis may be considered as one of the differential diagnosis in patients with biliary stricture especially in a geographical area with a high incidence of XGC, when a patient harbors gall stones and had thick-walled gall bladder on imaging. This stricture can be found anywhere in the biliary tree from hepatic hilum to the lower end. However, preoperative imaging and cytology are unreliable both in confirming the diagnosis or ruling out malignancy. Therefore, resection of the stricture should be attempted wherever feasible.

Keywords Xanthogranulomatous cholecystitis (XGC) · Xanthogranulomatous choledochitis · Biliary stricture

Introduction

Xanthogranulomatous cholecystitis (XGC) is a variant of chronic cholecystitis characterized by intense inflammation and accumulation of lipid laden macrophages.[1] The disease is benign but locally invasive and may involve adjacent organs such as liver, duodenum, colon, and common bile duct (CBD). Involvement of CBD by the inflammatory process, termed as xanthogranulomatous choledochitis, may lead to obstructive jaundice and mimic biliary malignancy. We herein describe the presentation and management of four such patients.

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Materials and Methods

A retrospective review of a prospectively maintained data base on xanthogranulomatous cholecystitis (XGC) was performed. Out of 6,150 cholecystectomies performed over a period of 18 years (1989 to 2006), 620 patients had histology of XGC. Among these patients, those with biliary strictures were identified. Other causes of biliary strictures such as associated gallbladder cancer, Mirrizzi's syndrome,

and post cholecystectomy iatrogenic bile duct injury were excluded. Four patients with xanthogranulomatous choledochitis on histology leading to biliary strictures were identified. Their presentation, preoperative investigations, surgical details, and histology were reviewed.

Results

Out of 620 patients with xanthogranulomatous cholecystitis, there were 290 women and 330 men (M/F, 1:1.1). Mean age at presentation was 48 years (14–84 years). Common presentation was pain in the majority (96%). Other associated symptoms were vomiting, anorexia, and weight loss in some. A number of patients (n = 598, 96%) had associated gallstone disease and 486 patients (79%) had a thick-walled gallbladder on preoperative imaging [ultrasonography and/or contrast-enhanced computed tomography (CECT)]. In 104(16%) patients, there was a preoperative suspicion of malignancy based on imaging findings of a mass lesion or focal thickening of gallbladder wall. On final histology, 6.5% (n=41) had carcinoma gallbladder in association with XGC. The incidence of fistulization into adjacent hollow viscus (cholecystoenteric fistula) and fistulization into CBD (Mirrizi's syndrome) was 6% (n=40) and 5.7% (n=36) respectively.

Four (0.6%) patients had biliary strictures due to xanthogranulomatous choledochitis in the absence of associated Mirrizi's or biliary malignancy. There were two men and two women with a mean age of 50 years. The clinical presentation, investigation, and operative details of these four patients are summarized in Tables 1 and 2 respectively.

Case 1 A 55-year-old man presented with a history of jaundice and recurrent fever of 2 weeks duration. Ultrasound and CT scan revealed a thick-walled gallbladder with cholelithaisis and a mid-CBD growth. Patient underwent endoscopic retrograde cholangiography (ERC) and stenting of CBD stricture. Brush cytology obtained during ERC revealed atypical cells suspicious for malignancy. At exploration, there were extensive pericholecystic and pericholedochal adhesions. Gall bladder was diffusely thick-walled with multiple calculi. CBD was thick-walled

Table 1 Details of Clinical Presentation and Preoperative Investigations

	Case 1	Case 2	Case 3	Case 4
Presentation	Jaundice, cholangitis	Pain abdomen, jaundice (fluctuating) cholangitis	Jaundice, cholangitis	Jaundice, cholangitis
Duration	2 weeks	9 months	3 weeks	4 weeks Rt lobe liver abscess 10 years ago
Liver function tests				
Se Bilirubin T/D	11.7/8.0 mg/dl	3.2/1 mg/dl	7.9/2.5 mg/dl	3.2/0.9 mg/dl
SAP	792 IU/dl	1,106 IU/dl	1,901 IU/dl	737 IU/dl
SGOT/ SGPT	89/54 IU/dl	86/ 100 IU/dl	187/284 IU/dl	18/12 IU/dl
Imaging				
Ultrasound	Gall bladder thick-walled contracted with calculi. Mid CBD mass.	GB thick-walled, contracted with calculi. Hilar stricture with hilar mass.	Gallbladder thick-walled with calculi mucocele. CBD dilated till lower end. PD also dilated	Contracted small GB. Right lobe atrophy with left lobe hypertrophy with coarsened echo texture
CECT/ MRCP	CECT: CBD thickening and narrowing at mid CBD. No e/o mass/calculus. Thick walled irregular enhancing GB wall	MRCP: Type 3 biliary stricture with suspicious mass at neck of gallbladder	CECT: "Double duct sign" with ill defined soft tissue density at lower end of CBD	MRCP: Hilar stricture with left IHBRD; Right side crowded ducts. Hepatolithiasis. No evidence of mass
Preoperative biliary drainage	ERCP stenting done–mid CBD stricture	None	ERCP stenting done. Lower CBD stricture	PTBD gram Hilar separation, left sided PTBD done
Preoperative cytology	Bile cytology atypical cells (suspicious of malignancy)	FNAC Hilar mass: negative	Papilla biopsy: No evidence of malignancy	None

LFT Liver function tests, *Se Bil T/D* serum bilirubin total/direct, *SAP* serum alkaline phosphatase, *SGOT* serum glutamate oxalate transferase; *SGPT* serum glutamate phosphate transferase, *ERCP* endoscopic retrograde cholangiopancreatography, *MRCP* magnetic resonance cholangiopancreatography, *GB* gallbladder; *PTBD* Percutaneous transhepatic biliary drainage, *IHBRD* intrahepatic biliary radical dilatation, *CBD* common bile duct

Table 2 Operative Diagnosis, Operative Details and Postoperative Course

	Case 1	Case 2	Case 3	Case 4
Preoperative diagnosis	Mid-CBD cholangiocarcinoma	Carcinoma GB neck/hilar cholangiocarcinoma	Periampullary malignancy	Hilar cholangiocarcinoma/ postinflammatory stricture
Peroperative findings	Extensive pericholecystic and pericholedochal adhesions. Diffusely thickened GB wall with multiple gallstones. Thick walled CBD with peri-choledochal nodes	Thick walled contracted gallbladder with extensive adhesions. Mass extending from GB neck to hilum. Common hepatic artery involved by mass. Frozen section, imprint and FNAC from mass-negative for malignancy	Gallbladder distended with mucocele. CBD dilated with extensive pericholedochitis. Severe desmoplastic reaction near uncinate process. 1.5 cm ampullary growth	Atrophy-hypertrophy. Pericholecystic, omental and duodenal adhesions. Thick walled contracted gallbladder with unhealthy necrotic tissue extending from GB fossa till hilum.
Surgery performed	Cholecystectomy, CBD excision and Roux-en-Y hepaticojejunostomy	Cholecystectomy and Roux-en-Y hepaticojejunostomy	Pancreaticoduodenectomy	Right hepatectomy with Roux-en-Y left hepaticojejunostomy.
Histology	Gallbladder and CBD–transmural xanthogranulomatous inflammation	Gallbladder and hilar tissue–xanthogranulomatous inflammation	XGC with xanthogranulomatous reaction extending along CBD till ampulla	Gallbladder and hilar tissue of right hepatectomy specimen revealed evidence of xanthogranulomatous inflammation
Follow-up	Asymptomatic, normal LFT at 2 year follow-up	Asymptomatic, normal LFT at 3 1/2 years follow-up	Asymptomatic, normal LFT at 4 year follow-up	Asymptomatic, normal LFT at 1 year follow-up

CBD Common bile duct, *FNAC* fine needle aspiration cytology, *GB* gallbladder, *XGC* xanthogranulomatous cholecystitis, *LFT* liver function tests

with multiple peri-choledochal lymph nodes. Patient underwent cholecystectomy and CBD excision with hepaticojejunstomy. Cut section of excised CBD revealed a mid-CBD stricture with mural thickening and mucosal ulceration. Final histology revealed XGC with xanthogranulomatous choledochitis. Postoperative recovery was uneventful. Patient is symptom-free with normal liver function tests (LFT) at 2 years follow-up.

Case 2 A 43-year-old woman presented with history of jaundice, recurrent upper abdominal pain, and fever of 9 months duration. Preoperative ultrasound revealed cholelithiasis, thick-walled contracted gallbladder, and a hilar stricture. Magnetic resonance cholangio pancreatography (MRCP) revealed a hilar stricture with a patent confluence. Fine needle aspiration cytology (FNAC) of hilar mass was negative for malignant cells. Preoperative diagnosis of hilar cholangiocarcinoma/carcinoma gallbladder (neck growth) with hilar involvement was considered. At exploration, a thick-walled contracted gallbladder with extensive pericholecystic adhesions was found. There was a mass extending from gallbladder neck to hilum. Resection could not be performed because of infiltration of the common hepatic artery by the mass. Intraoperative frozen section, imprint cytology, and FNAC obtained from mass was negative for malignancy. In view of unresectability, only a hepaticojejunstomy was performed (left hepatic duct). Postoperative course was smooth. Histology of hilar tissue revealed xanthogranulomatous choledochitis. Patient remained symptom-free with normal liver function tests at 3 1/2 years follow-up.

Case 3 A 48-year-old woman presented with jaundice and recurrent fever of 3 weeks duration. Ultrasound and CT scan (Fig. 1) revealed a lower CBD block with a dilated pancreatic duct (double duct sign) and a soft tissue mass at lower end suggestive of periampullary tumor. In view of

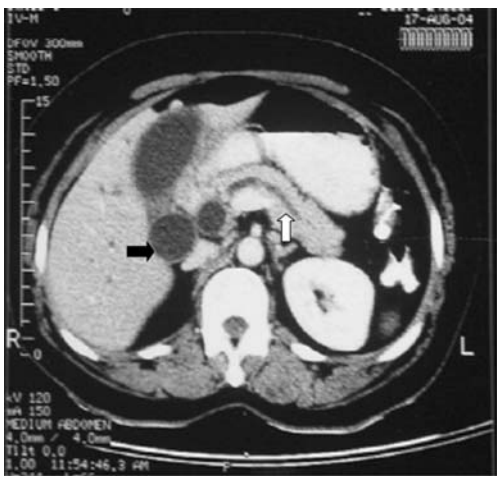

Figure 1 CT scan (case 3): Dilated common bile duct (*black arrow*) and pancreatic duct (*white arrow*) (double duct sign).

cholangitis and lower CBD stricture, patient underwent preoperative ERC and stenting. Biopsy of the papilla was negative for malignancy. Three weeks later, she was taken up for definitive surgery. Operative findings revealed mucocele of the gall bladder with a 3-cm impacted stone in the neck of GB. CBD was dilated with extensive pericholedochitis and severe desmoplastic reaction near uncinate process. With an operative impression of an ampullary tumor, patient underwent Whipple's pancreaticoduodenectomy. Cut section revealed a 2-cm ampullary growth. Histopathology revealed XGC with xanthogranulomatous reaction extending along CBD to the ampulla (Fig. 2). There was no evidence of malignancy. Patient is symptom-free with normal liver function at 4 years follow-up.

Case 4 A 56-year-old man presented with history of jaundice with recurrent cholangitis of 4 weeks duration. He had past history of percutaneous drainage of a right lobe liver abscess 10 years ago after which he developed an external biliary fistula. Subsequently, he required ERC and stenting of CBD after which the fistula closed and stent was removed. He remained asymptomatic for 10 years until the present symptoms. Preoperative imaging (ultrasound and MRCP) revealed a contracted and small gallbladder with calculi, hilar stricture with hilar separation, and right lobe atrophy and left lobe hypertrophy (Fig. 3). Patient underwent a percutaneous transhepatic biliary drainage (PTBD) of left duct, which further confirmed hilar separation (Fig. 4). Preoperative diagnosis was of a hilar cholangiocarcinoma/postinflammatory hilar stricture. Surgical findings revealed right lobe atrophy with left lobe hypertrophy and pericholecystic omental and duodenal adhesions. Gall bladder was thick-walled and contracted with unhealthy necrotic tissue extending from GB fossa to the hepatic hilum. Patient underwent right hepatectomy with hilar excision and left hepaticojejununostomy. Histology of gallbladder and hilar tissue revealed xanthogranulomatous inflammation. Patient is symptom-free with normal liver function tests at 1 year follow-up.

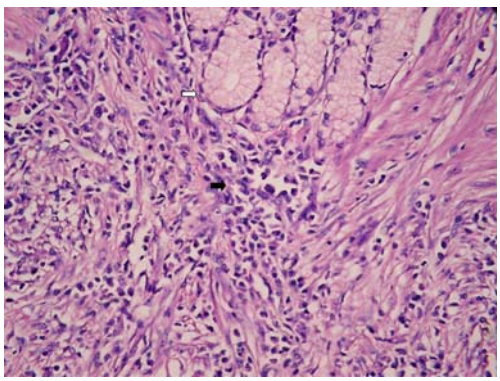

Figure 2 Histology of the ampullary stricture (case 3) shows Brunner's glands (*white arrow*) with mixed inflammatory infiltrate of histiocytes, lymphocytes, and plasma cells (*black arrow*) consistent with xanthogranulomatous inflammation.

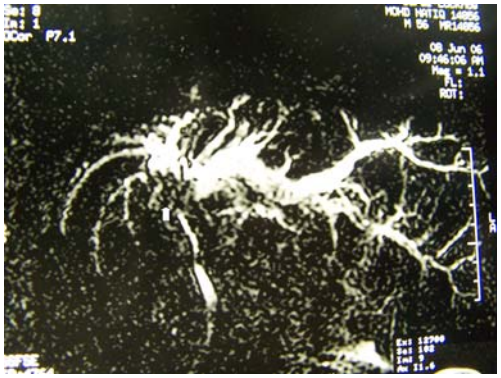

Figure 3 Magnetic resonance cholangiogram (*MRC*) (case 4): Hilar stricture with right lobe atrophy (*arrow*) and left lobe hypertrophy.

Discussion

XGC is a benign locally invasive inflammatory variant of chronic cholecystitis, which may be mistaken for malignancy. It is characterized by distinct pathological findings like fat laden macrophages, foamy histiocytes, and associated with severe fibrosis. Although traditionally considered rare,[1] our previously reported experience[2,3] and other reports[4] suggest that it occurs much more frequently in northern India where gallstone disease is common. Gallstones, biliary stasis, and chronic infection may be possible etiological factors.[1–3] The female-to-male ratio for XGC in

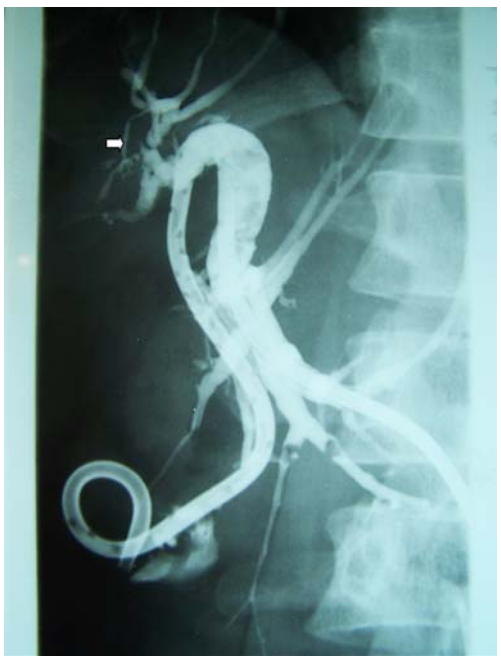

Figure 4 Percutaneous transhepatic cholangiogram (PTC) (case 4). Hilar stricture with non-filling of right system (*arrow*).

our series was 1.1:1 suggesting a male preponderance in comparison to chronic cholecystitis. As seen in our series and reported by others,[5,6] there is a disproportionately high incidence of local complications including fistulization into adjacent organs and CBD occurring in up to 10–20% of patients. The propensity of XGC to behave in a pseudo-malignant manner with local infiltration and fistulization is similar to xanthogranulomatous pyelonephritis.[7]

Biliary obstruction in patients with XGC is commonly caused by associated CBD stones, Mirrizzi's syndrome, or gallbladder cancer. Xanthogranulomatous choledochitis, caused by of xanthogranulomatous inflammatory involvement of biliary tree without any direct fistulization, is a rare cause of biliary stricture. These strictures along with other benign etiologies, such as primary sclerosing cholangitis, idiopathic inflammatory stricture, lymphoplasmocytic sclerosing cholangitis, and granulomatous strictures, have been reported in literature to masquerade as biliary malignancy.[8,9] Although a majority of patients who present with painless jaundice are ultimately proven to have cancer, it is now well established that approximately 5 to 10% of patients presenting with hilar obstruction harbor benign disease.[8,9] In a series of 22 such cases of benign strictures reported by Covera et al.,[8] there were two cases of xanthogranulomatous choledochitis. Data in literature has been limited to single case reports describing resections for xanthogranulomatous biliary strictures mimicking malignancy.[8,10–13]

The entity usually affects middle-aged adults as seen in our series. However, Kawana et al.[12] have reported an infant with xanthogranulomatous biliary stricture, so it seems that any age group may be affected. In addition to XGC, the association of xanthogranulomatous choledochitis with gallstone disease and biliary sepsis was a consistently observed feature in our four patients. All four patients had a thick-walled gallbladder and associated gallstones. Although all of them had history of cholangitis, bile culture was positive in only three patients (75%). Cholangitis is unusual in malignant biliary strictures in the absence of intervention. One patient (case 4) had a history of amoebic liver abscess with biliary complication needing intervention, which could have led to a stricture, but he had a symptom-free interval of 10 years before this presentation. Therefore, a clear causal relationship cannot be established. Majority of the cases described in literature have been hilar strictures,[8,10–13] but our experience suggests that xanthogranulomatous biliary strictures may occur anywhere in the extrahepatic biliary tree from the hilum to the lower end. Xanthogranulomatous pancreatitis has also been reported presenting with obstructive jaundice and masquerading as carcinoma head of pancreas.[14]

A preoperative diagnosis of xanthogranulomatous biliary stricture on imaging is difficult considering their rarity. In areas with high incidence of XGC such as ours, a biliary stricture in the setting of a thick-walled gallbladder and gall stones in the absence of associated CBD stones or Mirrizi's could be pointers toward XGC with xanthogranulomatous inflammatory biliary stricture. However, the presence of thick-walled gallbladder and gallstones in association with a biliary stricture may also suggest the possibility of carcinoma gallbladder with bile duct invasion. Xanthogranulomatous inflammation may often lead to formation of a mass mimicking a malignancy. In our series of XGC, 16% had a GB mass or focal thickening on preoperative imaging. However, only 6% had gallbladder malignancy on histology. Likewise, all four patients with xanthogranulomatous biliary strictures had an evidence of mass on preoperative imaging/operative findings, which led to suspicion of malignancy. Conventional imaging modalities such as CT scan cannot reliably distinguish these benign inflammatory strictures from malignancy.[4,8] Features such as adjacent organ infiltration and lymph nodes may be seen in the setting of xanthogranulomatous inflammation.[4–6] Covera at al.[8] suggested that positron emission tomography (PET) scan could be a potentially useful modality for hilar strictures because of poor uptake in benign strictures in contrast to cholangiocarcinoma, which is a fluorodexoxyglucose avid malignancy. However, in addition to limited availability, PET may be false positive in the presence of xanthogranulomatous inflammation.[15]

Xanthogranulomatous inflammation may be identified on preoperative FNAC as previously reported by us.[16] However, preoperative FNAC is unreliable if negative and has a limited role in resectable lesions. A report of xanthogranulomatous inflammation on preoperative FNAC or a preoperative cytology/frozen section biopsy may falsely reassure the surgeon that the lesion is benign while an associated cancer is missed.[4] In our experience, preoperative biliary drainage is frequently needed in these patients because of associated cholangitis. During the time of biliary drainage, brush cytology may be obtained. However, the accuracy of brush cytology for cholangiocarcinoma is only approximately 60%.[17] False positive cytology report showing atypical cells may occur in the presence of biliary obstruction as was seen in case 1. In our series, there was a strong suspicion of malignancy in all four cases based on clinical presentation/preoperative imaging and preoperative findings. In three (cases 1, 3, and 4) of the patients, resection was possible (Table 2). In one patient (case 2) where resection was not feasible, all attempts were made to establish histological diagnosis.

Xanthogranulomatous choledochitis should be considered as one of the differential diagnosis of biliary strictures in the presence of a thick-walled gallbladder and gall stones, especially in a geographical area where the incidence of XGC is high. It can be found anywhere in the biliary tree from the hilum to the lower end. Imaging

and cytology are unreliable both in confirming the diagnosis of xanthogranulomatous choledochitis and also in ruling out malignancy. Therefore, resection of stricture should be performed whenever feasible.

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Operative Mortality After Hepatic Resection: Are Literature-Based Rates Broadly Applicable?

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Abstract
Introduction Literature-based data on mortality after hepatectomy may be misleading, as poor outcomes are less likely to be published. The objective of the current study was to compare published vs public, nationally available mortality rates after hepatic resection.
Materials and Methods A systematic MEDLINE review was conducted to identify reports of hepatectomy outcome between January 1998–December 2004. Data were analyzed to calculate literature-based mortality rate and then compared with population-based mortality rate for hepatectomy using the Nationwide Inpatient Sample (NIS) dataset.
Results Twenty-three publications fulfilled screening criteria. The studies included 7,073 patients who had undergone hepatic resection (46.1% within USA vs 53.9% outside USA). Most patients were male (58.6%) with median age of 56 years. Indications for hepatic resection included hepatocellular carcinoma (47.7%), metastatic disease (34.3%), or other (18.1%). Cirrhosis was present in 23.2% of patients; 46.9% patients underwent either a hemi-hepatectomy or extended resection. The literature-based mortality rate was 3.6% (US centers only, 2.8%). Analysis of NIS revealed 11,429 hepatectomy cases. After controlling for gender, age, extent of hepatectomy, hepatocellular cancer diagnosis, and presence of cirrhosis, the adjusted NIS-based perioperative mortality rate for hepatectomy was 5.6% (95% CI, 5.0–6.2%). The relative mortality after hepatectomy was 1.6-fold higher based on population-based data compared with reports from the literature ($P<0.05$).
Conclusion Actual population-based mortality rates for major liver resections may be higher than those reported in the literature. Informed consent should reflect actual local and national mortality rates rather than selective reports from the literature.

Keywords Hepatic resection · Mortality · Perioperative · Population-based

Introduction

When appropriate, surgical resection remains the best therapeutic option in patients with both primary and secondary hepatic malignancies. In fact, over the past decade, the criteria for resectability of hepatocellular cancer (HCC) and colorectal metastasis (CRM) have expanded.[1] Specifically, some clinicians have begun to advocate a more "aggressive" surgical approach to the management of patients with hepatic malignancies.[1–8] For example, in otherwise "unresectable" patients with large HCC and underlying hepatic cirrhosis/fibrosis, portal vein embolization (PVE) is now advocated to induce hypertrophy of the future liver remnant to facilitate resection.[9,10] In addition, many patients with advanced CRM—who traditionally may

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not have been considered surgical candidates—are now undergoing hepatic resection through the selective use of PVE,[11] as well as the increased utilization of resection plus radiofrequency ablation,[12,13] two-stage hepatectomies,[14,15] and down-staging after chemotherapy.[6] Surgeons are now more willing to perform simultaneous colon and hepatic resections[16–18] and perform hepatic metastectomy in the presence of extrahepatic disease.[19] Various other studies have also advocated liver resection of metastatic neuroendocrine and even non-neuroendocrine neoplasms.[20,21]

The reason for this shift toward expanding the criteria of resectability for liver malignancies, and in turn the adoption of more "aggressive" surgical approaches, is multifactorial. For CRM, the introduction of new, more efficacious cytotoxic chemotherapeutic drugs has been important. However, another factor that is often cited is the reported decreased mortality rates associated with hepatic resection.[22–24] Traditionally, hepatic resection was associated with large-volume blood loss, varying degrees of liver failure, and significant morbidity. As such, the perioperative mortality associated with hepatic resection before the 1990s was reported to be as high as 10% to 20%.[25–27] However, over the past decades, more and more academic centers have reported lower and lower rates of mortality associated with hepatic resection[23,28] with some centers even reporting zero mortality for complex procedures such as extended hepatic resections.[22]

There has been some concern, however, that published, literature-derived mortality rates associated with hepatectomy may not accurately reflect actual population-based perioperative mortality. In fact, publication bias may be responsible for the tendency of academic centers preferentially to report favorable outcomes.[29–31] Previous studies examining carotid endarterectomy indeed suggested that such a bias may exist.[32] No study to date, however, has examined the generalizability of literature-derived mortality rates for hepatectomy compared with national, population-based data. The relative difference between published vs actual population-based mortality rates after hepatic resection has important implications. Such data are critical not only to the informed consent process on the individual patient level but also may have ramifications at the policy level. The objective of the current study was to compare published vs population-based mortality rates after hepatic resection—with the null hypothesis being that these mortality rates are the same.

Materials and Methods

Search Strategy and Data Extraction for Literature-Based Mortality Rates

We systematically searched available electronic databases including MEDLINE/PubMed for the period from January 1998 through December 2004. Specifically, we searched for all English language articles using the medical subject headings "liver resection/mortality/morbidity," "liver resection/outcomes," "hepatectomy/mortality/morbidity," "hepatectomy/outcomes," "liver resection/complications," and "hepatectomy/complications." Criteria for including an article were (1) English language, (2) human subjects, (3) main topic concerning hepatic resection, (4) reported in-hospital and perioperative death rate. Exclusion criteria included (1) hepatic resection not main topic of report and (2) study did not report perioperative survival. All potentially relevant articles were retrieved and reviewed by two independent investigators. Data were collected using standardized data extraction sheets. Data on location of treating institution (US vs non-US), single vs multi-institution involvement, patient demographics, type of hepatic malignancy (primary vs secondary), presence of underlying liver disease, and details of the operative procedure were collected. The primary outcome of interest was the incidence of perioperative death after hepatic resection. For the purposes of this study, perioperative mortality was defined as any in-hospital deaths (regardless of time from operation) or deaths within 30 to 90 days of discharge (dependent on that reported in the individual study). An aggregate literature-based mortality rate was calculated by simple pooling of the total number of perioperative death events over the total number of patients included in the selected studies.

National Population-Based Mortality Rates

To evaluate mortality rates for hepatic resection at the national level, we used the Nationwide Inpatient Sample (NIS) for the years 1998 through 2004. The NIS database is the largest all-payer in-patient care database in the USA, containing data from approximately 8 million hospital stays each year from a stratified sample of 20% of non-federal US community hospitals from participating states, including academic hospitals.[33] The NIS data elements include information on patient demographics, hospital characteristics, primary and secondary diagnoses, primary and secondary procedures, and information on in-patient and discharge mortality rates.

Through a structured query of the NIS database, all patients undergoing hepatic resection were identified based on the ICD-9 procedure codes for hepatic resection (Table 1). Data on demographics, type of operative procedure, diagnosis of the liver tumor, and the presence of underlying hepatic cirrhosis were collected. The primary measured outcome in the NIS dataset was in-hospital mortality. Specifically, mortality was defined as death from any cause before discharge regardless of time from operation.

Table 1 Diagnostic and Procedural Codes Utilized for Structured Query of the NIS Database

Procedural Codes	Diagnosis
Hepatectomy	
50.22	Partial hepatectomy
50.3	Hepatic lobectomy
Hepatic Cirrhosis	
571	Chr liver dis/cirrhosis
571.2	Alcohol cirrhosis liver
571.5	Cirrhosis of liver nos
Hepatocellular Carcinoma	
155.0	Mal neo liver, primary
Blood Transfusion	
99.0	Blood transfusion
99.01	Exchange transfusion
99.02	Transfus prev auto blood
99.03	Whole blood transfus nec
99.04	Packed cell transfusion
99.05	Platelet transfusion
99.06	Coag factor transfusion
99.07	Serum transfusion nec
99.08	Blood expander transfuse
99.09	Transfusion nec

Statistical Analyses

All data were analyzed using Stata/SE version 9 (College Station, TX, USA). Univariate analyses of categorical variables were performed using chi-square and *t* tests, where appropriate. All hepatic resections were first evaluated in aggregate form, and then separate univariate analyses were performed to evaluate less than hemi-hepatectomy (e.g., wedge) vs more than or equal to hemi-hepatectomy. Adjusted mortality rates and 95% confidence intervals (95% CI) were calculated based on regression coefficients from multivariable logistic regression analyses. Perioperative/in-hospital mortality was defined as the dependent variable; independent variables included patient age, gender, HCC diagnosis, presence of cirrhosis, type of hepatic resection (e.g., less than hemi-hepatectomy vs more than or equal to hemi-hepatectomy). When possible, certain hospital level characteristics including surgical volume, geographic region (e.g., Northeast, West, South, and Midwest as defined by the Census Bureau), and teaching status were also evaluated as independent variables. Three distinct adjusted statistical comparisons were assessed: entire literature-based mortality rate vs entire NIS rate; only US literature-based mortality rate vs entire NIS rate; only US literature-based mortality rate from teaching hospitals vs NIS rate from teaching hospitals. Literature vs actual mortality rates were compared by chi-square tests. Adjusted mortality rate and 95% CI were calculated based on regression coefficients from logistic regression analysis with death as dependent variable, and age, gender, HCC diagnosis, presence of cirrhosis, and receipt of more than or equal to hemi-hepatectomy as independent variables. In this manner, the NIS cohort was adjusted to match the average age, percent female, percent HCC as indication for surgery, percent with cirrhosis, and percent receiving more than or equal to hemi-hepatectomy among patients reported in the literature.

Results

Literature-Based Mortality Rates

Twenty-three publications were identified that fulfilled screening criteria (Table 2).[28,34–54] Overall, these studies included 7,064 patients who had undergone hepatic resection. The median number of patients in the 23 studies was 309 (range, 18 to 1,803). Eight reports were from centers within the USA (n=3257 patients; 46.1%), while 15 studies involved institutions from outside the USA (n=3,807 patients; 53.9%). The overwhelming majority of publications were single center reports (n=19 institutions; 82.6%) from academic institutions (n=17 institutions; 73.9%).

Table 3 shows the clinicopathologic features of the 7,064 patients included in the literature-based cohort. There were 2,835 (40.4%) women and 3,946 (58.6%) men with a median age of 56 years. Indications for hepatic resection included HCC (n=3,366; 47.7%), metastatic disease (n=2,420, 34.3%), and other (n=1,278, 18.1%). At the time of surgery, the extent of hepatic resection was less than a hemi-hepatectomy in 3,748 patients (52.1%) or more than or equal to hemi-hepatectomy in 3,316 patients (46.9%). The mean estimated blood loss was 993 ml (range, 400 to 1,940 ml); among those studies that reported such data (n=11), the mean proportion of patients receiving a blood transfusion was 56.8%.

The mean number of reported perioperative deaths was 11 (range, 0 to 75). Over one third (n=8; 34.8%) of studies reported a perioperative mortality rate of 0%. Of those studies that did report at least one perioperative death (n=15; 65.2%), the mortality rates ranged from 1.6% to 14.8% (Fig. 1). After pooling the total number of perioperative death events over the total number of patients included in the selected studies, the aggregate literature-based mortality rate was 3.6% (257 deaths in 7,064 patients). For single institution reports, the aggregate literature based mortality rate was 2.6% (151 deaths in 5,864 patients). The aggregate literature-based mortality rate of patients undergoing hepatectomy for HCC was 4.7% compared with 4.0% for non-cirrhotic patients (Fig. 2).

Table 2 Details of Studies Included in Literature-Based Mortality Rate

Author/Year Published	Institutional Setting	Number of Institutions	Location	Number of Patients	No. patients ≥ Hemi-hepatectomy (%)	Number of Postoperative Deaths (%)
Belghiti 1999[47]	Academic	Single	International	747	333 (44.6)	5 (1.6)
Bidan 2001	Academic	Single	International	100	42 (42.0)	4 (4.0)
Capusotti 1998[46]	N/A	Single	International	193	188 (97.4)	6 (3.1)
Choti 1998[52]	Both	Multiple	United States	606	232 (38.3)	31 (5.1)
Descotes 2002[44]	Both	Multiple	International	87	3 (3.4)	0 (0)
Fan 1998[36]	Academic	Single	International	330	229 (69.4)	21 (6.3)
Finch 1998[42]	Academic	Single	International	129	116 (89.9)	6 (4.6)
Glasgow 1999[53]	Both	Multiple	USA	507	208 (41.0)	75 (14.8)
Hanzaki 2000[37]	Academic	Single	International	386	62 (16.1)	27 (6.9)
Helling 2002[35]	Academic	Single	USA	147	101 (68.7)	5 (3.4)
Imamura 2003[40]	Academic	Single	International	915	305 (33.3)	0 (0)
Jacobs 2003[39]	Academic	Single	USA	33	8 (24.2)	1 (3.0)
Jarnagin 2002[28]	Academic	Single	USA	1,803	1072 (59.5)	55 (3.1)
Kammula 2001[41]	Academic	Single	USA	28	5 (17.9)	0 (0)
Kanematsu 2002[51]	Academic	Multiple	International	303	2 (0.7)	5 (1.6)
Mcall 2001[54]	Nonacademic	Single	International	123	80 (65.0)	3 (2.4)
Morino 2003[43]	Academic	Single	International	60	0 (0)	0 (0)
Pol 1999[50]	Academic	Single	International	100	100 (100)	7 (7.0)
Redaelli 2002[48]	Academic	Single	International	167	167 (100)	6 (3.6)
Stone 2000[34]	Nonacademic	Single	USA	18	4 (22.2)	0 (0)
Torzilli 1999[49]	Academic	Single	International	107	37 (107)	0 (0)
Yanaga 2003[45]	Academic	Single	International	60	20 (33.3)	0 (0)
Yoon 2003[38]	Academic	Single	USA	115	2 (1.7)	0 (0)

National Population-Based Mortality Rates

During the sample time period of 1999–2003, 11,429 patients were identified who had undergone hepatic resection. There were 5,941 (52.0%) women and 5,477 (48.0%) men with a median age of 59 years (range, 20 to 101; Table 4). Most individuals were white (n=6781; 76.3% of patients with race data); 788 (6.9%) patients were black and 1,313 (14.8%) were other races. Table 4 includes the distribution of diagnoses, medical comorbidities, and hospital type (teaching vs non-teaching). Most patients were treated at a teaching hospital (78.1%). At the time of surgery, the vast majority of patients (n=7,559, 66.1%) underwent a partial hepatectomy, while 3,870 (33.9%) patients had more than or equal to hemi-hepatectomy. Overall, 1,910 patients received a blood transfusion for an overall transfusion rate of 16.7%.

Table 3 Clinicopathologic Characteristics of Patients in the Literature-based Cohort

Variable	Number (Percent) Patients (n=7,064)
Patients characteristics	
Age (median, years)	56
Gender (% Male)	3,946 (58.6)
Indication for hepatic resection	
Hepatocellular carcinoma	3,366 (47.7)
Presence of cirrhosis	1,660 (23.5)
Type of hepatic resection	
<Hemi-hepatectomy	3,748 (52.1)
≥Hemi-hepatectomy	3,316 (46.9)
Estimated blood loss (mean, range) (ml)	993 (400–1940)

IQR Intra-quartile range, *CEA* carcionembryonic antigen

For all patients undergoing hepatectomy, the crude perioperative mortality rate was 4.9% (Fig. 3a). On single logistic regression, increased perioperative mortality after hepatectomy was associated with male gender (OR, 1.53; 95% CI, 1.29–1.82; P<0.001) and patient age (OR, 1.01 for every 1 year increase; 95% CI, 1.01–1.02; P<0.001). Institutional annual surgical volume also strongly correlated with mortality (OR, 0.99 for every one case increase in annual volume; 95% CI, 0.989–0.994). The high-volume centers (≥50 resections/year) had a mortality rate of 2.9% compared with 4.3% for medium-volume centers (10–49 resections/year) and 7.1% for low-volume center (<10 resections/year; P<0.001). Compared with high-volume centers, this translated into an unadjusted odds ratio for death at medium-volume centers of 1.25 (95% CI, 1.05–1.55; P=0.01) and a higher unadjusted odds ratio of 1.96 for low-volume centers (95% CI, 1.56–2.44; P<0.001). Perioperative mortality was also lower at teaching hospitals

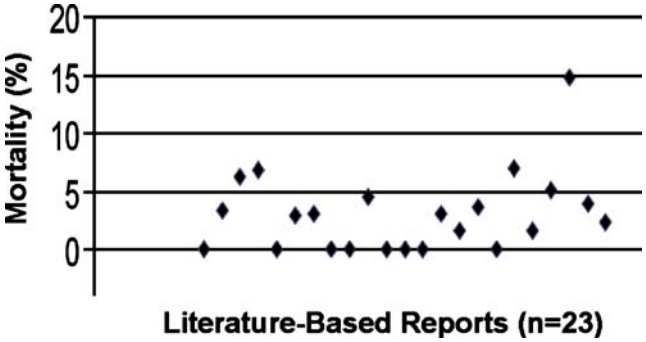

Figure 1 Distribution of mortality rates reported in the literature-based studies (n=23). Over one third (n=8; 34.8%) of studies reported a perioperative mortality rate of 0%, while greater than 80% of studies reported mortality rates less than 5%.

compared with non-teaching hospitals (OR, 0.79; 95% CI, 0.65–0.96; P=0.02). There was no significant difference in perioperative mortality between the different regions of the country (reference: Northeast; Mid-west, OR 0.87; South, OR 1.22; West, OR 1.02; all P>0.05).

In addition to volume and teaching status of the hospital, the type of operative procedure (more than or equal to hemi-hepatectomy vs less than hemi-hepatectomy; OR, 1.64; 95% CI, 1.37–1.92; P<0.001) was associated with in-hospital mortality. Specifically, patients who underwent less than a hemi-hepatectomy had a mortality rate of 4.1% compared with 6.5% for patients who underwent more than or equal to hemi-hepatectomy. Receipt of blood transfusion (OR, 1.80; 95% CI, 1.48–2.19; P<0.001) was also associated with increased risk of in-hospital mortality. Similarly, mortality rates were higher among cirrhotic vs non-cirrhotic patients (OR, 2.41; 95% CI, 1.87–3.09; P< 0.001). On univariate analyses, mortality rates were also associated with HCC as the indication for surgery (HCC vs non-HCC: OR, 2.00; 95% CI, 1.62–2.46; P<0.001).

Using multivariate logistic regression model, several independent predictors of in-hospital mortality were identified. After adjusting for competing risks, factors that remained significantly associated with an increased risk of in-hospital mortality included age (OR, 1.02; 95% CI, 1.01–1.02), male gender (1.50; 95% CI, 1.25–1.79), more than or equal to hemi-hepatectomy (OR, 1.71; 95% CI, 1.59–1.99), transfusion (OR, 1.48; 95% CI, 1.21–1.81), and cirrhosis (OR, 2.05; 95% CI, 1.54–2.74; all P<0.001). Hospital volume also continued to have a strong protective effect. Compared with low-volume centers, medium-volume (OR, 0.51; 95% CI, 0.42–0.63; P<0.001) and high-volume (0.34; 95% CI, 0.26–0.45; P<0.001) centers had a significantly lower risk of in-hospital mortality. In contrast, HCC diagnosis (OR, 1.18; 95% CI, 0.92–1.52) and teaching status of the hospitals (OR, 1.23; 95% CI, 0.98–1.54) did not have an independent association with in-hospital mortality (both P>0.05; Table 5).

Comparative Analyses: Published, Literature- vs Population-Based Mortality Rates for Hepatic Resection

The demographic and clinical profile of patients reported in the literature differed from that of patients reported in the NIS database. Importantly, among those literature-based studies where such data were reported, patients were more likely to be male (literature, 57.8%, vs NIS, 47.7%), have underlying cirrhosis (literature, 23.5%, vs NIS, 6.4%), have HCC as an indication for surgery (literature, 47.7%, vs NIS, 12.7%), and have undergone more than or equal to hemi-hepatectomy (literature, 47.7%, vs NIS, 35.2%; all P<0.05) compared with NIS patients. As such, a comparative analysis of the published, literature- vs population-based mortality rates for hepatic resection was performed that controlled for these factors. The adjusted death rate for patients in the NIS dataset undergoing hepatectomy was 5.6% (95% CI, 5.0–6.2%). This was significantly higher than the overall literature-based mortality rates reported in either multi-institutional (3.6%) or single institution studies (2.6%; both P<0.05; Fig. 3b).

As the NIS dataset includes data only on institutions in the USA, a secondary comparative analysis was performed that specifically compared outcomes from US centers. Literature-based mortality after hepatectomy in US centers only was 3.6% compared to an adjusted mortality rate of 4.9% (95% CI, 4.4–5.4%) for patients in the NIS dataset (P<0.05). Similarly, when analyses were restricted to a comparison of literature-based mortality rates only in USA teaching hospitals (3.6%) vs the adjusted mortality of NIS patients treated at like centers (4.5%; 95%, CI 4.0–5.1%), there was a significant difference in mortality after hepatectomy (P<0.05; Fig. 3b). In contrast, when the analysis was restricted to high-volume academic hospitals in the NIS, the adjusted mortality rate was 3.0% (95% CI,

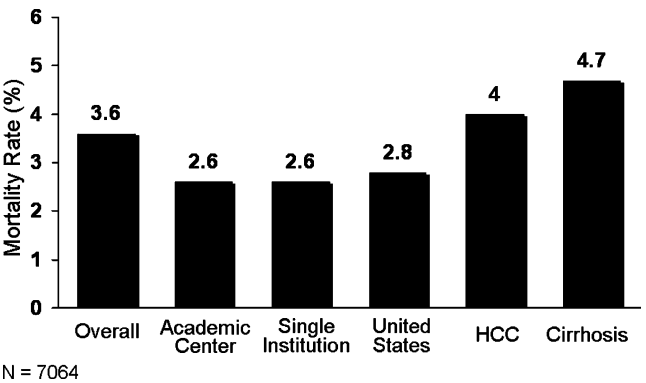

Figure 2 The aggregate crude mortality derived from literature-based series was 3.6%. Studies that involved academic centers, single institutions, and those specifically within the USA reported a lower overall mortality rate. In contrast, as expected, the mortality rate associated with hepatectomy in patients with HCC/cirrhosis was higher (4% to 4.7%).

Table 4 Clinicopathologic Characteristics of Patients in the Nationwide Inpatient Sampling (NIS) Cohort

Variable	Number (Percent) Patients (n=11,429)
Year	
1998	1,398 (12.2)
1999	1,595 (14.0)
2000	1,426 (12.5)
2001	1,457 (12.7)
2002	1,642 (14.4)
2003	2,022 (17.7)
2004	1,889 (16.5)
Patients characteristics	
Age (median, years)	59
Gender (% male)	5,477 (48.0)
Indication for hepatic resection	
Hepatocellular carcinoma	1,453 (12.7)
Presence of Cirrhosis	757 (6.6)
Type of hepatic resection	
<Hemi-hepatectomy	7,559 (66.1)
≥Hemi-hepatectomy	3,870 (33.9)
Geographic location of treating hospital	
Northeast	2,726 (23.9)
Midwest	2,276 (19.9)
South	3,995 (35.0)
West	2,432 (21.3)
Academic affiliation of treating hospital	
Non-teaching	2,502 (21.9)
Teaching	8,927 (78.1)
Surgical volume of treating hospital	
Low volume (<10 cases/year)	4,062 (35.6)
Middle volume (10–50 cases/year)	4,248 (37.2)
High volume (>50 cases/year)	3,109 (27.2)

2.4–3.8%), which was statistically the same as the literature-based 3.6% reported by US teaching hospitals (P>0.05).

Discussion

Accurate information regarding perioperative mortality is critical not only to inform patient consent but also to provide the proper context when assessing the relative risks and benefits of hepatectomy. Most data on mortality have traditionally come from single institution case series with few studies[55,56] investigating actual population-based mortality associated with hepatectomy. In addition, to our knowledge, no previous report has specifically investigated the relative differences in literature-based vs national mortality rates after major hepatic resection. Such data are important for several reasons. While the majority of data on perioperative mortality is derived from highly selected published series, it remains unclear whether these data can be extrapolated to the over 1,000 hepatectomies that are performed in the USA each year. Such data are particularly important at a time when many investigators are calling for an expansion of the criteria for resectability of liver tumors in light of improved self-reported outcomes.[1–8]

Self-reporting of institution-specific outcome data may, however, be susceptible to a significant reporting bias.[29,30] It has been well documented that positive outcomes are more likely to be published as compared to negative or poor outcomes.[29,57] Positive outcome bias has been associated with increased selection of data for national presentation and publication, independent of adequacy of study design or data quality.[58] Furthermore, publication bias has been demonstrated on post hoc analysis in cohort studies,[59,60] clinical trials,[61] and data presented at national meetings.[62] As such, self-reported data from academic institutions need to be carefully considered, as these data may preferentially tend to report more favorable outcomes.[59] Indeed, one prior study[32] convincingly has shown that such a positive outcome bias exists in the reporting of outcomes after carotid endarterectomy. The current study suggests that such a positive outcome bias may also exist in the reporting

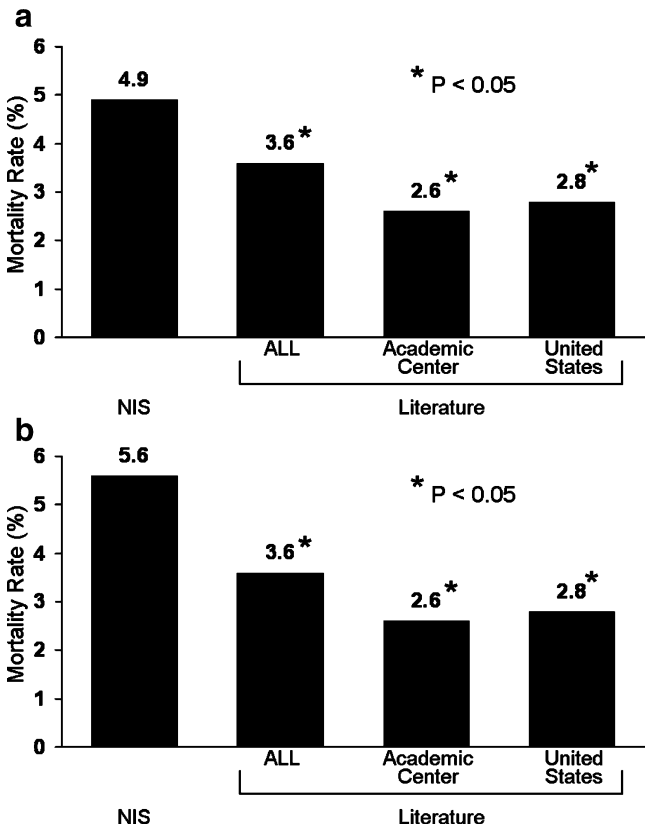

Figure 3 **a** The aggregate population-based crude mortality rate for hepatectomy was 4.9%, which was significantly higher than the literature-based overall rate of 3.6% and the US rate of 2.8%. **b** After adjusting for differences in clinicopathologic factors, the aggregate population-based mortality rate for hepatectomy increased to 5.6%. This represents a 1.6-fold increase in mortality compared to the overall literature-based mortality rate.

Table 5 Prognostic Factors Associated with Population-Based, Postoperative Mortality in Patients from the Nationwide Inpatient Sample (NIS)

Prognostic Factor	Odds Ratio	95% Confidence Interval	P-value
Patient factors			
Age (per year)	1.02	1.01–1.02	<0.001
Sex (male)	1.50	1.25–1.79	<0.001
Liver factors			
Presence of cirrhosis	2.05	1.54–2.74	<0.001
Hepatocellular carcinoma	1.18	0.92–1.52	0.35
Operative factors			
≥Hemi-hepatectomy	1.71	1.59–1.99	<0.001
Transfusion	1.48	1.21–1.81	<0.001
Hospital factors			
Non-teaching	1.23	0.98–1.54	0.23
Hospital surgical volume			
High volume (reference)	–	–	–
Middle volume	1.96	1.59–2.38	<0.001
Low volume	2.94	2.22–3.85	<0.001

of outcome data after hepatectomy. Of particular note was the finding that over one third of literature-based reports documented a zero mortality rate after major hepatectomy. While the root reasons for the reported 0% mortality are clearly multifactorial, such data need to be placed within the context of actual nationwide mortality data.

To assess the population-based mortality associated with hepatectomy, we utilized the NIS dataset. NIS is the largest all-payer in-patient care database in the USA. It contains data from approximately 8 million hospital stays with discharge data from 1,054 hospitals located in 37 states. Most patients (66.1%) in the NIS dataset underwent less than a hemi-hepatectomy and had favorable clinicopathologic characteristics (e.g., only 6.6% patients had documented cirrhosis). Despite the fact that the majority of patients did not have cirrhosis and underwent only a wedge/segmentectomy, the unadjusted crude population-based mortality rate after hepatectomy was 4.9%. Analyses revealed several factors that were associated with mortality, including both biologic and institutional factors. Those clinical factors associated with mortality included age, male gender, history of transfusion, and surgery involving more than or equal to hemi-hepatectomy (all $P<0.001$). Perhaps as important as the biologic factors, several institutional factors predicted mortality after hepatectomy (Table 5). Chief among these was case-center volume. In fact, patients who underwent hepatectomy at a low-volume institution (e.g., less than ten cases per year) had a nearly threefold (OR, 2.94; 95% CI, 2.22–3.85) increased risk of perioperative mortality compared with high-volume hospitals (e.g., more than 50 cases per year). Of note, when analyses were restricted to high-volume academic hospitals in the NIS, the adjusted mortality rate was 3.0% (95% CI, 2.4–3.8%), which was statistically the same as the literature-based 3.6% reported by US teaching hospitals. These data suggest that mortality rates reported in the literature are derived from high-volume teaching hospitals with lower-volume hospitals—and higher mortality rates—being under-represented (e.g., publication/reporting bias). Other investigators have similarly noted a strong relationship between hospital level hepatectomy case volume and outcome.[55] Of note, however, in the current report—while hospital volume was associated with mortality—teaching status of the hospital did not have an independent association with in-hospital mortality ($P>0.05$).

Compared to nationwide data, literature-based, academic institutional reporting of overall peri-operative mortality was significantly lower. As noted, over one third of institutions reported zero mortality and the overwhelming majority of studies (83%) reported a mortality rate well below 5% (Fig. 1). In aggregate, the overall crude mortality rate after hepatectomy reported in the literature was 3.6%. When only institutions within the USA were considered, the aggregate crude mortality rate was even lower (2.8%). It is important to note, however, that there were significant differences in the composition of patients reported in the literature as compared to those in the NIS dataset. Specifically, patients in the literature-based cohort were significantly more likely to be male, have cirrhosis, carry a diagnosis of HCC, and have undergone more than or equal to hemi-hepatectomy. Thus, even though patients in the literature-based cohort were noted to have more adverse clinical and biologic characteristics, they were paradoxically less likely to die after hepatectomy. Because of this, we performed an adjusted analysis to account for these disparate covariates, thereby allowing for a more appropriate comparison of the mortality rates between the literature- and population-based cohorts. After controlling for age, sex, presence of cirrhosis, HCC diagnosis, and extent of hepatectomy, the differences in the national vs literature-based mortality rates were even more pronounced. As expected, because patients in the NIS dataset initially had a more favorable clinical profile, after adjusting for the increased incidence of cirrhosis, HCC, and the greater extent of hepatic resection compared to literature-based patients, the population-based mortality rate increased from 4.9% to 5.6% (Fig. 3). Adjusted analyses therefore revealed a 56% or 1.6-fold increased risk of death (population-based, 5.6%, vs literature-based, 3.6%) based on actual, public data compared with reported data from the literature ($P<0.05$). If one took into account the fact that the NIS represents a population-based sample from the USA only and compared the NIS mortality rate vs the USA-only literature-based cohort, the disparity in mortality was even more striking (NIS, 5.6%, vs US literature, 2.8%).

The current study has several limitations. Although a systematic review of the literature was undertaken, it is possible that the literature-based cohort was not truly representative of the published data on outcomes after hepatic resection. This, however, is unlikely, as specific, prospectively chosen criteria were used to perform the literature search. In addition, the lack of variance in the reported mortality rates among the chosen studies (e.g., all studies reported a very similar mortality rate) strongly suggests that literature-based mortality rates were comparable and the addition of further studies would not have significantly changed the results. The inclusive dates of the current study also predate the International Committee of Medical Journal Editors uniform requirements for manuscripts submitted to biomedical journals. As such, we were unable to review unpublished trials, negative outcome trials, or trials presented only as abstracts. In addition, although the year of reporting (1998 to 2003) was used to select publications, some literature-based studies included data from patients undergoing hepatectomies before these dates. Inclusion of such patients, however, would, if anything, bias the results toward the null—as patients undergoing hepatectomy in earlier decades were more likely to have worse outcomes. Another limitation involved the definition of operative mortality. Whereas the calculated NIS mortality rate included only in-hospital deaths, literature-based mortality rates included both in-hospital and postoperative deaths. As such, the NIS mortality rate may actually underestimate the "true" population-based mortality rate associated with hepatectomy—thereby suggesting an even greater difference between population- vs literature-based mortality rates. Finally, although adjusted analyses were performed in an attempt to create more comparable pools of patients to compare in the national vs literature-based cohorts, only a limited number of factors (e.g., age, sex, cirrhosis, HCC, and extent of hepatectomy) were included in the multivariate model. Other unmeasurable confounders may have contributed to the differences between national vs literature-based mortality rates, but these inherently cannot be accounted for in a retrospective study.

In conclusion, our data strongly suggest that literature-based mortality rates underestimate actual national operative mortality rates after hepatectomy. The risk of perioperative mortality after hepatectomy was associated with age, sex, presence of cirrhosis, extent of hepatectomy, and hospital volume. Analyses of mortality data revealed that population-based mortality rates for hepatectomy were 1.5 to 2.0 higher than literature-based mortality rates. Furthermore, adjustment for patient, liver, and surgery characteristics did not explain the difference in literature- vs population-based mortality. At a population level, hepatic resection remains associated with about a 5% risk of mortality. Differences in literature- vs population-based mortality rates need to be considered when discussing the role of liver resection in patients with primary and secondary hepatic malignancies. Obviously, data from all population-based studies must be extrapolated with care when considering the individual patient. Conclusions derived from aggregate data must be individualized based on the clinicopathologic characteristics of the specific patient in question and the experience of the treating surgeon. When center-specific data are unavailable, however, informed consent should reflect actual local and national population-based mortality rates, as literature-based mortality rates tend to underestimate the risk associated with hepatic resection.

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ZM336372, A Raf-1 Activator, Causes Suppression of Proliferation in a Human Hepatocellular Carcinoma Cell Line

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Abstract Hepatocellular carcinoma has been described to exhibit characteristics similar to that of neuroendocrine tumors (NETs). This includes similar anti-neoplastic responses to extracellular signal-regulated kinase (ERK) activation. NET cells and HepG2 cells have both shown growth inhibition with ERK activation. ZM336372, a Raf-1 activating agent, has been shown to cause growth inhibition and suppression of hormone secretion in a neuroendocrine cell line. Here we examine treatment of the HepG2 cell line with ZM336732 to determine if a similar anti-proliferative response will be obtained. HepG2 cells were treated with ZM336372 or solvent (dimethyl sulfoxide). The resulting effect on the proliferation was measured using the 3,4-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Western blot analysis was performed to examine the activation of the Raf-1/mitogen-activated protein kinase kinase/ERK pathway, chromogranin A production, and $p21^{CIP1}$ level. Growth inhibition was observed with ZM336372 in a dose-dependent fashion. Minimal baseline phosphorylation of ERK 1/2 was observed; however, activation was observed after treatment with ZM336372. Chromogranin A secretion was suppressed due to treatment with ZM336372. A dose-dependent up-regulation of $p21^{CIP1}$ was observed in response to ZM336372 treatment. ZM336372 causes growth inhibition, suppression of hormone secretion, and up-regulation of cell cycle inhibitors in a human hepatocellular carcinoma cell line, similar to that previously seen in NETs.

Keywords ZM336372 · Hepatocellular carcinoma · Raf-1 · MAPK

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Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and a significant cause of cancer-related death throughout the world.[1,2] The only effective forms of treatment for this disease are locoregional; systemic therapies are generally ineffective. Therefore, studies looking at cellular mechanisms of tumor growth are essential in order to discover efficacious therapies.

Examinations into the biology of HCC have shown characteristics similar to those of neuroendocrine tumors (NETs). HCC and NETs share a similar response to Notch-1 activation. In both NETs and HCC, Notch-1 activation causes growth inhibition and cell cycle arrest.[3–5] This is unlike pancreatic adenocarcinoma, colon cancer, renal cell carcinoma, non-small cell lung cancer, and cervical cancer, where Notch1 activation causes cellular proliferation.[6] In addition, chromogranin A secretion occurs in both NETs and HCC. Chromogranin A has long been used as a marker

for NETs, but it has also been found to be elevated in the serum of patients with HCC.[7]

NETs and HCC uncommonly possess activating mutations of the Ras/Raf-1/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway [8–12] (Fig. 1), whereas activating mutations of this pathway are quite common in most other tumors.[13,14] ERK pathway activation has been shown to cause growth inhibition in NET and HCC cell lines. Studies have shown that inducing Raf-1 expression in neuroendocrine cell lines leads to suppression of hormone secretion and cellular growth.[15,16] Numerous other studies have also shown antineoplastic effects of activation of the Raf-1/MEK/ERK pathway on neuroendocrine tumors.[17–19]

Activation of ERK has previously been shown to cause growth inhibition in HepG2 cells due to treatment with hepatocyte growth factor (HGF) and induced constitutive expression of Ha-Ras.[20] In addition, HGF treatment has been shown to result in up-regulation of the cyclin-dependent kinase inhibitors $p21^{CIP1}$ and $p27^{KIP1}$ leading to cell cycle arrest in response to ERK activation.[21]

ZM336372 is a small molecule discovered by screening a chemical library for a Raf-1 inhibitor. It was shown to inhibit Raf-1 in solution; however, when tested in cell culture, ZM336372 was shown to cause Raf-1 activation by greater than 100-fold.[22] ZM336372 was previously tested in a neuroendocrine cell line. The H727 carcinoid tumor cell line was treated with ZM336372, causing diminished production of chromogramin A, suppression of cellular proliferation, and $p21^{CIP1}$ up-regulation.[23] Since ZM336372 has shown these effects in NETs and since NETs share a similar response to ERK activation as HCC, we decided to determine if Raf-1 activation due to ZM336372 treatment of a hepatocellular carcinoma cell line would result in antineoplastic effects similar to those previously seen in NETs.

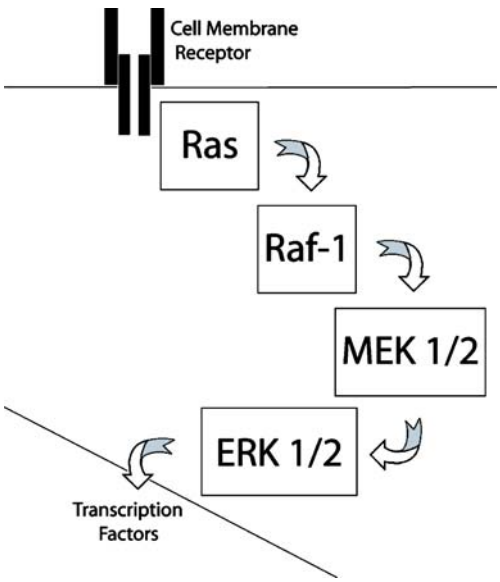

Figure 1 Schematic representation of the Ras/Raf-1/MEK/ERK pathway.

Methods

Cell Culture HepG2 cells (American Type Culture Collection, Manassas, VA, USA) were maintained in Dulbecco's modified Eagle's medium (Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (Hyclone, Logan, VT, USA), 100 IU/ml of penicillin, and 100 pg/ml of streptomycin (Gibco). The cell lines were incubated in a humidified atmosphere of 5% CO_2 at 37°C.

ZM336372 treatment Treatment of the cell lines with ZM336372 (Tocris, Ellisville, MO, USA) was performed by addition of the appropriate concentration of drug from a 100 mM stock dissolved in 100% dimethyl sulfoxide (DMSO; Sigma, St. Louis, MO, USA) to the culture media prior to adding the solution to cells plated the day before. The media and drug were exchanged every 2 days for the duration of the experiments.

MTT Assay MTT reagent, 3,4-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma), was reconstituted in phosphate-buffered saline (PBS) to a final concentration of 5 mg/ml. MTT reagent was added to each culture being assayed in phenol red free media to equal one tenth the original culture volume and incubated for 3 h at 37°C. The medium was then removed, and the dye was solubilized with 350 μl of 0.1 N HCl in isopropanol. The absorbance was then measured at a wavelength of 540 nm with background subtraction at 630–690 nm.

Cellular Extracts Media was aspirated, and the attached cells were washed once with PBS. PBS containing 0.5 M ethylenediamine tetraacetic acid was added to the cells, and then cells were removed using a cell scraper. Next, the cell suspension was centrifuged at 2,000 rpm for 5 min at 4°C. The supernatant was aspirated, and lysing buffer, consisting of Tris–sodium dodecyl sulfate buffer, phenylmethylsulfonyl fluoride, and a protease inhibitor cocktail, was added to the cell pellets and incubated for 20–30 min at 4°C. After centrifugation at 1,300 rpm for 30 min at 4°C, supernatant was collected, and protein concentrations were performed using the bicinchoninic acid (BCA) protein assay kit (Pierce, Rockford, IL, USA) following manufacturer's instructions.

Western Blot Analysis Approximately 40 μg of cellular extract from ZM336372-treated cells and controls were loaded onto pre-cast 10% polyacrylamide gels (Pierce). The gels were run at 100 V for 60 min and then transferred to

polyvinylidene difluoride Immobilon-P membranes (Millipore, Bedford, MA, USA) at 40 V for 90 min. The membranes were blocked with a 5% milk solution for 1 h, and the primary antibodies, p-MEK 1/2, p-MAPK p44/p42, p-c-Raf, p21, and Cg A (Cell Signaling Technology, Beverly, MA, USA), were incubated overnight in bovine serum albumin (Sigma) at a 1:1,000 ratio. Following incubation with the primary antibody, membranes were washed three times for 5 min in Tris-buffered saline Tween-20 (TBS-T) wash buffer (Tris-buffered saline, 0.05% Tween 20). Next, goat anti-rabbit horseradish peroxidase-labeled antibody (Pierce) was added at ratio of 1:7,000 in milk solution and incubated for 1–2 h. The membranes were then washed again three times, for 5 min with TBS-T. SuperSignal West Pico Chemiluminescent Substrate (Pierce) was added according to manufacturer's instructions and then incubated for 5 min. Following removal of the substrate, the membranes were placed in plastic sleeves and exposed to film. Anti-G3PDH antibody (Pierce) was utilized as a loading control at a ratio of 1:7,500.

MEK 1/2 inhibitor assay Cell cultures were plated out at 1 million cells per 100 mm culture dish. Cells were pretreated with UO126 (Cell Signaling Technology), a MEK 1/2 inhibitor, for 45 min at a concentration of 5 μM. Following UO126 treatment, ZM336372 was added from a 100-mM stock solution in DMSO directly to the culture media in the culture dish at a concentration of 15 μM and mixed. Controls containing only UO126 and ZM336372 were also incubated with the experiment. Cellular extracts and Western blot were then performed as above.

Results

ZM336372 Causes Activation of Raf-1/MEK/ERK Cascade in HCC Cell Line

To clarify the cellular effects of ZM336372 on the Raf-1/MEK/ERK pathway in the HepG2 cell line, Western blot using antibodies targeted for the activated forms of these kinases was performed. Minimal phosphorylation of ERK 1/2 was observed at baseline (Fig. 2a). However, an increase in phosphorylated ERK 1/2 was observed after ZM336372 treatment in a dose-dependent fashion for the concentrations from 5 to 25μM. In addition, phosphorylation of Raf-1 and MEK 1/2 were also observed. This confirms that ZM336372 is able to cause activation of the Raf-1/MEK/ERK1/2 pathway in HepG2 cells.

To determine if the ERK 1/2 activation by ZM336372 is dependent on phosphorylation of MEK 1/2, an inhibitor assay was performed using UO126. UO126 has previously been shown to prevent the phosphorylation of ERK 1/2 by both MEK1 and MEK 2. Since Raf-1 activation of ERK 1/2 is mediated through MEK 1/2, inhibition by UO126 should prevent ZM336372-mediated ERK phosphorylation if it occurs through this pathway. Incubation of HepG2 cells with UO126 prior to treatment with ZM336372 prevented the activation of ERK 1/2 by ZM336372 as demonstrated by Western blot in Fig. 2b. A concentration of 5 μM of UO126 was used to inhibit the ZM336372-induced phosphorylation of ERK 1/2. This correlates with the ZM336372-induced activation of ERK 1/2 being propagated through MEK 1/2.

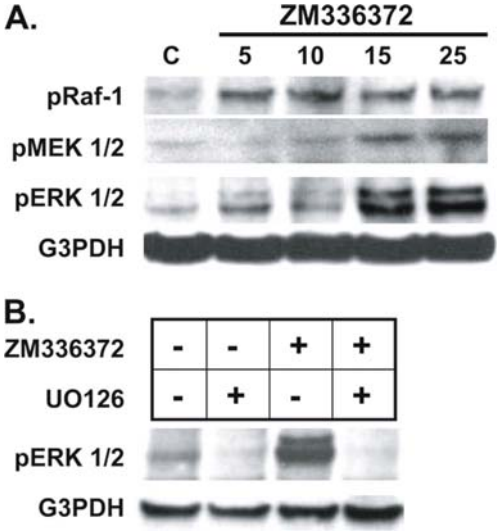

Figure 2 Activation of the Raf-1/MEK/ERK pathway secondary to treatment with ZM336372. **a** Total cellular extracts from HepG2 cells treated with ZM336372 or control show a dose-dependent increase in ERK 1/2 activation following treatment with ZM336372 after 2 days. In addition, ZM336372 activation of Raf-1 and MEK 1/2 is shown. **b** Following treatment with UO126, the ZM336372-induced activation of ERK 1/2 is inhibited.

ZM336372 Causes Growth Inhibition of the HepG2 Cell Line

The MTT assay was employed to determine if ZM336372 would cause an effect on cell growth, as previously described with HGF-induced ERK activation in this cell line.[20] The MTT assay after 8 days of treatment (Fig. 3a) shows a decrease in growth rate in proportion to the concentration of ZM336372 added. Significant growth reduction is observed at the 5 μM concentration of ZM336372, with complete suppression of proliferation at the 15 μM concentration. This confirms that ZM336372 is able to cause suppression of proliferation in HCC cells.

Since ZM336372 caused growth suppression in a cell line with minimal baseline ERK activation, the growth effects of ZM336372 when baseline ERK activation is present was investigated. Pancreatic adenocarcinomas com-

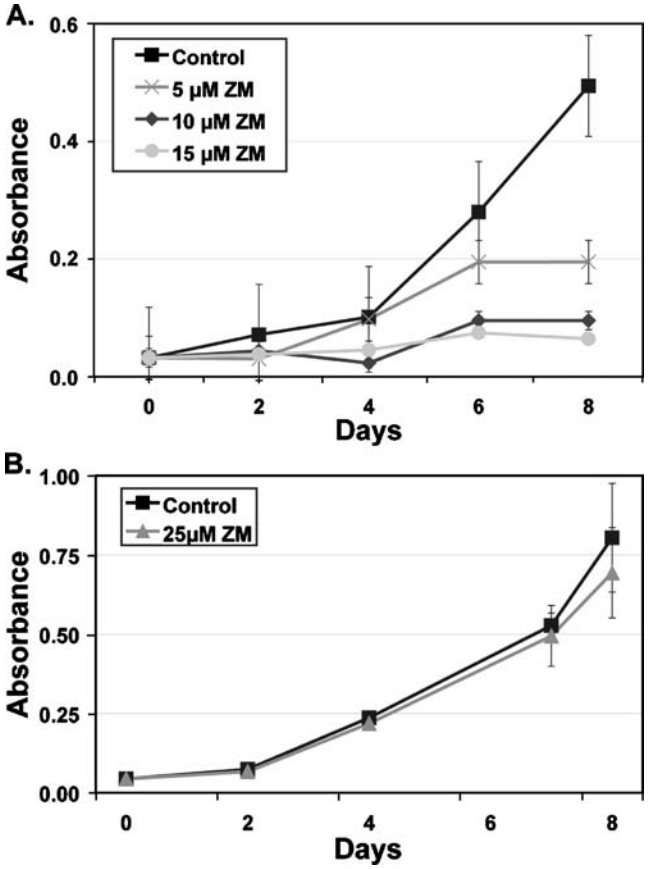

Figure 3 Growth suppression secondary to treatment with ZM336372. **a** The MTT assay after 8 days of treatment shows a reduction in proliferation after treatment with the 5 μM concentration of ZM336372. Complete growth suppression of the HepG2 cells is observed with the 15 μM concentration. DMSO treated HepG2 cells were used as a control. **b** ZM336372 treatment of a pancreatic adenocarcinoma cell line results in no change in growth suppression. Panc-1 cells treated with 25μM of ZM336372 for 8 days showed no significant difference between cells treated with the DMSO control.

monly possess activating mutations of the Ras/Raf-1/MEK/ERK pathway and thus would not be expected to respond to ZM336372 treatment with growth suppression. The MTT assay was utilized to evaluate the growth effects of ZM336372 on Panc-1 cells. Figure 3b shows that no change in growth was noted between 25 μM of ZM336372 and control cells after 8 days of treatment. Above-baseline activation of MEK 1/2 and ERK 1/2 was seen in the pancreatic cancer cells on Western blot (data not shown).

ZM336372 Causes Up-regulation of the Cell Cycle Inhibitor $p21^{CIP1}$

To determine if there is a ZM336372 treatment-induced effect on the cyclin-dependent kinase inhibitor $p21^{CIP1}$, Western blot analysis was performed. Figure 4a shows a dose-dependent elevation in the expression of $p21^{CIP1}$ in response to ZM336372 treatment. This correlates with previous studies showing a Raf-1-induced increase in $p21^{CIP1}$ expression resulting in inhibition of proliferation.[24] In addition, this also correlates with previous descriptions of ZM336372-induced cell cycle arrest in H727 cells and cell cycle arrest due to HGF treatment in HepG2 cells.

ZM336372 Treatment Results in Suppression of Hormone Secretion

Chromogranin A secretion is a marker of neuroendocrine differentiation but has also been observed in the serum of patients with HCC. Previously, ZM336372 treatment in H727 cells resulted in decreased chromogranin A secretion. Figure 4b shows confirmation of chromogranin A secretion along with a dose-dependent decrease in hormone production in HepG2 cells, similar to that seen with carcinoid cells.

Discussion

The Raf-1/MEK/ERK pathway controls cellular differentiation, proliferation, and survival. Numerous tumor types contain activating mutations of this pathway resulting in neoplastic transformation. However, in other tumor types that typically do not harbor activating mutations of this pathway, growth inhibition has been described in response to activation of ERK 1/2.[25]

In a study using an estrogen-inducible Raf-1 construct in NIH 3T3 cells, Raf-1 activation was shown to induce $p21^{CIP1}$ expression and elicit G_1 arrest.[24] In this same study, it is interesting to note that A-Raf activation led to cell cycle progression. Using a similar construct, activation of

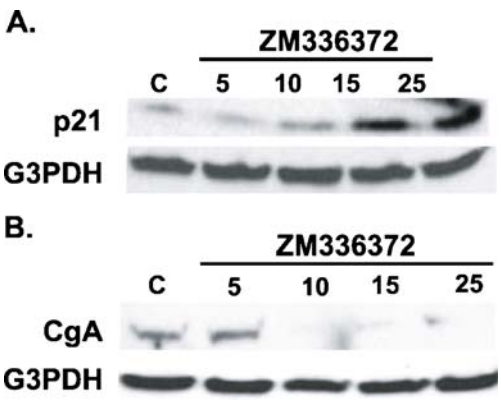

Figure 4 A. Up-regulation of $p21^{CIP1}$ after ERK 1/2 activation by ZM336372. Minimal $p21^{CIP1}$ is observed at baseline. Following 2 days of treatment with ZM336732, a dose-dependent increase in the level of $p21^{CIP1}$ is observed. **b** Chromogranin A secretion is suppressed following ZM336372 treatment. A low level of Cg A is present at baseline in HepG2 cells. This is suppressed by treatment with ZM336372. Suppression of Cg A is observed at the 10μM dose.

Raf-1 in NET cell lines has shown anti-neoplastic effects, including growth inhibition, decrease in hormone secretion, and morphologic changes.[15,16] This sparked the interest in ZM336372 as a Raf-1 activating agent for treatment of NETs. Previously, treatment of the H727 NET cell line with ZM336372 has resulted in growth inhibition, a decrease in hormone secretion, and $p21^{CIP1}$ up-regulation.[23]

In the HepG2 cell line, previous studies have shown a similar response to ERK 1/2 activation as compared to NETs. Ha-Ras induction leads to suppression of proliferation through ERK 1/2 in HepG2 cells.[20] It is interesting to note that partial inhibition with the MEK inhibitor PD98059, after Ha-Ras induction, leads to growth proliferation. This suggests that the proliferation response may be a dose-related effect of ERK 1/2 activation. In addition, treatment of HepG2 cells with HGF also led to ERK 1/2 activation and resulted in inhibition of cellular proliferation.[20] Activation of ERK 1/2 via HGF treatment resulted in up-regulation of $p21^{CIP1}$ and $p27^{KIP1}$ and cell cycle arrest at G_1.[21]

Here we show that ZM336372 can also cause growth inhibition in HepG2 cells. Raf-1/MEK/ERK pathway activation resulted as expected from ZM336372 treatment. Inhibition of this pathway via UO126 proves that the ERK 1/2 activation of ZM336372 is through MEK 1/2. The induced expression of $p21^{CIP1}$ seen here is similar to that seen previously with ZM336372 treatment and also similar to that seen with HGF, suggesting a possible mechanism for the observed suppression of proliferation.

In addition, CgA secretion was observed to be decreased in HepG2 cells in response to ZM336372 treatment. This is similar to that seen previously with the H727 cell line. In NET cells, CgA has been used as a marker for neuroendocrine differentiation. It has been shown that this suppression of Cg A has also been associated with hASH-1 down-regulation, but the exact mechanism by which this decrease in hormone secretion takes place has yet to be identified.

Conclusion

ZM336372 induces anti-neoplastic effects in HepG2 cells similar to those previously seen with ERK activation in this cell line and seen with NET cell lines. These data suggest that treatments that activate the ERK pathway may be effective in controlling this disease. Further studies with ZM336372 and other ERK activators are warranted as potential new agents in cancer therapy.

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Inclusion of Tumor Markers Improves the Correlation of the Milan Criteria with Vascular Invasion and Tumor Cell Differentiation in Patients with Hepatocellular Carcinoma Undergoing Liver Resection (#JGSU-D-07–00462)

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Abstract The currently used criteria, such as the Milan criteria, to select a candidate of liver transplantation for HCC consists of size and number of tumors because vascular invasion and poor differentiation, the strongest prognostic factors, are difficult to be assessed preoperatively. We hypothesized that inclusion of two tumor markers (alpha-fetoprotein and des-γ-carboxy prothrombin) into the criteria would increase the prediction accuracy of these factors. Our hypothesis was tested in 478 HCC patients undergoing liver resection. The models with or without markers, constructed at predicting vascular invasion (n=150) or poor differentiation (n=49), were compared. The model including markers was superior at predicting the absence of vascular invasion to either the Milan criteria alone [at 81.2% sensitivity; specificity, 52.4 vs 43.3%; difference, 9.1%(95% CI, 1.3–14.2%)] or a model in which size and number varied freely [AUCs of receiver operating characteristic curves, 75.2 vs 69.1%; difference, 6.1%(2.33–10.7%)]. The model incorporating markers was also superior at predicting well to moderate differentiation to either the Milan criteria [at 74.5% sensitivity; specificity, 57.1 vs 38.8%; difference, 18.3%(2.4–32.7%)] or a model with size and number [AUCs, 71.5 vs 59.0%; difference, 12.5%(5.84–21.4%)]. In conclusion, the tumor marker levels should be considered when selecting patients with HCC for liver transplantation.

Keywords Hepatocellular carcinoma · Alpha-fetoprotein · Des-γ-carboxy prothrombin · Liver transplantation · Milan criteria · Vascular invasion · Tumor differentiation

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Abbreviations

HCC	hepatocellular carcinoma
UCSF	University of California at San Francisco
AFP	alpha-fetoprotein
DCP	des-γ-carboxy prothrombin
ROC	receiver operating characteristic
AUC	area under the curve

Introduction

Liver transplantation is a good therapeutic option in patients with hepatocellular carcinoma (HCC), because the entire potentially tumor bearing liver can be resected, cirrhosis can be eliminated, and the possibility of future oncogenesis can be eradicated.[1–3] Given the severe shortage of donor livers, however, it can be offered only to patients whose post-transplant survival is expected to be similar to that of

patients with benign end-stage liver disease. The predicted long-term results depend on adequate selection criteria.

Bismuth et al.[4] were the first to report that a small number and size of HCC in cirrhotic liver (less than three nodules, each <3 cm) led to a favorable outcome. Subsequently, a landmark study conducted by Mazzaferro et al. in 1996 established liver transplantation as a viable option for the treatment of HCC; the selection criteria that they developed (Milan criteria; single nodule ≤5 cm or three or less nodules, each ≤3 cm) have become the standard de facto criteria used worldwide.[5–7] Other selection criteria, such as the University of California at San Francisco (UCSF) criteria (single nodule ≤6.5 cm or three or less nodules, each ≤4.5 cm, and a total diameter of ≤8 cm), are also based on the size and number of tumor nodules.[8]

Post-transplant tumor recurrence is by definition metastatic and is presumed to develop via the dissemination of malignant cells into the systemic circulation either before or at the time of liver transplantation. Vascular invasion by the tumor is thought to play a pivotal role in this process.[9,10] In fact, vascular invasion is the strongest independent prognostic factor after liver transplantation for HCC.[9–13] This variable is also consistently reported as being indicative of a poor prognosis after liver resection, especially during the early postoperative phase.[14–20] Furthermore, other recent studies have shown that a poor tumor grade is another strong independent factor predicting a poor outcome after transplantation.[21–24] Tumor histology and presence of microvascular invasion cannot be identified before transplantation, with the exception of gross vascular invasion identifiable by preoperative imaging. Thus, the size and number of tumors can be regarded as surrogate markers for these difficult-to-quantify parameters.[3,10,11,13,23,25,26]

HCC is oncologically unique in that it is independently associated with two tumor markers: alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP).[27–33] Both markers are associated with a poor prognosis after liver resection for HCC.[17,18,20,30] In particular, AFP is related to the grade of differentiation,[18,22–24,27–30] whereas DCP is linked to the presence of vascular invasion.[22,30,34] Therefore, we hypothesized that the inclusion of these tumor markers into the selection criteria for transplantation candidates would increase the accuracy of predicting vascular invasion and/or the grade of tumor cell differentiation. In this study, we attempted to verify this hypothesis in a cohort of patients who had undergone liver resection for HCC.

Patients and Methods

Population

The base population consisted of 549 consecutive patients who underwent curative liver resections for HCCs without any extrahepatic metastases in our institute during 8 years from 1994 to 2002. The HCC diagnosis and operative indication was made based on the imaging findings, although they were later confirmed by a pathological assessment of the resected specimen in all of the patients.[35] Curative resection was defined as the removal of all recognizable tumors with a clear margin. Preoperative imaging studies revealed vascular invasion in 71 patients. These patients would not have been candidates for liver transplantation a priori, and thus, they were excluded, and the remaining 478 cases were utilized in the subsequent analyses.

"Macroscopic" vascular invasion was defined as invasion detectable on preoperative imagings, whereas "microscopic" vascular invasion was defined as invasion identified by postoperative assessment of the resected specimen. Both of them were later confirmed histologically. Vascular invasion includes the presence of a tumor thrombus in the portal veins, hepatic veins, and/or the bile ducts. Satellite nodules were also included with vascular invasion in the statistical analyses because they are presumed to develop from vascular invasion,[36,37] and these two variables are thought to represent the same pathological entity.

Multiple primary tumor nodules and satellite nodules were differentiated using the guidelines proposed by the Liver Cancer Study Group of Japan; these guidelines are based on macroscopic and microscopic findings.[38] Briefly, multiple tumors were classified as intrahepatic metastases if they were (a) tumors that had apparently grown from portal venous tumor thrombi or (b) multiple satellite nodules surrounding a main tumor with a similar or poorer grade of cell differentiation. Multiple tumors that were not classified as intrahepatic metastases according to the above criteria were classified as multiple primary tumors.

The liver function of the patients was evaluated by indocyanine green retention rate at 15 min and Child–Pugh classification, regardless of the presence or absence of cirrhosis. The background characteristics of the 478 patients are presented in Table 1. The series comprised 370 men and 108 women with a median age of 65 years (range, 13–87 years).

Assessment

The tumor size and the number of nodules were determined based on the preoperative imaging findings. Serum AFP and plasma DCP levels were simultaneously measured using standard methods at the time of the imaging studies.[39–41] Vascular invasion was classified as a binary categorical variable (presence or absence of invasion). The grade of differentiation was classified as well, moderate, or poor. If tumor cells with various grades of differentiation were present in a single nodule, the least differentiated grade was used to represent the nodule. Likewise, if multiple nodules with different grades of differentiation

Table 1 Background Characteristics

Variables	n=478
Gender	
Male	370 (77%)
Female	108 (23%)
Age (years)[a]	65 (58–70)
Alanine aminotranferase (IU/l)[a]	45 (28–69)
Indocyanine green retention rate at 15 min (%)[a]	15 (10–22)
≤20%	337 (71%)
>20%	141 (29%)
Child–Pugh class	
A	369 (77%)
B	109 (23%)
Hepatitis B virus infection[b]	
Yes	89 (19%)
No	389 (81%)
Hepatitis C virus infection[b]	
Yes	322 (67%)
No	156 (33%)
Background liver status	
Cirrhosis	310 (65%)
Non-cirrhosis	168 (35%)

[a] Median with inter-quartile range.
[b] Two patients were positive for both hepatitis B and C virus infections.

were present, the lowest grade was used to represent the patient. The grade of differentiation of each patient was classified as a binary categorical variable (well to moderately differentiated or poorly differentiated) for the later statistical analyses, according to the protocol of former studies.[12,22–24]

Analyses

As a baseline analysis, the correlation between AFP and DCP levels was investigated. We then tested the ability of several models to predict the absence of vascular invasion. First, we evaluated the prediction accuracy of the Milan criteria. Then, we used logistic regression analysis to compose a model that incorporated the AFP and DCP tumor marker levels into the Milan criteria. The overall prediction accuracy was assessed by drawing a receiver operating characteristic (ROC) curve taking various cut-off points for the AFP and DCP values into account. We compared the prediction accuracy of these models. Of course, one may argue that this comparison was not fair because the Milan criteria utilized predetermined values (i.e., ≤5 cm and/or three or less nodules), whereas the cut-off points for the AFP and DCP values were freely set in the latter model. With this possible criticism in mind, we made another comparison between two models that were both based on similar logistic regression analyses: The first model was based on the size and number of lesions, with variable cut-off points, whereas the second model was based on the size and number of lesions, as well as the AFP and DCP levels.

In a second set of analyses, we examined the ability of the models to predict patients with well to moderately differentiated tumors. We first compared the prediction accuracies of the Milan criteria and the model incorporating the AFP and DCP tumor marker levels into the Milan criteria. Then, we compared the model consisting solely of information on the size and number of tumors with the one that incorporated the AFP and DCP levels.

Statistical Analysis

All statistical analyses were performed using SAS computer software, version 9.1 (SAS Institute Inc., Cary, NC, USA). The prediction accuracies of the Milan criteria and the Milan criteria plus the tumor marker levels were compared by assessing the difference in specificity at the same sensitivity point. The confidence intervals (CI) of the differences were calculated using the Jackknife method.[42] When the prediction accuracies of two models were compared using ROC curves, the difference between the area under the curves (AUCs) was calculated to compare the accuracies.[43,44]

Table 2 Tumor-Related Factors

Variables	n=478
Tumor size (cm)[a]	3.0 (2.0–4.2)
≤ 3.0	280 (59%)
3.0–5.0	112 (23%)
> 5.0	86 (18%)
Tumor number[a]	1 (1–2)
1	331 (69%)
2 or 3	120 (25%)
≥4	27 (6%)
Milan criteria	
Compatible	352 (74%)
Incompatible	126 (26%)
Vascular invasion	
Yes	150 (31%)
No	324 (68%)
Unknown	4 (1%)
Differentiation of tumor	
Well or moderate	419 (88%)
Poor	49 (10%)
Unknown	10 (2%)
AFP (ng/ml)[a]	29 (9–207)
DCP (AU/ml)[b]	62.5 (23–284)

AFP α-Fetoprotein, *DCP* des-γ-Carboxy prothrombin
[a] Median with inter-quartile range
[b] Des-γ-carboxy prothrombin was not measured in four patients

Results

Size, Number, Vascular Invasion, Grade of Tumors, AFP, and DCP

The variables that are thought to be contributing factors to tumor recurrence after transplantation are summarized in Table 2. Overall, 352 out of 478 (74%) patients met the Milan criteria. The correlation between AFP and DCP is shown in Fig. 1. No association was seen between these markers.

Prediction of the Absence of Vascular Invasion

The sensitivity and specificity of the Milan criteria for predicting the absence of vascular invasion were 81.2 and 43.3%, respectively (Table 3). A model incorporating the tumor markers levels into the Milan criteria was constructed using logistic coefficients for the respective parameters as follows:

$$p = \frac{1}{1 + \exp\{-2.5101 - 0.4378 \times \text{Milan} + 0.1551 \times \log(\text{AFP}) + 0.2865 \times \log(\text{DCP})\}},$$

where p denotes the probability of the absence of vascular invasion in each patient and Milan is assigned a value of 0 if the patient meets the Milan criteria and 1 if the patient exceeds the criteria.

This equation signifies that when the patient meets the Milan criteria and when the AFP and DCP levels are relatively low, the probability that vascular invasion is absent increases. The prediction accuracy of this model is delineated together with that of the Milan criteria in Fig. 2a.

At the sensitivity of the Milan criteria (81.2%), the difference in the specificity of the Milan criteria (43.3%) and the Milan criteria plus the tumor markers (52.4%) was 9.1% (95% CI, 1.3–14.2%; Fig. 2a).

Logistic regression analyses were also used to construct a prediction model composed of the size and number of tumors (model 1A) and a model composed of the size and number of tumors plus the AFP and DCP levels (model 1B) as follows:

(Model 1A)

$$p = \frac{1}{1 + \exp\{-5.073 + 0.586 \times \log(\text{Number}) + 1.180 \times \log(\text{Size})\}}, \text{ and}$$

(Model 1B)

$$p = \frac{1}{1 + \exp\{-4.479 + 0.542 \times \log(\text{Number}) + 0.483 \times \log(\text{Size}) + 0.151 \times \log(\text{AFP}) + 0.254 \times \log(\text{DCP})\}},$$

where p denotes the probability of the absence of vascular invasion.

The prediction accuracies of these models are shown in Fig. 2b together with those of the Milan, UCSF, and Bismuth criteria. The difference between these AUCs (model 1A, 69.1%; model 1B, 75.2%) was 6.1% (95% CI, 2.33–10.7%).

Prediction of a Well to Moderate Grade of Tumor Cell Differentiation

The sensitivity and specificity of the Milan criteria for predicting a well to moderate grade of tumor differentiation were 74.5 and 38.8%, respectively (Table 4). A model

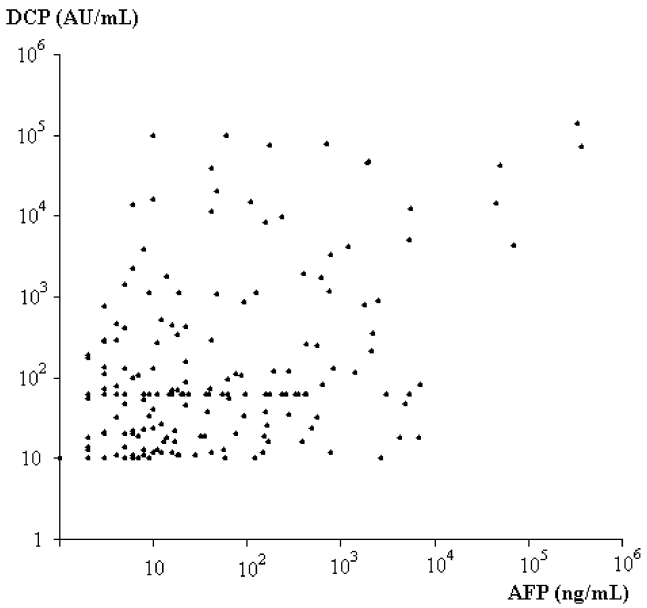

Figure 1 Association between the AFP and DCP levels in the present 478 cases. The correlation between the two markers was calculated after a logarithmic transformation of the data. No association between the two markers was found (Spearman correlation coefficient, r=0.242).

incorporating the tumor marker levels into the Milan criteria was constructed as described above as follows:

$$p = \frac{1}{1 + \exp\{-2.9913 - 0.2317 \times \text{Milan} + 0.2441 \times \log(\text{AFP}) - 0.0241 \times \log(\text{DCP})\}},$$

where p denotes the probability of a well to moderate grade of differentiation.

The prediction accuracy of this model is compared with that of the Milan criteria in Fig. 3a. At the sensitivity of the Milan criteria (74.5%), the difference in the specificity of the Milan criteria (38.8%) and the Milan criteria plus the tumor markers (57.1%) was 18.3% (95% CI, 2.4–32.7%).

Prediction models composed of the size and number of tumors (model 2A) and of the size and number of tumors plus the AFP and DCP levels (model 2B) were constructed as follows:

(Model 2A)

$$p = \frac{1}{1 + \exp\{-3.283 - 0.291 \times \log(\text{Number}) + 0.348 \times \log(\text{Size})} \quad \text{and}$$

(Model 2B)

$$p = \frac{1}{1 + \exp\{-2.837 - 0.452 \times \log(\text{Number}) - 0.141 \times \log(\text{Size}) + 0.260 \times \log(\text{AFP}) + 0.021 \times \log(\text{DCP})\}},$$

where p denotes the probability of a well to moderate grade of tumor cell differentiation.

The prediction accuracies of these models are shown in Fig. 3b. The difference between these AUCs (model 2A, 59.0%; model 2B, 71.5%) was 12.5% (95% CI, 5.84–21.4%).

Discussion

The aim of the selection criteria for determining whether HCC patients are candidates for liver transplantation is to prevent transplantation in patients destined to develop recurrences and to maximize transplantations in patients with a high likelihood of being cured after transplantation and without any alternative treatment modalities.

Table 3 Milan Criteria Predictions for the Absence of Vascular Invasion

		Pathological Vascular Invasion		
		Negative	Positive	
Milan criteria	Meet	263	85	
	Exceed	61	65	
	Total	324	150	474

Sensitivity of Milan criteria for vascular invasion (−)=263/324=81.2%.
Specificity of Milan criteria for vascular invasion (+)=65/150=43.3%

The tumor size limits for selecting transplantation candidates have been expanded in recent criteria, e.g., USCF criteria.[8,45] Nevertheless, it is important to note that patients with small HCC, selected rather strictly on the basis of the Milan criteria, still carry a 10–15% risk of recurrence at 5 years that can appear shortly after transplantation in some patients.[3,46] Although the selection of recipients using the UCSF criteria reportedly resulted in a patient survival rate similar to that obtained using the Milan criteria, the recurrence rate per se was significantly higher when the selection criteria was expanded from the Milan criteria to the UCSF criteria.[3] In addition, if the size and number of tumors increases, the possibility of being dropped from the transplantation waiting list will also increase.[47] These results illustrate the limitations of using the size and number of tumors as ultimate components of the selection criteria for identifying transplantation candidates and raise an alarm regarding the optimistic expansion of candidate criteria relying solely on these variables.[10]

Post-transplant HCC recurrence is thought to derive from cancer cells in the systemic circulation at the time of total hepatectomy, which is presumed to be directly related to vascular invasion.[48,49] In fact, vascular invasion is reportedly the strongest independent factor associated with HCC recurrence and poor patient survival after liver transplantation.[9–13] The definitions of macroscopic and microscopic vascular invasion remain controversial; some definitions are based on whether vascular invasion can be detected using preoperative imaging studies,[9,13,24] whereas others depend on whether the invasion extends to the main

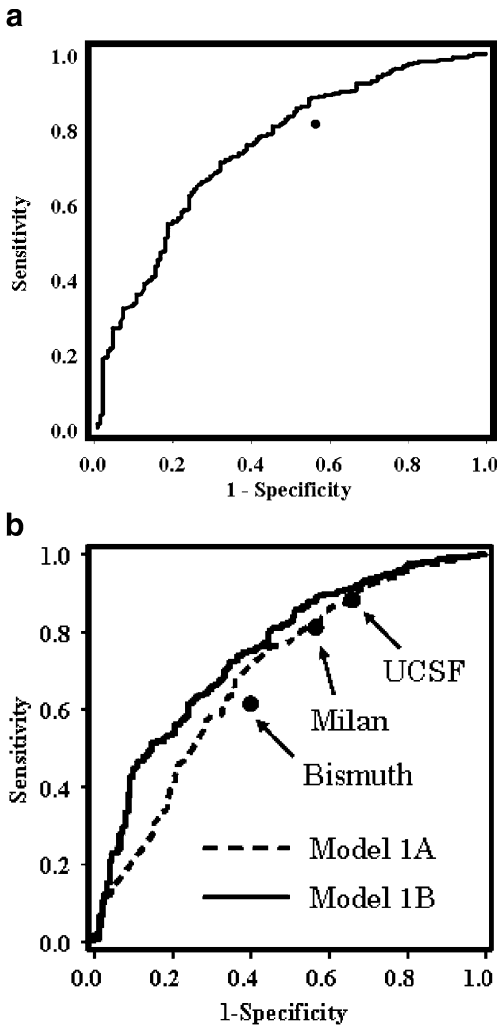

Figure 2 Accuracies for predicting the absence of vascular invasion. **a** Milan criteria (*closed circle*) and a model incorporating AFP and DCP into the Milan criteria (ROC curve). The Milan criteria had a sensitivity of 81.2% and a specificity of 43.3%. At the sensitivity of the Milan criteria, the specificity of the model incorporating the tumor markers was 52.4%. The difference in the specificity of the Milan criteria (43.3%) and the Milan criteria plus the tumor marker criteria (52.4%) was 9.1% (95% CI, 1.3–14.2%). **b** A model consisting of the size and number of nodules (model 1A, *dotted line*) and a model consisting of the size and number of nodules plus the AFP and DCP levels (model 1B, *solid line*). The accuracies of the two models are shown by the ROC curves. The points indicated by the *arrows* represent the sensitivity and specificity of the Milan, UCSF, and Bismuth criteria. The area under the curve (AUC) for model 1A was 69.1%, whereas that for model 1B was 75.2%. The difference in the AUCs was 6.1% (95% CI, 2.33–10.7%), which was significant.

branches of the portal and/or hepatic veins or remains in the peripheral tributaries.[10,23,26,46] Likewise, although many have agreed that the presence of "macroscopic" vascular invasion is the single strongest prognostic factor for predicting a poor outcome, a consensus concerning the significance of "microscopic" vascular invasion has not been reached.[10–12] On the contrary, the influence of satellite nodules, which is presumed to develop from vascular invasion, as a risk factor for recurrence have been reportedly underestimated.[46] Taken together, it is highly reasonable to conclude that (1) all categories of vascular invasion are associated with an increased risk of HCC recurrence, although the magnitude of invasion may be correlated with the degree of recurrence risk,[26] and (2) the statistical insignificance of microscopic invasion and/or satellite nodules as risk factors reported in some studies[10,11,13,22,24] is attributable to the separation of these two variables representing the same pathological entity.[37] From the viewpoint of constructing a model that preoperatively forecasts the presence of unidentified vascular invasion and based on the above considerations, we excluded patients with vascular invasion identified by preoperative imagings from the analyses and defined other vascular invasions detected solely by postresectional examination as microscopic vascular invasion, together with microscopic satellite nodules. The importance of vascular invasion as a direct biological indicator is further supported by the observations that tumor diameter was linearly correlated with the incidence of vascular invasion[10,13,23,26] and that the likelihood of metastasis rose exponentially with an increasing number of tumors.[50,51]

Recent reports have emphasized the importance of poorly differentiated HCC as another or the sole independent risk factor for posttransplant recurrence,[21,22,24] advocating assessment by pretransplant needle biopsy.[24] However, needle biopsy is associated with a high risk of dissemination of cancer cells[52]; furthermore, the small specimen obtained by needle biopsy may not be representative of heterogeneously differentiated HCC nodule.[26,37] The biological association between the grade of differentiation and tumor cell dissemination into the systemic circulation is not clear. Some studies have shown a close relationship between the grade of differentiation and the incidence of vascular invasion, suggesting that the grade of differentiation is another surrogate marker for vascular invasion.[23,26] The high-risk ratio of poorly differentiated

Table 4 Milan Criteria Predictions for a Well to Moderate Grade of Tumor Cell Differentiation

		Grade of Differentiation		
		Well to Moderate	Poor	
Milan criteria	Meet	312	30	
	Exceed	107	19	
	Total	419	49	468

Sensitivity of Milan criteria for a well to moderate grade of differentiation=312/419=74.5%. Specificity of Milan criteria for a well to moderate grade of differentiation=19/49=38.8%

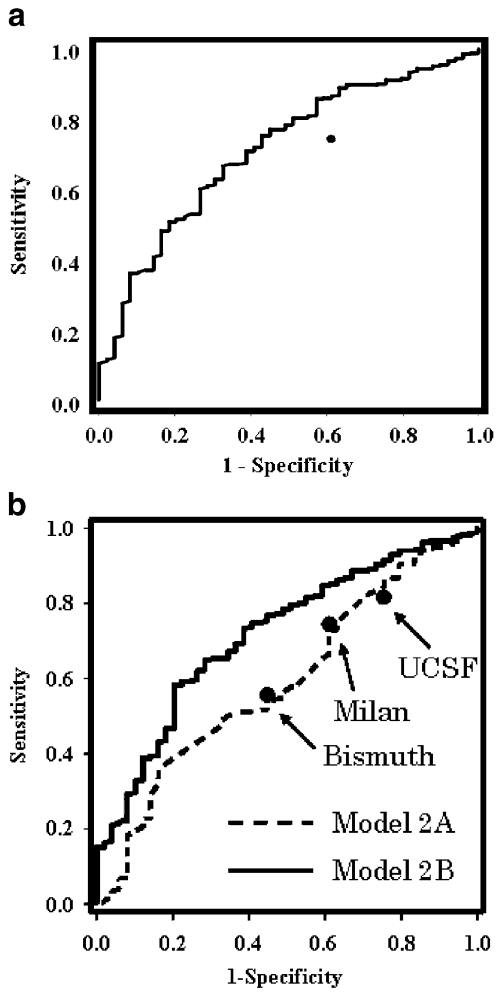

Figure 3 Accuracies for predicting a well to moderate grade of tumor differentiation. **a** Milan criteria (*closed circle*) and a model incorporating AFP and DCP into the Milan criteria (ROC curve). The sensitivity and specificity of the Milan criteria were 74.5 and 38.8%, respectively. At the sensitivity of the Milan criteria, the specificity of the model incorporating the tumor markers was 57.1%. The difference in the specificity of the Milan criteria (38.8%) and the Milan criteria plus the tumor marker criteria (57.1%) was 18.3% (95% CI, 2.4–32.7%), which was significant. **b** A model consisting of the size and number of nodules (model 2A, *dotted line*) and a model consisting of the size and number of nodules plus the AFP and DCP levels (model 2B, *solid line*), as depicted by the ROC curves. The accuracies of the Milan, UCSF, and bismuth criteria are also shown (*solid circles*). The AUC of model 2A was 59.0% and that of model 2B was 71.5%. The difference in the AUCs was 12.5% (95% CI, 5.84–21.4%), which was significant.

tumors that has nevertheless been statistically demonstrated as being independent of vascular invasion can most probably be explained by the following considerations. First, patients with poorly differentiated tumors, comprising a relatively minor population (10% in the present study), represent a specific cohort associated with a markedly poor prognosis. Second, the grade of differentiation is rarely misdiagnosed, whereas small vascular invasion or satellite nodules occasionally remain unidentified in explanted liver. In view of these issues, we treated the grade of differentiation as an independent variable related to a poor posttransplant prognosis and searched for a model capable of predicting poor differentiation.

AFP has been accepted as a useful tumor marker for HCC, both for diagnosis and follow-up after treatment,[53] and is presumed to reflect the grade of differentiation.[18,54–56] In contrast, although the first report referring to the significance of DCP as a specific marker of HCC dates back to 1985,[40] DCP has not received much attention in Western countries until recently.[31,32] Reports from countries where HCC is endemic have shown that DCP is a variable marker of HCC,[27–29,33] is closely associated with vascular invasion and intrahepatic metastases,[18,30,34] and is a variable prognostic variable.[14,17,18] Most importantly, the DCP and AFP levels were not correlated (Fig. 1).[11,27–30,33] This mutual independence signifies that they are, in theory, complementary markers of HCC and that the combination of them increases the sensitivity without sacrificing the specificity.[27,28,30,33]

From the results of the present investigation, it can be concluded that the inclusion of tumor marker (AFP and DCP) levels into the morphologic selection criteria currently in use, like the Milan criteria, increased the accuracy of predicting the presence or absence of pathological parameters. The complete separation of the ROC curves for models with or without the inclusion of the tumor markers, shown in Figs. 2b and 3b, further signifies that the prediction accuracy increases at any sensitivity and/or specificity level. In other words, the increment in the prediction accuracy is significant, irrespective of the original model (i.e., Milan, UCSF, Bismuth, etc.), as long as the original models are based on the size and number of tumor nodules.

One limitation of this investigation is that the present study population consisted of HCC patients who underwent liver resection. In this regard, the possible bias and validity must be clearly discriminated when discussing data obtained from an HCC cohort undergoing liver resection. From a practical point of view, most clinicians' interest lies in the expected probability of negative vascular invasion in each patient if the patient meets a given set of selection criteria, and vice versa. These probabilities are expressed statistically as positive and negative prediction values and may vary depending on the incidence of the parameters of interest. For example, the incidence of vascular invasion in the present cohort (150/474; 31.6%) appears to be higher than the reported figures in transplant recipients. Therefore, the positive prediction value of the Milan criteria for the absence of vascular invasion in the present series (263/3848; 75.6%) cannot be simply extrapolated to other cohorts, such as HCC patients who are transplant candidates. Thus, we did not propose concrete selection criteria incorporating specific cut-off values for tumor markers (i.e.,

AFP<1,000 ng/l) in the present study. Nevertheless, it must be emphasized that the trade-off between sensitivity and specificity represents the prediction accuracy of a given test, i.e., the criteria, independent of the disease incidence. Therefore, the discussion based on the sensitivity and specificity is still valid, although the data were derived from patients with HCC who were undergoing liver resection. Further investigation is necessary to determine the concrete cut-off values in constructing new selection criteria with tumor markers for transplantation candidates for HCC. And this investigation has to be conducted in patients with HCC undergoing liver transplantation.

In conclusion, the inclusion of information on tumor markers, i.e., AFP and DCP, to selection criteria based on information of size and number, improves the accuracy of predicting the presence of vascular invasion and the grade of tumor differentiation. These markers can be measured during routine preoperative work-ups and provide objective data. The present selection criteria for HCC transplant recipients should incorporate information on tumor markers regardless of whether the current criteria are expanded or not.

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Albendazole is Not Effective for Primary Treatment of Hepatic Hydatid Cysts

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Abstract
Introduction In current practice, minimal invazive interventions such as percutaneous drainage and laparoscopic surgery in adjunct treatment with benzimidazoles have been gaining acceptance in treatment of hydatid cystic disease with minimal morbidity and mortality. In this prospective study, the efficacy and validity of primary medical therapy in the treatment of hydatid cystic disease has been investigated.
Patients and methods Sixty-five patients with hepatic cystic disease were treated with albendazole alone between January 2004 and June 2007. All of the patients were administrated albendazole as 10 mg kg^{-1} day^{-1} divided into two equal doses for 6 months with ultrasonography (USG), serological tests, full-blood cell count and hepatic function tests performed in 2 months intervals in the course of treatment.
Results Fifty of the patients were female and 15 were male with a mean age of 47.0±16.9 (17–80). A total number of 106 cysts were present in 65 patients. Mean cystic diameter was 5.5±3.6 (1–16). In 41 of the patients, cysts were solitary and in remaining 24 patients cysts were multiple. Mean follow-up period was 28.3±8.6 (12–42) months. The overall success rate of albendazole therapy was 18 % (12/65) in the study.
Conclusion Albendazole therapy for hepatic hydatidosis is not effective in the vast majority of patients and, therefore, should not be used as the primary therapy for patients who are surgical candidates.

Keywords Hepatic hydatid disease · Albendazole therapy · Recurrence

Introduction

Benzimidazole derivatives have been widely used both in the medical treatment of hydatid cystic disease and in the prevention of recurrences after surgery in recent years, with albendazole being superior to mebendazole in clinical efficacy.[1–4] Most of the studies suggest albendazole as an effective and safe agent in hydatidosis. The WHO Informal Working Group on Echinococcosis published "Guidelines for treatment of cystic and alveolar echinococcosis in humans" in which chemotherapeutic methods for the treatment of echinococcosis and their significance were highlighted.[5–7]

In current practice, minimal invasive interventions such as percutaneous drainage and laparoscopic surgery in adjunct treatment with benzimidazoles have been gaining acceptance in treatment of hydatid cystic disease with minimal morbidity and mortality.[2,3,6] In this prospective study of 65 patients, the efficacy and validity of primary medical therapy in treatment of hydatid cystic disease has been investigated.

Patients and Methods

This prospective study was performed in our clinic between January 2004 and June 2007. Sixty-five patients with a

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regular follow-up among 102 cases with uncomplicated hepatic hydatid cysts treated primarily by albendazole therapy were included in the study. Patients with hepatitis, nephritis, abnormal hepatic or renal function tests, pregnant patients, and patients having degenerative signs of cysts (Gharbi 5) were excluded. Diagnosis was made by ultrasonography (US), computerized tomography (CT), and positive serological tests (detection of specific antibodies, circulating antigen and immune complexes). All of the patients were administrated albendazole as 10 mg kg^{-1} day^{-1} divided into two equal doses for 6 months. In every 2 months, US, serological tests, full blood cell count and hepatic function tests as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) were obtained. During the follow-up period, patients were evaluated regarding persistency or improvement with imaging studies. Evaluation in imaging studies was done in three groups with modification of criteria in a study performed by Chai et al.[1] These criteria are shown in Table 1. After treatment, patients were called for control every 6 months with indirect hemaglutination (IHA) and US/CT.

Results

Sixty-five patients with hepatic cystic disease treated with albendazole between January 2004 and June 2007 were included in this study. Fifty of the patients were female and 15 were male with a mean age of 47.0±16.9 (17–80). A total number of 106 cysts were present in 65 patients. Mean cystic diameter was 5.5±3.6.[1–16] In 41 of the patients, cysts were solitary and in the remaining 24 patients cysts were multiple. In 3 of 65 patients, extrahepatic involvement was also present with splenic involvement in one patient, pulmonary involvement in one patient, and both splenic and pulmonary involvement in another. The remaining 62 patients had only hepatic hydatidosis. Forty-seven patients had their cysts in the right hepatic lobe, 34 in the left lobe, and 14 patients had cysts in both lobes. Nine of the patients (9/65) were referred to our hospital from other hospitals with recurrences after surgical therapy. Gharbi classification[8] and diameters of cysts at first admission is presented in Tables 2 and 3, respectively. IHA tests were positive in 53 patients and negative in the remaining 12 patients at the first admission. At the end of the treatment, IHA results were still positive in 41 of the formerly positive patients, in 12 patients who were cured, IHA results were switched to negative. Among 12 formerly negative patients, a switch to positive occurred in three patients. Moreover, in patients with recurrences IHA results were all positive at the diagnosis of recurrence. All of the patients were given albendazole 10 mg kg^{-1} day^{-1} divided into two equal doses. The mean follow-up period was 28.3±8.6 (12–42) months. The evaluation of albendazole therapy regarding imaging studies during the follow-up period was given in Table 4. Surgical treatment was planned for 45 of 65 patients resistant to albendazole therapy. In 20 of these patients, cystotomy and drainage was performed, three had percutaneous drainage, one had laparoscopic pericystectomy, and one had laparoscopic drainage. In one patient, because of intrabiliary rupture of the cyst, endoscopic retrograde cholangiopancreatography (ERCP) with nasobiliary drainage was performed. The remaining 19 patients were scheduled for surgery. In eight patients with improvement at the end of 6 months treatment, albendazole therapy was continued for another 6 months. Three of these patients were cured, whereas the remaining five patients were planned for surgery because of ineffectiveness in the grade of cysts and persistency of positive serology at the end of 12 months. Recurrence occurred in 3 of 12 patients, who were cured in the 10th, 12th, and 18th months after cessation of treatment. In two patients, transient elevation of hepatic enzymes occurred; however, a 15-day discontinuation of therapy resulted in rapid reversal in both patients. The overall success rate of albendazole therapy was 18% (12/65) in the study. Gharbi classification of these patients who were cured revealed that six patients had Gharbi III, four had Gharbi II, and two had Gharbi I cysts. Ten of these patients had solitary cyst and two of them had multiple

Table 1 Classification According to Imaging Studies Modified from Chai et al.[1]

Changes obtained by imaging studies during medical therapy	
I. Ineffectiveness	a. No changes of hepatic hydatid cysts
	b. Increase in cystic diameter
II. Improvement	Decrease in cystic diameter by 25% or more, or detachment of endocyst or increase in echogenicity of cystic contents
III. Cure	Disappearance of cysts, full echogenity within cyst, significant calcification

Table 2 Gharbi Classification of 106 Cysts in 65 Patients[8]

Gharbi classification	Number of cysts (*n*)
Gharbi 1 (Pure fluid collection)	26
Gharbi 2 (Fluid collection with a split wall)	40
Gharbi 3 (Fluid collection with septa)	34
Gharbi 4 (Heterogeneous echo patterns)	6

Table 3 Cyst Diameters at the Beginning of the Study

Cystic diameter (cm)	Number of cysts (*n*)
0–5	62
5–10	34
>10	10

cysts. The mean diameters of cysts in these 12 patients were 5.1±2.0 (2–8) and correlated with the mean diameter of the whole series. The mean cost of the 6-month medical treatment was approximately 250–300$ depending on the weight of the patients.

Discussion

Since the introduction of benzimidazole derivatives as broad-spectrum anthelmintics in veterinary medicine in the 1960s, many studies have been done regarding the efficacy of these drugs in the control of human parasitic diseases.[6] In general, the solubility of benzimidazoles in water is poor, resulting in limited absorption from the intestine. Therefore, these drugs are safe without drug toxicity in host animals and do not retain in the food chain. Mebendazole and the newer benzimidazole derivative—albendazole—were developed for the treatment of human intestinal helminthiasis.[6] The primary mode of action takes place with β-tubulin—an eukaryotic cytoskelatal protein—inhibiting its polymerization into microtubules, reducing glucose uptake, leading to depletion of glycogen storage with degenerative changes in the endoplasmic reticulum and mitochondria of germinative membrane resulting in cellular autolysis.[6,7,9]

As a result of being poorly absorbed after oral administration, benzimidazole derivatives are very effective in intestinal helminthiasis. Administration with fatty meals is required for the treatment of tissue parasites.[2,4,6,10]

Multicenter open clinical trials about efficacy of benzimidazole derivatives were initiated by WHO in the 1980s. However, comparative efficacy studies were not performed; instead a number of cohort studies and case reports addressing different aspects of medical treatment of echinococcosis have been published. It is generally accepted that the choice of one or the other benzimidazole is not of major importance, as both mebendazole and albendazole presumably are equally effective. Case definitions, diagnostic procedures and defined monitoring procedures for the long-term follow-up were not standardized.[6]

The usual dosage of albendazole is generally suggested to be 10–15 mg kg^{-1} day^{-1} in two equal doses in courses of 3 months, separated by intervals of 1 or 2 weeks.[2,6,11] In this study, we administered albendazole 10 mg kg^{-1} day^{-1} in two equal doses in courses of 2 months. At the end of each course, imaging studies with hematological and biochemical analysis as hemogram, AST, ALT, ALP, and GGT were performed and in patients with normal hematological and biochemical analysis albendazole therapy was continued without interruption.

Similar to mebendazole, albendazole has a low absorbance in the gastrointestinal system; however, serum concentrations are as much as 15–50 times more than mebendazole. Unlike mebendazole designed as a broad spectrum anthelminthic drug against intestinal nematodes, albendazole has a scolocidal effect with better absorption and tissue distribution than mebendazole; however, cystic fluid concentrations of albendazole sulfoxide—the active metabolite—are much lower than the plasma levels.[4,9]

Hepatic metabolization is rapid, and albendazole sulfoxide, as the primary metabolite, has anthelminthic activity. Long-term administration of both derivatives causes side effects as hepatic function abnormalities, leucopenia, and alopecia. Being teratogenic in rats and rabbits, albendazole is contraindicated in pregnancy and lactation.[2,4,10] Liu et al.[12] suggested long-term high dose albendazole treatment was effective and safe without any side effects in their study consisting of 20 patients with a follow-up period of 2–8 years. They suggested that continuous long-term therapy with regular monitoring of hepatic function tests was safe and more effective than other regimens, but the power of this study could be challenged in terms of the

Table 4 Response to Albendazole Therapy

Changes obtained in imaging studies	At the end of the medical therapy (*n*)	In follow-up period
I. Ineffectiveness		
a	22	Planned for surgery
b	23	Planned for surgery
II. Improvement	8	3 cure 5 planned for surgery
III. Cure	12	9 no recurrence 3 recurrence

limited number of patients. Similarly, in our study of 65 patients with normal hematological and biochemical analysis, the therapy of 63 patients was continued for 6 months without any interruption.

The main adverse effects of albendazole therapy are changes in hepatic enzyme levels, as approximately 10–20% of patients develop mild to moderate, self-limiting rises in transaminases, but these changes are reversible on cessation of treatment.[5,9] In our study, we observed an increase in hepatic transaminases in only two patients (3%), and after 2 weeks interruption of treatment, transaminases of both patients rapidly declined thereafter; however, we did not observe any other mentioned side effects. To our knowledge, albendazole regimen with a dose of 10 mg kg^{-1} day^{-1} is safe and does not cause notorious side effects as reported in the literature.

In current practice, indications of benzimidazole therapy are inoperable primary hepatic hydatidosis, multiple cysts in two or more organs, multiple small liver cysts, cysts located in deep hepatic parenchyma, prevention and management of secondary hydatidosis, management of recurrent hydatidosis, unilocular cysts in unfit elderly patients, in adjunct therapy with surgery or percutaneous interventions, pulmonary echinococcosis, and long-term treatment for cystic echinococcosis in specific organs like the bone, brain, or eye. Large cysts, honeycomb cysts, superficial cysts with tendency to rupture, infected cysts, inactive cysts, calcified cysts, severe chronic hepatic disease, bone marrow depression, and early pregnancy are the contraindications.[10]

Benzimidazoles are shown to kill the entire metacestode stage of the parasite. Continuous or intermittent treatment with albendazole is recommended for a period of up to 6 months. Kern[6] suggested that degenerative changes in the cyst occur in approximately 75% of the patients by the end of the treatment; however, in our study we observed that in only 18% of the patients cure and cystic degeneration occurred.

Horton[13] classified the clinical outcome of patients treated with albendazole as cure, improvement, no change and worsening and reported that 30% of the patients were cured, 30–50% had improvement and 20–40% had no change.

Gil-Grande et al.[14] from Spain suggested that initial medical therapy to be a good alternative to surgical therapy in uncomplicated hepatic hydatid cysts in their study of 55 patients.

Keshmiri et al.[15] treated 29 patients with 240 cysts intermittently for 6 months and reported a cure rate of 10%, reduction in cyst size 60%, and improvement in morphological appearance 62%. They also stated that patients in the placebo group were observed to have shown an improvement of 10%.

In our series of 65 patients, the success rate of medical therapy is not as high as stated in the literature. After the first 6-month therapy, cure occurred in 12 of 65 (18%) patients and partial improvement was achieved in eight patients (12%). In these eight patients with partial improvement, therapy was continued for another 6 months. After a 12-month therapy, only in 3 of 8 patients were cured; the remaining five patients were scheduled for surgery because of lack of improvement. Moreover, among 12 patients who were cured at the end of first 6 months, three recurrences occurred during the follow-up period and they were also planned for surgical therapy. In our opinion, serological evaluation is not effective alone in the follow-up of period as radiological evaluation is more reliable in the course of treatment; however, in the follow-up of patients with cure according to radiological evaluation with negative serological tests, switching to positive serology is highly suggestive of recurrence.

There are also studies reporting that albendazole therapy was more successful in small, young, and multiple cysts instead of worse prognosis in cysts with daughter vesicles. However, in our study, in 12 patients who were cured, six had Gharbi III cysts, four had Gharbi II cysts and two had Gharbi I cysts. Moreover, in only 2 of 12 patients, cysts were multiple; the remaining patients had solitary cysts. Mean cystic diameters in cured patients were also correlated with cystic diameter of whole series as 5.5±3.6 (1–16) and 5.1±0.6 (2–8) respectively. These results in our series suggested that in patients with hydatid cystic disease Gharbi classification, the number of cysts or cystic diameter does not change the efficacy of primary albendazole treatment.[16]

In hydatid cystic disease, incubation period varies and may last months to years. In large series, it was shown that 38–60% of the cases remain asymptomatic and the diagnosis was accidentally. Maximum survival time of a cyst observed in humans was 53 years. Asymptomatic liver cysts may remain symptom-free for over 10 years regardless of the cyst size or type. It is generally accepted that many cysts degenerate spontaneously over time as the parasite may lose its biological potential over time.[6] Therefore, considering that some of the cysts in our cure cases might have died spontaneously, the success rate of albendazole is not as high as suggested.

In our previous study of 172 patients with primary hepatic hydatidosis treated surgically, the mean follow-up period was 60.5±1.3 (25–84) months with a mean period of recurrence development of 23.4±5.3 (8–48) months, suggesting that recurrences occur after 2 years even in the surgically treated patients.[17] In this study, the mean follow-up period of 28 months seems to be enough; however, prolonging the follow-up period may increase recurrence rates.

Some authors suggest that patients with recurrence after surgery with comorbid diseases or recurrences smaller than 5 cm in diameter benefit from medical therapy for 6 months, but in our study among nine patients referred to our hospital with recurrences, cure was achieved in only one patient.[17,18]

Conclusion

Based on our findings, we suggest that albendazole seems to be a cost-effective alternative in the treatment of hydatid cystic disease in which surgical or percutaneous treatment is contraindicated; however, it should not be used as primary treatment because of low success rates. Moreover, Gharbi classification, the number of cysts, or the cystic diameter does not change the efficacy of medical treatment.

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Treatment of High Output Cardiac Failure by Flow-Adapted Hepatic Artery Banding (FHAB) in Patients with Hereditary Hemorrhagic Telangiectasia

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Abstract Involvement of abdominal organs in Osler's disease may lead to the development of hepatic arteriovenous shunts with a dilatation of the hepatic artery. Right and subsequent global heart failure due to cardiac valvular insufficiency, pulmonary artery hypertension, and hepatomegaly as well as increased cardiac output may result. This hyperdynamic hepatic blood flow can be reduced by ligature or banding of the hepatic artery or by orthotopic liver transplantation. We report on two female patients suffering from Osler's disease (68 and 76 years old) with severe heart insufficiency (NYHA III-IV) caused by the high hepatic shunt volumes. A gradual banding of the hepatic artery directed by intraoperative flow measurement in the hepatic artery and control of the systemic hemodynamics by Swan–Ganz or COLD catheters was performed in these patients. The banding was achieved by encasing the hepatic artery in a PTFE cuff (length, 1.0 cm). The high cardiac output could be reduced from 11.2 to 7.0 l/min and from 10.7 to 6.0 l/min, respectively. The respective hepatic artery flow was reduced from 2.0 to 0.3 l/min and from 4.0 to 0.7 l/min. An improvement of heart insufficiency, a reduction in the severity of the cardiac valvular insufficiency, and a reduction of the pulmonary arterial hypertension could be already observed intraoperatively. One patient died of right cardiac failure after an orthotopic liver transplantation 7 months later. The other one died 3 years after the banding. The banding of the hepatic artery controlled by hepatic arterial flow measurement can be considered as an effective and safe palliative procedure in intrahepatic HHT compared to therapeutic alternatives such as hepatic artery ligation or embolization.

Keywords HHT · Flow-adapted banding · Hepatic artery

Introduction

The hereditary hemorrhagic teleangiectasia (HHT), also known as Morbus Osler (Osler–Weber–Rendu's disease), is an autosomal dominant transmitted fibrovascular dysplasia with diverse manifestations.[12,17] Three types of HHT are distinguished by genetic differences. Despite its genetic heterogenitiy, the risk of recurrence in the next generation is 50%. The clinical manifestation is age-dependent and complete at the age of 45, although primary manifestations after the age of 65 years are reported.[13,21,23]

According to more recent trials, the incidence of this disease is quoted as >1/1,0000, whereas it was estimated at 1/50,000–1/100,000 before. The incidence is region-dependent.[13,21]

HHT is very variable in its clinical presentation, and the most common manifestation is recurrent epistaxis (>90% of all affected persons). The diagnosis of HHT is proved by clinical findings summarized in the Curaçao criteria (Table 1). HHT is characterized by typical teleangiectasia of the face (cheek, lips, tongue, nose, and ears) and on the fingers.[24] The pathophysiological mechanism has been described as a primary dilatation of postcapillary venols continuing in capillaries and arterioles and finally forming arterio-venous

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Table 1 Curaçao Criteria for HHT

Curaçao criteria (Shovlin et al. [22])
1. Heritability (at least one affected relative in first degree of relationship with that criterion)
2. Recurrent, spontaneous epistaxis, >90%
3. Multiple, typical teleangiectasia (characteristic on lips, nose, fingers, and in the mouth)
4. visceral involvement, including:
gastrointestinal teleangiectasia, possible bleedings, 15–44%
pulmonal arteriovenous malformations, 33%
cerebral vascular malformations, 1–15%
intrahepatic arteriovenous malformations, 8–31% (often HHT types 2 and 3)
If two of four criteria are met, Osler's disease is likely; if more than two criteria are met, Osler's disease is certain according to Shovlin et al. If only one criterion is fulfilled, Osler's disease is unlikely

shunts.[7,9] These arterio-venous malformations (AVM) may develop in the lungs, the gastrointestinal system (mainly stomach), the brain, and the liver.[12,14,24,25]

Liver involvement in HHT occurs in 8–31%. Women and the HHT type 2 appear to be affected more frequently. Intrahepatic AVM are formed between hepatic artery or portal veins and hepatic veins leading to an increased hepatic blood flow with hepatomegaly, abdominal pain, and a higher right heart preload. Shunts between hepatic artery and the portal vein may result in portal hypertension. Fifty percent of the patients with intrahepatic HHT become symptomatic showing a right heart insufficiency, secondary pulmonary hypertension, portal hypertension, cholestasis, ascites, and cirrhosis or fibrosis. [21] Complications of intrahepatic Osler's disease are right heart failure, portosystemic encephalopathy, recurrent bleeding from esophageal varices or bleedings from mucocutaneous teleangiectasia, and AVM. Predominantly, impaired liver function and cardiocirculatory stress influence the prognosis and treatment of intrahepatic HHT.[8,10,15,25] Intrahepatic HHT is diagnosed by means of B-mode ultrasound of the abdomen, power and color mode Doppler ultrasound, spiral computed tomography (CT) scan, magnetic resonance imaging (MRI) scan with angio-sequence and/or angiography of the abdominal vessels.[4,12,14,18,19,24]

The treatment of symptomatic intrahepatic HHT includes arterial embolization, ligation (dearterialization), or banding of the proper hepatic artery or a branch of hepatic artery to prevent right heart insufficiency or failure. [2,3,11,18,20,25,26] The only curative therapy in intrahepatic HHT with promising long-term results is liver transplantation.[3,5,11,20,21,23]

We report on two cases of symptomatic intrahepatic HHT treated by an intraoperatively ultrasound-controlled gradual banding of the hepatic artery to reduce the high cardiac output improving the clinical conditions for the patients during the waiting time for liver transplantation.

Materials and Methods

Two female patients (68 and 76 years old) with intrahepatic HHT and high intrahepatic arteriovenous shunts underwent a gradual banding of the hepatic artery controlled by intraoperative flow measurement. All patients suffered from proven HHT with high output cardiac insufficiency, relative cardiac valvular insufficiency, and pulmonary hypertension. Both patients showed the classic cutaneous stigmata of the syndrome and mucocutaneous teleangiectasia in the oro- and nasopharynx, one patient had gastrointestinal AVM, and one patient had cerebral AVM. Both suffered from recurrent epistaxis. There was no evidence of portal hypertension. The liver synthesis was not altered yet (Table 3). They showed severe symptoms of right heart insufficiency NHYA III-IV° and ascites. The preoperative angiography of intra-abdominal vessels showed multiple AVM in both hepatic lobes with an early flush of contrast medium from the hepatic artery into the hepatic veins.

After median laparotomy, the proper hepatic artery was dissected and its arterial flow was measured. The flow controlled banding of the hepatic artery was performed by using an ultrasound based flow measuring device (Transsonic, Ithaka, USA). While measuring the flow distally, a more proximally put non-resorbable (Prolene®) stitch surrounding the hepatic artery was tightened until the desired flow was achieved. To avoid an hourglass-shaped stenosis, the banding was encased for hemodynamic reasons by a PTFE cuff (length, 1.5 cm). Intraoperatively, the patients were given nitrates to reduce the pulmonary pressure and dobutamine for cardiac support (dosages: nitrate, 0.5–3.0 μg/kg body weight and min; dobutamine, 2–8 μg/kg body weight and min) intravenously.

Measurements

Preoperatively, systemic flow and circulatory pressure parameters such as pulmonary arterial pressure, right ventricular diameter and pressure, systemic blood pressure, central venous pressure, and the cardiac output were measured. Therefore, both patients underwent echocardiography, right heart catheterization, and duplex ultrasound with pulsed wave Doppler mode of the abdominal vessels. They were evaluated for arteriovenous malformations in other organs by endoscopy, CT, and MRI scan of the brain and the abdominal organs.

Intraoperatively, systemic flow and circulatory pressure parameters as above and the hepatic flow and hepatic pressure parameters were measured. Apart from the right heart catheterization the preoperative hemodynamic and radiological examinations were repeated within the following 5 postoperative days.

Table 2 Intraoperative Hemodynamic Measurements Before and After Banding of the Hepatic Artery

	Patient 1		Patient 2	
	Preoperative	Postoperative	Preoperative	Postoperative
Age	76 years		68 years	
Arteriovenous shunting	60%	60%		
Diameter of proper hepatic artery	11 mm	6 mm	15 mm	10 mm
Hepatic arterial flow	2.0 l/min	0.3 l/min	4.0 l/min	0.7 l/min
Cardiac Index	7.0 l min^{-1} m^{-2}	4.5 l min^{-1} m^{-2}	6.6 l min^{-1} m^{-2}	3.9 l min^{-1} m^{-2}
Cardiac output	11.2 l/min	7.0 l/min	10.7 l/min	6.0 l/min
PAP	78/33/50 mmHg	48/18/30 mmHg	28/14/21 mmHg	22/12/17 mmHg
LVEF	71%	66%	70%	68%
LVEDP	10 mmHg	10 mmHg	9 mmHg	7 mmHg
RVEDP	11 mmHg	5 mmHg	6 mmHg	4 mmHg
Diameter of proper hepatic artery	11 mm	6 mm	15 mm	10 mm

LVEF Left ventricular ejection fraction; *PAP* pulmonary arterial pressure; *LVEDP* left ventricular enddiastolic pressure; *RVEDP* right ventricular enddiastolic pressure

Results

The follow-up time of the two patients was 7 (patient 2) and 24 (patient 1) months after the gradual banding, which was performed in both patients in 2001. Patient 2 stayed in improved conditions for 3 months after the banding operation. Thereafter, she developed severe portosystemic encephalopathy and a renal failure within the following 4 months due to impaired liver function and newly forming AVM leading to listing for liver transplantation. Upon receiving an organ 7 months after arterial banding, she unfortunately developed an acute cardiac failure intraoperatively and died without being transplanted. The hepatic artery was found to be patent.

The other patient (patient 1) was still alive 24 months after the banding operation and was in improved cardiopulmonary conditions (NYHA II); the secondary pulmonary hypertension had also improved. She was free of any bleeding within 2 years after the operation and enabled to walk again after having laid and sit all day before the operation. Pre- and postoperative data are shown in Tables 2 and 3.

Preoperative measurements showed intrahepatic arteriovenous shunting of 50 and 60% in both patients, an increased cardiac output (10.7 and 11.2 l/min), and an enlarged end-diastolic right ventricular diameter (39 and 43 mm). The pulmonary pressure was 50 and 21 mmHg preoperatively.

After the gradual banding, the hemodynamic parameters and right heart diameters improved or normalized in both patients within 2 months. The cardiac output was reduced by 37.5% to 6.0 l/min and by 44.0% to 7.0 l/min. The mean pulmonary pressure was decreased to 30 and 17 mmHg. The end-diastolic right ventricular diameter could be decreased to 31 and 25 mm. The flow in the hepatic artery was reduced by 85% to 0.3 l/min and by 82.5% to 0.7 l/min. Comparing the

Table 3 Preoperative and Postoperative (2 months) Liver Function Tests

	Patient 1		Patient 2	
	Preoperative	Postoperative	Preoperative	Postoperative
Age	76 years		68 years	
Total bilirubin in serum	0.66 mg/dl	1.76 mg/dl	0.76 mg/dl	1.49 mg/dl
Protein in serum	62 g/l	56 g/l	72 g/l	64 g/l
Quick test	105%	93%	124%	120%
INR	1.0	1.1	1.0	0.9
GPT	18	10	16	23
GOT	14	8	15	16
CHE	3296	2365	2040	2245
γ-GT	68 U/l	12 U/l	133 U/l	37 U/l

Quick test–Prothrombin time

INR International normalized ratio; *GPT* glutamate pyruvate transaminasis; *GOT* glutamate oxalacetate transaminasis; *CHE* cholinesterasis; *γ-GT* gamma-glutamyl transferasis

pre- and postoperative values, there was a significant reduction of cardiac output ($p=0.02$), a significant reduction of mean pulmonary pressure ($p=0.03$), and a significant decrease in the end-diastolic right-heart ventricular diameter ($p=0.01$). The reduction of the intrahepatic arterial flow was also significant ($p=0.008$). Clinically, we could observe an improved cardiac function, as patients were put to stage II of their heart disease compared stage IV before the procedure.

Discussion

Only a small number of case reports concerning intrahepatic involvement of HHT are found in the literature. Therefore, there is no standard recommendation in the treatment on the intrahepatic HHT. Intrahepatic HHT involves the stem or branches of hepatic artery, vein, and the portal vein causing the development of intrahepatic arteriovenous malformations. It is agreed that only symptomatic patients should be treated.[3,8,12,16,17,20] The indication for hepatic arterial banding in our two cases was severe stage IV heart failure, which could be attributed to intrahepatic shunting along with well-preserved liver function.

The therapeutic opportunities in intrahepatic Osler's disease include percutaneous embolization, ligature or banding of the hepatic artery as palliative procedures, and liver transplantation as a curative procedure. Percutaneous embolization of the hepatic artery has been used in several cases.[2,3,11,14,25] However, the embolization or coiling often fails to reduce the shunting volume sufficiently, as new AVM may develop at short notice. Additionally, ischemia of the biliary system with subsequent cholangitis and destruction of the biliary system may occur. The same problem is imminent after ligation of the hepatic artery. Embolization or hepatic artery ligation is only effective in patients with predominant shunting from the hepatic artery to the hepatic veins. In cases of shunting from the portal vein to the hepatic veins, only the hepatic artery delivers blood to the liver parenchyma and its embolization may cause hepatic necrosis. In addition, some patients with intrahepatic HHT have fibrosis or cirrhosis of the liver with impaired liver function leading to acute liver failure after embolization or ligation of a hepatic artery.[2,11,13,14,20,23,25,26]

Liver transplantation is the only curative option in intrahepatic HHT, but this may be complicated by perioperative decompensation of the right-heart insufficiency or pulmonary hypertension. Some authors published encouraging long-term results in patients with intrahepatic HHT after liver transplantation.[3,5,20,23] However, the indication for liver transplantation in patients with intrahepatic HHT and high arteriovenous shunting should be considered early, before the pulmonary hypertension becomes irreversible. Otherwise, the pulmonary hypertension and the right-heart insufficiency may preclude the long-term survival in patients with intrahepatic HHT after liver transplantation. In case of irreversible pulmonary hypertension, only a combined liver and heart–lung transplantation allows a successful treatment.[21,23]

As long as the liver function is fair, we suggest the gradual banding of the hepatic artery to avoid or bridge the time until liver transplantation. The sonographically flow controlled gradual banding of the hepatic artery maintains arterial hepatic flow. On one hand, the surgeon is enabled to control the arterial flow to the liver during the banding operation to prevent liver ischemia or necrosis. On the other hand, the banding operation decreases the right-heart stress and pulmonary hypertension, possibly improving the outcome of the presumptive liver transplantation.[3,5,20,21,23]

Two methods of saving the arterial banding of the hepatic artery are described: encasing in a balloon expander[27] similar to the gastric banding procedure or encasing in a PTFE cuff as shown here. The first one has the advantage of adjustability but the disadvantage of local complications for its size. The latter method has the advantage of low complication rate but the disadvantage of missing external adjustability. The results of both methods are similar, although the first method was described in only one patient.[27] The aim of arterial hepatic flow reduction was to achieve a physiological hepatic artery flow being estimated between 200 and 400 ml/min in humans.[15,16]

The objective criteria to perform a flow-adapted hepatic artery banding (FHAB) could be an arteriovenous shunting of more than 50% and/or a cardiac output of more than 8 l/min, pulmonary artery pressure more than 20 mmHg, end-diastolic right ventricular diameter more than 35 mm as long as they are combined with severe clinical symptoms such as a heart insufficiency stage III or IV. Because there are only a small number of case reports in the literature, general objective indication criteria for the hepatic artery banding cannot be given. According to our experiences with the two patients, we suggest the hepatic artery banding as a palliative procedure in patients with debilitating severe cardiac insufficiency. The decision should be made in collaboration with the treating hepatologists and cardiologists when conservative treatment does not offer further options anymore. The option and risk of liver transplantation should be evaluated. As cardiac output and pulmonary arterial pressure decreased promptly after reducing hepatic artery flow, a causal mechanism can be assumed, which was not compensated for by collateral flow or increased portal vein flow. The hepatic artery banding should not be done in mainly portovenous-venous shunting, in anatomic variations of the hepatic artery like a particular origin of the right or left hepatic artery from the gastroduodenal artery, a fixed pulmonary hypertension, or cardiac valvular failure with calcifications.

To our knowledge, this is the first description of a flow-adapted gradual banding of hepatic artery by a PTFE cuff in hepatic HHT. There are only reports about flow-adapted pulmonary artery banding recommended for patients with transposition of the great arteries who have lost the chance for the arterial switch operation or whose systemic (right) ventricle failed after the atrial switch.[1,6]

Conclusion

Compared to the ligation or embolization of the hepatic artery, the arterial banding provides the advantage of sonographically controlled adjustable reduction of the hepatic arterial perfusion with a comparable operative risk. The question whether the arterial banding of the hepatic artery provides long-term advantages over arterial embolization or ligation cannot be answered at present due to a lack of comparable data. At present, we advocate the indication for the described sonographically controlled gradual banding in those patients in whom the arterial embolization failed or appears hazardous in respect to liver function.[2,3,21,23,27]

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Clinical Analysis of Ectopic Pancreas with Endoscopic Ultrasonography: An Experience in a Medical Center

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Abstract
Objective To describe the endosonographic features of gastrointestinal ectopic pancreas, especially when histopathological diagnosis is unachievable with nonsurgical modalities.
Methods Endoscopic ultrasonography was performed in 20 patients with endoscopically recognized ectopic pancreas. We then analyzed the endosonographic features of the lesions and the clinical aspects of the patients, including age, gender, symptoms, and lesion locations.
Results Endoscopic ultrasonography revealed that the lesions originated from the second, third, and/or fourth layers of the gastrointestinal wall. Most lesions (95%, 19/20) were heterogenous, mainly hypoechoic or mixed, in echogenicity. The borders of the lesions were indistinct in 13 (13/20, 65%) and distinct in 7 (7/20, 35%) patients. Anechoic cystic or tubular structures within the lesions appeared in 7 of the 20 lesions (35%).
Conclusion Ectopic pancreas usually appears as a submucosal lesion with characteristic central dimpling. Furthermore, characteristic endoscopic ultrasonographic features can readily assist in the diagnosis of ectopic pancreas without having to perform endoscopic biopsy or surgery. However, either endoscopic ultrasonography-guided fine needle aspiration or endoscopic removal of lesions should still be considered mandatory for the differential diagnosis of ectopic pancreas whenever typical endosonographic features cannot be well demonstrated.

Keywords Ectopic pancreas · Aberrant pancreas · Endoscopic ultrasonography

Introduction

Ectopic pancreas, a relatively rare benign developmental anomaly, is defined as pancreatic tissue that has neither vascular nor anatomic continuity with the normally located pancreas proper.[1] This lesion is also termed aberrant pancreas, heterotopic pancreas, pancreatic rest, and pancreatic heterotopia.[2] Ectopic pancreas has been found in 0.55% to 13% of autopsies and has also been noted in approximately one of every 500 surgical operations involving the upper abdomen.[3] In addition, it is most commonly located in the upper gastrointestinal (UGI) tract adjacent to the normal pancreas.[4,5]

Pathological diagnosis of ectopic pancreas is usually unachievable for two reasons: because adequate tissue samples cannot usually be taken during endoscopic biopsy using standard forceps[6] and because surgery is usually unnecessary for most asymptomatic patients. In contrast, imaging techniques are helpful in establishing an early and definite differential diagnosis. Correlations between sonographic and histopathological patterns of ectopic pancreas have been previously established in the literature.[7,8] Endoscopic ultrasonography (EUS) combines the techniques of gastrointestinal endoscopy and ultrasonography and provides

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clear and nonsurgical visualization of various subepithelial lesions in the UGI tract.[9–13] In this study, we present our experience of using EUS in diagnosing ectopic pancreas and evaluate the role of EUS in determining these lesions.

Materials and Methods

From April 2004 to October 2007, a total of 10,257 patients underwent panendoscopy; of them, ectopic pancreas was diagnosed endoscopically in 114 (1.1%) patients based on characteristic features of the lesions.[14] Of the 114 patients, 20 underwent EUS examination. All EUS procedures were performed by two experienced endosonographers.

EUS was performed using a radial echoendoscope at a scanning frequency of 7.5 or 12 MHz (Olympus GF-UM 240; Olympus, Tokyo, Japan), as well as an ultrasonic miniprobe at a scanning frequency of 12 MHz (Olympus UM-2R; Olympus, Tokyo, Japan) introduced via an electronic esophagogastroduodenoscope (Olympus XQ-240; Olympus, Tokyo, Japan). EUS was performed to determine the location and size of the lesion, wall layer(s) involved, internal echotexture, and outer margin. Biopsy specimens were taken from all lesions with conventional biopsy forceps and sent for pathological diagnosis. Two patients also underwent exploratory laparotomy. Written informed consent to undergo EUS was obtained from all patients.

Results

The 20 patients ranged in age from 19 to 58 years (mean, 39 years), and comprised 11 men and 9 women. Thirteen patients presented with epigastric pain or dyspepsia. Ectopic pancreas was incidentally diagnosed in the other seven patients without preceding symptoms (Table 1).

Endoscopy revealed that the lesions were localized in the antrum in 19 of the 20 patients; only one lesion was found in the duodenum. Eighteen lesions were centrally umbilicated (Fig. 1). Two lesions without central dimpling were diagnosed as ectopic pancreas based on the EUS findings and pathological confirmation of resected specimens (Fig. 2). Conventional biopsies were performed on all 20 lesions, but only 2 lesions (10%) were diagnosed as ectopic pancreas based on pathology (Table 1). EUS revealed lesions ranging in size from 8 to 20 mm (mean 12±3 mm). Heterogenous, hypoechoic, or mixed echogenic lesions were seen in 19 patients. Only one patient had a homogenous echogenic lesion. The borders were indistinct in 13 (13/20, 65%) and distinct in 7 (7/20, 35%) lesions. Anechoic cystic or tubular structures within the lesions appeared in 7 (35%) of the 20 lesions (Fig. 2). Nine lesions involved only one sonographic layer of the gastrointestinal wall: three originated in the second (muscularis mucosae) layer, five in the third (submucosa) layer, and one in the fourth (muscularis propri) layer. Ten lesions involved both the

Table 1 Summary of Clinicopathologic Features of Patients with Ectopic Pancreas

Case	Age	Gender	Symptoms	Location	PES	Surgery	Biopsy Pathology
1	37	M		S (antrum)	U+	N	CG
2	39	M	Epigastric pain	S (antrum)	U+	N	CG
3	50	F	Epigastric pain	S (antrum)	U+	N	CG
4	33	M		S (antrum)	U+	N	CG
5	38	M	Epigastric pain	S (antrum)	U+	N	CG
6	29	F	Epigastric pain	S (antrum)	U+	N	CG
7	36	F		S (antrum)	U+	N	CG
8	51	F	Dyspepsia	S (antrum)	U+	N	CG
9	43	M		S (antrum)	U+	N	CG
10	50	M	Epigastric pain	D (bulb)	U−	Y	EP
11	24	M		S (antrum)	U−	Y	CG
12	42	F	Epigastric pain	S (antrum)	U+	N	CG
13	47	M	Epigastric pain	S (antrum)	U+	N	CG
14	40	M		S (antrum)	U+	N	CG
15	23	F	Epigastric pain	S (antrum)	U+	N	EP
16	54	F	Dyspepsia	S (antrum)	U+	N	CG
17	58	M	Dyspepsia	S (antrum)	U+	N	CG
18	35	F	Epigastric pain	S (antrum)	U+	N	CG
19	19	M	Dyspepsia	S (antrum)	U+	N	CG
20	33	F		S (antrum)	U+	N	CG

S stomach, *D* duodenum, *PES* panendoscopy, *U+* with central umblication, *U–* without central umblication, *N* no, *Y* yes, *EP* ectopic pancreas, *CG* chronic gastritis

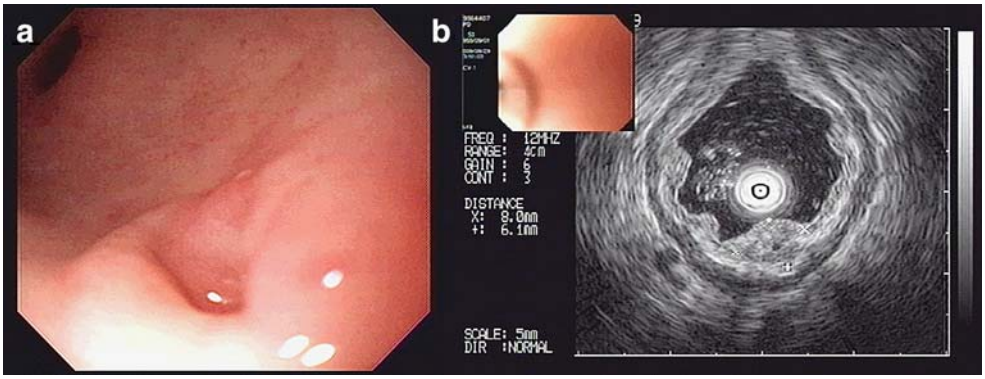

Figure 1 Ectopic pancreas of stomach (case 8). **a** Endoscopic image showing a submucosal lesion with central dimpling at the greater curvature of the antrum. **b** Corresponding EUS images showing an indistinct, heterogenous, and intermediate hypoechoic lesion with an anechoic space involving the second and third sonographic layers of the stomach.

second and third layers. Only one lesion involved the second, third, and fourth layers (Table 2).

Based on Hase's classification, 18 out of 20 lesions were S-type lesions; the other 2 lesions were M-type lesions.[8] Based on Changchien's classification,[15] there were 14 type 1 lesions, 4 type 2 lesions, and 2 type 3 lesions.

Discussion

Ectopic pancreas, an uncommon benign developmental anomaly, is characterized by the presence of pancreatic tissue in ectopic locations at various sites of the body, but most frequently in the GI tract adjacent to the pancreas proper. In 90% of cases, ectopic pancreas is found in the stomach, the duodenum, and the proximal jejunum.[16] Although rare, ectopic pancreas has also been found in the appendix, ileum, Meckel's diverticulum, gall bladder, bile ducts, liver, spleen, omentum, mesentery, perigastric, and periduodenal locations.[17] In our series, ectopic pancreas was diagnosed during panendoscopy in about 1% (1.1%, 114 of 10,257) of patients. The most common location was the antrum of the stomach.

Grossly, ectopic pancreas in the stomach and duodenum can display a central depression, which corresponds to the opening of a duct. The gross appearance of so-called central dimpling implies the presumptive diagnosis of ectopic pancreas for an endoscopist during preoperative endoscopy. As in our series, 90% of the lesions were visualized endoscopically to be centrally umbilicated. The appearance of a "bull's eye" can also be typically visualized on barium studies.[7,18]

Ectopic pancreatic tissue may be functionally active and secretive.[19] Ectopic pancreas may also give rise to benign and malignant ectopic pancreatic tumors.[20] In addition, rare complications resulting from ectopic pancreas have been reported, including gastric outlet obstruction, obstructive jaundice, intestinal obstruction, and intussusception.[21,22] However, ectopic pancreas is usually asymptomatic and found incidentally during routine endoscopic or radiographic studies. Although most of our patients (13/20) complained of some gastrointestinal symptoms, e.g., epigastric pain and dyspepsia, none of the patients presented with specific symptoms attributable to ectopic pancreas. However, two patients (case 10 and 11) benefited from surgical resection of ectopic pancreas, with subsequent loss of the symptoms postoperatively. The need for surgical treatment depends on the symptoms, definitive diagnosis regarding the possibility of malignancy and other attributable complications, such as gastrointestinal obstruction or bleeding. Definitive patholog-

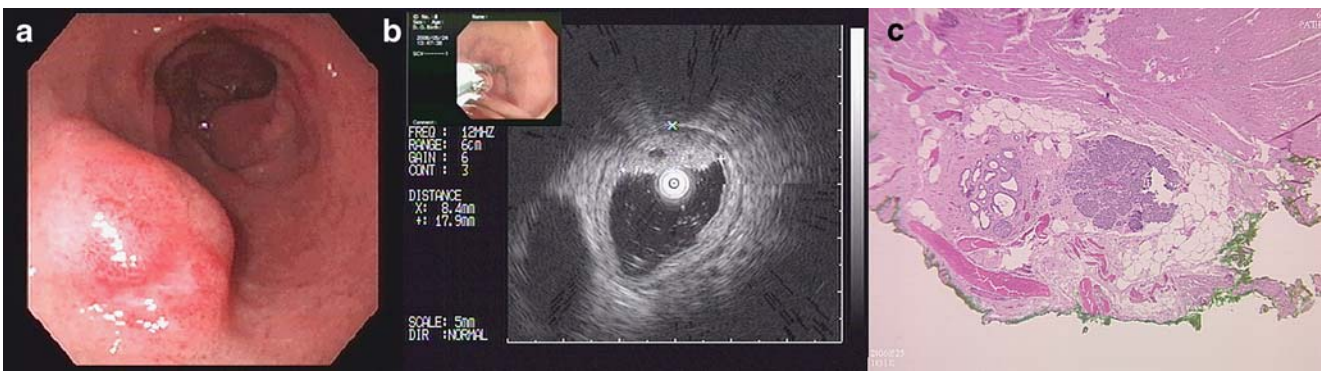

Figure 2 Ectopic pancreas of duodenum (case 10). **a** Endoscopic image of a submucosal tumor without central umblication in the duodenal bulb. **b** Endosonographic view of an indistinct, heterogenous, and mixed echogenic mass with an anechoic space involving the second, third, and fourth layers of duodenum. **c** Microscopically, the ectopic pancreatic tissue, which is composed of pancreatic acini and ducts with focal cystic change, is located in the muscularis mucosae, submucosa, and muscularis propri of duodenal wall.

Table 2 Summary of EUS Features and Classification of Ectopic Pancreas

Case	Size (mm)	Layer	Echogenecity		Border	Anechoic space	4th layer thickening	Hase	Changchien
1	10	2, 3	Hypo	Hetero	Distinct	−	−	S	1
2	10	2, 3	Hypo	Hetero	Indistinct	+	+	S	2
3	8	2, 3	Hypo	Hetero	Indistinct	−	−	S	1
4	10	2	Hypo	Hetero	Distinct	−	−	S	1
5	10	3	Mixed	Hetero	Distinct	−	−	S	1
6	15	3	Mixed	Hetero	Indistinct	+	−	S	1
7	15	2, 3	Hypo	Hetero	Indistinct	−	−	S	1
8	8	2, 3	Hypo	Hetero	Indistinct	+	−	S	1
9	10	2, 3	Mixed	Hetero	Distinct	−	−	S	1
10	18	2, 3, 4	Mixed	Hetero	Indistinct	+	−	M	3
11	20	4	Hypo	Homo	Indistinct	−	−	M	3
12	14	3	Mixed	Hetero	Indistinct	+	+	S	2
13	14	2, 3	Mixed	Hetero	Indistinct	+	−	S	1
14	10	3	Mixed	Hetero	Indistinct	−	−	S	1
15	14	2, 3	Mixed	Hetero	Indistinct	−	+	S	2
16	8	3	Mixed	Hetero	Indistinct	−	−	S	1
17	10	2, 3	Mixed	Hetero	Distinct	+	−	S	1
18	15	2	Mixed	Hetero	Distinct	−	−	S	1
19	10	2, 3	Mixed	Hetero	Indistinct	−	+	S	2
20	10	2	Hypo	Hetero	Distinct	−	−	S	1

Hypo hypoechoic, *Mixed* intermediate echogenicity, *Hetero* heterogenous, *Homo* homogenous

ical diagnosis was only possible in two of our patients because none of the others required surgical intervention.

Histological diagnosis of ectopic pancreas is usually difficult when tissue specimens are obtained using conventional endoscopic biopsy forceps. For precise histological diagnosis, endoscopic techniques for obtaining deeper specimens are necessary, such as EUS-guided biopsy or combined strip biopsy and bite biopsy.[23,24] Endoscopic removal of gastric aberrant pancreas is also useful for accurate diagnosis and treatment.[25] The diagnosis of ectopic pancreas was based on the pathological appearance of specimens taken with standard endoscopic biopsy forceps in only two cases in our series.

EUS can clearly identify the structure of the intestinal wall, visualize sonographic features of the lesion and its layer(s) of origin, and thus readily assist in the differential diagnosis of subepithelial tumors. Based on the correlations between endosonographic and histopathological patterns of ectopic pancreas that have been established in the literature,[7,8] endoscopists may benefit from EUS to determine the anatomic nature of an endoscopically recognized ectopic pancreas. Hase et al.[8] described two types of aberrant pancreas: an M-type and an S-type. When we classified the EUS patterns in our 20 cases (lesions) into these two types, we found that the ectopic pancreatic tissue penetrated into the muscularis propria in the 2 M-type lesions and solely originated from the submucosal layer in the 18 S-type lesions, respectively. The latter type is therefore a good candidate for safe endoscopic removal, although none of our patients underwent the procedure.

In a study by Changchien et al.,[15] 13 cases of gastric aberrant pancreas were classified into three types based on the morphology of the muscular (the fourth) layer: type 1 (six cases), indicated an intact fourth layer with normal thickness; type 2 (four cases), indicated a thickened fourth layer; and type 3 (three cases), indicated a thickened fourth layer composed of some hyperechoic densities (tubular-like structures). Mucosectomy was performed without any complications in six cases (four type 1 and two type 2). They concluded that EUS provides practical information for selecting patients for a safe endoscopic mucosectomy.

The characteristic EUS features of ectopic pancreas, including indistinct margin, heterogeneous echogenicity (mainly hypoechoic accompanied by scattered small hyperechoic areas), an anechoic area and fourth-layer thickening, and location within the second, third, and/or fourth layers are very useful in establishing a preoperative diagnosis of ectopic pancreas. The heterogeneous hypoechoic or mixed echogenicity, resembling that of the normal pancreatic parenchyma, corresponds to the acinous tissue with scattered adipose tissue within the lesion. Anechoic areas indicate duct dilatation, and fourth-layer thickening is considered a consequence of the hypertrophy of the muscularis propria. The fact that the margins were mostly indistinct in our patients correlates with the histological findings of a lobular structure of the acinous tissue at the

margin. However, the atypical features of homogenous hypoechoic echogenicity solely within the fourth layer on EUS in case 11 led to a misdiagnosis of gastrointestinal stromal tumor (GIST); ectopic pancreas was later diagnosed based on pathology of the resected specimen.

Conclusion

The characteristic endosonographic features of ectopic pancreas correlate well with specific histological components, making EUS a useful diagnostic modality without having to perform endoscopic biopsy or surgery. However, either EUS-guided fine needle aspiration or endoscopic removal of the lesion should still be considered mandatory for the differential diagnosis of ectopic pancreas whenever endosonographic features cannot be well demonstrated.

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Effect of BioGlue® on the Incidence of Pancreatic Fistula Following Pancreas Resection

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Abstract
Background Despite numerous modifications of surgical technique, pancreatic fistula remains a serious problem and occurs in about 10% of patients following pancreas resection. BioGlue is a new sealant that creates a flexible mechanical seal within minutes independent of the body's clotting mechanism.
Hypothesis Application of BioGlue sealant will reduce the incidence of pancreatic fistula following pancreas resection.
Methods A retrospective cohort study was performed with 64 patients undergoing pancreas resection. BioGlue sealant was applied to the pancreatic anastomosis (Whipple) or resection margin (distal pancreatectomy) in 32 cases. Factors that could affect the rate of postoperative pancreatic fistula were recorded. Pancreatic fistula was defined as greater than 50 ml of drain output with an amylase content greater than three times normal serum value after postoperative day 10. To improve the sensitivity of our study, we also examined pancreatic fistula with a strict definition of any drain output on or after postoperative day 3 with a high amylase content and graded the fistulas in terms of clinical severity. Grade A leaks were defined as subclinical. Grade B leaks required some response such as making the patient *nil per os*, parenteral nutrition, octreotide, antibiotics, or a prolonged hospital stay. Grade C leaks were defined as serious and life threatening. They were associated with hemorrhage, sepsis, resulted in deterioration of other organ systems, and mandated intensive care. Comparisons between the two groups were made using the chi-square test or Fisher's exact test for categorical variables and by the Wilcoxon rank-sum test for continuous variables. *P* values of 0.05 or less were deemed statistically significant.
Results There were no differences between the patients who received BioGlue and the control cohort in terms of comorbid conditions, tumor location, texture of the pancreas, size of the pancreatic duct, or surgical technique. By the common definition, pancreatic fistula occurred in 6% (control) vs. 22% (BioGlue). By the strict definition, a fistula occurred in 41% (control) vs. 60% (BioGlue). In the control group, ten were subclinical (grade A) and two were clinically apparent leaks (grade B). In the BioGlue group, seven were subclinical (grade A), five were clinically apparent (grade B), and three were severe (grade C). There were no statistically significant differences in the incidence or severity grades of postoperative pancreatic fistulas between the two groups.
Conclusion Application of BioGlue sealant probably does not reduce the incidence of pancreatic fistula following pancreas resection.

Keywords Pancreatic fistula · BioGlue sealant · Pancreas resection

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Introduction

In recent years, the mortality rate of pancreatic resection has decreased to less than 5% in high-volume centers.[1–5] Although mortality has been reduced, complications of pancreatic surgery such as pancreatic anastomotic leak and associated postoperative hemorrhage and infection continue to be problematic. The morbidity of pancreatic surgery remains relatively high at 30% to 60%, and much of this

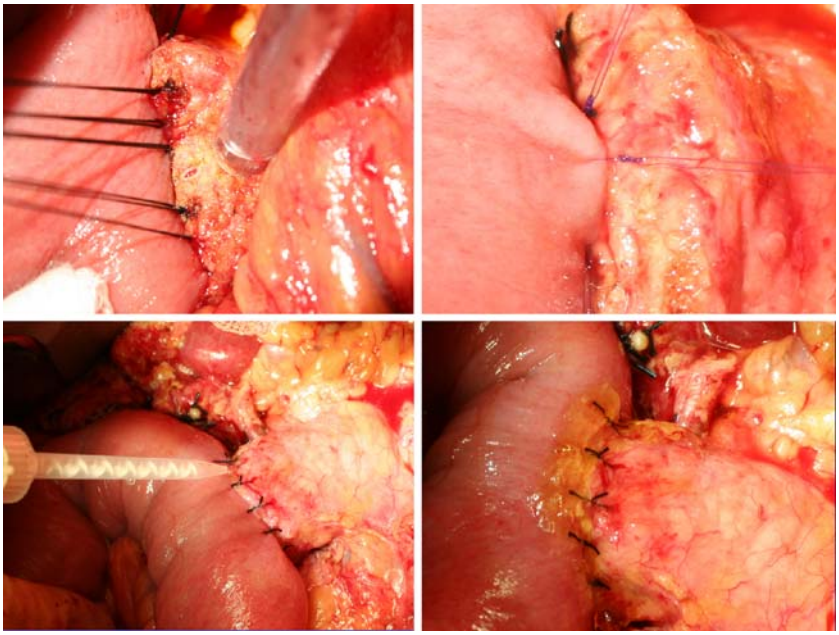

Figure 1 A back row of 4-0 interrupted silk sutures was placed, followed by a duct-to-mucosa anastomosis between the pancreatic duct and the jejunum using 6-0 PDS, followed by an anterior row of interrupted silk sutures. BioGlue was applied after the anastomosis was complete. The suture line was coated with a thin layer of the glue and it was allowed to polymerize without contacting any other tissue.

morbidity is attributed to a leak from the pancreatic anastomosis.[5–10]

The rate of pancreatic fistula after pancreatic resection varies widely in the literature from 0% to 40% depending on the definition used for pancreatic leak.[2,4,6,10,14,16,17,20,25,28,31,35–37] Pancreatic leak is more common after distal pancreatectomy than pancreaticoduodenectomy. The indication for resection also influences the leak rate with leaks being more common in pathology such as cystic lesions than pancreatitis or pancreatic cancer where the pancreas is firm and the duct is dilated. Although most pancreatic leaks resolve spontaneously without further intervention, decreasing the incidence of pancreatic fistula would potentially reduce the morbidity and mortality of pancreatic resection.[11–13]

Many attempts have been made to find a reliable method to prevent a pancreatic fistula and the associated complications. These range from injection of perioperative octreotide[14–19] to technical modifications of the pancreatic anastomosis,[2,20–26] application of a topical sealant to the pancreatic duct[27] or at the site of pancreatic anastomosis,[28–31] and irradiation.[19] The usefulness of a topical sealant to reduce the rate of pancreatic fistula is still controversial. Several non-randomized studies and one randomized prospective trial by Suzuki have suggested that fibrin glue can decrease the incidence of pancreatic fistula.[30,31,32,33] However, several recent prospective randomized trials have not shown a benefit with fibrin glue application.[28,29] Fibrin glue is composed of thrombin, fibrinogen, factor XIII, and an antifibrinolytic agent originally intended to be used for hemostasis and subsequently used for wound closure and tissue sealing.[34] Although there are no obvious adverse effects associated with fibrin glue, technically it is a poor adhesive for pancreatic surgery because it takes a long time to set up and is easily wiped or washed away.

BioGlue is a new sealant mostly used by cardiovascular surgeons for sealing graft anastomoses. Upon application, the glutaraldehyde molecules covalently bond (cross-link) the bovine serum albumin molecules to each other and to the tissue proteins at the repair site, creating a flexible mechanical seal independent of the body's clotting mechanism. The transformation of liquid glue on the anastomotic surface to a flexible hydrogel is quick, reaching maximal strength in 2 min. This study was designed to evaluate the safety of BioGlue in pancreatic surgery and the effect of topical BioGlue sealant on the rate of pancreatic leak following pancreatic resection.

Methods

Study Design and Patient Population

This study was a single-institution, retrospective, non-randomized cohort study. Our prospective database includes all patients undergoing pancreas resection. Records were retrospectively reviewed for all patients (64) who underwent open pancreatic resection from April 2004 to July 2006. Approval for this study was obtained from our institutional review board (Baylor IRB #H-16313). Patients undergoing laparoscopic pancreatic surgery were excluded. Patients in the study group (n=32 consecutive patients) had 5 ml of BioGlue applied to the pancreatic anastomosis (Whipple procedure) or pancreatic resection margin (distal pancreatectomy). A subsequent additional group (n=32 consecutive patients) underwent surgery without the use of

BioGlue. A single experienced pancreatic surgeon (WEF) performed all 64 of the resections during the above time period, thus minimizing technical variation. Patients who required total pancreatectomy or patients who underwent completion pancreatectomy were excluded.

Surgical Technique

The anastomotic technique was left to the discretion of the surgeon. Ninety-five percent of the anastomoses were performed using an end-to-side pancreatico-jejunostomy. A back row of 4-0 interrupted silk sutures was placed, followed by a duct-to-mucosa anastomosis between the pancreatic duct and the jejunum using 6-0 polydioxanone (PDS), followed by an anterior row of interrupted silk sutures. The end of the pancreas was intussuscepted into the open end of the jejunum in 5% of the cases because the pancreatic duct was difficult to identify at the time of surgery, and the texture of the pancreas was soft. Pancreatic duct stents were not used. The resection margin in cases of distal pancreatectomy was controlled with a combination of the use of a surgical stapler, a running locked suture in some cases, and direct suture of the pancreatic duct when it could be identified.

Prophylactic octreotide was used in 26% of the cases. An infusion of 10 μg/h was initiated intraoperatively and continued for 7 days when the surgeon felt the anastomosis was at risk due to a small duct (less than 3 ml) and soft pancreas. All patients had a single dose of prophylactic intravenous antibiotics before the skin incision.

BioGlue was applied after the anastomosis was complete. The surface was patted dry with a laparotomy pad. The suture line or pancreatic margin was then coated with a thin layer of the glue, and it was allowed to polymerize without contacting any other tissue. An effort was made to control the glue and keep it just at the anastomotic site. Drains were placed at the end of the procedure after the glue had completely polymerized (Fig. 1).

Data Collection

Patient age, smoking history, alcohol consumption, comorbidities such as body mass index (BMI), preoperative weight loss, preoperative diabetes, preoperative albumin and bilirubin levels, the use of octreotide, the type of surgery and anastomosis, pancreatic texture, pancreatic duct size, estimated blood loss, and pathology were recorded. All patients had Jackson–Pratt drains placed intraoperatively at the surgical site. The daily amount of drainage and amylase content of the fluid was recorded from the medical record. All postoperative complications within 30 days of operation and the length of hospital stay were recorded.

Definition of Pancreatic Fistula

The primary end point of the study was the incidence of pancreatic fistula. Pancreatic fistula was defined using two definitions. The first definition was greater than 50 ml of drain output with an amylase content greater than three times normal serum value after postoperative day 10. We also used a recent classification and grading system for pancreatic fistula proposed by an international study group.[1] By this system, a fistula was defined as a drain output of any volume with an amylase level greater than three times the normal serum value on or after postoperative day 3. The grading system categorizes pancreatic fistulae by clinical conditions such as infection, sepsis, or hemorrhage, specific treatments such as antibiotics, octreotide, total parenteral nutrition, or reoperation. Grade A fistulas were subclinical and required no treatment. Grade B fistulas required some intervention such as octreotide, total parenteral nutrition, or antibiotics and prolonged the hospital stay. Grade C fistulas resulted in life-threatening infection, sepsis, hemorrhage, or required a return to the operating room.

Statistics

Descriptive statistics were used to summarize demographics and patient characteristics for the two study groups. The incidence of complications was calculated separately for both groups. Any complication was defined as occurrence of any complications. Comparisons between the two groups were made using the chi-square test or Fisher's exact test for categorical variables and by the Wilcoxon rank-sum test for continuous variables. P values of 0.05 or less were deemed statistically significant.

Results

Although this was a retrospective cohort study, there were no significant differences between the patients in the control group and the group treated with BioGlue in terms of factors that may affect the incidence of postoperative pancreatic fistula. There were no differences in demographics, nutritional status (BMI, preoperative weight loss, hypoalbuminemia), renal function (creatinine clearance), tobacco or alcohol use, history of chronic pancreatitis, diabetes, preoperative bilirubin, or the use of preoperative stents. The difference in creatinine was statistically significant but not clinically significant. Although retrospective data regarding the texture of the pancreas or size of the pancreatic duct was not always available, we detected no difference between the two groups with the available data (Table 1).

Table 1 Demographics and Patient Characteristics

	BioGlue (n=32)	Control (n=32)	P value*
Gender, no. (%)			
Male	15 (46.9)	14 (43.8)	1.000
Female	17 (53.1)	18 (56.3)	
Race, no. (%)			
Caucasian/Non-Hispanic	27 (84.4)	22 (68.8)	0.176
Caucasian/Hispanic	4 (12.5)	4 (12.5)	
African-American	1 (3.1)	6 (18.8)	
Age at surgery (years)	61.5 (53.0–69.5)[a]	66.0 (54.0–69.5)[a]	0.616**
BMI	26.7 (22.1–30.2)[a]	27.3 (25.0–34.2)[a]	0.204**
Pre-operative weight loss, no. (%)			
>10%	11 (37.9)	13 (41.9)	0.797
≤10%	18 (62.1)	18 (58.1)	
Missing	3	1	
Tobacco history, no. (%)			
Ever	6 (19.3)	9 (28.1)	0.365
Never	25 (80.7)	23 (71.9)	
Missing	1	0	
Alcohol consumption, no. (%)			
Yes	15 (50.0)	14 (43.8)	0.799
No	15 (50.0)	18 (56.3)	
Missing	2	0	
Chronic pancreatitis, no. (%)			
Yes	4 (12.9)	7 (21.9)	0.509
No	27 (87.1)	25 (78.1)	
Missing	1	0	
Pre-operative diabetes, no. (%)			
Yes	6 (19.4)	9 (29.0)	0.554
No	25 (80.7)	22 (71.0)	
Missing	1	1	
Serum albumin (mg/dl), no. (%)			
≤3.0	1 (3.3)	4 (12.9)	0.159
>3.0	29 (96.7)	27 (87.1)	
Missing	2	1	
Serum creatinine (mg/dl)	0.9 (0.7–1.0)[a]	1.0 (1.0–1.3)[a]	0.001**
Pre-operative bilirubin (mg/dl)	0.5 (0.3–0.8)[a]	0.5 (0.3–1.1)[a]	0.982**
Texture of pancreas, no. (%)			
Soft	8 (50.0)	9 (64.3)	0.484
Hard	8 (50.0)	5 (35.7)	
Missing	16	18	
Pancreatic duct size, no. (%)			
Large (>3 mm)	7 (21.9)	13 (40.6)	0.177
Small (<3 mm)	25 (78.1)	19 (59.4)	

*P values were based on Fisher's exact test.
**P values were based on Wilcoxon rank-sum test.
[a] Values were expressed as median (interquartile range).

We also analyzed the technical factors that may affect the incidence of postoperative pancreatic fistula (Table 2). There were almost equal numbers of Whipple procedures and distal pancreatectomies in each study group. Five Whipple procedures also included resection of the portal vein/superior mesenteric vein; two in the control group and three in the BioGlue group. Among the subset of patients who had a pancreatico-duodenectomy, there was no difference between the number of patients in the control group and the BioGlue group who had a duct-to-mucosa anastomosis versus an intussusception. We reserved the latter technique for patents with a soft pancreatic parenchyma and pancreatic duct that was too small to find. This subset would be anticipated to have a higher risk for postoperative pancreatic fistula. Among the subset of patients who had a distal pancreatectomy, there were no significant differences in the use of sutures or a stapling device to control the pancreatic resection margin. When staples were not used, the pancreatic duct was identified and directly sutured, followed by a running locked suture across the resection margin.

The pathology for which the resection was performed could also be a factor related to postoperative pancreatic fistula. Resections performed for chronic pancreatitis would

Table 2 Technical Factors

	BioGlue (n=32)	Control (n=32)	P value*
Procedure, no. (%)			
Whipple	23 (71.9)	21 (65.6)	0.788[a]
Type of anastomosis			
Duct to mucosa	21 (91.3)	20 (95.2)	1.000
Invagination	2 (8.7)	1 (4.8)	
EBL (ml)	500 (300–800)[b]	500 (265–825)[b]	0.910**
Distal pancreatectomy	9 (28.1)	11 (34.4)	
Type of closure			
Stapled	5 (55.6)	2 (18.2)	0.160
Sutured	4 (44.4)	9 (81.8)	
EBL (ml)	300 (300–600)[b]	550 (100–900)[b]	0.970**
Octreotide, no. (%)			
Prophylactic	6 (18.8)	11 (34.4)	0.361
Therapeutic	1 (3.1)	2 (6.3)	
None	25 (78.1)	19 (59.4)	

*P values were based on Fisher's exact test.
**P values were based on Wilcoxon rank-sum test.
[a] Comparison of procedures (Whipple and distal pancreatectomy) between the two groups.
[b] Values were expressed as median (interquartile range).

be expected to be associated with a lower incidence of pancreatic fistula since the gland is more firm and holds sutures better, and the pancreatic duct is often dilated. In contrast, resections performed for ampullary lesions or cystic neoplasms are frequently associated with a more normal pancreatic resection margin and higher incidence of pancreatic fistula. There were no statistically significant differences in the pathology for which the resections were performed between the two study groups (Table 3). We categorized each case as high or low risk based on these factors, but this categorization was not predictive of the incidence of fistula.

Postoperative complications are summarized in Table 4. When the data was analyzed using a common definition of postoperative pancreatic fistula, (>50 ml/day of drain output with a high amylase content after postoperative day 10), pancreatic fistula occurred in 6% (control) vs. 22% (BioGlue). Although the use of BioGlue almost quadrupled the incidence of pancreatic fistula, the difference was not statistically significant. If we separate the Whipples (n=44) from the distal pancreatectomies (n=20), there was 1 fistula out of 21 Whipples (5%) in the control group and 6 fistulas out of 23 Whipples (26%) in the BioGlue group. Among the distal pancreatectomies, there was 1 fistula among 11 cases (9%) in the control group and 1 among 9 cases (11%) in the BioGlue group. These differences were also not significant.

To increase the sensitivity of our observations for postoperative pancreatic fistula, we adopted a very strict definition suggested by a recent international conference. Any drain output on or after postoperative day 3, no matter how small, with an amylase content three times greater than the normal serum value, was considered a pancreatic fistula. By the strict definition, a fistula occurred in 41% (control) vs. 60% (BioGlue). In the control group, ten (37%) were subclinical (grade A), and two (7.4%) were clinically apparent leaks (grade B). In the BioGlue group, seven (28%) were subclinical (grade A), five (20%) were clinically apparent (grade B), and three (12%) were severe (grade C). Although there again seemed to be a trend toward more clinically significant leaks in the BioGlue group, there were no statistically significant differences in the incidence or severity grades of postoperative pancreatic fistulas between the two groups.

In addition to pancreatic fistula, all other complications within 30 days of the operation were also recorded (Table 4). The incidence of any complication did not differ between the groups, and pancreatic fistula was not associated with additional complications. Among patients with a pancreatic fistula, there was no difference in the length of stay. In the subgroup of patients with a pancreatic fistula, the BioGlue® group had a mean hospital stay of 13.5 days compared to 10.7 days in the control group (P=0.4688, Wilcoxon rank-sum test). The presence of a pancreatic fistula was not associated with a prolonged hospital stay.

Discussion

The word fistula is defined as an abnormal passage from one epithelialized surface to another, congenital or created surgically. The anastomosis created after pancreatic resec-

Table 3 Pathology[a]

	BioGlue (n=32)	Control (n=32)
Lower leak risk, no. (%)	18 (56.2)	16 (50.0)
Pancreatic adenocarcinoma	12 (37.5)	11 (34.4)
Pancreatitis	5 (15.6)	3 (9.4)
Pancreatic pseudocyst	1 (3.1)	2 (6.3)
Higher leak risk, no. (%)	14 (43.8)	16 (50.0)
Ampullary neoplasm	9 (28.1)	6 (18.8)
Mucinous cystic neoplasm	1 (3.1)	2 (6.3)
Serous cystadenoma	1 (3.1)	3 (9.4)
Intraductal papillary mucinous neoplasms	0 (0.0)	3 (9.4)
Other	3 (9.4)	2 (6.3)
Neuroendocrine tumor	2 (6.3)	0 (0.0)
Lymphangioma	1 (3.1)	0 (0.0)
Gangliocytic paraganglioma	0 (0.0)	1 (3.1)
Adenomatoid ductal hyperplasia	0 (0.0)	1 (3.1)

[a] P values were not significant.

Table 4 Complications

	BioGlue (n=32)	Control (n=32)	P value*
Pancreatic fistula, no. (%)			
Traditional definition			
Yes	7 (21.9)	2 (6.2)	0.148
No	25 (78.1)	30 (93.8)	
New definition			
Yes	15 (60.0)	12 (41.4)	0.275
No	10 (40.0)	17 (58.6)	
Missing	7	3	
New definition-graded fistula			
Grade A	7 (28.0)	10 (34.5)	0.141
Grade B	5 (20.0)	2 (6.9)	
Grade C	3 (12.0)	0 (0.0)	
No Fistula	10 (40.0)	17 (58.6)	
Missing	7	3	
Any complication, no. (%)	13(40.6)	13 (40.6)	1.000
Specific complications, no. (%)			
Wound infection	8 (25.0)	5 (15.6)	
Urinary tract infection	0 (0.0)	5 (15.6)	
Pneumonia	0 (0.0)	4 (12.5)	
Intra-abdominal abscess	2 (6.3)	2 (6.3)	
Arrhythmia	1 (3.1)	2 (6.3)	
Fever (>102.3°F)	1 (3.1)	2 (6.3)	
Biliary leak	1 (3.1)	0 (0.0)	
Gastroparesis	1 (3.1)	1 (3.1)	
Line sepsis	1 (3.1)	1 (3.1)	
Deep venous thrombosis	0 (0.0)	1 (3.1)	
Hospital stay (days)	8.5 (7.0–10.5)	8.5 (7.0–12.0)[a]	0.6509**

*P values were based on Fisher's exact test.
**P values were based on Wilcoxon rank-sum test.
[a] Values were expressed as median (interquartile range).

tion is therefore technically a desired fistula between the pancreatic duct and the jejunum (or stomach). The term pancreatic leak is a more common way to describe a fistula that develops after pancreatic resection connecting the pancreatic duct to the skin surface, usually via a drain placed at the time of surgery or placed percutaneously after surgery. This leak or escape of pancreatic juice is the result of either a technical insufficiency of the surgical anastomosis or, more likely, a breakdown of that anastomosis in the postoperative period.

This retrospective nonrandomized single-institution trial was designed to evaluate the efficacy of topical administration of BioGlue sealant to prevent pancreatic anastomotic leak after pancreas resection. The primary end points of this study included pancreatic fistula and other intra-abdominal complications, death, and the length of postoperative hospital stay. During this period, we recruited 64 patients in two consecutive cohorts. The two groups were comparable with respect to patient characteristics and preoperative parameters, intraoperative parameters, and pathologic findings. Using a common definition of fistula, we found that 6% of our patients developed a pancreatic fistula in the control group compared to 22% in the BioGlue group. The 6% incidence of postoperative pancreatic fistula observed in our control group is comparable to numerous other studies. Using a more strict definition, fistulas were stratified into three grades (A–C) depending on severity. Although there was a trend toward an increase in severity of fistulas with the use of BioGlue, there was no statistically significant difference in the incidence of grade A (clinically silent), grade B (clinically apparent but not severe), and grade C (severe or life-threatening) fistulas.

The results of this study indicate that topical application of BioGlue sealant to a completed pancreatic anastomosis or resection margin is not likely to decrease the rate of pancreatic fistula, total complications, the overall length of postoperative stay, or the length of stay for patients in whom a fistula develops. There was no statistically significant increase in adverse effects associated with the use of BioGlue. However, the trend was not in favor of its use. Anecdotally, there were three patients in the BioGlue group who had a completely uneventful initial recovery with no evidence of a fistula. Between the seventh and ninth postoperative days, the drains were removed from these patients, and within 24 h, they returned with abdominal pain and were diagnosed with a pancreatic leak. One of them also developed a bile leak, and another eventually had to be returned to the operating room to drain an intra-abdominal abscess. The patient with the bile leak had a percutaneous transhepatic cholangiogram demonstrating no leak from the choledochojejunostomy, and the bile was thought to be coming from the pancreaticojejunostomy site. Although we made sure the glue was completely set before placing the drains at the end of the procedure, this experience raises the question of whether or not the drains may have been adherent to the pancreatic anastomosis and removal of the drain caused the leak.

Our experience with this product would suggest that such treatment would be unlikely to be associated with substantial benefit and may potentially increase short-term or long-term complications. Avoidance of the routine use of this product will decrease the hospital cost by $700 per resection at our hospital.

Although there have been dramatic improvements in the mortality following pancreatic resection in recent decades, the morbidity of the operation remains high with most series reporting complication rates of about 40%. The most frequent complications reported are gastroparesis, wound infection, and pancreatic leak. Considerable attention has been focused on the prevention of pancreatic leak after

pancreas resection. Modifications of the anastomotic technique (end-to-side or end-to-end, duct-to-mucosa or invaginated), the use of jejunum or the stomach for drainage, the use of pancreatic duct stents, the use of octreotide, and various sealants have all been evaluated.

Octreotide, a synthetic analog of somatostatin with a longer half-life, has been evaluated as a pharmacologic therapy to reduce pancreatic secretion and the rate of pancreatic fistula after pancreatic resection. European studies advocate the routine use of octreotide, while North American trials conclude that octreotide is useless.[14–19,38–41] In our study, we used octreotide as a prophylactic measure in high-risk patients when the pancreas was found to be soft with a small (<3 mm) duct. Octreotide was started intraoperatively when these findings were noted as a continuous drip of 10 μg/h. In cases where a clinically significant pancreatic fistula was diagnosed postoperatively, "therapeutic" octreotide was given at a dose of 100 μg by subcutaneous injection every 8 h.

Many technical modifications to the classic pancreaticoduodenectomy have been described. However, more than 70 technical variations to the pancreaticoenteric anastomosis have not clearly demonstrated an objective method to consistently decrease the rate of fistula which varies from 0% to 40%.[2,7,10,14,16,20,21,25–26,28,31,42] In our study, we preferred to perform a pancreaticojejunosomy. Other options to consider when performing the pancreatic anastomosis are the duct-to-mucosa versus the invagination techniques. Many surgeons choose the technique at the time of operation depending on the size of the pancreatic duct and the texture of pancreas.[22] The duct-to-mucosa anastomosis results in a low pancreatic fistula rate in patients with a large pancreatic duct and a fibrotic pancreas.[8] However, the end-to-end invagination technique may be more secure in patients with a small duct and soft pancreas. In our study, more patients had a duct-to-mucosa anastomosis than invagnation because the latter technique was employed only in patients with a soft pancreas and very small pancreatic duct. The use of BioGlue with other anastomotic techniques has not been studied.

Although there has been little convincing evidence for the use of a pancreatic duct stent, proponents suggest that a stent may discourage a pancreatic leak and aid in technical precision.[23,43] Both internal stenting as well as external stenting have been shown to reduce the incidence of pancreatic fistula in some clinical studies.[8] None of the procedures in our study included use of a stent.

Avoiding the pancreatic anastomosis altogether by ductal ligation or occlusion has also been evaluated as a potential technique to reduce the rate of postoperative pancreatic fistula. Ductal occlusion with neoprene or prolamine, which are non-resorbable glues, has been abandoned due to pancreatic atrophy and loss of exocrine function.[44] Another study by Tran et al.[27] comparing duct occlusion and pancreaticojejunostomy showed that duct occlusion significantly increases the risk of endocrine insufficiency without a decrease in the postoperative complication rate. To avoid long-term loss of function, absorbable glues, such as fibrin glue, have been evaluated to limit the action of pancreatic enzymes until the anastomosis is healed. Fibrin glue has been used for both duct occlusion and has also been applied to the surface of the pancreatic stump and anastomotic site. Different amounts of aprotinin have been added to the glue.[17, 28–31,44] Aprotinin is an anti-fibrinolytic agent which was added to the system to delay the dissolution of the glue by the pancreatic enzymes. Some studies with surgical adhesives have suggested that the method of application is important. Application of the glue between surfaces rather than coating the completed anastomosis was more effective in one trial.[30] Although earlier studies[30,31,44] suggested that fibrin glue may be useful in preventing pancreatic fistula, the recent studies[28,29] have not been able to reproduce similar results. In this study, we chose to apply the glue to the completed anastomosis because we did not want to risk occlusion of the main pancreatic duct with BioGlue. Another strategy would be to complete the duct to mucosa sutures then apply the glue before placing the anterior row of interrupted sutures.

BioGlue is a recent addition to the list of synthetic tissue sealants that can be used during surgery. The characteristics of this glue are markedly different than fibrin glue sealants. The glue polymerizes very rapidly creating what appears to be a "weld" between the pancreas and intestine unlike fibrin glue which wipes off easily and may be removed with irrigation even after prolonged waiting. These characteristic encouraged us to evaluate the safety and efficacy of BioGlue applied at the pancreatic resection site to reduce postoperative pancreatic fistula.

The mortality rate following a pancreaticoduodenectomy may be higher than with distal pancreatectomy. However, the rate of pancreatic fistula may be higher following distal pancreatectomy and was reported to be 22.9% in a recent meta-analysis.[5] Some of the technical variations to manage the pancreatic resection margin after distal pancreatectomy include use of a mechanical stapler for resection and closure, use of an ultrasonic dissector especially for a nonfibrotic pancreas, ligation of the main pancreatic duct, and use of an omental plug.[36] In some cases, particularly when there is concern about downstream pancreatic duct obstruction, the resection margin is anastomosed to a defunctionalized Roux-en-Y limb of jejunum. A meta-analysis of distal pancreatic stump closure techniques, however, did not reveal a statistically significant difference between the incidence of pancreatic fistula with any particular stump management: suture closure, suture closure plus fibrin glue, suture closure plus Prolene mesh, stapler

closure and pancreaticojejunostomy.[5] The stapler closure is simple, quick, and secure compared to other methods, and although existing data is insufficient to draw any firm conclusions, there was a trend in favor of the stapled technique.

Conclusion

To our knowledge, this is the first report on the use of BioGlue as a topical sealant after pancreatic resection. The obvious weaknesses of this trial are the limited sample size and nonrandomized, retrospective study design. Our preliminary results do not encourage the use of BioGlue to prevent pancreatic leak after pancreas resection. However, a more powerful, larger randomized prospective trial may be required to definitively answer this question.

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Serum Paraoxonase Undergoes Inhibition and Proteolysis During Experimental Acute Pancreatitis

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Abstract Oxidative stress has a primary role in the pathogenesis of severe acute pancreatitis. Then, the antioxidant capacity is a critical factor in the progression of this disease. Serum paraoxonase-1 (PON1) is an esterase associated with high-density lipoprotein, which clinical interest resides in its ability to prevent or limit the lipid oxidation. The aim of this study was to investigate changes in PON1 activity in the early stages of acute pancreatitis and to find out if its alteration is related with the severity of the disease. To this purpose, we used an experimental model of taurocholate-induced mild and severe acute pancreatitis. Our results showed that serum activity and PON1 concentration decreased 18 h after the induction of a severe acute pancreatitis. In vitro analysis revealed that incubation with oxidized lipids obtained from pancreatitis samples results in the inactivation of the enzyme in a concentration-dependent manner. In addition to oxidative inactivation, we observed by Western blot, an immunoreactive band suggestive of proteolytic degradation of the enzyme, altogether indicating that during severe acute pancreatitis, there is a significant decrease in serum PON1 activity. This decrease is related with inactivation of the enzyme by oxidized lipids, probably followed by proteolytic degradation of the enzyme.

Keywords Paraoxonase-1 · Pancreatitis · Inflammation · Oxidized lipids · Arylesterase

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Introduction

Acute pancreatitis is a multiple-stage disease resulting in substantial morbidity and mortality.[1] Severe acute pancreatitis is a result of a primary damage in pancreatic acinar cells that triggers the intrapancreatic activation of hydrolytic enzymes from their inactive zymogens. This fact induces the rapid autodigestion of the gland and is followed by a local inflammation that could progress to a systemic inflammatory response and, in the worst case, in multi-organic dysfunction. So, in addition to the activation of pancreatic enzymes, the severity of the acute pancreatitis depends on the extent of inflammatory response mediated by cytokines, bioactive lipids, and oxidative stress.[2,3]

The relationship between acute pancreatitis and oxidative stress was first studied by Sanfey et al.[4,5] when using an isolated perfused ex vivo canine pancreas preparation for the induction of three models of acute pancreatitis showing the beneficial effects of free radical scavengers. Other works reported similar results in different models of acute pancreatitis, and now, it is accepted that free radicals are mediators of tissue damage and also play a role in the progression of the disease.[6,7] Even though these highly

reactive molecules are not the inductors of acute pancreatitis, the interaction between oxidative stress and pro-inflammatory cytokines has been suggested to be the major cause leading to amplification of inflammatory cascade and initiation of systemic inflammatory response.[8–10]

One of the main consequences of oxidative stress appears to be the induction of lipid peroxidation. Several studies reported that the level of lipid peroxidation increases in different stages of acute pancreatitis.[11] In spite of the number of studies reporting on the generation of lipid peroxides in pancreas, there are a few studies focused on the importance of these products on the progression of the disease. This is of importance because during pancreatitis, the activation and release of lipolytic enzymes as lipase and phospholipase A2 results in the generation of free fatty acids and lysophospholipids that could easily be oxidized. The final metabolic fate of these oxidized lipids is to be absorbed into the portal system, carried to the liver, and there, incorporated to lipoproteins to be redistributed throughout the body.[12]

For this reason, it is important to identify changes in the enzymatic mechanisms that regulate the levels of lipid oxidation in the lipoproteins during pancreatitis. In this sense, serum paraoxonase-1 (PON1) is an enzyme associated with high-density lipoprotein (HDL), which clinical interest resides in its ability to prevent or limit the oxidation of HDL.[13] This ability is of particular relevance, as HDLs appear to be the primary transporters of oxidized lipids in plasma.[14] This enzyme has been shown to be expressed mainly in liver, and in some inflammatory pathologies such as atherosclerosis or chronic liver diseases where the expression and the activity of PON1 is downregulated.[13,15] This could be important during pancreatitis because the liver also showed changes in the expression of inflammatory mediators.[16] In this sense, a recent study focusing on acute pancreatitis has reported that PON1 activity and HDL level were lower in acute pancreatitis, whereas the mean levels of total cholesterol, low-density lipoproteins, and malonyldialdehyde were significantly higher.[17]

A decrease in PON1 activity could be related with changes in liver expression, but also with the increase in oxidative stress. As what occurs with other antioxidant enzymes, such as superoxide dismutase, the inhibitory action of PON1 has been shown to be associated to an inactivation reaction that results in the lost of the functional active sites in the enzyme.[18] Finally, the effect of circulating hydrolytic enzymes released in the early stages of acute pancreatitis could result in the proteolytic degradation of PON1.

In the present study, we evaluated the changes in the enzymatic activity of PON1 during acute pancreatitis and its relation with the severity of the disease. We also evaluated if the alteration in PON1 activity was related with changes in the protein genetic expression or if it was due to an increase of PON1 degradation related with oxidative processes or the pancreatitis-associated proteolytic activity.

Material and Methods

Animal Model of Acute/Mild Pancreatitis

All experiments were approved by the Institutional Committee of animal care and research (CEEA; University of Barcelona). Thirty-six male Wistar rats (250–300 g b/w) were anesthetized with pentobarbital and randomized in six experimental groups (n=6). The biliopancreatic duct was cannulated through the duodenum, and the hepatic duct was closed by a small bulldog clamp. Severe acute pancreatitis was induced by retrograde infusion into the biliopancreatic duct of 5% sodium taurocholate (Sigma Chemical, St. Louis, MO) in a volume of 0.1 ml/100 g b/w using a *Harvard* '22' infusion pump (Harvard Instruments, Edenbridge, UK).[19] Mild pancreatitis was induced by injecting into the pancreatic duct 1% of sodium taurocholate. Control animals received an intraductal infusion of saline solution (0.9% NaCl). We have previously reported that in this model, systemic inflammation occurs 3 h after the induction of pancreatitis; therefore, this time point is considered to be representative of the early stages of disease.[20] Regarding the 18-h period, we consider this stage as representative for the full-developed disease.

Plasma, serum, and the pancreatitis-associated ascitic fluid (PAAF) were collected 3 or 18 h after induction. Serum and plasma samples were centrifuged, and the supernatant was stored at −40°C until used. Tissue samples of liver, pancreas, and lung were also obtained, immediately frozen, and maintained at −80°C until processed. Liver samples were also obtained and stored for histological analysis.

Lipase Measurement

Pancreatic damage results in an increase of plasma lipase. Plasma lipase was determined by using commercial kits from Randox (Antrim, UK), according to the supplier's specifications.

Myeloperoxidase Assay

We have analyzed myeloperoxidase levels to measure the inflammatory response. Myeloperoxidase was measured photometrically employing 3,3′,5,5′-tetramethylbenzidine as a substrate.[21] Samples were homogenized with 0.5% hexadecyltrimethylammonium bromide in 50 mM phosphate buffer pH 6.0. Homogenates were then disrupted for 30 s using a Labsonic (B.Braun) sonicator at 20% power

and subsequently snap frozen in dry ice and thawed on three consecutive occasions before a final 30 s sonication. Samples were incubated at 60°C for 2 h and then spun down at 4,000×*g* for 12 min. Supernatants were collected for myeloperoxidase assay. Enzyme activity was assessed photometrically at 630 nm. The assay mixture consisted of 20 µl supernatant, 10 µl tetramethylbenzidine (final concentration 1.6 mM) dissolved in dimethyl sulfoxide, and 70 µl H_2O_2 (final concentration 3.0 mM) diluted in 80 mM phosphate buffer pH 5.4. An enzyme unit is defined as the amount of enzyme that produces an increase of 1 absorbance unit per minute.

Assay of PON1 Activity

Total serum arylesterase activity was measured using phenylacetate as substrate.[22] The reaction buffer contained 0.5 ml of 50 mM Tris buffer, pH 7.4, containing 1 mM $CaCl_2$ and 10 mM phenyl acetate (Sigma-Aldrich, Barcelona, Spain). Serum arylesterase (PON1) activity was calculated by subtracting the unspecific calcium-independent arylesterase activity. The latter was determined using 1 mmol/L ethylenediaminetetraacetic acid in the reaction buffer instead of $CaCl_2$, which was used to determine total arylesterase activity. The rate of generation of phenol was monitored at 270 nm.[23] One unit of arylesterase activity is expressed as 1 µmol of phenol produced by the hydrolysis of phenyl acetate per minute.

Concentration of PON1

The serum PON1 concentration was determined by enzyme-linked immunosorbent assay (ELISA).[24] Microtiter plate wells were coated with 100 µL of rat plasma diluted at 1/1,000 with 50 mmol/L carbonate buffer, pH 9.6 and incubated overnight. Afterwards, they were washed with 0.1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS; pH 7.2) for three times, and the remaining absorption sites were blocked with 1% BSA in PBS for 1 h. This was followed by incubation for 1 h with a rabbit polyclonal antibody against PON1 at a dilution of 1:6,400 in PBS with 1% BSA. The wells were washed three times and incubated for 1 h with anti-rabbit IgG peroxidase conjugate (Sigma Chemical Co.; 200 µL per well diluted 1/2,500 in 1% BSA/PBS). Afterwards, they were washed again, and 200 µL of hydrogen peroxide (5 µL diluted in 10 mL citrate buffer, pH 5.0, containing tetramethylbenzidine-HCl) were added. The plate was incubated with shaking for 15 min. Then, the reaction was stopped with sulfuric acid 2 N, and the absorbance at 405 nm was measured with a multiwell plate reader. All the procedures were developed at room temperature. The inter-assay coefficient at variation was 15%.

PON1 RT-PCR Analysis

RNA from 100 mg of liver was extracted using the TRizol® reagent (Invitrogen, Carlsbad, CA). One microgram total RNA was used for amplification using the Invitrogen one-step reverse transcriptase-polymerase chain reaction (RT-PCR) System according to the manufacturer's instructions. The following primers were used: PON1 forward 5′-TGCT GGCTCACAAGATTCAC-3′ and reverse 5′-GGCC TCACTTTCCATGATGT -3′; fragments were amplified using 20 cycles of PCR, each cycle consisting of 15 s at 94°C, 30 s at 55°C, and 1 min at 72°C. The resulting RT-PCR products were electrophoresed on 2% agarose gels with DNA markers, stained with ethidium bromide, and visualized under UV light. GAPDH was used as internal control for stable expression (housekeeping gene) in all experiments: The forward primer was 5′-TCCTCTGACTT CAACAGCGACACC-3′ and the reverse primer was 5′-TCTCTCTTCCTCTTGTGCTCTTGC-3′.

PON1 Immunohistochemistry

Hepatic PON1 expression was assessed by immunohistochemistry with a polyclonal anti-PON1 antibody as previously reported.[25] Serial sections (4 µm thick) of paraffin-embedded samples were deparaffined in xylene and rehydrated through a series of graded alcohols. Sections were then rinsed in PBS (pH 7.4) and H_2O_2 to inactivate endogen phosphatase activity. Sections were blocked in 2% BSA in PBS for 2 h. Antibody against PON1 was diluted 1/300 in PBS–BSA 1% and incubated overnight at 4°C. After the overnight incubation, tissue sections were washed with PBS and incubated with 1:200 biotinylated goat anti-rabbit antibody for 1 h at room temperature. After additional washes, the secondary antibody was detected using the avidin–biotin complex reaction (ABC Elite Kit from Vector Laboratories) and developed with a solution of 0.025% DAB in phosphate buffer (pH 7.4) and 0.005% H_2O_2. The sections were rinsed in PBS and mounted in DPX.

Negative control samples underwent the same procedure without being incubated with the PON1 antibody but with PBS–BSA 1% solution.

Western Blot

To analyze the status of the protein 18 h after induction, HDL fractions were isolated by ultracentrifugation, delipidated with chloroform–methanol solution diluted (3:1), and the obtained protein fraction resuspended in a sodium dodecyl sulfate (SDS)–dithiothreitol (DTT) solution. Then, 10 µg of protein were boiled at 100°C for 5 min under reducing conditions. Proteins were separated on a 10%

SDS-polyacrylamide gel (run at constant voltage, 100 mV for 1 h) and electrophoretically transferred to a nitrocellulose membrane (Hybond P, Amersham Biosciences). After several washes in Tris-buffered saline (TBS, Tris–HCl 50 mM, 150 mM NaCl, pH 7.4), the membrane was incubated with the anti-PON1 antibody in TBS-0.05% nonfat milk at 4°C overnight. The following day, membranes were washed with TBST (0.05% Triton X-100 in TBS buffer) and TBS with 3% nonfat milk. Immunoreactive proteins were detected by incubation with horseradish peroxidase-conjugated antirabbit IgG (dilution 1:4,000; Dako, Denmark) using enhanced chemiluminiscence system (ECL Plus, Amersham Biosciences).

TBARS Levels

Lipid peroxidation was determined by the thiobarbiturate (TBA) reaction measuring the formation of thiobarbiturate acid reacting substances (TBARS). For this purpose, 1 ml of trichloroacetic acid (20%) was added to 1 ml of lipid extract. After mixing and centrifuging, 0.5 ml of a TBA solution in water was added to the supernatant and boiled for 60 min. Optical density was recorded at 530 nm.[26]

Lipid Extraction and Analysis of Arylesterase Activity with Lipids Presence

Lipids were extracted from pancreatitis-associated ascitic fluid (PAAF) using the lipid extraction method described by Bligh and Dyer.[27] Final lipid extract was resuspended in saline solution containing 1% of sodium cholate. To evaluate whether PAAF-extracted lipids had an inhibitory effect of PON1 arylesterase activity, increasing concentrations of lipids were preincubated with plasma from control rats for 1 h at RT. Thereafter, the procedure was performed as described above.

Densitometric Analysis

ImageJ 1.32 software (obtained from http://rsbweb.nih.gov/ij/download.html) was used to quantify the intensities of the bands obtained in Western blots and RT-PCR experiments.

Statistical Analysis

Data have been expressed as mean±SEM. Means of different groups were compared using a one-way analysis of variance. Tukey's multiple comparison test was performed for evaluation of significant differences between groups. Differences were assumed to be significant when $P<0.05$.

Results

Induction of Severe and Mild Pancreatitis

Pancreatic damage results in an increase of plasma lipase. Thus, we analyzed plasma lipase levels to ascertain the induction of pancreatitis. We also corroborated the inflammatory response that occurs during pancreatitis analyzing myeloperoxidase activity.

Administration of sodium taurocholate at 1% and at 5% induces mild pancreatitis and severe acute pancreatitis, respectively. As shown in Fig. 1a, 3 h after induction, plasma lipase levels increased until 1,500 U/L in mild pancreatitis and 5,000 U/L in severe pancreatitis. Lipase levels remained significantly increased 18 h after induction in the case of severe pancreatitis, but they returned to control values in mild pancreatitis.

To evaluate the systemic effects of pancreatitis, we measured the inflammatory process in the lung by measuring MPO activity (Fig. 1b). No significant increases were observed after induction of mild pancreatitis. By contrast, a significant increase in MPO activity was observed 3 and 18 h after induction of severe pancreatitis.

PON1 Arylesterase Activity

The catalytic capacity of PON 1 (measured by arylesterase activity) was analyzed. Total serum arylesterase activity is shown in Fig. 2a. No changes were observed in arylesterase activity 3 h after induction of both mild and severe pancreatitis. By contrast, a significant decrease in arylesterase PON1 activity was observed 18 h after induction, but only in the severe form of acute pancreatitis (Figure 2a).

Concentration of PON1

As what occurs with the enzymatic activity, protein concentration of PON1 shows decreased values 18 h after induction of pancreatitis only in the severe from of the disease. By contrast, no changes were observed at any time point after the induction of the mild acute pancreatitis (Fig. 2b).

PON1 RT-PCR Analysis

To see whether changes in PON1 concentration were due to a decrease of PON1 synthesis, we analyzed liver PON1 RNA expression by RT-PCR. We detected a slight increase of PON1 RNA levels in all samples of severe acute pancreatitis suggesting that PON1 is upregulated 3 h after induction (Fig. 3). This result indicates that there is an increase of genetic expression of the protein, despite the decrease of serum arylesterase activity. This increase is transient, and PON1 RNA levels 18 h after induction

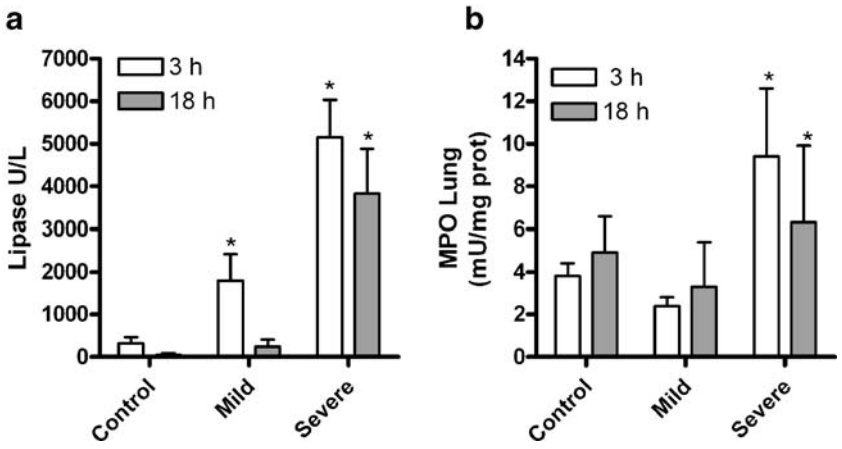

Figure 1 Plasma lipase (**a**) and lung MPO (**b**) activities 3 and 18 h after induction of pancreatitis. Mild pancreatitis courses with a transient increase in lipase activity. By contrast, in the severe form of the disease, lipase shows significant increases 3 and 18 h after induction. MPO in lung significantly increases only in the severe form of the disease. Data are expressed as mean±SEM. *$P<0.01$ vs control.

yielded no differences when compared to controls, as shown also in Fig. 3.

Histological Analysis

In addition to the mRNA expression of PON1, we analyzed the hepatic protein expression by immunohistochemistry. For this purpose, we performed liver serial sections from animals with mild and acute pancreatitis and compared them with controls (Fig. 4). At expected, the labeling pattern revealed the presence of PON1 in the centrilobular vessels of the liver. Three hours after pancreatitis induction, PON1 immunostaining showed a stronger positive stain in most of all parenchymal cells. This increase was more evident in severe acute pancreatitis (Fig. 4f) than in the mild model of the disease (Fig. 4e). By contrast, 18 h after the induction of pancreatitis, the staining was similar in all samples studied as what occurs with the RNA expression (data not shown).

Western Blot

The previous analysis indicates that the decrease in serum PON1 concentration was not caused by an inhibition of PON1 synthesis. To analyze whether the decrease of PON1 concentration in severe pancreatitis (18 h after induction) was related with PON1 proteolytic cleavage, we performed Western blot analysis.

In control animals, SDS-PAGE analysis revealed the presence of two immunoreactive bands of PON1 (Fig. 5). It has been reported that this double pattern represents two oxidation states of the enzyme.[28] We observed that the PON1 staining was remarkably lower 18 h after severe pancreatitis induction. Interestingly, a concomitant increase in a band of lower molecular weight (35 Kd) could also be detected in pancreatitis samples. This fragment possibly represents degradation products of PON1.[29]

Semiquantitative densitometric analysis revealed that in control animals, the cleaved fragment account only for the 25% of the total staining. This percentage increased to 75% after induction of severe pancreatitis (Fig. 5). Consequently, this result indicates that the decrease in PON1 concentration in severe pancreatitis was related with PON1 degradation rather than a downregulation in the protein synthesis.

Lipid Peroxidation

Having seen that the increased proteolytic degradation of PON1 could be related to an increase in oxidation

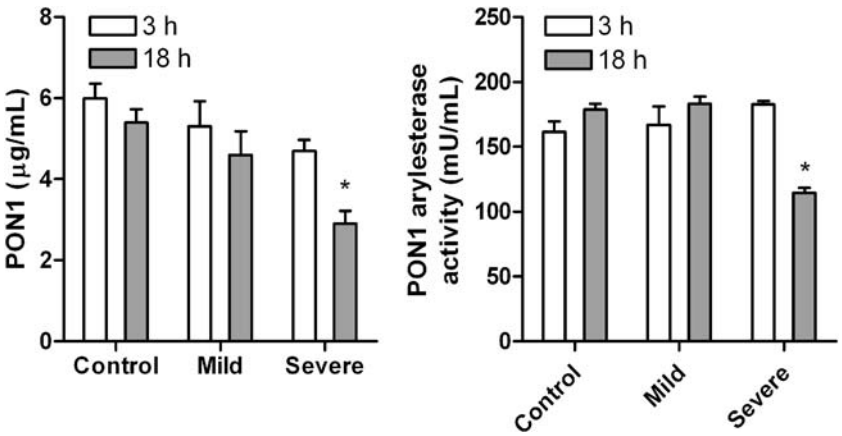

Fig. 2 Serum PON1 concentration and activity. No changes were observed in the mild acute pancreatitis. By contrast, a significant reduction in serum concentration and enzymatic activity was detected in the severe acute pancreatitis 18 h after induction. Data are expressed as mean±SEM *$P<0.01$ vs control.

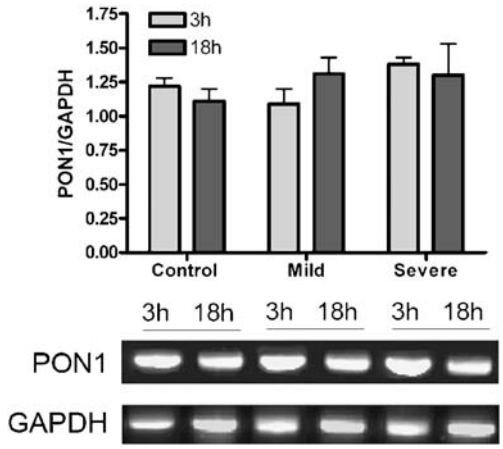

Figure 3 PON1 RNA expression in liver. There are no significant changes in the hepatic expression of the enzyme during acute pancreatitis. Only a moderate and transient increase of PON1 expression could be observed 3 h after induction. The *upper graph* shows the semiquantitative densitometric analysis of the RT-PCR bands. Data are expressed as mean±SEM.

processes,[30] we analyzed the levels of serum lipid peroxidation by assessing TBARS formation.

Results indicated that there were no significant increases in TBARS in the mild model of acute pancreatitis. By contrast, in the severe model of acute pancreatitis, a significant increase was observed 3 h after the induction, and levels of TBARS still remained significantly higher than controls 18 h after the induction (Fig. 6).

Effect of Oxidized Lipids on Arylesterase Activity

Our next aim was to investigate the effect of oxidized lipids generated during severe acute pancreatitis on the arylesterase activity of PON1. Different concentrations of PAAF-extracted lipids were incubated for 1 h with control rat serum. We selected the lipids present in ascitic fluid of pancreatitis because they show a high level of oxidation, and they easily achieve the bloodstream. We observed that

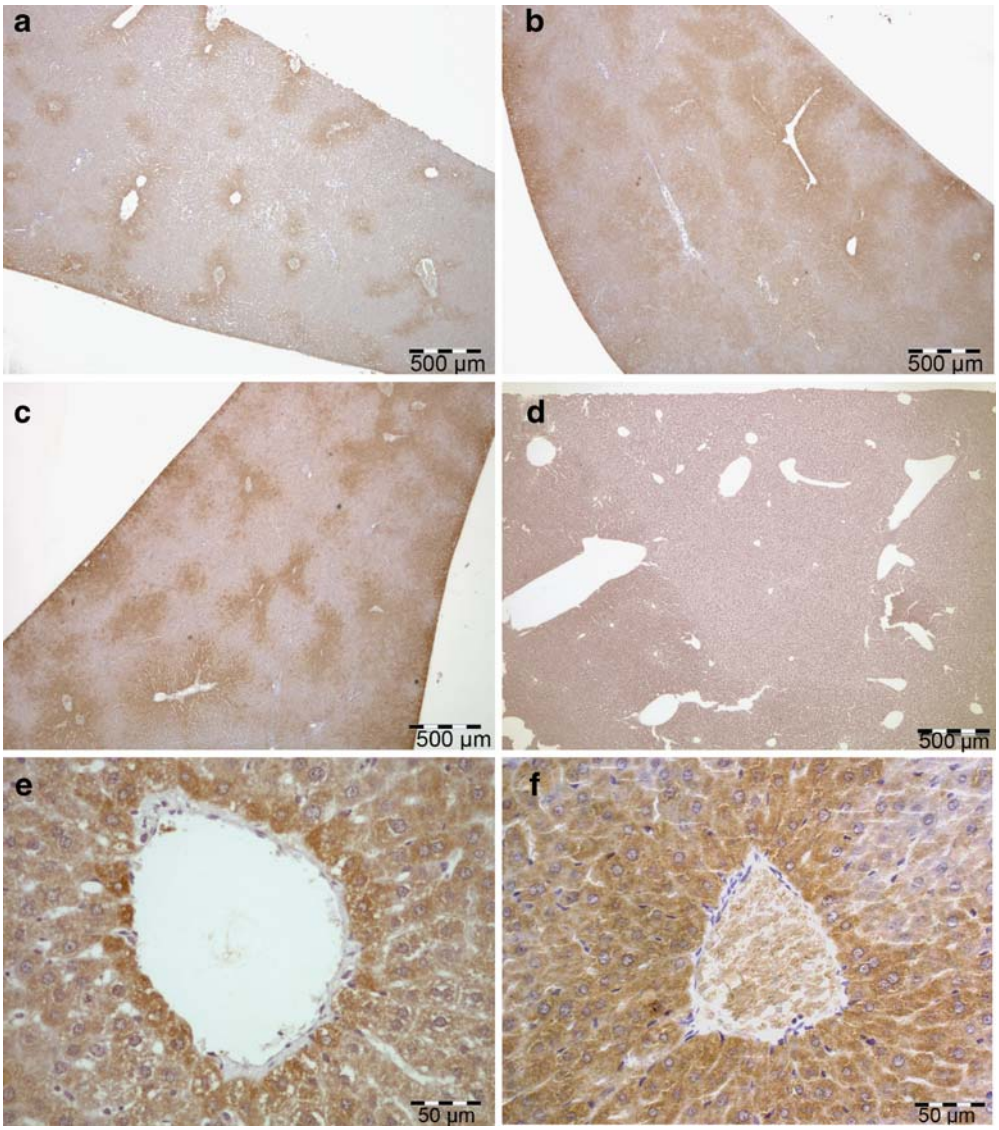

Figure 4 Representative micrographs of PON1 liver immunostaining of control (**a**), mild (**b**) severe (**c**) pancreatitis 3 h after induction. Note the different staining between them in the centrilobular veins of the liver, being the most intense staining the picture corresponding to severe pancreatitis rats. A detail of the liver region analyzed corresponding to a mild (**e**) and severe pancreatitis (**f**) are shown. Image (**d**) shows a negative control for PON1 immunostaining.

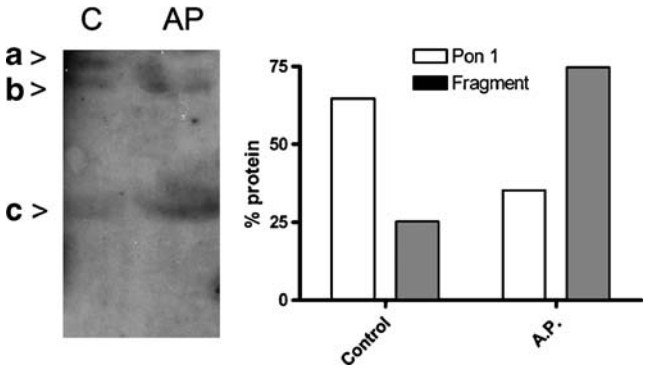

Figure 5 *Left*: Western blot analysis of PON1 18 h after the induction of pancreatitis. The plasma samples were delipidated, and it could be observed that there are two immunoreactive bands of approximately 45 kDa (**a**, **b**) that have been reported to correspond to two different oxidation states of the enzyme. An additional band of lower molecular weight, approximately 35 kDa (**c**) could also be detected in pancreatitis samples. This fragment could represent degradation products of PON1. The *right* figure shows semiquantitative densitometric analysis.

those lipids inhibited arylesterase activity in a dose-dependent manner (Fig. 7). This finding agrees with the fact that the enzyme could be inactivated by oxidized lipids leading to a decrease in PON1 arylesterase activity.

Discussion

The role of oxygen-free radicals in the pathogenesis of acute pancreatitis is well-known. After the initial report of Sanfey et al.,[5] pointing out the involvement of free radicals in different models of pancreatitis, a number of articles have been demonstrating that these highly reactive molecules participate in the local tissue damage and inflammation. By contrast, the involvement of free radicals in the systemic effects of the disease remains unclear. It is known that there is an increase in the plasma concentrations of free radical generating enzymes as xanthine oxidase[31] and in the levels of products of the free-radical activity, such as lipoperoxides.[19,32] Regarding antioxidant enzymes, no significant changes in circulating superoxide dismutase have been reported in the early stages of the disease.[33] However, there are other circulating enzymatic mechanisms involved in the defense against the oxidative damage.

In this sense, PON1 is an enzyme that catalyzes the hydrolysis and inactivation of man-made organophosphates. Obviously, this activity cannot be its primary physiological function, and other roles have been proposed. As it is known that PON1 inhibits lipid oxidation in LDL, it has been suggested that PON1 could protect LDL from oxidative modifications. This protection seems to be related to the ability of PON1 to hydrolyze some oxidized phospholipids and hydroperoxides that are present in oxidized LDL.[34,35] For this reason, we wanted to characterize the alteration of PON1 enzymatic activity during the progression of mild and severe acute pancreatitis, and we also wanted to know if PON1 could be used as a biological index of the severity of the disease.

Our results indicate that as what occurs with SOD,[33] no significant changes in the serum enzymatic activity were observed in the early stages of mild acute pancreatitis. By contrast, we detected a downfall in serum arylesterase

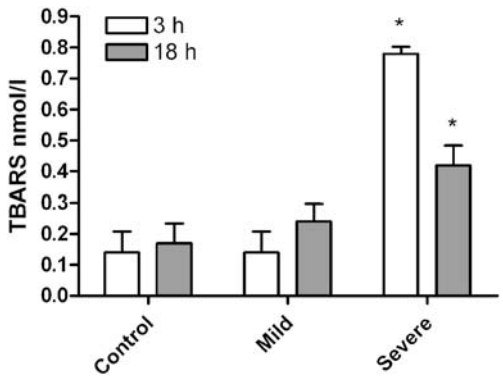

Figure 6 Serum TBARS levels in mild and severe pancreatitis. Results indicate that there was a significant increase in circulating lipid peroxides only in the severe form of pancreatitis. Data are expressed as mean±SEM. *$P<0.01$ vs control.

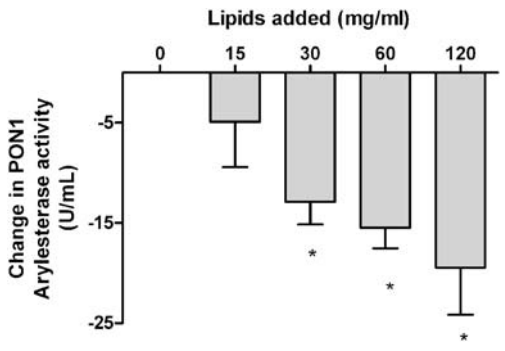

Figure 7 Arylesterase activity assay in the presence of increasing concentrations of lipids obtained from pancreatitis associated ascitic fluid. Results indicate that these lipids have an inhibitory effect on the PON1 arylesterease activity of the enzyme. Data are expressed as mean±SEM. *$P<0.01$ vs control.

activity and protein concentration 18 h after the induction of a severe acute pancreatitis. Similar results have been recently reported[17] using a different model of experimental acute pancreatitis. This decrease renders the circulating lipid fraction more susceptible to free-radical alterations. This is of importance, as oxidized lipids are important modulators of the activation of macrophages and other cells involved in the inflammatory response.[36,37]

The observed decrease in serum PON1 activity could be explained by several factors, including degradation of PON1 due to high proteolytic activity associated with acute pancreatitis or through oxidative inactivation and modification of the enzyme, but it could also be related with an inhibition in hepatic PON1 synthesis.

The latter possibility is related with the fact that liver is the main source of PON1.[28] On the other hand, it has been reported that during the early stages of acute pancreatitis, a sort of acute-phase response occurs resulting in changes in the expression of different proteins in the liver.[38] In addition, during pancreatitis, concentrations of IL-6 increases significantly, and this interleukin acts as inhibitor of liver expression of PON1.[39] However, when we measured the RNA levels (Fig. 3) of PON1 in liver, we observed that there were no significant changes at any time point. In fact, only a slight increase was observed after 3 h of induction of pancreatitis. This result was confirmed by the PON1 immunohistochemistry (Fig. 4) which yielded also the strongest staining 3 h after induction and only in the severe form of pancreatitis.

The other possible explanation for the decrease of PON1 activity is the proteolytic degradation of the protein, considering that during acute pancreatitis, there is an important release of hydrolytic enzymes into the bloodstream. Despite that the liver immunohistochemistry analysis suggests an increase in hepatic PON-1 generation, ELISA results yielded a decrease in PON1 protein concentration in serum, indicating a higher rate of degradation in serum. In addition, Western blot analysis revealed the presence of two bands in the control group. The presence of these bands had been previously described and suggested that they correspond to two different oxidation states[28] or different glycosylation states of the enzyme.[22] Interestingly, there was also another band, corresponding approximately to 35 KDa, which shows an important increase when compared to controls in the severe pancreatitis group. This increase paralleled with a decrease in the intensity of the two bands of high molecular weight.

This result is similar to that obtained by Leviev et al. when analyzing the stability of human PON1 isoforms.[29] The 35 KDa fragment was identified as a proteolytic fragment of the protein. Thus, the decrease observed in both PON1 activity and concentration during severe acute pancreatitis could be explained by the proteolytic degradation of the enzyme. PON1 is a particularly susceptible target for proteases because the active site for lipid peroxide hydrolysis requires a free sulfhydryl group at cysteine 284, and lipid peroxides might react covalently with this site leading to enzyme inactivation.[18] This fact might modify PON1 structure yielding to proteolytic recognition and degradation, following a similar pattern reported to other antioxidant enzymes.[30]

It is noteworthy that in different diseases, serum PON1 activity appears to be inversely correlated to plasma malondialdehyde levels.[40–42] As we observed, this also occurs during pancreatitis, and the increase in MDA levels (Fig. 6) precedes the downfall in PON1 activity. This fact could only be observed in the severe model of the disease.

To further investigate the role of oxidized lipids in the modification of PON1, we analyzed the inhibition of arylesterase activity in presence of increasing concentration of the oxidized lipids obtained from pancreatitis. For this purpose, we used the lipid extract from pancreatitis-associated ascitic fluid, which contains a high concentration of these lipids owing to the effect of lipase and other lipolytic enzymes in the peritoneal cavity.[12] As expected, we observed an inverse correlation between lipid concentrations and arylesterase activity. This result strongly suggests that enzymatic inactivation because of the effect of oxidized lipids, precedes the proteolytic PON1 degradation during severe acute pancreatitis.

Conclusion

In conclusion, our results indicate that during severe acute pancreatitis, there is a significant decrease in serum PON1 activity. This decrease is related with inactivation of the enzyme by oxidized lipids, probably followed by proteolytic degradation of the enzyme.

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Intravital Microscopic Characterization of Suramin Effects in an Orthotopic Immunocompetent Rat Model of Pancreatic Cancer

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Abstract
Objectives We investigated the effect of suramin on tumor growth and spread in an immunocompetent, orthotopic rat model of pancreatic cancer and analyzed the tumor vasculature by intravital microscopy.
Methods and Methods In vitro, rat ductal pancreatic cancer cells (DSL-6A) were incubated with suramin (10–800 μg/ml), and cell proliferation was assessed. In vivo, DSL-6A tumors were induced in the pancreas of Lewis rats. Animals received suramin (60 mg/kg, weekly i.p.) or the vehicle (controls). Treatment started after 3 days. Intravital microscopy after 1, 4, and 8 weeks quantified diameter, density, and permeability of tumor vessels. Primary tumor volume, local infiltration, and metastatic spread were determined at autopsy. Microvessel density was analyzed by immunohistochemistry.
Results In vitro, proliferation was inhibited by suramin up to 95%. In vivo, all controls developed extensive tumor growth and spread. No tumor was detectable in half of the suramin-treated animals after 8 weeks; tumor dissemination was almost completely depressed. Suramin therapy resulted in a complete regression of tumor macrovessels and a significant reduction of microvessel density.
Conclusion Suramin significantly reduces primary tumor growth and dissemination in a clinically relevant rat model of pancreatic cancer and seems to play an important role for the inhibition of tumor angiogenesis.

Keywords Pancreatic cancer · Suramin · Intravital microscopy · Orthotopic rat model

Introduction

Adenocarcinoma of the pancreas is the fifth leading cause of cancer-related death in Western countries. The poor overall 5-year survival rate of less than 5% is due to the tumors propensity toward aggressive tumor growth, early metastasis, and its resistance to cytotoxic agents and radiation. More than 80% of patients are diagnosed with pancreatic cancer at a locally advanced or metastatic stage, which excludes a curative surgical resection.[1] Therefore, novel therapeutic strategies are required to improve the prognosis of patients with pancreatic cancer.

Angiogenesis, the development of vascular supply by sprouting from existing vessels, is a critical step for tumor growth and appears to impact prognosis. Control of angiogenesis with pharmacological drugs represents an alternative approach to the management of solid malignancies. The complex process of angiogenesis involves many growth factors [including vascular endothelial growth factor (VEGF)],[2] extracellular matrix molecules, enzymes, and several cell types in vivo.[3,4] Anti-angiogenic agents decrease tumor growth and metastatic dissemination of numerous solid tumor types.

One potential anti-angiogenic agent is suramin. This polysulfonated napthylurea derivative, originally developed in 1916[5] to treat trypanosomiasis, has been extensively evaluated over the past 15 years as an anticancer agent. On the molecular level, suramin is able to bind to several

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growth factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors alpha and beta (TGF), insulin-like growth factor I (IGFI), and influences growth factor-receptor interactions.[5–8] Suramin can also interfere in processes involved in cellular adhesion and migration and with different signal transduction pathways, and in addition, it has been shown to be a strong inhibitor of angiogenesis.[9] Previous studies from our group have shown that suramin reduces tumor growth and neoangiogenesis in a T-cell-deficient nude mouse model of pancreatic cancer.[10]

To improve the existing knowledge on the therapeutic activity of suramin and to characterize in more detail its anti-angiogenic potential in pancreatic cancer, we tested this drug in vitro by evaluating the effects on proliferation and cell viability of a ductal rat pancreatic cancer cell line. Furthermore, we studied the therapeutic and anti-angiogenic potential of suramin in a clinically relevant, fully immunocompetent, orthotopic rat model of pancreatic cancer. We determined parameters like microvessel density, vessel diameter, and vessel permeability by intravital microscopy with a novel computer-assisted image analysis system for quantitative assessment of microcirculation after 1, 4, and 8 weeks of tumor implantation. Tumor growth and metastatic behavior were analyzed at the autopsy of each animal, and microvessel density of the whole tumor was determined by immunohistochemistry.

Materials and Methods

Cell Line and Culture Conditions

The rat pancreatic adenocarcinoma cell line of ductal origin DSL/6A was obtained from the European Collection of Cell Cultures (Salisbury, UK). The cells were cultured in Waymouth's medium (Invitrogen, Karlsruhe, Germany), supplemented with 10% heat-inactivated fetal bovine serum (FBS-Gold, PAA, Cölbe, Germany), penicillin G (100 U/ml), streptomycin (100 µg/ml; PAA), and amphothericin B (0.25 mg/ml). DSL/6A cells were incubated at 37°C in humified air with 5% CO_2. The medium was replaced twice a week, and cells were maintained by serial passaging after treatment with 0.1% trypsin.

Drug

Suramin was a generous gift from Bayer AG (Leverkusen, Germany), as a sodium salt and stored at room temperature. For in vitro assays and intraperitoneal injection, suramin was first dissolved in 0.9% NaCl (pH 7.5). Further dilutions for in vitro studies were made with Waymouth's medium and filtered before use.

In Vitro Assessment of Cell Proliferation and Viability

To examine the effect of suramin on in vitro cell proliferation, 2×10^5 cells from the DSL-6A cell line were seeded in six-well culture plates in 2 ml of the respective cell culture medium. The medium was changed the next day (day 1), and suramin was added in the following concentrations: 10, 100, 200, and 800 µg/ml. After 72 h (day 4), the cells were trypsinized and counted in a standard hemocytometer. Cell viability was assessed by a colorimetric dye reduction assay with monotetrazolium (MTT, Boehringer, Mannheim, Germany) according to the manufacturer's instructions. Briefly, cells were seeded in 96-well plates at a density of 5×10^3 cells in 0.2 ml of the respective medium. Medium was changed the next day (day 1), and suramin was added as described above. After 72 h (day 4), 10 µl of MTT (5 mg/ml) solution, and after additional 4 h, 100 µl of 10% SDS were added to the cells. The plates were allowed to stand overnight (37°C, 5% CO_2). The change in absorbance measured at 550 nm with an enzyme-linked immunosorbent assay reader (Biotek Instruments Inc., Burlington, VT, USA) has been shown to strongly correlate with the number of viable cells. All experiments were generated in triplicates and repeated three times.

Orthotopic Rat Model of Pancreatic Cancer

As previously described for an orthotopic nude mouse and rat model of pancreatic cancer,[11,12] we used the same transplantation technique in this study. Four-week-old male Lewis rats were obtained from Charles River Laboratories (Charles River, Sulzfeld, Germany). Donor rats were anesthetized with isoflurane (Forene, Abbott, Wiesbaden, Germany) inhalation. Ten million cells of the DSL/6A cell line were injected subcutaneously into the animals' flanks. The animals were killed by a lethal dose of isoflurane inhalation and opening of the thorax after 8 weeks, when the subcutaneous tumors had reached a size of 1 cm in largest diameter. The donor tumors were harvested and minced by a scalpel (no. 11) into small (1 mm^3) fragments. Tumor recipient Lewis rats were anesthetized with isoflurane, followed by intraperitoneal injection of xylazinhydrochloride (Rompun, 12 mg/kg BW; Bayer, Leverkusen, Germany) and Esketaminhydrochloride (Ketanest S, 40 mg/kg BW; Parke-Davis/Pfizer, Karlsruhe, Germany). The animals' abdomens were opened by a midline incision, and the pancreatic tail with the spleen was gently exteriorized. Five small tissue pockets were prepared in the pancreatic parenchyma as an implantation bed with a microscissor (RS-5610 VANNAS; Roboz, Rockville, MD, USA). One donor tumor fragment was placed into each pancreatic tissue pocket in such a way that the neoplastic tissue was completely surrounded by pancreatic paren-

chyma. The pancreas was relocated into the abdominal cavity, which was then closed in two layers with 3-0 absorbable suture (Vicryl, Ethicon, Germany). For pain relief, a subcutaneous injection of Carprofen (Rimadyl, 4 mg/kg BW; Pfizer) was given after surgery.

In Vivo Treatment with Suramin

The animals were allocated randomly into a treatment group and a control group, and intravital microscopy was done 1, 4, and 8 weeks after tumor induction (12 rats per group and time point). The dosage of suramin administration was chosen according to the references in the literature and the manufacturers' recommendation and had been tested in previous studies.[10,13] Treatment with suramin (60 mg/kg weekly i.p.) or the vehicle (0.9% saline) was started 3 days after orthotopic tumor implantation. Suramin was administered by intraperitoneal injections twice per week in the first 2 weeks and once a week subsequently. The rats were monitored daily to evaluate their clinical conditions.

Intravital Microscopy

Intravital microscopy of the pancreas was studied as previously described.[14–18] Briefly, the animals were anesthetized with Rompun and Ketamine as described above. Polyethylene catheters (inside diameter, 0.5 mm; B.Braun, Germany) were inserted into the right jugular vein and the left carotid artery for monitoring heart rate, blood pressure, and injection of substances needed for intravital microscopy. The animals were placed on a heated operating table and relaparotomized through a small midline incision. The spleen and the tail of the pancreas with the growing tumors were mobilized and exteriorized, placed in an immersion chamber with Ringer's lactate maintained at 37°C, and positioned under a fluorescence microscope (Leitz, Wetzlar, Germany) with a heat protection and excitation filter (450 to 490 nm) connected to a video recorder. After exposure of the pancreas, 1 ml/kg body weight 0.02% rhodamine 6G (Sigma-Aldrich, Deisenhofen, Germany) was injected intraarterial, and after a 5-min stabilization period, five randomly chosen regions on the tumor site were recorded for off-line analysis of vessel density and vessel diameter. Capillary permeability was determined after an intraarterial injection of 0.2 ml of 5% FITC-Dextran (molecular weight, 150,000; ICN, Aurora, OH, USA). Heart rate and arterial pressure were continuously monitored during intravital microscopy. Only the data from animals with stable cardiovascular conditions were included in the analysis of the microcirculatory parameters to avoid bias possibly resulting from systemic cardiovascular derangement. Exclusion criteria were mean arterial pressure <80 mmHg, PO_2 <80 mm Hg, PCO_2 >50 mmHg, and pH <7.3 or >7.5.

Image Analysis

All images were analyzed offline using the software CAP-Image (Zeintl, Heidelberg, Germany).[19] This computer-assisted video frame analysis system for dynamic capillaroscopy allows the off-line analysis of a variety of microcirculatory parameters and calculates vessel density, vessel diameter, and capillary permeability from the changes in perivascular density caused by extravasation of the fluorescent-labeled dextran over a defined observation period. Details of the equipment, techniques, and methods of calculating the microcirculatory parameters have been described elsewhere.[18]

Quantification of Tumor Growth and Spread

All animals underwent autopsy after intravital microscopy. The perpendicular diameters of the primary orthotopic tumor were measured with calipers, and the volume was calculated using the following formula: volume=length×width×depth/2. A dissemination score was used to assess local tumor infiltration and distant metastasis.[11,12] Local infiltration was determined at the following sites: spleen, stomach, liver (hilus), kidney, retroperitoneum, diaphragm, mesentery loops, and abdominal wall. Isolated tumor nodules with no anatomic connection to the primary tumor were considered distant metastases. The sites of evaluation included liver, kidney, spleen, lung, diaphragm, mesentery, retroperitoneum, mediastinum, and the suture line. Tumor dissemination was quantified as follows: Each manifestation of tumor infiltration or metastatis was counted with one point. Additional points were awarded for massive local infiltration (e.g., including more than half of the circumference of the spleen), multiple metastatic nodules (more than one in parenchymal organs; more than ten in diaphragm, mesentery, and retroperitoneum), and metastatic nodules >50 mm^3. Clinical consequences of tumor growth were incorporated into this scoring system: formation of ascites (two points if volume >5 ml), development of jaundice, ileus, and cachexia. The primary tumor and all sites of potential infiltration or metastasis were harvested, fixed in 4% formaldehyde, and embedded in paraffin. Then, 3-μm thick tissue sections were obtained and stained with hematoxylin and eosin for microscopic examination. The sections were reviewed to confirm the findings of the macroscopic dissemination score.

Microvessel Density

Anti-CD31 was used as an endothelial marker to highlight intratumoral microvessels. Immunohistochemical staining was performed on paraffin-embedded tissue of the collected primary tumor tissue. Three-micrometer-thick

sections were cut, using a rotation microtom (Leica, RM2125RT). The sections were deparaffinized in xylene and rehydrated in graded alcohols and distilled water. After antigen retrieval with 0.01% ethylenediaminetetraacetic acid, pH 8.0, endogenous peroxidase activity was blocked with 1% hydrogen peroxide in distilled water for 25 min followed by washing with distilled water and finally phosphate-buffered saline (PBS)+0.1% Tween for 5 min. To bind nonspecific antigens, the sections were incubated with 1× Power Block (BioGenex, San Ramon, CA, USA) for 5 min. The primary antibody was a purified anti rabbit CD-31 (PECAM) and was purchased from Santa Cruz Biotechnology, (Santa Cruz, CA, USA). Antibody dilution was 1:150 in PBS for 30 min at 37°C. As a negative control, sections were incubated with PBS instead of the primary antibody. This was followed by incubation with biotinylated anti-rabbit immunoglobulin G (1:200, Santa Cruz) for 30 min at 37°C and after washing with PBS+Tween by peroxidase-conjugated avidin-biotin complexes (KPL, Gaithersburg, MD) and 3,3′-diaminobenzidine (Sigma, DE). The sections were then counterstained with Mayer's hematoxylin, upgraded alcohols, mounted and analyzed by standard light microscopy. Microvessel density was quantified as described by Weidner.[20] Areas of highest neovascularization were found by scanning the sections at a magnification of ×100; individual microvessel counts were made on ten fields at ×200 magnification (≈0.74 mm^2 per field).

Statistical Analysis

All results are presented as mean±standard error of the mean (SEM). Continuous normally distributed variables were analyzed by the Student's *t* test. Discontinuous variables (dissemination score, microvessel density) were analyzed by the Mann–Whitney rank sum test. A p value<0.05 was considered as statistically significant.

Results

Effect of Suramin on Proliferation and Cell Viability In Vitro

The effect of suramin on the proliferation and viability of the rat pancreatic cell line DSL-6A was studied over a time period of 72 h. The chemotherapeutic agent was applied to the cells using four different concentrations: 10, 100, 200, and 800 µg/ml. Figure 1 shows proliferation and viability changes during drug treatment. Suramin inhibited the proliferation of the ductal pancreatic cancer cell line DSL-6A in a dose-dependent manner. The highest concentration of suramin reduced cell proliferation to less than 10% in this cell line. Loss of cell viability was not detected by low concentrations of suramin, but viability was reduced at high concentrations up to 60% (Fig. 1b)

Effect of Suramin on Tumor Growth and Spread

All control animals developed extensive tumor growth (9,118±3,011 mm^3), local infiltration, and distant metastasis. In contrast, there was no tumor detectable in half of the suramin-treated animals after 8 weeks; the other animals harbored small tumors (56±38 mm^3; p<0.001; Fig. 2a). Tumor dissemination in treated animals was almost completely depressed after 8 weeks (0.4±0.2 points vs 10.3±2.8 points in control animals; p<0.05; Fig. 2b).

Effect of Suramin on Tumor Macro- and Microvasculature

Pancreatic carcinomas of control animals displayed irregular blood vessels, which are characteristic for tumor macrovasculature (Fig. 3). Vessel permeability (Fig. 4) was significantly higher in suramin-treated animals after 1 and 4 weeks in comparison to controls (113.8±3.2 gray-scale points vs 105.6±1.4 points after 1 week, and 122.6±

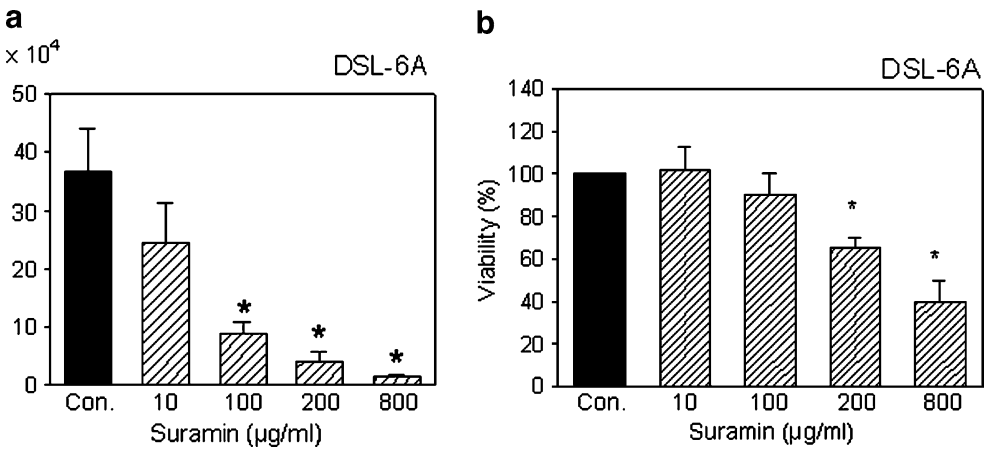

Figure 1 **a** In vitro effects of Suramin on proliferation of DSL-6A pancreatic cancer cells as assessed by cell count after 72 h of incubation. **b** In vitro effects of Suramin on viability of DSL-6A pancreatic cancer cells as assessed by MTT assay after 72 h of incubation.

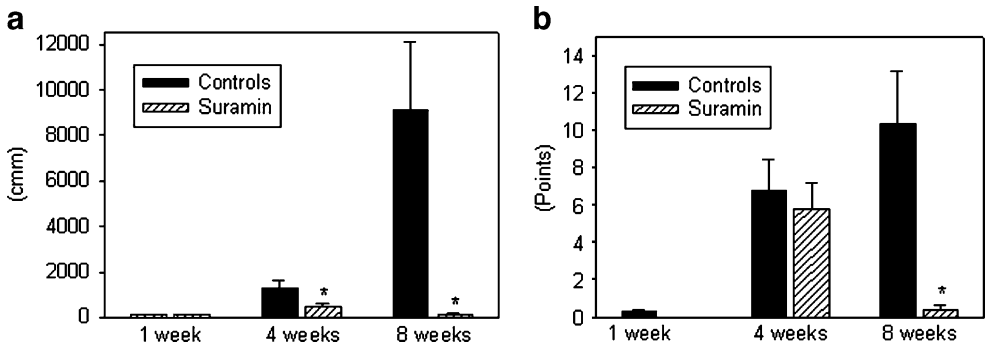

Figure 2 Primary tumors were derived from the rat ductal pancreatic cancer cell line DSL-6A. **a** The volumes of the orthotopic primary tumors in controls and animals treated with Suramin were assessed after 1, 4, and 8 weeks (n=12 per group and time point; *p<0.05). **b** Local infiltration and metastatic spread in controls (n=8) and animals treated with Suramin were evaluated after 1, 4, and 8 weeks and summarized in a dissemination score (n=12 per group and time point; *p<0.05).

2.8 grayscale points vs 112.8±2.4 points after 4 weeks, p< 0.05, respectively; 100 grayscale points are defined by normal pancreatic tissue).

Vessel diameter (Fig. 5) and vessel density (Fig. 6) measured by intravital microscopy showed no significant differences in suramin-treated animals vs control animals after 1 and 4 weeks (vessel diameter: 20.1±3.2 vs 30.9± 4.6 µm after 1 week, and 29.8±5.1 vs 28.4±4.0 µm after 4 weeks; vessel-density: 82.4±5.8 vs 72.4±7.9/cm after 1 week, and 83.6±7.0 vs 80.3±5.1/cm after 4 weeks).

Eight weeks of suramin therapy resulted in a complete regression of tumor macrovessels. Permeability, diameter, and density of tumor blood vessels (Figs. 4, 5, and 6) could therefore not be determined at this time point by intravital microscopy.

Microvessel density, as quantified by immunohistochemistry, revealed no differences between suramin treatment and control groups after 1 and 4 weeks, whereas 8 weeks of suramin treatment led to a significant reduction of microvessels in the remaining small tumors (30.2±13.4/0.74 vs 89.4±5.4/0.74 mm^2; Fig. 7).

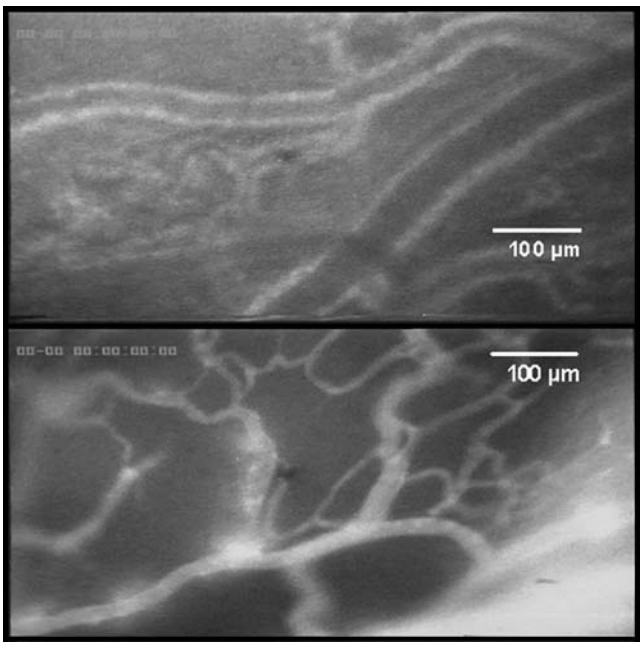

Figure 3 Primary tumors were derived from the rat ductal pancreatic cancer cell line DSL-6A. Irregularly shaped tumor (macro) vessels as visualized by intravital microscopy in an untreated control animal (×200).

Discussion

Suramin is a drug with a long history. Initially developed to treat sleeping sickness and onchoceriasis, the drug exhibited anti-tumor activity first in the treatment of patients with HIV-associated lymphomas and Kaposi's sarcoma. This raised the possibility of using suramin in the therapy of solid tumors. The ability of suramin to decrease proliferation rates in vitro has been demonstrated in several types of cancer cells, including cells derived from stomach cancer, esophageal cancer, breast cancer, and non-small-cell lung cancer.[21–24] The anti-angiogenic effect of

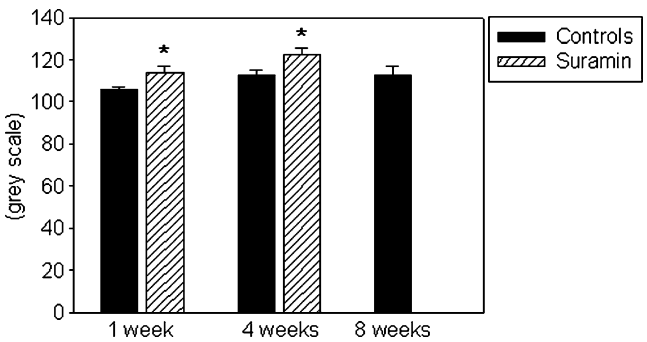

Figure 4 Primary tumors were derived from the rat ductal pancreatic cancer cell line DSL-6A. Tumor vessel permeability was evaluated by intravital microscopy after 1, 4, and 8 weeks (n=12 per group and time point; *p<0.05).

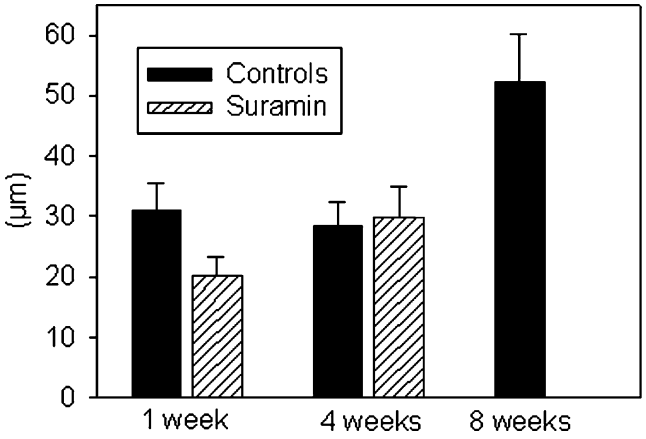

Figure 5 Primary tumors were derived from the rat ductal pancreatic cancer cell line DSL-6A. Tumor vessel diameter was evaluated by intravital microscopy after 1, 4, and 8 weeks (n=12 per group and time point; *p<0.05).

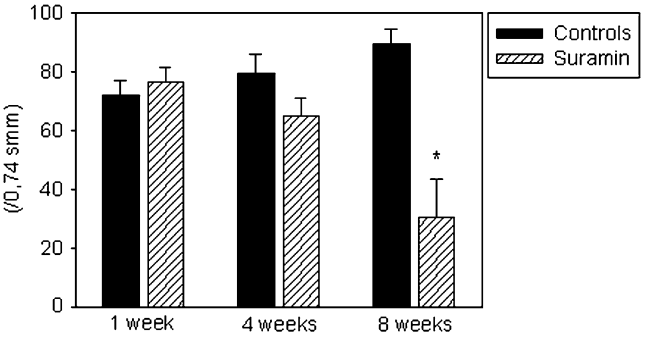

Figure 7 Primary tumors were derived from the rat ductal pancreatic cancer cell line DSL-6A. Tumor microvessel density was evaluated by immunohistochemistry for the endothelial cell marker CD31 after 1, 4, and 8 weeks (n=12 per group and time point; *p<0.05).

suramin has been analyzed both in vitro and in vivo and documented in the chick chorioallantoic membrane assay and in a bFGF-induced model with gel sponges subcutaneously implanted in mice.[25,26] Our group showed recently the inhibitory effect of suramin on tumor growth, metastasis, and angiogenesis in a orthotopic nude mouse model of pancreatic cancer.[10] The present study is the first to visualize the effect of suramin on tumor blood vessels in a clinically relevant, fully immunocompotent model of pancreatic cancer in rats by intravital microscopy. Our in vitro results demonstrated the inhibitory action of suramin on the rat pancreatic cancer cell line DSL-6A (Fig. 1). Proliferation was decreased dose-dependently by suramin and cell viability was influenced at high doses of suramin treatment. These results indicate that suramin acts in a cytostatic, rather than in a cytotoxic manner.

The effects of suramin were further evaluated in an orthotopic immunocompetent rat model of pancreatic cancer, which was established in our laboratory.[12] The in vivo results showed that suramin had an influence on

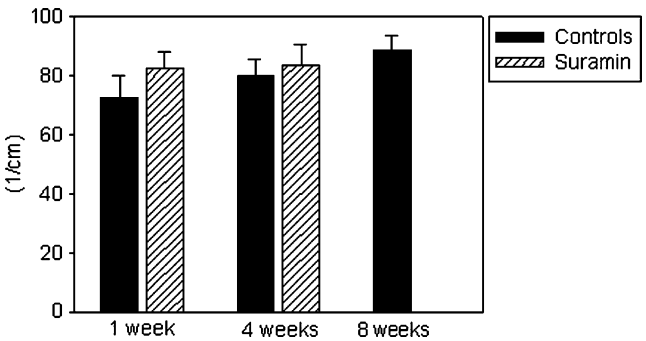

Figure 6 Primary tumors were derived from the rat ductal pancreatic cancer cell line DSL-6A. Tumor (macro) vessel density was evaluated by intravital microscopy after 1, 4, and 8 weeks (n=12 per group and time point; *p<0.05).

primary tumor growth, metastasis, and microvessel density in tumor bearing rats. The volumes of DSL-6A tumors in the treated groups were significantly smaller than those of the control animals after 4 and 8 weeks, and in half of the suramin-treated animals, there was no tumor detectable after 8 weeks. Dissemination in treated animals was almost completely depressed after 8 weeks. Intravital microscopy showed that control animals displayed irregular tumor blood vessels. It has been shown that tumor blood vessels have multiple abnormalities, like sprouting, proliferation, and remodeling, resulting from the bizarre environment in which they grow.[27] Treatment of tumors with angiogenesis inhibitors can stop new vessel growth, cause regression of some vessels, and normalize others. Suramin therapy resulted in a complete regression of tumor macrovessels and a significant reduction of microvessel density. This results confirm that suramin inhibits angiogenesis by affecting tumor blood vessels. It is known that suramin interacts with a number of peptide growth factors, such as PDGF and bFGF,[8,28] and acts as a functional VEGF-antagonist by binding to VEGF receptor-2 (KDR).[9] We recently reported the inhibitiory effect of suramin on the VEGF-level in human pancreatic cancer cells, and these results strongly argue that tumor vessel permeability was significantly higher in treated animals vs control animals.

We did not note any apparent side effects of suramin such as a change in food intake or activity in our study. As a surrogate marker of toxicity, animal weights were observed throughout the in vivo study and were not found to be different at autopsy in any group. Other investigators claim that the clinical use of suramin is limited by its toxicity, which is mainly characterized by the development of a polyneuropathy.[25] As a consequence of suramin's toxicity, a new generation of suramin analogs is currently being investigated and seems to be a promising approach to circumvent toxic side effects while preserving the advantages of suramin's anti-tumor activities.[29,30] A reasonable alternative to suramin analogs is the application of suramin

in low concentrations. Recently, it has been reported that low-dose administration of suramin as a chemosensitizer was able to improve the effects of chemotherapy in a mouse model of human breast cancer without enhancing host toxicity. However, this concept of a combination therapy has yet to be investigated in pancreatic cancer.

Conclusion

The present report demonstrated an inhibitory effect of suramin on proliferation and viability of the rat pancreatic cancer cell line DSL-6A in vitro. In a clinical relevant immunocompetent orthotopic rat model of pancreatic cancer, therapy with suramin resulted in a decrease of tumor size and metastatic spread. In addition, we assumed an anti-angiogenic effect of suramin as verified by the reduction of microvessel density in primary tumors of animals. In summary, our results strongly argue for further investigation of suramin as a part of novel treatment strategies for human pancreatic cancer.

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Portal Vein Resection in Surgery for Cancer of Biliary Tract and Pancreas: Special Reference to the Relationship Between the Surgical Outcome and Site of Primary Tumor

Isao Kurosaki · Katsuyoshi Hatakeyama · Masahiro Minagawa · Daisuke Sato

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Abstract
Background Early and late outcomes after superior mesenteric-portal vein resection (VR) combined with pancreaticoduodenectomy, major hepatectomy, or both for pancreaticobiliary carcinoma were retrospectively evaluated. VR is the most frequently used vascular procedure in this field, but an exact role of VR has not been compared according to the primary site of tumor.
Materials and Methods Postoperative outcomes were compared between surgery with and without VR in each of the three disease-based groups: hilar cholangiocarcinoma and intrahepatic cholangiocarcinoma with hilar extension (HIC, 56), middle and distal cholangiocarcinoma and gallbladder carcinoma (DGC, 118), and pancreatic head adenocarcinoma (PHC, 77).
Results VR was performed in 19.6% of HIC, 8.5% of DGC, and 45.5% of PHC. In-hospital death was 7.1% (4 of 56) patients with VR (3 of DGC and 1 of PHC). Operations with VR in DGC showed a larger amount of blood loss and more increased ratio of R1operation than those with no VR. In HIC, DGC, and PHC, median survival time of patients with VR was 37, 6.8, and 20 months and that of patients without VR was 42.9, 28.6, and 20.3 months, respectively. VR did not affect survival either in HIC or in PHC; however, in DGC, VR was accompanied with dismal outcome compared with no VR ($p=0.001$).
Conclusions Aggressive surgery with VR can be justified both in HIC and in PHC but should not be recommended for DGC. Surgical outcomes of VR differed considerably, depending on the sites of the primary tumor.

Keywords Portal vein resection · Morbidity · Mortality · Biliary tract cancer · Pancreatic cancer

Introduction

Resection of superior mesenteric-portal vein (VR) is the most frequently used vascular procedure in aggressive surgery for cholangiocarcinoma,[1–8] gallbladder cancer,[8,9] and pancreatic cancer.[10–26] Especially in surgery for pancreatic cancer, VR is an indispensable surgical technique and VR itself does not worsen the postoperative survival.[15,16,18–25] However, clear discrimination from tumor adherence to cancer invasion is often difficult.[11,15,22] Several reports pointed out that the surgical outcome after VR is closely related to the depth of cancer invasion into the wall of the portal vein,[11,12,26,27] and patient survival after VR is preferable to cases without microscopic invasion compared to those with the invasion.[16,20,28] Furthermore, it was reported that tumors requiring VR increases the likelihood of association with margin-positive resection.[21,19] Considerable variance regarding the incidence of concomitant VR, 0–28%, was pointed out from a domestic survey of seven large volume centers in Germany.[29] This variance may involve differences in surgical strategies for pancreatic cancer.[30,13]

Similarly, in hilar cholangiocarcinoma, the incidence of VR combined with aggressive surgery varied among large-volume studies, ranging from 6.3 to 43%.[2,3,5,6,31–34] As for survival after VR, Neuhaus et al.[3,4] said that VR more frequently occurred in left-sided hepatectomy and was accompanied by favorable outcome when compared with no VR. Also, Hemming et al.[6] revealed that there was no difference in survival between patients who had VR and

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those who did not. Contrary to this view, Ebata et al. demonstrated in their series, which included the largest number of VRs, that there was negative prognostic factor regardless of the presence or absence of microscopic invasion.[3] In gallbladder cancer and distal-sided bile duct cancer, a few studies focus on VR.[7–9,35]

Although serious complications related to VR were documented only in a few reports,[24,36,37] it is generally considered a safe vascular procedure that does not exacerbate short-term results. Aggressive surgery for cholangiocarcinoma, gallbladder carcinoma, and pancreatic head adenocarcinoma involve the potential risk of VR intrinsically. However, differences in postoperative outcomes after VR have not been compared based on the site of the primary tumor. In the present study, we have evaluated short- and long-term outcomes of VR combined with aggressive surgery for biliary tract and pancreatic carcinomas, and we have discussed the variance of clinical implication of VR based on differences in the primary disease.

Materials and Methods

From 1987 to 2005, 56 patients underwent superior mesenteric and portal vein resection combined with radical surgery for cholangiocarcinoma, gallbladder carcinoma, and invasive ductal carcinoma of pancreas. Operations performed concomitant with 56 VRs were major hepatectomy (more than 2 hepatic sections) with hilar dissection (n=11), pancreaticoduodenectomy with or without gastrectomy (n=38), or hepatopancreaticoduodenectomy (n=7). For comparative analyses of morbidity, mortality, postoperative liver function, and survival outcomes in the 56 patients with VR, 195 patients who underwent major hepatectomy (62), pancreaticoduodenectomy (118), or hepatopancreaticoduodenectomy (15) without VR during the same period were reviewed and investigated as the control. Operations with only minimal probability or necessity for VR were excluded from the analyses to ensure fair and accurate comparison: bile duct resection, cholecystectomy with partial hepatectomy, or partial hepatectomy without the hilar dissection. Totally, this retrospective study included 251 patients (56 with VR and 195 without VR) who underwent major hepatectomy, pancreaticoduodenectomy, or hepatopancreaticoduodenectomy with curative intent.

This study focused on VR and investigated the difference in surgical results of VR according to site of the primary tumor. For this, the 251 tumors were firstly dichotomized to pancreatic head carcinoma (PHC, n=77) and biliary tract carcinoma (174), and then the latter was divided into two disease-based groups: HIC (n=56), hilar cholangiocarcinoma (49) and intrahepatic cholangiocarcinoma involving the porta hepatis (7), and DGC (118), middle and distal cholangiocarcinoma (68) and gallbladder carcinoma (50). Preoperative variables, surgical findings, postoperative complications within the same hospital stay, and survival were analyzed and compared between patients with VR and those without in each of the three disease-based groups. Operative mortality and in-hospital deaths were defined as death within 30 days and within the same hospital admission, respectively.

Pathologic characteristics of primary tumor, including extent of tumor, lymph node metastasis, final tumor stage, surgical margin status, and tumor differentiation were described according to the American Joint Commission on Cancer (AJCC) classification. Microscopic invasion of the vein was defined as positive when a tumor infiltrated into the adventitia of the vein or beyond it. Continuous variables were compared using the Mann–Whitney U test and categorical variables with a chi-square test or Fisher's exact test. Survival probabilities were calculated from date of surgery and estimated using the Kaplan–Meier method and compared by the log-rank test (significant difference, $p<0.05$). Cox regression was used to determine independent predictors of outcome, using survival as the dependent variable and factors significant on univariate analysis as covariates. Operative mortality was excluded from survival analyses. Statistical calculations were performed using Statistical Package for the Social Sciences (SPSS), version 9.0 (SPSS, Chicago, IL, USA).

Vascular Procedures for Portal Vein

The type of surgery according to the site of the primary tumor is listed in Table 1. VR was performed when the obvious involvement of the vein was demonstrated by preoperative imaging examination or when the tumorous invasion to the vein wall was suspected during surgery. To perform an en-bloc resection, the tight adhesion of the vein to tumor was not separated before the vein resection. VR was carried out in 11 (19.6%) patients of HIC, in 10 (11.8%) of DGC (5 each in the middle and distal cholangiocarcinoma and in the gallbladder carcinoma), and in 35 (45.5%) of PHC (Table 1); 44 (78.6%) were segmental resections and 12 (21.5%) were tangential resections. About 75% of 56 vascular procedures were performed by the first author (I.K.). Vein graft was used for reconstruction in two patients. A median length±standard deviation of excised portal vein was 3.0±1.2 cm (1–6 cm) in 40 segmental resections (length of the remaining four cases before 1994 were not stated in the operation record). Median time of the portal clamping was 20±5.7 min (11–

Table 1 Operations Performed in 251 Patients

Type of Operation	VR (+), *n*=56	VR (−), *n*=195	Total, *n*=251
Major hepatectomy	11 (15%)	62 (75%)	73
(Extended) Left hemihaptectomy	2	20	
Left trisectionectomy	1	1	
(Extended) Right hemihepatectomy	7	39	
Right trisectionectomy	1	2	
Pancreaticoduodenectomy	38 (24.4%)	118 (75.6%)	156
Pyloric-preserving procedure	12	51	
With partial hepatectomy	–	20	
Hepatopancreaticoduodenectomy	7 (31.8%)	15 (68.2%)	22
Pancreaticoduodenectomy + extended right hemihepatectomy	7	13	
Pancreaticoduodenectomy + left hemihaptectomy	–	2	

Major hepatectomy, hepatectomy of 2 or more than 2 sections; VR, superior mesenteric vein resection or portal vein resection

40 min) in 35 patients (the clamping time was not available in 9 cases before 1994). In all 44 patients who underwent the segmental resection, the end-to-end anastomosis of the vein was carried out by the running suture technique with 5–0 or 6–0 nonabsorbable threads.

In this series, preoperative portal embolization technique was not used. In addition, the intraoperative catheterization into both hepatic artery and portal vein was performed for the adjuvant liver perfusion chemotherapy with 5FU in 14 patients with pancreatic carcinoma: 4 patients (11.4%) of VR group and 10 (23.8%) of no VR group.

Results

Preoperative and Operative Findings

The average age, male-to-female ratio, percent of patients with jaundice (total bilirubin level >3 mg/dl), hemoglobin concentration, and serum total protein and albumin levels were similar between patients with VR and those without, in each of the three disease-based groups (Table 2). In DGC, the frequency of VR did not differ from gallbladder carcinoma (10%) to middle and distal cholangiocarcinoma (7.4%).

Table 2 Comparison of Preoperative and Intraoperative Variables Between Surgeries With and Without VR

	HIC		DGC		PHC	
	VR, *n*=11	No VR, *n*=45	VR, *n*=10	No VR, *n*=108	VR, *n*=35	No VR, *n*=42
Age (mean±SD)	64.1±10	63.8±11	66.4±8.9	66.5±10	66.2±9.2	64.1±8.8
Female % (*n*)	36.4 (4)	33.3 (15)	40.0 (4)	50 (54)	45.7 (16)	42.8 (18)
Preoperative jaundice % (*n*)	63.6 (7)	86.7 (39)	90.0 (9)	67.6 (73)	82.9 (29)	85.7 (36)
Hemoglobin g/dl [median (IQR)]	13.1 (11.6–13.9)	12.7 (11.2–13.5)	12.8 (11.8–13.7)	12.6 (11.8–13.4)	12.6 (11.9–13.4)	12.4 (11.4–13.4)
Total protein mg/dl [median (IQR)]	7.1(6.5–7.6)	7.0 (6.6–7.5)	7.3 (6.7–7.9)	7.1 (6.7–7.4)	7.2 (6.8–7.5)	6.9 (6.6–7.5)
Albumin mg/dl [median (IQR)]	3.9 (3.6–4.2)	3.8 (3.5–4.1)	4.0 (3.5–4.3)	3.8 (3.5–4.1)	4.1 (3.6–4.5)	4.0 (3.7–4.2)
Operation						
Major hepatectomy	81.8 (9)	91.1 (41)	20.0 (2)	19.4 (21)	–	–
Hepatopancreaticoduodenectomy	18.2 (2)	8.9 (4)	50.0 (5)*	10.2 (11)	–	–
Pancreaticoduodenectomy			30.0 (3)	70.4 (76)	100	100
Operation time [min, median (IQR)]	560 (480–670)	570 (520–627)	645 (582–735)**	550 (480–700)	510 (480–634)	510 (450–594)
Blood loss [ml, median (IQR)]	1,600 (1,300–3,700)	1,595 (1,095–2,376)	1,601 (1,499–2,398)***	1,280 (700–1,917)	1,200 (800–1,950)	1,130 (845–1,413)

HIC Proximal cholangiocarcinoma and intrahepatic cholangiocarcinoma with hilar extension; *DGC* middle and distal cholangiocarcinoma and gallbladder carcinoma; *PHC* pancreatic head adenocarcinoma; *VR* superior mesenteric vein resection or portal vein resection; *IQR* interquartile range; pancreaticoduodenectomy including pylorus preserving type

*0.002

**0.081

***0.027

Hepatopancreaticoduodenectomy was carried out in a total of 22 patients, in whom 32% (7) underwent combined portal vein resection. Of the 22 hepatopancreaticoduodenectomy, 16 (73%) were carried out for DGC: 7 (10.3%) for middle or distal cholangiocarcinoma and 9 (18.0%) for gallbladder carcinoma (no significant difference). The estimated blood loss in DGC was significantly higher in patients with VR compared with those without (p=0.027).

Liver Function After Surgery

The maximal levels of serum aspartate aminotransferate (AST) and alanine aminotransferate (ALT) in VR group were 366 and 310 IU/l in HIC, 148 and 119 IU/l in DGC, and 69 and 65 IU/l in PHC, respectively. Maximal total bilirubin (TB) levels were 3.4 mg/dl in HIC, 3.1 mg/dl in DGC, and 69 and 65 IU/L in PHC. Regardless of VR or no VR, the maximal AST and ALT values were higher in HIC and DGC compared with that in PHC. When dividing the 251 patients into two groups who underwent surgery with major hepatectomy (156) or without major hepatectomy (95), median values of AST, ALT, and TB showed a significant increase in patients with major hepatectomy (380, 325 IU/l, and 5.7 mg/dl) compared to those without (210, 208 IU/l, and 3.9 mg/dl; p=0.001, 0.030, and <0.001, respectively). However, VR did not influence maximal values of AST, ALT, and TB after surgery in any one of the three disease-based groups (Table 3).

Complications After Surgery

Of the 251 patients, 6% (15) had operative or in-hospital deaths. The operative death was recorded in two (3.6%) patients of VR group and in four (2.1%) patients of no VR, and in-hospital death was observed in two (3.6%) patients of VR and in seven (3.6%) patients of no VR; there was no statistical difference of incidence between VR and no VR. In VR group, two operative deaths (one each in the gallbladder carcinoma and in PHC) were due to intra-abdominal hemorrhage, and two in-hospital deaths were caused by early recurrence of the gallbladder carcinoma. According to disease-based group, the in-hospital death

Table 3 Comparison of Postoperative Liver Function Tests and Complications Between Surgeries With and Without VR

	HIC		DGC		PHC	
	VR (11)	No VR (45)	VR (10)	No VR (108)	VR (35)	No VR (42)
Postoperative liver function						
Maximal AST, IU/l [median (IQR)]	366 (205–451)	306 (215–417)	148 (76–284)	162 (78–295)	69 (48–102)	84 (64–113)
Maximal ALT, IU/l [median (IQR)]	310 (241–485)	258 (199–478)	119 (65–278)	166 (87–218)	65 (41–106)	76 (56–106)
Maximal TB, mg/l [median (IQR)]	3.4 (2.1–4.6)	4.1 (2.3–7.1)	3.1 (1.9–6.3)	5.0 (3.7–3.6)	2.2 (1.3–3.2)	2.5 (1.5–3.6)
Postoperative complications						
Postoperative bleeding						
Intraperitoneal, % (n)	–	11.1 (5)	10.0 (1)	7.4 (8)	2.9 (1)	2.4 (1)
Gastrointestinal or biliary (2), % (n)	9.1 (1)	4.4 (2)	–	4.6 (5)	5.7 (2)	–
Pancreatic fistula, % (n)	–	–	25.0 (2)$	17.2 (15)$	5.7 (2)	2.4 (1)
Bile leak, % (n)	36.4 (4)	35.6 (16)	0 (0)	11.1 (12)	–	–
High bilirubinemia>10 mg/dl, %(n)	9.1 (1)	13.3 (6)	10.0 (1)	7.4 (8)	–	4.8 (2)
Intra-abdominal infection, % (n)	9.1 (1)	17.8 (8)	20.0 (2)	13.0 (14)	5.7 (2)	2.4 (1)
Pulmonary disorders, % (n)	18.2 (2)	15.6 (7)	30.0 (3)*	5.6 (6)	8.6 (3)	4.8 (2)
Acute renal failure, % (n)	–	2.2 (1)	18.2 (2)**	0.9 (1)	–	–
Bowel necrosis, % (n)	–	4.4 (2)	–	–	–	–
Ileus, % (n)	9.1 (1)	2.2 (1)	–	–	–	–
SVC thrombosis, % (n)	–	–	–	0.9 (1)	–	–
Anastomotic leakage, % (n)	–	–	–	0.9 (1)	2.9 (1)	4.8 (2)
Portal vein thrombosis, % (n)	–	–	–	–	2.9 (1)	2.4 (1)
Reoperation, % (n)	9.1 (1)	13.3 (6)	20.0 (2)	10.2 (11)	5.7 (2)	4.8 (2)
Morbidity rate, % (n)	72.7 (8)	71.1 (32)	30.0 (3)	43.5 (47)	34.3 (12)	23.8 (10)
In-hospital death (n)	0 (0)	11.1 (5)	30.0 (3)***	5.6 (5)	2.9 (1)	0 (0)
Mortality rate, % (n)	0 (0)	4.4 (2)	10.0 (1)	1.9 (2)	2.9 (1)	0 (0)

VR Superior mesenteric vein resection or portal vein resection; *IQR* interquartile range
*0.029 (Fisher's exact test)
**0.019 (Fisher's exact test)
***0.028; percentage for 95 patients who underwent pancreaticoduodenectomy

including operative mortality occurred more frequently in HIC (8.9%) and in DGC (7.6%) compared to that in PHC (1.3%), although there were no statistical differences (p= 0.092 and 0.082, respectively; Table 3). Especially in the gallbladder carcinoma, three of the five patients who required VR died early after surgery, although surgery-related mortality was only one; two deaths were caused by tumor recurrence. Of 45 gallbladder carcinomas in no VR group, the surgery-related death was recorded in a patient (2.2%).

Overall morbidity was significantly higher in HIC among the three disease-based groups but did not differ between VR and no VR in any of the three disease-based groups. Only the pulmonary disorder requiring intensive treatment and acute renal failure developed frequently in VR group compared with no VR group (DGC; Table 3). Occurrence of intra-abdominal hemorrhage after surgery was not affected by the portal vein resection because the incidence was 3.6% (2) in VR group and 7.2% (14) in no VR (not significant difference). The hemorrhage in the two patients who underwent VR was caused by the rupture of pseudoaneurysm. Gastrointestinal hemorrhage from peptic ulcer after VR occurred in 9.1% of HIC and 5.7% of PHC; the figures were not statistically different to the incidence in no VR.

Regardless of VR or no VR, the pancreatic fistula after pancreatic resection was more frequent in DGC (20.0%, 19 of the 95 patients), compared with that in PHC (3.9%, n=3, p= 0.004). However, VR itself did not influence the occurrence of pancreatic fistula (Table 3). The occurrence of bile leakage also did not differ between VR and no VR. The hyperbilirubinemia >10 mg/dl occurred in 3.6% (2) of the 56 patients with VR and in 8.2% (16) of the 195 patients without VR, with no statistical difference (p=0.378; Table 3). Reoperation was performed in 8.9% (five) after surgery with VR, for adhesive ileus, intra-abdominal hemorrhage, intra-abdominal abscess, peritonitis due to the small bowel perforation, and leakage of colo-colostomy. Any causes for reoperations were not related to vascular procedure.

No early complication specific to VR was observed. Intrahepatic portal vein thrombosis occurred in two patients in whom the plastic tube was placed in the portal vein for liver perfusion chemotherapy; one (1.8%) was in VR group and another (0.5%) was in no VR group (no significant difference; Table 3). The thrombosis disappeared immediately after removal of the tube and anticoagulant therapy.

A symptomatic late complication specific to the portal vein resection during long-term follow-up period has been rarely observed in this series. In VR group, there was a patient who had sinistral portal hypertension due to tumor recurrence.

Table 4 Comparison of Final Pathologic Diagnoses Between Surgeries With and Without VR

	HIC		DGC		PHC	
	VR, n=11	No VR, n=45	VR, n=10	No VR, n=108	VR, n=35	No VR, n=42
Histological differentiation, pap-well	63.6 (7)	48.9 (22)	10.0 (1)*	54.6 (59)	51.4 (18)	42.9 (18)
Positive microlymphatic permeation	72.7 (8)	82.2 (37)	100 (10)	78.7 (85)	85.7 (30)	95.2 (40)
Positive microvenous permeation	54.5 (6)	40.0 (18)	80.0 (8)	53.7 (58)	40.0 (14)	54.8 (23)
Perineural invasion	90.9 (10)	75.6 (34)	100 (10)	73.1 (79)	97.1 (34)	88.1 (37)
pT factor						
T1, T2	9.1 (1)	51.1 (23)	–	36.1 (39)	–	–
T3	27.3 (3)	37.8 (17)	–	49.1 (53)	100 (35)	100 (42)
T4	63.6 (7)**	11.1 (5)	100 (10)	14.8 (16)	–	–
pN factor						
N1	27.3 (3)	42.2 (19)	50.0 (5)	61.1 (66)	57.1 (20)	71.4 (30)
pM factor						
M1	-	2.2 (1)	20.0 (2)	12.0 (13)	14.3 (5)	16.7 (7)
Final stage						
<IIa or IIa	9.1 (1)	48.9 (22)	–	31.5 (34)	45.7 (16)	31.0 (13)
IIb	9.1 (1)	31.1 (14)	–	35.2 (38)	34.2 (12)	52.4 (22)
III or III<	81.8 (9)****	20.0 (9)	100 (10)	33.3 (36)	20.0 (7)	16.7 (7)
Positive surgical margin	27.3 (3)	31.1 (14)	60.0 (6)***	18.5 (20)	14.3 (5)	14.3 (6)
Microscopic portal vein invasion	45.5 (5)	–	70.0 (7)	–	42.9 (15)	–

HIC Proximal cholangiocarcinoma and intrahepatic cholangiocarcinoma with hilar extension; *DGC* middle-distal cholangiocarcinoma and gallbladder carcinoma; *PHC* pancreatic head adenocarcinoma; *VR* superior mesenteric vein resection or portal vein resection

*0.008

**0.002

***0.008 (Fisher)

****0.004

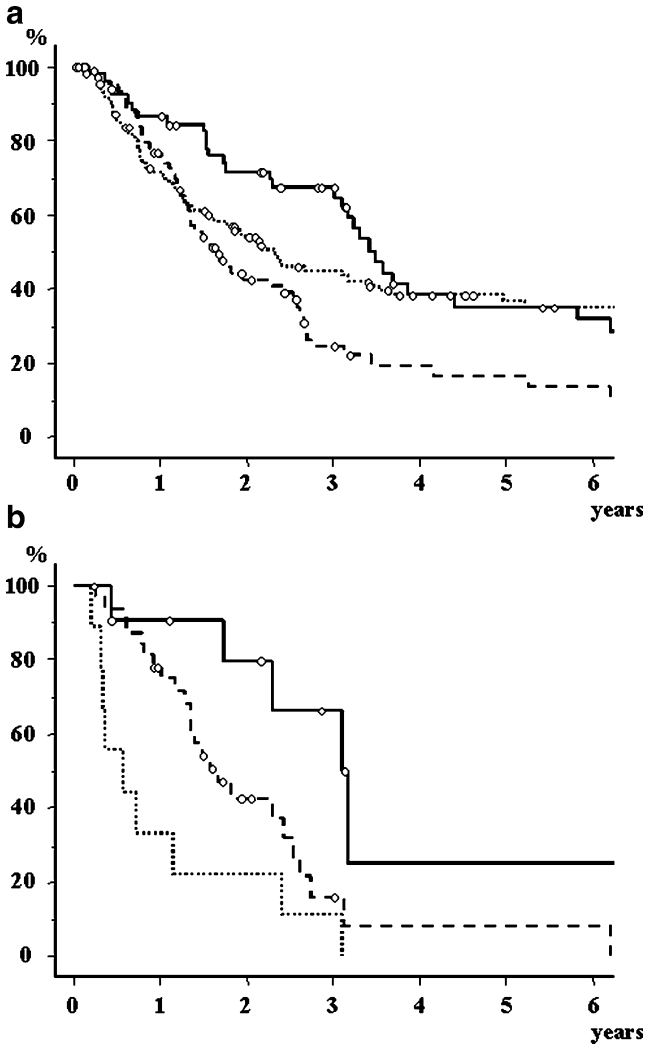

Figure 1 Survival curves in the three disease-based groups. In analyses for all patients (**a**), a median survival time (95% CI, months) was 41.8 months (36.4–47.3) in HIC (*black line*), 27.7 months (18.9–36.5) in DGC (*dotted line*), and 20.1 months (14.2–26.3) in PHC group (*broken line*). Statistical significances were HIC vs PHC, 0.003; DGC vs PHC, 0.0368; and HIC vs DGC, 0.2151. In analysis of patients who underwent VR (**b**), DGC showed significantly worse survival of a median of 6.8 months among the three disease-based groups (37.0 months in HIC and 20.0 months in PHC; $p=0.0016$ and $p=0.0316$, respectively). There was also a significant difference in survival between PHC and HIC ($p=0.0307$).

Pathologic Features

Positive rates of lymphatic permeation, microvenous permeation, perineural invasion, and lymph node metastasis were similar between VR and no VR groups in each of the three disease-based groups (Table 4). In DGC, VR group was accompanied with higher positivity of surgical margin compared with no VR ($p=0.008$). When analyzing tumors of DGC separately, the middle and distal cholangiocarcinoma in VR group showed 60% (three of the five tumors) of positive surgical margin, whereas that in no VR was 15.9% ($p=0.045$). Also in gallbladder carcinoma, margin positivity was so high in VR (60% of the five tumors), but there was not statistical difference compared with no VR (22.2%, $p=0.064$).

In PHC, no significant difference was observed in all the parameters evaluated between VR and no VR. The tumor size of pancreatic adenocarcinoma also did not differ between tumors excised with VR and without (a mean value±SD, 38.4±12.2 mm and 35.5±13.2 mm, respectively, $p=0.323$). Microscopic invasion of the vein was more frequently observed in DGC (70%) among the three disease-based groups (45.5% in HIC and 42.9% in PHC); however, there were no statistical differences.Positivity of microscopic invasion did not differ between middle-distal cholangiocarcinoma and gallbladder carcinoma.

Survival Analyses

Among the three disease-based groups, PHC was associated with significantly worse median survival time (20.1 months) compared to others (41.8 months in HIC and 27.7 months in DGC, Fig. 1a). When analyzing the 54 patients who underwent VR, survival probabilities of DGC and of PHC were inverted, and DGC showed most dismal outcome (a median of 6.8 months) among the three groups (37.0 months in HIC and 20.0 months in PHC; $p=0.0016$ and $p=0.0316$ to DGC, respectively, Fig. 1b). In DGC with VR, five patients with middle or distal cholangiocarcinoma all died of tumor recurrence within 14 months after surgery, and also four patients with gallbladder carcinoma were succumbed to the disease at 37, 29, 4, and 3 months after surgery, respectively.

In Table 5, univariate analyses for multiple prognostic parameters were calculated. Positive surgical margin and lymph node metastasis were important prognostic factors common to the three disease-based groups. The negative prognostic value of VR itself was prominent in DGC (surgeries with VR and without, $p=0.001$) but was not demonstrated in HIC or in PHC (Fig. 2). In DGC, VR was a negative prognostic factor regardless of positive or negative microscopic invasion of the vein (Table 5). When performing subgroup analyses, portal vein invasion showed striking negative impact in the middle-distal cholangiocarcinoma ($p=0.001$), whereas it was marginal difference in the gallbladder carcinoma ($p=0.055$).

In PHC, microscopic invasion was a significant prognostic factor, but a median survival time of VR group without microscopic invasion was similar to that of no VR (Table 5). In HIC, median survival time in VR with microscopic invasion was shorter than that in no VR, although no statistical difference (27.5 months with 95%C.I.; 17–37 vs 41.8 months with 36–48). The median survival time in VR without microscopic invasion was 38.1 months, 95% confidence interval (CI) 36.6–39.4, with no significant

Table 5 Univariate Analyses of Prognostic Factors in Each of Three Disease-based Groups

	HIC (n=54)		DGC (n=115)		PHC (n=76)	
	Median Survival Time					
	Month (n)	p value	Month (n)	p value	Month (n)	p value
Age, 70 >/70 < year-old	53.0 (36)/38.9 (18)	0.1477	23.3 (72)/37.1 (43)	0.6828	16.1 (47)/28.2 (29)	0.0672
Male/Female	41.1 (35)/70.0 (19)	0.4481	25.8 (57)/27.7 (58)	0.5925	16.1 (42)/28.2 (34)	0.1768
Adjuvant chemotherapy (-/+)	42.9 (42)/36.3 (12)	0.9771	25.1 (101)/37.1 (14)	0.6233	16.7 (38)/29.2 (38)	0.2958
Differentiation; pap-well/others	41.1 (29)/41.8 (25)	0.9376	59.7 (58)/16.8 (57)	0.0011	31.9 (36)/15.7 (40)	0.0023
Microlymphatic permeation; −/+	41.1 (11)/41.8 (43)	0.2849	76.1 (23)/22.1 (92)	0.0734	74.5 (7)/16.7 (69)	0.0629
Microvessle permeation; –/+	42.9 (31)/37.2 (23)	0.9442	76.1 (50)/18.2 (65)	0.0011	25.4 (40)/18.1 (36)	0.7844
Perineural invasion; –/+	38.1 (12)/41.8 (42)	0.5240	– (29)/23.3 (86)	0.0121	14.4 (6)/20.3 (70)	0.4350
Surgical margin; negative/positive	53.0 (38)/21.1 (16)	0.0004	42.4 (89)/13.3 (26)	0.0001	21.8 (65)/10.7 (11)	0.0011
Lymph node metastasis; –/+	70.0 (33)/27.5 (21)	0.0012	76.1 (47)/16.2 (68)	0.0005	30.6 (27)/16.1 (49)	0.0842
Preoperative jaundice; –/+	37.2 (10)/41.1 (44)	0.4010	41.0 (36)/25.8 (79)	0.3942	32.1 (12)/17.7 (64)	0.2045
Operation time; 600 >/600< (min)	46.6 (30)/36.3 (24)	0.0914	38.1 (63)/21.3 (52)	0.0285	21.8 (56)/16.1 (20)	0.0473
Blood loss; 1600 >/1600< (ml)	42.9 (28)/38.1 (26)	0.5008	28.9 (68)/21.7 (47)	0.0857	23.5 (61)/16.1 (15)	0.0363
VR (−/+)	42.9 (43)/37.2 (11)	0.5406	28.3 (106)/6.8 (9)	0.0001	20.3 (42)/20.0 (34)	0.3298
Microscopic vein invasion (−)/(+)	41.1 (49)/27.5 (5)	0.2209	28.6 (108)/6.8 (7)	0.0008	20.3 (62)/12.2 (14)	0.0228
VR (+) without microscopic invasion	38.1 (6)		4.0 (3)		20.0 (20)	

VR Superior mesenteric vein resection or portal vein resection

HIC Proximal cholangiocarcinoma and intrahepatic cholangiocarcinoma with hilar extension; *DGC* middle-distal cholangiocarcinoma and gallbladder carcinoma; *PHC* pancreatic head adenocarcinoma; *VR* superior mesenteric vein resection or portal vein resection; *pap-well* papillary and well-differentiated adenocarcinoma

difference to that in no VR. Multivariate analyses demonstrated two negative independent predictors each in DGC and in PHC, respectively: positive surgical margin and positive nodal metastasis, and positive surgical margin and histological differentiation (Table 6). The depth of tumor infiltration into the vein was evaluated in PHC; median survival time in nine tumors infiltrating into the tunica media or intima [11.1 months with 95%CI, 7–15.1] was significantly lesser than that in 25 tumors infiltrating up to the tunica adventitia (21.8 months with 95%CI, 14.4–29.2, p= 0.0301). The survival difference was not observed between the patient's group of PHC with liver perfusion chemotherapy and that without in this series.

When analyzing all 54 patients who underwent VR, univariate analyses revealed 9 prognostic parameters with statistical difference as shown in Table 7. Among these parameters, multivariate analyses disclosed four negative prognostic predictors: site of the primary tumor (no HIC), surgical margin, microvenous permeation, and microscopic invasion to the vein (Table 8).

Discussion

Portal Vein Resection in Pancreatic Head Adenocarcinoma

VR has been widely performed for pancreas carcinoma since the report of the regional pancreatectomy,[10] but its survival benefit has been still controversial. In general, incidence of VR seems to be inversely proportional to that of microscopic tumor invasion; more than 40% of VR rate was associated with 50–60% of microscopic vein wall invasion,[12,20,27,38] whereas less than 40% of VR rate was accompanied by more than 70% of microscopic invasion.[16,17,22,26,39] Although much variance was seen in the incidence of VR, the true venous infiltration was not so widely distributed; estimated figures calculated from several reports were 16–33%.[12,16,17,20,22,26,27,38,39] Nevertheless, the low probability of true infiltration could not preclude the aggressive attitude to pancreaticoduodenectomy combined with VR.

Increased intraoperative blood loss with VR was pointed out,[13,22,24] but the operative morbidity and mortality did not differ between operation with VR and without.[14,22,25] In a recent report by Carrere et al.,[14] VR did not influence the blood loss, but 22% of reoperation rate and 15% of postoperative hemorrhage rate after VR seems to be somewhat high because of 5.5 and 2.9% in our series, respectively. The incidence of pancreatic fistula significantly decreased in patients who underwent VR.[14,28] More advanced pancreatic tumors and more decreased pancreatic function may reduce the probability of pancreatic fistula. However, pancreatic fistula after pancreaticoduodenectomy for pancreatic carcinoma is generally less frequent, compared to that for biliary tract carcinoma with normal pancreas. The vascular procedure showed no impact on

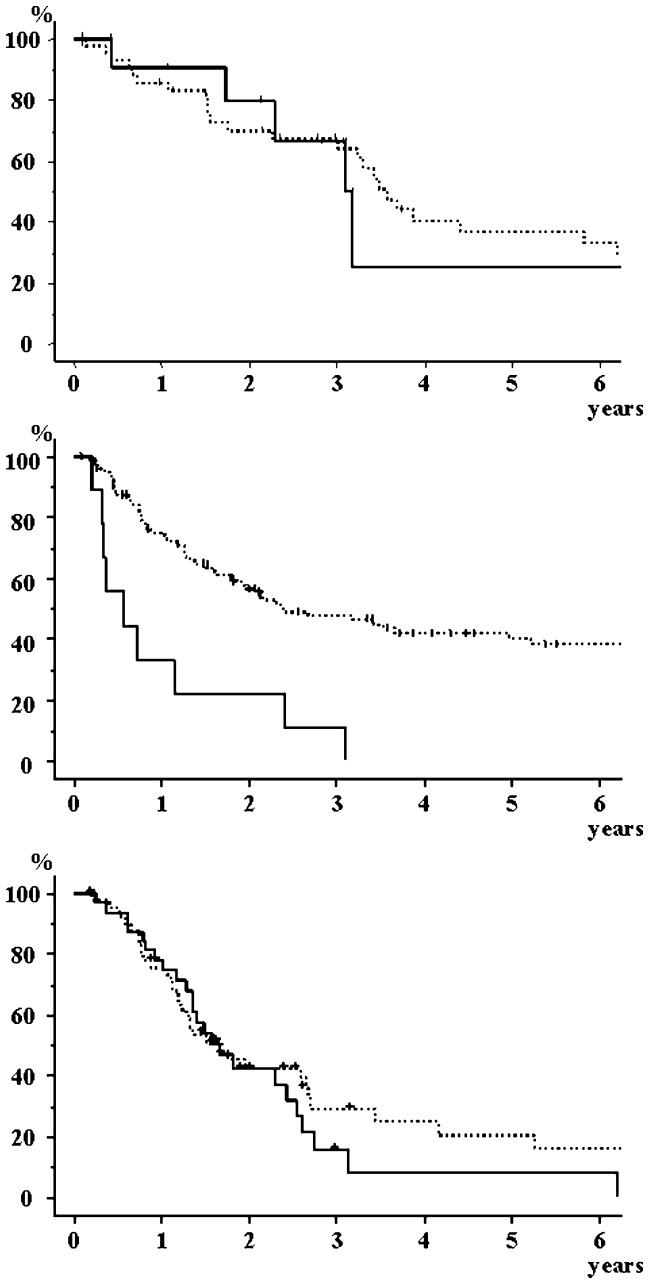

Figure 2 Postoperative survival in each of the three disease-based groups. A median survival time of patients without VR (*dotted line*) was 42.9 months (95%CI, 37–48.8 months) in HIC, 28.6 months (95% CI, 13.3–43.8 months) in DGC, and 20.3 months (95%CI., 11.4–29.1 months) in PHC. A median survival time of patients with VR (*black line*) is described in Fig. 1. Statistical difference in survival between surgeries with and without VR was observed only in DGC (p=0.0001).

increased risk of pancreatic fistula. On the other hand, superior mesenteric ischemia,[22] bowel edema caused by prolonged venous occlusion time,[18] or sinistral portal hypertension[24,37] appear to be infrequent complications after VR. Leach et al.[24] reported that the venous occlusion after VR occurred in 22% (7) of 31 patients: 5 were asymptomatic and the remaining 2 died of the condition.

Table 6 Mutivariate Analyses for DGC and for PHC

	p value	Risk Ratio	95% CI
DGC			
Positive surgical margin	<0.001	3.30	1.84–5.91
Positive lymph node metastasis	0.006	2.18	1.26–3.76
PHC			
Positive surgical margin	0.002	3.38	1.59–7.19
Histological differentiation	0.001	2.62	1.49–4.62

Although we experienced portal thrombosis with liver perfusion chemotherapy, the vein occlusion or sinistral portal hypertension caused by VR itself was not encountered. VR for pancreatic carcinoma is a safe vascular procedure, but we should take care of unexpected pathologic conditions related to the vascular procedure.

Exact correlation between long-term survival and concomitant VR remains unclear. Several reports have stated that true microscopic invasion into the vein wall was accompanied by lower probability of survival.[11,12,16,20,26,27] Furthermore, the depth of tumor infiltration into the vein wall also affected postoperative survival.[11,12,26,27] In the present study, VR itself showed no disadvantage on

Table 7 Prognostic Factors in 54 Patients Who Underwent VR: Univariate Analyses

Analyzed factors (n)	Median survival time [month, (95% CI)]	p value
Histological grade, pap-well (25)/others (29)	29.2 (20.2–38.1)/16.7 (10.4–23.0)	0.0044
Microlymphatic permeation, −(8)/+(46)	27.7 (15.3 -40.0)/16.7 (11.5–21.9)	0.0189
Microvenous permeation, −(27)/+(27)	30.6 (26.2 -35.0)/15.3 (10.1–20.6)	0.0042
Surgical margin, negative (40)/positive (14)	28.9 (15.8 -42.0)/13.8 (1.5–26.0)	0.0218
Lymph nodal metastasis, −(28)/+(26)	32.8 (24.5–41.1)/16.1 (13.2–19.0)	0.0016
Microscopic invasion to vein wall, −(28)/+(26)	29.2 (12.8–45.6) /12.2 (0.0–29.6)	0.0041
Operation time, 600 min > (32)/< (22)	25.4 (12.8–38.0) /16.1 (4.6–27.7)	0.0382
No DGC, yes (45)/no (9)	27.5 (18.5–36.5)/6.8 (0.0–14.3)	0.0032
No HIC, yes (43)/no (11)	16.7 (11.7–21.7)/37.2 (31.8–42.5)	0.0134

VR Superior mesenteric vein resection or portal vein resection; *pap-well* papillary and well-differentiated adenocarcinoma
CI Confidential interval. (excluding two operative deaths)

Table 8 Prognostic Factors in 54 Patients Who Underwent VR: Multivariate Analysis

	p value	Risk Ratio	95% CI
No HIC	0.002	5.46	1.91–15.6
Positive microvenous permeation	0.001	4.18	1.76–9.96
Positive surgical margin	0.023	2.35	1.13–4.90
Microscopic portal vein invasion	0.033	2.19	1.06–4.51

CI Confidential interval. (excluding two operative deaths)

postoperative survival, but the probability of prognosis decreased when microscopic invasion was positive or when tumor infiltrated beyond the tunica adventitia. Fuhrman et al.[13] stated that the portal vein involvement was a function of tumor location rather than aggressiveness of cancer biology. However, microscopic true infiltration should be considered as an indicator that reflects the local invasiveness of the primary tumor and poor prognosis. Interestingly, Hartel et al.[16] mentioned that survival of the patients who underwent VR for a lesion with no microscopic invasion was superior to that of patients who did not undergo VR, whereas Shimada et al.[28] described the results opposite to that of Hartel el al. In general, R0/R1 ratio did not differ between surgeries with and without VR, and en-bloc resection permits extirpation with potentially negative margins and may reduce the risk of local recurrence.[13,20,22,24] In the report by Shimada et al.,[28] the higher positivity of R1 operation, extrapancreatic neural invasion, and widespread nodal diseases in the VR group seems to influence their surgical outcomes. In treatment for pancreatic tumors with portal vein invasion, it was reported from the randomized control trial that resection surgery was superior to chemoradiotherapy alone.[40] On the basis of safe performance in vascular procedure, VR combined with aggressive surgery can be justified in cases with potential risk of vein invasion.

Portal Vein Resection in Biliary Tract Carcinoma

In many studies for hilar cholangiocarcinoma, in-hospital mortality after major hepatectomy with VR ranged from 9 to 17%, with no significant difference compared to that with no VR.[2,6,41] Zero mortality series with 40 consecutive major hepatectomies was reported by Kondo et al.,[5] in which 14 patients underwent concomitant VR. In our series, in-hospital deaths were not observed after major hepatectomy with VR in HIC. Morbidity with VR was similar to that with no VR.[2,5,6] In gallbladder cancer, it is reported that major hepatectomy combined with VR for cases with obstructive jaundice was accompanied with high in-hospital mortality of 20–36% due to postoperative hepatic coma.[9,41] Also in our series, mortality significantly increased in surgery with VR than in without VR, but we did not encounter hepatic coma as the primary presentation of postoperative morbidities. Portal vein embolization was not carried out in our institution until 2005, but this technique is thought to be a modality of choice for improving postoperative outcome regardless of VR or no VR.[42,43]

The incidence of VR combined with hepatectomy for hilar cholangiocarcinoma widely ranged from 6.3 to 43%.[2–6,8,31,33,34] Similarly in pancreatic cancer surgery, the difference in the treatment strategy seems to be a possible explanation for this variance. Neuhaus et al.[3] reported that VR improved long-term survival, and only VR was identified as an independent predictor in patients who underwent R0 operation. Although microscopic infiltration of the portal vein was approximately 20% in their series, the curative right trisectionectomy with VR yielded a surprising outcome of 72% 5-year survival.[4] On the other hand, Ebata et al.[2] stated that macroscopic involvement of the portal vein affected postoperative survival statistically, but absence or presence of microscopic involvement had less impact on survival. More recently, Kondo et al.[5] and Hemming et al.[6] mentioned that there was no difference in survival between surgeries with and without VR, and our study also showed a similar tendency. An en-bloc resection with VR appears to enhance surgical clearance of tumor cells in porta hepatic.[3,44] A routine use of VR is not standardized in the current status, but VR should not be precluded in cases with portal vein involvement detected before or during operation.

With regard to gallbladder carcinoma, only a few studies focused on the surgical outcome of surgery with VR and reported its unfavorable results.[1,8,9,45] More than 3-year survival was rarely encountered even with aggressive surgery.[1,9,45] In several studies about middle and distal cholangiocarcinoma amenable to pancreaticoduodenectomy, the description of VR was lacking[46,47] or only the number of cases with VR was provided.[48,49] Reported figures of 13,[46] 13.5,[47] and 18%[35] appear to be higher than in many other studies. Tseng et al.[18] described that distal cholangiocarcinoma was found only in 2% (three) of 141 patients who underwent pancreaticoduodenectomy with VR but was carried out in 79% of the 141 patients with pancreatic head adenocarcinoma. Roder et al.[35] stated that seven cases with pancreaticoduodenectomy with VR showed no survival benefit because of high incidence of positive surgical margin (71%) and of limited survival of less than 12 months. Tashiro et al.[7] reported two patients who had widespread nodal disease and died of tumor recurrence at 3 and 25 months after surgery, respectively. In gallbladder

carcinoma and middle-distal cholangiocarcinoma, lymph node metastasis and surgical margin status are well-established prognostic factors.[50,51] Adjuvant chemotherapy after aggressive surgery seems to be a practical and promising strategy that can improve the prognosis,[52] but the indication of an extensive surgery with vascular procedure is limited when tumors have obvious negative prognostic predictors.

Portal Vein Involvement in Pancreatic and Biliary Tract Carcinoma

In gallbladder carcinoma, portal vein involvement occurs in the far advancing margin of tumor extension, and true vascular invasion is seen more frequently compared to hilar cholangiocarcinoma.[9] In surgery for advanced gallbladder carcinoma, we seldom encounter solitary portal vein involvement, and multiple visceral resections are required for tumor resection. In middle and distal cholangiocarcinoma, tumors with deep invasion were associated with poor prognosis compared with those with superficial invasion.[53] Furthermore, the depth of invasion of the primary tumor correlated well with patient survival in middle and distal cholangiocarcinoma, whereas it did not in hilar lesion.[54] Considering these biological characteristics, portal vein invasion in these lesions should be regarded as the depth of invasion of the primary tumor. In DGC, the clinical requirement of VR itself is thought to represent a high malignant potential with the primary tumor.

Both in HIC and in PHC, VR was associated with no survival disadvantage in cases of tumor infiltration within the tunica adventitia of vein. The superior mesenteric vein, portal vein, or its tributaries run closely across the pancreatic head and proximal bile duct, and these veins are in direct contact with pancreatic parenchyma or with structures of porta hepatis, respectively. Because of this anatomical proximity, the vein can be regarded as a regional vessel of "porta hepatic" or "pancreatic head." Hence, the tumorous infiltration up to the most superficial layer of the vein does not seem to show strong impact on survival.

Conclusions

The superior mesenteric-portal vein resection combined with major hepatectomy, pancreaticoduodenectomy, or both was technically feasible without complications specific to vascular procedures. However, surgery with portal vein resection for middle-distal cholangiocarcinoma and gallbladder carcinoma was accompanied by a dismal outcome; these operations should not be recommended for lesions with obvious noncurative factors. In hilar cholangiocarcinoma and pancreatic head carcinoma, the vein resection is not contraindicated because of minimal adverse effects on postoperative outcome. In the pancreatic and biliary tract adenocarcinoma, surgical outcomes after aggressive surgery with VR differed considerably, depending on the sites of the primary tumor. It is suggested that difference in the anatomical relationship between the primary tumor and superior mesenteric-portal vein is a probable reason for the explanation of variance in surgical outcome after vein resection.

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Bowel Cleansing Before Bowel Surgery: Major Discordance Between Evidence and Practice

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Abstract Mechanical bowel cleansing (preparation) before colorectal surgery is commonly practiced, and medical care guidelines consent to this regimen. This has been an incontestable routine for surgeons for more than 100 years. However, during the last years, several randomized control trials and three meta-analyses led to the accumulation of enough evidence to conclude that no significant benefit is derived from this practice and thus, elective colorectal surgery can be safely done without mechanical bowel cleansing. Furthermore, several complications are attributed to mechanical bowel cleansing including anastomotic leakage, wound infections, and septic and non-septic complications that sometimes lead to the need for reoperation. Surgeons around the world may have to seriously reconsider the common practice of preoperative mechanical bowel cleansing. Despite the unquestionable practical value of mechanical bowel cleansing for bowel handling during anastomotic confection, we believe that current literature provides strong evidence that passed the line where this time-honored tradition may be finally called into question.

Keywords Bowel cleansing · Bowel surgery

Decision-making of clinicians is influenced mainly by knowledge of the evidence and medical tradition. In the era we live, evidence-based medicine has gained popularity among clinicians, leading to a simplified and rigid standardization of medicine ("cook book medicine"). We certainly believe that medical tradition has a value in modern medicine. However, one should draw a line where evidence, calling into question time-honored traditions, suppresses dogmas based only on observation and experts opinion.

Mechanical bowel cleansing (MBP) before colorectal surgery is an incontestable routine for surgeons for more than 100 years. Medical care guidelines and scientific papers still consent to this regimen as requisite to colorectal surgery. However, during the last three decades, a series of scientific papers put into question the medical value of MBP and even attributed complications to this practice. The first studies that challenged the principle of MBP were severely criticized for flawed methods. In the following years, several prospective studies, randomized controlled trials (RCTs), and reviews of the literature also put into question the value of MBP for colorectal surgery. However, none was considered powered enough to change the established surgical tradition and guidelines.

Review of the current evidence in PubMed database reveals three meta-analyses[1–3] of RCTs studying the role of MBP in colorectal surgery. In 2004, Slim et al. published in the *British Journal of Surgery* a meta-analysis of seven RCTs of colorectal surgery with or without MBP, including 1,454 patients. MBP was significantly associated with anastomotic leakage in comparison with surgery performed without bowel cleansing. Wound infections, septic and non-septic

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complications were endpoints in favor of the no-preparation procedure, although without statistically significant difference. The authors, after having calculated the quality score for the included RCTs, excluded in their sensitivity analysis two trials of poor quality, without substantial change of the results, still in favor of the non-MBP surgery.

In 2004, the *Archives of Surgery* published a second meta-analysis. Bucher et al., retrieved seven prospective RCTs including 1,297 patients. Anastomotic leakage was significantly more frequent in patients undergoing surgery with bowel preparation in comparison with patients that did not receive MBP. Several other end-points, intra-abdominal infection, wound infection, reoperation, postoperative morbidity and mortality were all in a nonsignificant proportion higher in the MBP group. Despite the unquestioned methodological problems in many of the RCTs included, the funnel plot homogeneity test of the meta-analysis is symmetrical indicating considerable sensitivity. The authors concluded to an even more heretic point of view; MBP is not supported by current evidence and might as well be harmful for patients undergoing colorectal surgery.

Finally in 2005, Wille-Jorgensen et al published an updated meta-analysis regarding MBP in the *Colorectal Disease* Journal. This study included nine RCTs and a total of 1,592 patients. The group of patients that received MBP preoperatively developed anastomotic leakage in a proportion of 3.2% in comparison with 6% for the group of patients that underwent surgery without any kind of bowel preparation; this is a statistically significant difference. Wound infections and mortality were studied as endpoints in meta-analysis as well, and recorded nonsignificant higher proportions for the MBP group in comparison with the non-MBP group of patients. In the sensitivity analysis of the meta-analysis, the exclusion of four methodologically weak RCTs did not substantially change the results mentioned above. The authors conclude calling for abolishment of the dogma of MBP.

However, it is noteworthy that in 2005, Nichols et al. kept faithful to the surgical tradition and concluded, in their review of the mechanical and antibacterial bowel preparation in colon and rectal surgery,[4] to the "steadfast" necessity of MBP despite the fact that they cited in their contribution two of the three meta-analyses described in our commentary. The above conclusion, as well as the every day practice of the vast majority of colorectal surgeons and the current consensus guidelines[5–7] of many medical associations, clearly show that in this case, the accumulated evidence in dozens of RCTs and three meta-analyses has not been enough to change medical practice supported by traditional medical dogmas. In fact, in a survey regarding bowel preparation practices before elective procedures among 808 board certified colorectal surgeons, 100% of the respondents used MBP.[8] It should be acknowledged that among the reasons that may influence surgeons' decisions regarding the use of MBP are tradition and the fact that MBP facilitates surgeons' work by improving bowel handling during anastomotic confection.

In conclusion, we believe that surgeons around the world may have to seriously reconsider the common practice of preoperative MBP because the available data from RCTs do not seem to support this old medical dogma.

Conflict of interest None.

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Sacral Nerve Stimulation in Patients After Rectal Resection—Preliminary Report

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Abstract
Introduction Sacral nerve stimulation is a widely accepted therapeutic option for neurogenic fecal incontinence. More recently, case reports showed a positive effect of sacral nerve stimulation in patients with fecal incontinence following low anterior resection. The purpose of this study was to gain more information for this selected indication for sacral nerve stimulation through a nationwide survey.
Material and methods In the period 2002 to 2005, three Austrian departments reported data of patients who underwent SNS for fecal incontinence following rectal resection. Data were available of seven patients (two female, five male) with a median age of 57 years (min 42; max 79). Six patients had undergone rectal resection as a treatment for low rectal cancer. One patient had undergone rectal resection for Crohn's disease, one patient subtotal colectomy and ileorectostomy for slow colon transit constipation.
Results Test stimulation was performed in the foramen S3 unilaterally over a median period of 14 days (2–21 days). Seven patients reported a marked reduction of episodes of incontinence during the observation period and received a permanent stimulation system. After a median follow-up of 32 months (17–46), five patients reported a marked improvement of their continence situation.
Conclusion Despite a nationwide survey experiences with SNS as a treatment for fecal incontinence following rectal resection is still limited. Our observations show an improvement of the continence function following SNS. However, the promising results of our series as well as others need further research and more clinical data by a larger number of patients in a prospective trial.

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Keywords Fecal incontinence · Sacral nerve stimulation · Rectal resection

Introduction

Due to the increasing progress in surgical technique for the treatment of rectal cancer more and more patients can be treated with sphincter preserving procedures, thus avoiding the formation of a permanent colostomy.[1] Furthermore, standardization of the surgical technique have also led to a better preservation of urinary and sexual function. However, postoperative fecal incontinence in patients who have undergone anterior resection for rectal cancer has been reported in up to 40%.[2–7] Although the majority of studies describing this problem following anterior resection have shown that fecal incontinence is significantly more likely in patients with a resection less than 6 to 8 cm from the anal verge, the full etiology of postoperative fecal incontinence

is complex and not yet fully understood.[8] While the loss of the rectal ampulla as well as iatrogenic lesions of the sphincter muscles are obvious reasons, damage of the autonomic nerves as well as the effect of chemoradiation could also play a role even in patients with no evidence of sphincter lesions.

Sacral nerve stimulation (SNS) is a widely accepted therapeutic option for patients suffering from fecal incontinence based on a neurogenic dysfunction.[9–13] More recently, case reports have been published showing a positive effect of this treatment in patients suffering from fecal incontinence after low anterior rectal resection.[8,14,15] The purpose of this paper was to perform a nationwide survey for this selected indication for SNS in order to gain more information by recruiting a larger number of patients.

Material and Methods

All Austrian Surgical Departments performing SNS for fecal incontinence (n=15) were contacted. In the period 2002 to 2005, three Austrian departments reported data of patients who underwent SNS for fecal incontinence following rectal resection. Data were available of seven patients (two female, five male) with a median age of 57 years (min 42; max 79) (Table 1). Six patients had undergone rectal resection as a treatment for low rectal cancer. All of these patients had been treated with neoadjuvant chemoradiation (radiation dose ranging between 40 and 50 Gy). One patient had undergone rectal resection for Crohn's disease. All patients had normal anal sphincter function before these procedures and did not report any episodes of fecal incontinence in their previous history.

The median anastomotic height from the dentate line following low rectal resection was 3 cm. Three patients had straight coloanal anastomosis, one patient received a J-Pouch and coloanal anastomosis after intersphincteric resection, and two patients had a longitudinal coloplasty and coloanal anastomoses. All patients who had resections for rectal cancer were under regular oncologic follow-up and showed no evidence of recurrence.

Table 1 Patients Characteristics

Characteristics of Patients	*N*
Male:female	5:3
Median age (min–max)	57 (42–79)
Indication for rectal resection	
Rectal cancer	6
Crohn's disease	1
Chronic constipation	1
Preoperative (neoadjuvant) therapy	6
Median anastomotic height from dentate line (cm)[a]	3 (1,5–8)
Median history of fecal incontinence (min–max) (months)	23 (12–48)

[a] One patient who underwent subtotal colectomy with ileorectostomy is excluded

The median history of fecal incontinence following rectal resection or closure of the protective stoma, respectively was 23 months (min 12; max 48).

The incontinence status was classified in four patients as stage 4 according to the modified Williams classification, and one patient had a score of 13 according to Wexner.[16,17] Two patients reported to have a minimum of one incontinence episode for either solid or liquid stool every week. One patient following ISR showed incontinence during application of a test substance via the descending loop of the protective ileostomy as well as markedly reduced values in anal manometry.

All patients had failed to improve with maximal medical treatment (loperamide medication, dietary counseling) as well as with behavioural (biofeedback) therapy.

Before SNS, all patients underwent endoscopy (proving no anastomotic complications leading to incontinence), anal physiology testing (including measurement of maximal resting and contraction pressure, anal canal length and rectal compliance, respectively). Integrity of the anal sphincter was tested in all patients with endoanal ultrasound and/or pelvic magnetic resonance imaging. In four patients, preoperative quality of life evaluation (e.g. before SNS) using the fecal incontinence questionnaire of the American Society of Colon and Rectal Surgeons (ASCRS) was available.[17]

Technique of Sacral Nerve Stimulation

Test Stimulation

Under general anesthesia, four to six needles were positioned into the foramina S2 to S4 bilaterally, and stimulation was performed by the use of an external pulse generator (Screener, model 3625, Medtronic, Minneapolis, USA). The muscular response of the pelvic floor and the anal sphincters were visually evaluated with both buttocks fixed firmly in order to differentiate pelvic floor response from a possible gluteal contraction.

Following a positive stimulation response of the pelvic floor and/or the anal sphincters (i.e. contraction of the pelvic floor in a cranial–ventral direction and circular contraction of the anal sphincter) temporary (test-) stimulation was performed in order to evaluate the functional relevance of a positive electric stimulation, as follows: In four patients, a percutaneous nerve evaluation (PNE) was performed by application of a temporary stimulation wire (Model 3057 CL Test stimulation lead, Medtronic, Minneapolis) introduced into the stimulation needle and fixed to

the skin. The other four patients received immediately the permanent, quadripolar lead (tined lead electrode 3093, INTERSTIM, Medtronic, Kerkrade, Netherlands) which was connected via a subcutaneous extension with the external test stimulator.

The external stimulation was started on the first postoperative day in a continuous stimulation mode, with a pulse width of 210 μs, a frequency of 20 Hz, and a stimulation amplitude of 1.5 to 8.5 V (median, 5 V).

Permanent Implantation

The permanent electrodes (tined lead electrode 3093, INTERSTIM, Medtronic, Kerkrade, Netherlands) were placed into the sacral foramina by use of a percutaneous introducer device set. Exact positioning of the permanent quadripolar electrodes was confirmed by external testing as described above. Patients who became candidates for permanent implantation based on an improvement of their continence situation received either the permanent electrode plus the stimulation generator (3023, twin 7427 T; INTERSTIM, Medtronic, Kerkrade, Netherlands) under general anesthesia (n=3) or got the generator connected to the already implanted permanent electrode under local anesthesia (n=4).

Follow-up

Patients were followed 3, 6, and 12 months following the permanent implantation. Continence was assessed by continence diaries as well as by use of the Williams (n:4) or Wexner incontinence score (n:1), respectively (depending on the individual institution's preference). Postoperative quality of life evaluation by use of the ASCRS/quality of life (QOL) instrument in patients with fecal incontinence was available in five patients.

Stimulation parameters for permanent stimulation were set at a frequency of 16 Hz, pulse width of 210 ms, and an amplitude at which the patients reported the first sensation in the perianal region (threshold value). The median stimulation amplitude was 1.7 V (0.7 to 2.8). Stimulation was performed on a continuous mode with no deactivation during defecation.

Statistics

Continuous variables were documented as median, minimum, and maximum values. Statistical analysis of measured preoperative versus postoperative (12 months following implantation) anal physiology values as well as QOL scales were performed using the Wilcoxon paired rank test. A P value of <0.05 was regarded as a statistically significant level.

Results

In all patients, test stimulation was performed in the foramen S3 unilaterally over a median period of 14 days (12–21). All patients reported a marked reduction of incontinence in the observation period. Retention tests were performed in six patients showing an ability to retain 150 ml of a semisolid test substance for more than 15 min in five patients.

Permanent implantation was performed in seven patients. One patient developed postoperative hematoma and underwent hematoma evacuation under local anesthesia on the same day. One patient needed an explant of the pulse generator due to infection one month after the implant procedure. He was successfully reimplanted 3 months later after resolution of the infectious situation.

Postoperative Follow-up

After a median follow-up of 32 months (17 min; 46 max), six patients reported a marked improvement compared to the baseline (e.g. before test stimulation) of their continence situation. Three patients had no further incontinence episodes following the permanent implant. Their incontinence score improved from grade 4 to grade 0–1 according to the Williams classification.[16] Three patients reported "rare events" (1–2 incontinence episodes/month). In this group, one patient with a Cleveland score of 13 at baseline improved to 5. The other two patients had preoperatively reported about incontinence episodes of at least once per week in their diaries. One patient who had previously reported an improvement of his continence function during his test stimulation complained about repeated urgency problems as well as incontinence episodes. The patient has changed to retrograde colonic irrigation, thus, reaching an acceptable (pseudo) continence and explant of the stimulation system is presently discussed.

Anal Physiology Data

Postoperative (12 months) anal manometry and rectal compliance values were available in five patients. Anal manometry showed an increase of maximal resting and squeeze pressure 12 months following implant compared to baseline without reaching the level of statistical significance (Table 2).

Table 2 Anal Physiology (Median Values)

	Pre-SNS	Post-SNS (12 months)
Anal resting pressure (mm Hg)	44 (20–92)	48 (30–89)
Anal squeeze pressure (mm Hg)	72 (37–112)	79 (42–125)
Anal canal length (cm)	3 (2–4)	3 (2–4)

Median threshold, urge, and maximum tolerated rectal volumes revealed also an increase when compared to baseline values. However, the level of significance ($p<0.01$) was also not reached (Table 3).

Quality of Life

Assessment of QOL by use of the ASCRS questionnaire was available in five patients showing a significant improvement in all domains compared to baseline values (available in four patients) (Table 4).

Table 4 Results of Quality of life Evaluation 12 Months Following Permanent Implantation

Scale	Baseline Median (Min–Max) (n=4)	12 months post SNS Median (Min–Max) (n=5)
Lifestyle	2.0 (1.0–2.5)	4.0 (2.7–4.5)*
Coping/Behavior	2.0 (1.3–2.5)	3.6 (3.2–4.4)*
Depression/ Self perception	2.2 (1.5–3.1)	3.7 (3.1–4.2)*
Embarrassment	1.5 (1.0–2.4)	3.8 (3.3–4.7)*

*$p<0.01$

Discussion

The mechanism of deterioration of continence following rectal resection is not completely clear and seems to be multifactorial. While the importance of the rectal ampulla has been discussed controversially, other functions of anal rectal physiology have been investigated more recently to be also of important influence. Kakodkar and coworkers found the recto-anal inhibitory reflex (RAIR), the length of the high pressure zone (HPZ), as well as the maximum threshold volume (MTV) as main predictors for the functional outcome following anterior rectal resection.[18] These parameters are all dependent of the autonomic nerval system. Rectal sensation to the distension is transmitted along the S2, S3, and S4 parasympathetic nerves which are independent of the pudendal nerve. Therefore, in case of an undamaged anal sphincter fecal incontinence could be a result of neurogenic lesions in the autonomic pelvic nerves (either during surgery or due to neoadjuvant treatment) and SNS could positively influence this problem.

Although the efficacy of sacral nerve stimulation as a treatment of fecal incontinence has been proved repeatedly in larger series of patients, the mechanism leading to the improvement of fecal incontinence is not yet completely understood and partly speculative. This is also the case in the subset of patients treated for fecal incontinence following rectal or sigmoid resection in this and previous publications. In our series, six of seven patients showed a marked, persistent improvement of their continence situation following SNS.

It is widely accepted that the efficacy of SNS is based on a stimulation of efferent (sensory) nerve fibers although it is not yet clear if the stimulation reaches via this pathway spinal or cortical centers.[19] However, it has been repeatedly shown by us and others that the rectal sensory function is affected by SNS. This is also in accordance with the observations of Ratto and coworkers who observed an increase in "neorectal" sensation parameters during sacral nerve stimulation when the preoperative value was normal or below normal.[8] Contrary to this, the sensation parameters decreased after SNS when the preoperative value was higher than normal. In accordance with these findings, all four patients treated with SNS for fecal incontinence following rectal resection in Ratto's series showed a marked improvement.[8] In our own patients, we were able to observe an increase in all parameters of rectal compliance (threshold, urge, and maximum tolerated volume) following sacral nerve stimulation compared to the baseline. Furthermore, we have been able to show in patients with fecal incontinence based on a neurogenic (spinal) etiology that SNS led to a significant improvement of the rectal sensory function.[13]

Table 3 Median Threshold, Urge, and Maximum Tolerated Rectal Volumes to Balloon Distension (ml Air) (Median Values, Min–Max)

	Pre-SNS	Post-SNS (12 months)
Threshold	60 (25–75)	75 (40–110)
Urge	88 (40–120)	115 (70–140)
Maximal volume	115 (70–140)	145 (90–170)

Conclusion

Despite our observations, the promising results of this retrospective series have to be seen cautiously as the number of patients is very limited. Therefore, the role of SNS in the treatment of fecal incontinence following rectal resection needs further research as well as more clinical data by a larger number of patients.[8,14–15]

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Conservative Management of Adhesive Small Bowel Obstructions in Patients Previously Operated on for Primary Colorectal Cancer

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Abstract This study aimed to determine the incidence of adhesive small bowel obstruction (SBO) after primary colorectal cancer surgery and the outcomes of conservative management using gastrointestinal tubes in such cases. Between October 2000 and December 2005, 2,586 primary colorectal cancer patients underwent consecutive operations and were followed up completely for a median of 38 months. During the follow-up periods, 119 patients with 130 consecutive cases of adhesive SBO underwent conservative management using nasogastric tubes and long intestinal tubes. The overall adhesive SBO rate was 5.0% in 38 months of follow-up, and the observed incidence rate was 0.0013 per patient-month. Of the 130 cases, 104 cases (80%) were successfully treated by conservative management, and the symptoms of SBO were resolved by the sixth day (range 1 to 22). Twenty-six cases (20%) underwent surgery because of lack of clinical improvement (17) or signs of strangulation (9). The high success rate indicates that initial conservative management with intestinal decompression using gastrointestinal tubes is recommended for patients with adhesive SBO after primary colorectal cancer surgery.

Keywords Small bowel obstruction · Colorectal cancer · Long intestinal tube

Introduction

Previous abdominal operations are the most common cause of adhesive small bowel obstruction (SBO),[1–4] and colorectal surgeries are reported to result in more adhesions compared to other procedure because of the wide range of surgical field.[3,5–7] Ryan et al.[8] reported that the overall SBO rate requiring readmission after colorectal surgery was 3.6% per patient in the 3 years after surgery, and Edna et al.[9] reported that about 9% of patients developed SBO after colorectal cancer surgery. These values, however, were derived from analysis of diverse colorectal procedures, including stoma formations or arorectal procedures[8] or from analysis of SBO data caused by recurrent disease or carcinomatosis.[9] Therefore, the values do not reflect the accurate incidence of benign adhesive SBO after primary colorectal cancer surgery.

In terms of management of SBO, some recommend early operative intervention,[9,10] but many others favor initial conservative management with intestinal decompression using gastrointestinal tubes in the belief that this approach is safe and may ultimately avoid operations in the majority of patients.[1,2,11,12] However, there are large discrepancies in success rates of conservative management reported (20–73%),[1,5,6,11,13] and there are considerable controversies regarding adequate durations of tube placement. Some surgeons suggest that the duration of tube decompression should not exceed 24–48 h,[12,14–16] whereas others advocate a longer period of 5–7 days.[4,17,18] Reported differences in success rates, or in methods of conservative management, may be because previous studies included patients with a variety of causes of SBO. The earlier studies included SBO in patients with inflammatory bowel diseases, such as Crohn's disease, malignancies, incarcerated hernias, and in patients who had undergone various types of prior abdominal surgeries, which influenced the development and outcome of SBO.[6] To date, reports on SBO developed after colorectal surgery are limited,[8,9,19] and, to our

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knowledge, there is no published report on the outcomes of conservative management with intestinal decompression using gastrointestinal tubes for benign adhesive SBO after primary colorectal cancer surgery. The aim of the present study was to determine the incidence of benign adhesive SBO after primary colorectal cancer surgery and the outcomes of conservative management using gastrointestinal tubes in such cases.

Materials and Methods

Patients

Between October 2000 and December 2005, 2,835 primary colorectal cancer patients underwent consecutive operations at the Center for Colorectal Cancer, National Cancer Center, Korea. Those who had not visited our center for follow-up more than 6 months at September 2006 were defined as follow-up loss and excluded from further analysis. Of the 2,835 patients, 2,586 (91.2%) were followed up completely for a median of 38 months (range 9 to 66), allowing us to measure the incidence rate of SBO after primary colorectal cancer surgery. Of the included 2,586 patients, 157 were readmitted with a diagnosis of SBO during this follow-up period (Oct 2000–Sep 2006) and recruited as the subject of the present study. The diagnosis was made when the patients presented with at least four of the following clinical findings: colicky abdominal pain, constipation or obstipation, nausea or vomiting, abdominal distension, and increased bowel sounds on auscultation. In addition, all patients were confirmed with SBO when plane abdominal X-ray showed dilated small bowel loops with fluid levels. Patients were also checked for serum carcinoembryonic antigen levels. Abdominopelvic computed tomography and F18-fluorodeoxyglucose positron-emission tomography procedures were used if required for the detection of possible tumor recurrence or carcinomatosis. If the SBO was caused by malignant tumor recurrence or peritoneal carcinomatosis based on imaging workup (computed tomography or positron-emission tomography scan) or operative findings, the patients were excluded from further analysis (n=36, 22.9%). Of the remaining 121 patients with benign adhesive SBO, two (1.3%) underwent emergent laparotomies because signs of bowel compromise (rebound tenderness of abdomen, a body temperature above 37.5°C, a heart rate of greater than 100 beats per minute, a white blood cell count of 12,000/μl or greater) were evident at presentation. These patients were also excluded from analysis. The remaining group of 119 patients, with 130 episodes of adhesive SBO (nine had two episodes, one had three episodes), was the subjects of the present study. Each episode was considered and analyzed as an individual SBO case.

Data on demographics and the details of the colorectal cancer surgery and conservative management were collected. The incidence of SBO and the outcomes of conservative management were analyzed retrospectively. The observed incidence rate of adhesive SBO was calculated by dividing the total number of adhesive SBO cases by the total number of follow-up months, after colorectal cancer surgery, for all patients.

Conservative Management of Adhesive SBO

Postoperative adhesive SBO cases without evidences of bowel compromise at readmission received initial conser-

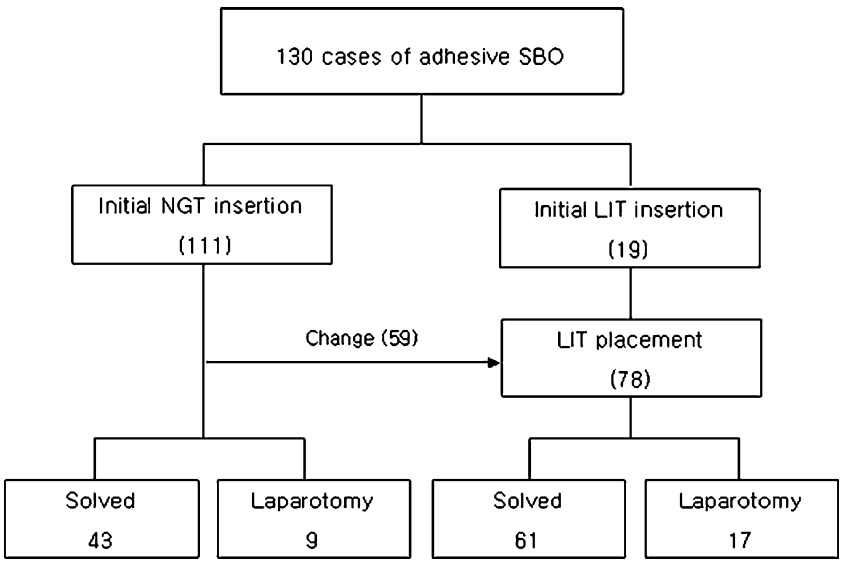

Figure 1 Scheme of conservative management for adhesive SBO using gastrointestinal tubes. *SBO* Small bowel obstruction, *NGT* nasogastric tube, *LIT* long intestinal tube.

Table 1 Demographics and Previous Colorectal Cancer Surgery Data of 130 Cases With Adhesive Small Bowel Obstruction

Variables		
Median age	Years (range)	60 (19–79)
Gender (*n*, %)	Male	91 (70)
	Female	39 (30)
Location of primary lesion (*n*, %)	Rectum	74 (56.9)
	Sigmoid colon	28 (21.5)
	Descending colon	6 (4.6)
	Transverse colon	4 (3.1)
	Ascending colon	7 (5.4)
	Synchronous multiple	4 (3.1)
	Familial adenomatous polyposis	7 (5.4)
Tumor grade (n, %)	Well differentiated	18 (13.8)
	Moderately differentiated	102 (78.5)
	Poorly differentiated	6 (4.6)
	Unknown	4 (3.1)
Tumor stage (*n*, %)	I	20 (15.4)
	II	50 (38.5)
	III	42 (32.3)
	IV	14 (10.8)
	Unknown	4 (3.1)
Radiation therapy	Yes	41 (31.5)
	No	89 (68.5)
Surgical approach (*n*, %)	Conventional open	112 (86.2)
	Laparoscopic	18 (13.8)
Operations (*n*, %)	Anterior resection	80 (61.5)
	TPC/total/subtotal	18 (13.8)
	Hartmann's procedure	10 (7.7)
	Abdominoperineal resection	9 (6.9)
	Right hemicolectomy	9 (6.9)
	Left hemicolectomy	2 (1.5)

TPC Total proctocolectomy, *total* total colectomy, *subtotal* subtotal colectomy

vative management with bowel rest, administration of intravenous fluids, and intestinal decompression using nasogastric tubes (NGTs, Levin tube, Yushin medical, Seoul, Korea) and long intestinal tubes (LITs) 220 cm in length (Ileus tube, Create medic, Yokohama, Japan). The scheme of conservative management is summarized in Fig. 1. Of the 130 SBO cases, 111 (85.4%) placed NGTs initially. If SBO was not resolved with NGT decompression, an LIT was substituted for the NGT (53.2%, 59/111 NGT cases). The median time to tube change was 2 days (range 1 to 10). If the adhesion causing SBO seemed to be located at the distal small bowel and gastric dilatation was not present (based on the imaging by plane abdominal X-ray and computed tomography), an LIT was initially placed (14.6%, 19/130 cases). Fluoroscopic guides were used to advance the LIT through the pylorus. Conservative management was considered to have failed when patients showed a lack of clinical improvement after adequate bowel decompression or when cases developed signs of intestinal strangulation (tachycardia, fever, continuous abdominal pain, leukocytosis). Failed cases underwent laparotomies.

Statistical analysis was performed using Pearson's chi-square test, Fisher's exact test, or Student's *t* test, depending on the nature of the data. A two-tailed p value<0.05 was considered to indicate a significant difference.

Results

During the median 38-month follow-up period, 119 patients were readmitted with 130 cases of adhesive SBO, and the median time to SBO development after initial colorectal cancer surgery was 3 months (range 1 to 66). The demographics, and previous colorectal surgery data, are summarized in Table 1. The overall adhesive SBO rate was 5.0% (130 cases/2,586 procedures), and, when presented as an SBO rate per patient, the incidence was 4.6% (119 patients/2,586 procedures) in the 38 months of the follow-up period. The observed incidence was 0.0013 adhesive SBOs per patient-month (130 cases in 98,268 months).

Of the 130 cases, 104 (80%) were successfully treated by conservative management as detailed above (Table 2, Fig. 2). When these 104 cases were analyzed, radiologic improvements in SBO were apparent, on average, on the fifth day (range 1 to 17) after management commenced. The symptoms of SBO were resolved, on average, by the sixth day (range 1 to 22). Fluoroscopic guides were used in all 78 LIT cases to advance the LIT through the pylorus, and, in 60 (76.9%) cases, the LIT passed into the small bowel on initial insertion. In the remaining 18 cases, 14 (77.8%) had delayed passage of LIT through the pylorus into the small bowel, after a median time of 2 days (range 1 to 5). SBO recurred during the follow-up period in ten cases (9.6%, 10/104), after initial resolution by conserva-

Table 2 Outcomes of Conservative Management for Adhesive SBO Using Gastrointestinal Tubes

Type of tubes applied	No. of cases	No. of resolution (success rate, %)*	Time to resolution (days, median, range)	Time to laparotomy in failed cases (days, median, range)
NGT only	52	43 (82.7)	7 (1–23)	4 (1–12)
NGT followed by LIT	59	48 (81.4)	11 (2–26)	8 (3–25)
LIT only	19	13 (68.4)	6 (3–13)	11.5 (7–22)
Total	130	104 (80.0)	8 (1–26)	8.5 (1–25)

NGT Nasogastric tube, *LIT* Long intestinal tube
*By chi-square test, $p=0.379$

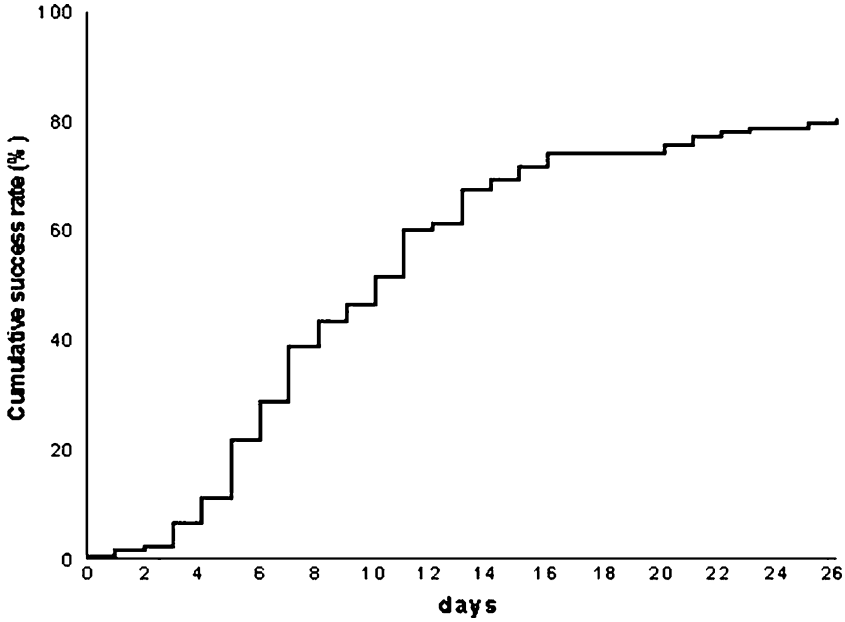

Figure 2 The cumulative success rate of conservative management with intestinal decompression using gastrointestinal tubes for an adhesive SBO after colorectal cancer surgery.

tive management, and the median time to SBO recurrence after discharge was 129 day (range 2 to 570). Of the ten recurring cases, eight were resolved by further conservative management, and two underwent laparotomies.

During observation, 26 cases (20%) underwent surgery because of lack of clinical improvement (17) or signs of strangulation (9; Table 3). In cases with signs of strangulation, operative times were longer (175±71 min vs. 111± 69 min, p=0.038), bowel resections were performed more frequently (77.8 vs. 17.6%, p=0.009), and postoperative hospital stays were longer (22.2±9.7 days vs. 15.7± 5.7 days, p=0.041). There were two postoperative morbidities of wound problems (7.7%, 2/26 cases), but there was no postoperative mortality.

Discussion

Although colorectal surgery is the most common procedure preceding development of SBO,[3,5–7] reports on the accurate incidence of SBO after colorectal surgery are limited.[8,9,19] Reported frequencies of SBO after colorectal resections vary from 1.5–12.5[9,20–22] to 24–32.6%.[18,23] In the present study, the SBO rate after the primary colorectal cancer surgery was 6.1% (157/2568), and the benign adhesive SBO rate was 4.7% (121/2,568). These rates seem to agree with the lower rates reported in the literature and possibly reflect improvements in operative techniques over time, as mentioned by Ryan et al.[8] The follow-up period in our study was short (median 38 months), however, and this might influence the observed low adhesive SBO rate. Williams et al.[6] reported that the mean time interval between initial colorectal surgery and SBO were 8.4 years. If an interval of 8.4 years is applied to our observed incidence rate of 0.0013 adhesive SBOs per patient-month, the adhesive SBO rate in 8.4 years is calculated to be 13.2% (339 SBOs in 2,586 patients in 260,669 months), and this SBO rate is now similar to that of previous studies. The median time to adhesive SBO after colorectal cancer surgery in the present study was only 3 months, however, and this interval is quite different from the interval reported by Williams et al.[6] A long-term follow-up study is needed

Table 3 Clinical Outcomes of Cases Who Underwent Laparotomies Because of Failure of Conservative Management

Variables	Total (n=26)	Cause of laparotomy		p value
		Lack of clinical improvement (n=17)	Signs of strangulation (n=9)	
Gender (male/female)	14:11	10:7	4:5	0.683
Mean age (years, SD)	57.6 (12.6)	58.9 (13.7)	55.1 (10.6)	0.473
Mean op. time (min, SD)	133.2 (75.0)	111.4 (69.2)	174.6 (71.0)	0.038
Bowel resection (n, %)	10 (38.5)	3 (17.6)	7 (77.8)	0.009
Postop. hosp. stay (days, mean, SD)	18.0 (7.8)	15.7 (5.7)	22.2 (9.7)	0.041
Morbidity (n, %)	2 (7.7)	0 (0)	2 (22.2)	0.111

SD Standard deviation

to determine an accurate SBO incidence rate in patients who have undergone primary colorectal cancer surgery.

Management of SBO after colorectal surgery is controversial. Ellis et al.[19] suggested aggressive early surgical intervention; however, these authors focused on SBO associated with metastatic colorectal carcinoma, and such patients were not included in our study. Many colorectal surgeons faced with postoperative SBO cases have used initial conservative management, unless the patients presented with signs of bowel compromise. In the present study, we also applied conservative management to all SBO patients without signs or symptoms of bowel compromise at readmission. Indeed, the number of patients with acute bowel compromise needing emergent laparotomy was very small, and only two of our patients (1.7%, 2/121 adhesive SBO patients) underwent emergent laparotomies. The success rate of conservative management in the present study was 80.0% (104/130 cases), a rate that is somewhat high in comparison with previous studies (20–73% success).[1,5,6,11,13] Our expected 80% success rate should be applied with caution to other patients with SBO of diverse causes or to other institutions with different management strategies for adhesive SBO. We worked with a very specific group of patients (those with benign adhesive SBO after primary colorectal cancer surgery), and we used rather aggressive conservative management. Gastrointestinal tubes (NGTs, LITs) were employed, following the management strategy of our center.

There are conflicting data regarding the clinical effectiveness of NGTs in comparison with LITs in the treatment of SBO. Brolin et al.[1] reported that patients treated with LITs had significantly longer postoperative ileus and higher morbidity compared to patients treated with NGTs. Conversely, Bizer et al.[2] found no difference in clinical outcomes between patients with SBO who were treated with LITs or NGTs. To resolve this issue, Fleshner et al.[24] performed a prospective, randomized trial of short versus long tubes in adhesive SBO patients and reported that these tubes were equally effective in patients with adhesive SBO, when the failure of nonoperative treatment was measured (failure rate of NGTs 46% [13/28] vs. LITs 30% [8/27], $p=0.16$). There was no difference in success rates between the types of tubes used (NGT only 82.7%, NGT followed by LIT 81.4%, LIT only 68.4%, $p=0.379$) in the present study. However, this was not designed with enough power to address this relationship. We believe that concern over the use of one type of tube over another is irrelevant in the management of adhesive SBO; the NGTs and LITs are not confronted with but complementary to each other in function. Many surgeons dealing with adhesive SBO manage patients with initial NGT decompression. When clinical improvement of SBO is not seen in spite of adequate decompression by NGT, attending surgeons have found it difficult to decide between laparotomy and a change to LIT placement. The unique feature of our strategy for adhesive SBO management is the application of LIT in a manner that complements the use of NGT. The details of our strategy have been described above.

The LIT has several advantages in the management of SBO. First, a properly positioned LIT provides suction close to the point of obstruction.[25] A small bowel distension is resolved more effectively by an LIT than by an NGT, because an LIT can approach the point of obstruction more closely than can an NGT. In an analysis of the LIT mechanics, Paine et al.[26] found that the effectiveness of intraluminal decompression in the bowel varies inversely with the measured distance between the tip of the tube and the site of blockade. Because this distance could not be easily measured, we measured the inserted length of tube instead. Even if the inserted length is associated with effective decompression of a dilated bowel, however, there was no relationship between inserted length and the success rate of conservative management in the present study (<140 cm: 77.5%, 69/89 cases vs. ≥140 cm: 85.4%, 35/41 cases, $p=0.353$). LITs also have other advantages. As a dilated small bowel can be adequately decompressed by LIT, and as general patient conditions (e.g., nutritional status, electrolyte balance) can be optimized during conservative management, outcomes tend to be favorable when operations are required. In the present study, we noted only two (7.7%, 2/26 cases) instances of postoperative morbidity (both because of wound problems), and these patients were managed conservatively.

LIT has some disadvantages associated with relatively uncommon complications, including rupture of the weighted reservoir resulting in mercury intoxication and intussusception of the small bowel with the weighted tip serving as the lead point.[27] A mercury bag is used in old-fashioned LITs, but we used LITs with weighted tips instead of mercury bags. Another possible disadvantage of LIT is the lack of gastric decompression. A properly positioned LIT provides no direct means of gastric decompression, because the suction ports are located within the small bowel. Lack of effective gastric decompression in patients with SBO may result in gastric dilatation and aspiration pneumonia.[25] For prevention of this possible complication, we used a sequential approach, where an NGT was followed by an LIT. We placed an NGT, rather than an LIT, initially, and if no improvement in SBO was apparent, we changed from an NGT to an LIT. This strategy decompressed dilated stomachs, and no patient suffered aspiration pneumonia. Gastric dilatation developing after the tube change could not be prevented; hence, it is necessary to take serial radiographs to check gastric dilatation.

In the present study, the median duration of conservative management for 17 cases undergoing laparotomy because

of lack of clinical improvement was 11 days (range 7 to 25). This duration was longer than recommended in the literature, and this may be explained by the use of LITs. It took time for the LIT to distally advance to the obstruction site and to adequately decompress the dilated bowel. Advancement of a tube beyond the pyloric sphincter is usually not easy. We used fluoroscopic guides in all 78 cases of LIT usage, to advance the LITs through the pylorus, and, in 60/78 cases (76.9%), the LIT passed into the small bowel at first attempt, with a trial time of 10–20 min. An alternative method used to advance LIT into the small bowel is gastrointestinal endosocpy,[28] and Gowen et al.[29] reported a good success rate of 90% using an improved tube designed for endoscopic placement.

During the observation period after tube placement, 9/130 cases (6.9%) developed signs of strangulation and underwent urgent laparotomies. These cases were associated with unfavorable outcomes (longer operative times, more frequent bowel resections, and longer postoperative hospital stays). Although not significant statistically, the two cases with wound problems were included in this group. We were unable to accurately identify these patients before progression of strangulation. Further study on the issues of surgical timing, and identification of candidates for surgical intervention, are needed.

Conclusion

The overall adhesive SBO rate was 5.0% in 38 months of follow-up, and the observed incidence rate was 0.0013 per patient-month. Conservative management using tube decompression for adhesive SBO after primary colorectal cancer surgery had a success rate of about 80%. This suggests that initial conservative management, with intestinal decompression using gastrointestinal tubes, is indicated for such patients. An LIT insertion guided by fluoroscopy adds to the ease of the procedure. A laparotomy with enterolysis or bowel resection is indicated for those patients who fail conservative management, and careful patient observation during decompression is of the outmost importance for a good outcome.

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Local Recurrence after Laparoscopic Resection of T3 Rectal Cancer without Preoperative Chemoradiation and a Risk Group Analysis: An Asian Collaborative Study

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Abstract Risk factors for local recurrence and indication for preoperative radiation therapy have not been well evaluated for patients undergoing laparoscopic rectal cancer operation. From 1998 to 2004, 497 T3 rectal cancer patients with tumor located within 12 cm from the anal verge who had undergone laparoscopic surgery without preoperative radiation therapy by eight experienced laparoscopic surgeons in four Asian countries were reviewed retrospectively for the incidence of local recurrence and related factors. The median follow-up was 29.0 months (range, 6.0 to 92.3), and 31 cases of local recurrence were observed during the follow-up period (6 anastomosis site, 6 perineum, 17 pelvic wall, and 2 unclassified). The estimated local recurrence rates at 24 and 60 months were 5.42 and 9.41%, respectively. Patient's gender, tumor location, lymph node metastasis, and tumor perforation were independent factors for local recurrence by multivariate analysis. The local recurrence rate was comparable to previous studies using conventional open surgery with preoperative chemoradiation, except for a subgroup of male patients with the tumor located within 7 cm from the anal verge. The indication for preoperative radiation therapy would be different from those who will undergo conventional open surgery, and further evaluation of the benefits of preoperative radiation therapy is required for those with low risk tumor.

Keywords Laparoscopy · Local recurrence · T3 Rectal cancer

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Introduction

Local recurrence has been one of the difficult problems in rectal cancer surgery, and the related risk factors such as tumor, patient, and surgeon have been evaluated on

conventional open surgery.[1–4] The control of risk factors has resulted in the improvement of outcome during the last few decades. The improvement was achieved mainly by subspecialization and training associated with meticulous pelvic dissection or total mesorectal excision (TME)[2,5,6] and judicious application of perioperative radiation therapy.[7–9] However, the combined morbidities of treatment, especially radiation therapy, is not negligible, and careful patient selection is necessary for optimal outcome.[10]

Laparoscopic surgery has widely been accepted for colon cancer. Acceptable outcomes and the safety of laparoscopic surgery for rectal cancer under experienced surgeons have been reported.[11–16] Meticulous dissection with minimal tumor manipulation under a magnified pelvic view obtained through laparoscopic surgery would be of considerable benefit for rectal cancer operation.[17] In laparoscopic rectal cancer surgery, the local recurrence and the related risk factors would be different from those of conventional open surgery, and therefore, the indication for radiation therapy could also be different from those of conventional open surgery.

In this study, we evaluated the local recurrence and the related risk factors with those who had received laparoscopic resection for T3 rectal cancer without preoperative radiation therapy and classified the risk groups according to these factors.

Materials and Methods

The data were collected from eight experienced laparoscopic colorectal surgeons from seven institutions in four Asian countries. Five hundred and four patients met the following inclusion criteria: received potentially curative laparoscopic rectal resection from January 1998 to December 2004, histopathologically proven T3 adenocarcinoma, distal margin of tumor located within 12 cm from the anal verge, preoperative radiation therapy was not given, and postoperative follow-up of more than 6 months. Seven cases were excluded for insufficient medical record, and 497 patients were finally enrolled for the study.

The data were filled up by each surgeon according to the protocol including patients' characteristics (age and gender), tumor characteristics (location, size, histopathologic features and resection margins), operation (duration and kind of procedure, extent of lymph node dissection, conversion to open surgery, protective stoma, and related complications), adjuvant therapy (chemotherapy and postoperative radiotherapy), and tumor recurrence. Anastomotic leakage was defined as any clinical evidence of anastomotic dehiscence including the color change of drain with or without radiological confirmation. The longest diameter of the tumor was used for measuring the tumor size, and the shortest distance was used for measuring the resection margin. Measurements were done after formalin fixation. Anterior resection (AR) was defined as the operation with anastomosis located above the peritoneal reflection, while low anterior resection (LAR) was defined as operation with the anastomosis located below the peritoneal reflection and above the levator ani muscle. When the anastomosis was located at the level of the levator ani muscle or at the anal canal, it was considered as ultralow anterior resection (uLAR) including both the hand-sewn colo-anal anastomosis and the stapled anastomosis. Lower margin of tumor located at 7 cm or less from the anal verge was considered as low located tumor, and those located more than 7 cm from the anal verge was considered as high located tumor. Follow-up was performed on regular visits of 3-month interval for the first two postoperative years, then of 6-month interval for the next 3 years. Follow-up studies included physical examination and serum CEA assay every 3 months for the first 2 years and thereafter every 6 months. Chest X-ray and abdominopelvic computed tomography was taken every 6 months. Rigid proctoscopy, flexible sigmoidoscpy, or colonoscopy was performed every 6 or 12 months, based on the institutional policy. Additional tests were performed on an as-needed basis. Local recurrence was defined as clinically or histopathologically verified recurrent tumor within the pelvis or perineum after potentially curative resection, and this included intraluminal recurrence (at anastomosis site), intrapelvic recurrence (pelvic organ, pelvic wall, and lymph node), and perineal wound recurrence.

Statistical analysis was performed using the SPSS statistical package (SPSS 11.0 for Windows; SPSS, Chicago, IL). Categorized variables were analyzed by using the Chi-square test and Fisher's exact test, while continuous variables were analyzed using *t* test and ANOVA. The local recurrence rates were estimated by Kaplan–Meier analyses and compared by the log rank test. Cox proportional hazards model was used for multivariate analysis. Confidence intervals (CI) were taken at 95%, and probability values less than 0.05 were considered significant.

Results

Patient Characteristics and Operative Results

The number of cases contributed by each surgeon ranged from 24 to 139. There were 289 male patients (58.1%) and 208 female patients (41.9%). The age of the patients ranged from 59.0 to 66.8 years. When the characteristics were analyzed according to gender, the operation time was found to be significantly different (Table 1).

Table 1 Clinicopathological features according to gender

Factor	Male (289)	Female (208)	*p*
Age (year)	62.2±11.6	60.9±12.5	NS
Tumor size (cm)	4.7±1.4	4.6±1.6	NS
Distance from anal verge (cm)	7.1±3.0	6.9±3.0	NS
Operation(n=495)			
AR(59)	32 (54.2%)	27 (45.8%)	NS
LAR(221)	125 (56.6%)	96 (43.4%)	
uLAR(105)	64 (61.0%)	41 (39.0%)	
APR(110)	67 (60.9%)	43 (39.1%)	
Operation time (min)	228.2±85.9	202.1±82.1	<0.05
Blood loss (ml)	139.9±228.6	115.9±170.5	NS
Conversion			
Yes	4	5	NS
No	285	203	
Distal resection margin (cm)	3.0±1.4	3.2±1.8	NS
Lymph node metastasis			
Yes	125 (43.2%)	103 (49.5%)	NS
No	164 (56.8%)	105 (50.5%)	

Abdominoperineal resection (APR) was performed in 22.1% of the patients. The sphincter preservation rate was 55.5% for low located tumor and 100% for highly located tumor. Temporary defunctioning stoma was fashioned in 29.6% of the 385 sphincter preserved patients (excluding Hartmann's operation), and its frequency was significantly different depending on the type of operation performed (43.8% of uLAR, 19.9% of LAR, and 6.8% of AR). Anastomotic leakage occurred in 11.7%, and it was not significantly different according to the type of operation (p=0.055) or whether a temporary stoma was made or not (11.3% of the patients without stoma vs 12.8% of the patients with stoma). Conversion to open laparotomy occurred in 1.8% of the operations, and it was not significantly different according to the tumor location or the tumor size. Tumor perforation during the operation occurred in four cases (0.8%), all of which occurred on highly located tumors. The mean number of harvested lymph nodes was 18.0 (±11.36), and lateral pelvic node dissection was performed in 1.4% of the patients. There were 269 N0 patients (54.1%), 132 N1 patients (26.6%), and 96 N2 patients (19.3%). Distal resection margin was significantly different according to the operation: uLAR, 3.3 (±1.4) cm; LAR, 2.13 (±1.9) cm; and AR 3.43 (±1.3) cm, and it was also significantly different according to the tumor location: low located tumor, 2.76 (±1.6) cm; and high located tumor, 3.55 (±1.4) cm.

Adjuvant chemotherapy was given to 58.6% of N0 patients and 76.8% of N1 or N2 patients. 5-Fluorouracil (5-FU) was the most frequently used agent which was given orally (73.7% of N0 patients) or by intravenous infusion (61.7% of N1 or N2 patients). Postoperative radiation therapy was given to 4.2% of N0 patients and 23.6% of N1 or N2 patients.

Local Recurrence and Risk Group Analysis

The median follow up period was 29.0 months (range, 6.0 to 92.3). Thirty-one cases of local recurrence were found during the follow-up period. Four of the 31 patients developed systemic recurrence simultaneously or before the local recurrence, while ten of them developed systemic recurrence after the local recurrence was diagnosed. The estimated local recurrence rates at 24 and at 60 months after the operation were 5.42 and 9.41%, respectively. The locations of the recurrence were at the anastomotic site (n=6), perineum (n=6), pelvic wall (n=17), and unclassified (n=2). The significant prognostic factors for local recurrence by univariate analysis were patient's gender, surgeon, operation method, tumor location, lymph node metastasis, and tumor perforation during the operation (Table 2), whereas postoperative radiation therapy and chemotherapy were not significant factors for the development of local recurrence. Multivariate analysis was performed on factors such as gender, surgeon, tumor location, tumor size, operation method, lymph node metastasis, tumor grade, distal resection margin, anastomotic leakage, and tumor perforation during the operation. The gender, tumor location, lymph node metastasis, and tumor perforation were found to be independent prognostic factors (Table 3). Because gender and tumor location are the factors which can be clearly defined before surgery, the risk group was classified according to these two factors. When the local recurrence was calculated according to the risk group, significant difference was found among the four groups;

Table 2 Prognostic factors for local recurrence by univariate analysis

Factor	Recurrence-free survival rate		*P*
	(24 months)	(60 months)	
Gender (*n*=497)			
Male (289)	92.5	89.6	0.009
Female (208)	97.4	92.7	
Age (*n*=497)			
Younger than 60 (195)	95.4	84.4	NS
60 or more (302)	94.1	92.2	
Operation(*n*=436)			
LAR(221)	97.6	96.4	0.0005
uLAR(105)	87.8	83.6	
APR(110)	91.8	83.6	
AV (*n*=420)			
≤7 cm (225)	90.2	83.7	0.0006
>7 cm (195)	97.9	96.7	
Tumor size (*n*=463)			
≤5 cm (326)	94.5	92.9	NS
>5 cm (137)	94.3	84.3	
Distal resection margin (n=359)			
≤2 cm (104)	90.1	94.8	NS
>2 cm (255)	88.4	90.5	
N (*n*=497)			
N0 (269)	97.1	92.4	0.02
N1 (132)	91.5	88.0	
N2 (96)	91.4	89.5	
Leakage (*n*=497)			
Yes (45)	95.2	91.4	NS
No (452)	94.5	90.6	
Tumor perforation (*n*=497)			
Yes (4)	25.0	0	0.000
No (493)	95.1	91.1	

however, the significant difference was not found when group IV (male patients with the tumor located within 7 cm from anal verge) was excluded (Table 4).

Discussion

In the present study, we evaluated the local tumor recurrence after laparoscopic rectal cancer surgery by analyzing 497 T3 rectal cancer patients who did not receive preoperative radiation therapy. The patient's gender, tumor location, lymph node metastasis, and intraoperative tumor perforation were found to be independent factors, whereas the surgeon factor was not. During the last 20 years, the local recurrence has decreased due to the efforts for standardization and education of TME in conventional open surgery. In laparoscopic rectal surgery, the magnification and better identification of structures deep in the pelvis is beneficial not only for rectal dissection but also for education and standardization because it can provide a common visual field for all members of the operating team,

Table 3 Prognostic factors for local recurrence by multivariate analysis (Cox's proportional hazard model)

Factor	Odds ratio	95% Confidence interval	*P*
Gender (male/female)	4.445	1. 682–11.749	0.001
Tumor Location (≤7 cm/>7 cm)	6.789	2.574–17.910	0.000
Lymph node tumor involvement (negative/positive)	2.839	1.260–6.396	0.012
Tumor perforation (no/yes)	11.220	3.149–39.972	0.000

Table 4 Local recurrence according to the risk group (Kaplan–Meier's method)

Group	Local recurrence (%)		*P*
	(24 months)	(60 months)	
I (Tumor >7 cm from anal verge, female)	0	0	0.0001*
II (Tumor >7 cm from anal verge, male)	3.5	5.3	
III (Tumor ≤7 cm from anal verge, female)	4.6	14.2	
IV(Tumor ≤7 cm from anal verge, male)	13.5	17.5	

*The significance was not found when group IV was excluded.

recorded images for review and discussion after the operation or whenever a review may be convenient.[19,20] In earlier randomized studies of laparoscopic colon cancer surgery, rectal cancer was excluded because of difficulties associated with pelvic dissection and the surgeon's operative skill; and these difficulties were frequently emphasized in studies involving laparoscopic rectal caner surgery.[11–18] The patients in this study were operated by experienced laparoscopic surgeons, and the surgeon factor should be minimal. Nevertheless, the indication and preference of preoperative radiation therapy were different between surgeons or between hospitals, resulting in significant differences in the patient's characteristics and the local recurrence rate in univariate analysis.

The estimated local recurrence rate in this study was 5.42% at 24 months and 9.41% at 60 months. Considering the inclusion criteria, this is comparable to recent studies with laparoscopic rectal cancer surgery (range, 2.9 to 6.8%).[11–16] Tumor perforation during the operation was an independent risk factor for local recurrence. This is in agreement with those found in previous studies involving conventional open surgery,[3,21,22] and tumor perforation has been reported as an indication for the conversion to laparotomy in the study with laparoscopic surgery.[16] The significance of the operation method found in the univariate analysis was not found in the multivariate analysis; therefore, a combination of different poor prognostic factors for those with low located tumor should be considered.[21,23] The tumor location is reported in many studies as an independent risk factor, while controversies still exist for the patient's gender.[3,4,6,21,23] We also found significantly different operation time and local recurrence in female patients. There are possible benefits for female patients during laparoscopic pelvic operation due to the fact that females have a wider pelvis and lower peritoneal reflection level which provide improved field of view, resulting in lesser pelvic organ injuries and complications.[24,25,26] During the subgroup analysis according to gender and tumor location, significant difference was found on recurrence-free survival; however, the significance was not found among groups I, II, and III. The 5-year local recurrence rate of T3 or locally advanced low rectal cancer with preoperative chemoradiation therapy ranges from 8.1 to 15.6%[27–29] in conventional open surgery, and this was similar with groups I, II, and III in this study. Preoperative radiation therapy for the locally advanced rectal cancer is generally accepted in conventional open surgery; however, in laparoscopic surgery, further evaluation and larger studies on female patients or male patients with tumor located more than 7 cm from anal verge are needed.

This study was retrospectively performed with the data collected from seven hospitals in different Asian countries. Consequently, there are possible biases and limitations. The exact measurement of circumferential resection margin was available in only a few cases, and follow-up duration was not enough in some cases. The rate of APR was lower than in other studies. The significances of other risk factors reported in open surgery were not found with 31 local recurrences among 497 patients in this study, and studies with larger number of cases would be required. However, studies on local recurrence and related risk factors for laparoscopic rectal surgery are rare; therefore, this study would be valuable and helpful, especially for studies concerned with preoperative radiation therapy for laparoscopic surgery.

Conclusions

In conclusion, tumor perforation, low tumor level, male gender, and lymph node metastasis were independent risk factors for developing local recurrence in T3 rectal cancer without preoperative radiation therapy after laparoscopic surgery. Further studies on the impact of preoperative radiation therapy on laparoscopic rectal resection are needed for female patients with a rectal cancer at any level and male patients with a rectal cancer located more than 7 cm from the anal verge.

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Comparison of Stapled versus Handsewn Loop Ileostomy Closure: A Meta-analysis

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Abstract The purpose of this study was to compare the rates of small bowel obstruction, anastomotic complications, and wound infections between stapled and handsewn closures of loop ileostomies. A literature search in Embase, PubMed, and Cochrane Database for Clinical Trials using search terms "closure," "loop ileostomy," and "stapled" was performed. All abstracts were reviewed to identify relevant articles, and their references were hand searched for additional studies. Six articles were identified for inclusion. Three independent reviewers extracted the following data: rates of small bowel obstruction, anastomotic complications, wound infection; length of hospital stay; and operative time. Data analysis was performed using Stata statistical software. Comparing stapled versus hand-sewn closures, there were no statistically significant differences in bowel obstruction (relative risk [RR] 0.69, 95% confidence interval [CI] 0.44 to 1.09), wound infection (RR 0.91, 95% CI 0.53 to 1.97), or anastomotic complication rates (RR 1.01, 95% CI 0.99 to 1.03). Two studies showed shorter operative times favoring stapled anastomoses. No difference was seen in length of stay. Current literature suggests no statistically significant differences between stapled and hand-sewn loop ileostomy closures, but there may be a trend favoring stapled closures with regard to lower small bowel obstruction rates and shorter operative time.

Keywords Meta-analysis · Loop ileostomy · Closure · Complications · Morbidity

Introduction

The diverting loop ileostomy is a commonly used stoma, often employed to diminish the consequences of an anastomotic leak in low colorectal anastomoses, ileal pouch-anal anastomoses, and in situations where reversible patient factors increase the risk of an anastomotic dehiscence. They are also used to divert the fecal stream in the event of an anastomotic leak and, occasionally, in severe fistulizing perianal disease.

Once anastomotic healing has been confirmed, systemic factors corrected, or fistulizing disease controlled or corrected, these ileostomies are typically closed usually through the stoma site without a formal laparotomy. Both loop ileostomy construction and subsequent closure are, in general, felt to be fairly straightforward, safe procedures, with relatively low associated morbidity and mortality.[1] Many opinions exist about the optimum method of performing these anastomoses, with proponents of differing methods claiming several advantages including diminished risk of anastomotic complications, small bowel obstructions (SBOs), and operative time, among others.

Proponents of sutured anastomoses often claim that, because many sutured closures do not require bowel resection, the intact bowel wall along with its blood supply, which comprises part of the anastomosis, should contribute to better healing, compared to completely divided bowel, as in the case with stapled anastomoses. Some also argue that the cost of these anastomoses is far less than that of stapled anastomoses.

Conversely, those in favor of stapled anastomoses often claim that these have a larger diameter compared to sutured anastomoses and, thus, will likely have a lower risk of SBO. Stapled proponents will also claim that these

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anastomoses are typically faster to construct and, thus, result in decreased operative times and potential cost savings in that regard.

Several studies have examined these differing surgical techniques in closing loop ileostomies to find the method that minimizes perioperative morbidity, including bowel obstruction, wound infection, and anastomotic leak, as well as operative time. Unfortunately, most of these studies are underpowered, and they either do not demonstrate a significant difference or report conflicting results.[1] As a result, there is no consensus on the superior method of loop closure. Thus, we performed a meta-analysis on these studies in an attempt to answer this question.

Materials and Methods

This analysis was performed using the quality of reporting of meta-analyses criteria for reporting meta-analyses. Studies that compared stapled versus sutured ileostomy closures were considered for inclusion. Studies that did not report data separately between the two groups were excluded.

All searches were performed in duplicate on multiple databases: Embase, Medline (PubMed), and Cochrane Clinical Trials Registry. The search terms "loop ileostomy," "closure," and "stapled" were used, with the Boolean operator "and." A total of 32 studies were identified. The abstracts were reviewed, and six studies met our inclusion criteria.[1–6] The bibliographies of these were hand searched to identify three additional studies; none of which fit our inclusion criteria. We also hand searched abstracts from international colorectal meetings in the past 10 years and contacted experts in the field in an attempt to identify any unpublished data available.

Data extraction was performed by three independent reviewers. Differences were resolved by consensus. Assessment of randomized controlled trials (RCTs) was performed using the Jadad scoring system.[7] The non-RCT studies were not scored. Each study was graded based on its level of evidence, adopted from the scale by Sackett et al.[8] Data collected included lead author, date of publication, study design, number of patients in each arm, mean follow-up period, length of stay (LOS), operative (OR) time, bowel obstruction rates, wound infection rates, and anastomotic complication rates (leak, abscess, and fistula).

Data analysis was performed using Stata (version 8.0). As we were unable to obtain standard deviations for LOS and OR time data from the authors, these were reported as mean differences. Statistical significance was defined as $p < 0.05$. Complication rates were approximated with a fixed-effects model and calculated using Mantel–Haenzsel risk ratios.

Results

The characteristics of the included studies are shown in Table 1. There are two RCTs, one retrospective study, and three nonrandomized prospective audits. Heterogeneity was not significant between the studies ($p>0.34$). There was no strong evidence of publication bias seen on the funnel plot in Fig. 1.

Three prospective audits and a retrospective study were included in this analysis. The two RCTs available on the topic do not include sample size calculations and do not appear properly powered to answer a clinically meaningful question. As a result of the methodologic limitations of these two RCTs, they have been included in this study with the prospective cohort studies and the retrospective study. Although there is significant heterogeneity in the design of the included studies, they are all of similar methodologic quality (level 2B[8]).

A single perioperative mortality was reported in each of the studies by Wong et al.[2] and Garcia-Botello et al.[5] Neither was specified in which group the deaths occurred, and these were attributed to cardiac events and pulmonary embolism, respectively. Details of the other perioperative complications are shown in Table 2.

A fixed-effects model depicting the rates of SBO is shown in Fig. 2. All six of the studies reported SBO rates. Of these, one study showed an increased risk in SBO after sutured

Table 1 Study Characteristics

Study	Journal	Year	Study design	*N* stapled	*N* sutured	Jadad score[7]	Level of evidence[8]	Mean follow-up (months)
Hull[1]	DCR	1995	RCT	31	30	2	2B	>30 days
Wong[2]	DCR	2005	Retrospective	226	1,278	n/a	2B	n/a
Bain[3]	Ann R Coll Surg Eng	1996	Nonrandomized audit	20	20	n/a	2B	15 stapled, 36 sutured
Hasegawa[4]	Ann Surg	2000	RCT	71	70	1	2B	n/a
Garcia[5]	Dig Surg	2004	Nonrandomized audit	47	62	n/a	2B	18.93 days
Feinberg[6]	Am J Surg	1987	Nonrandomized audit	9	101	n/a	2B	n/a

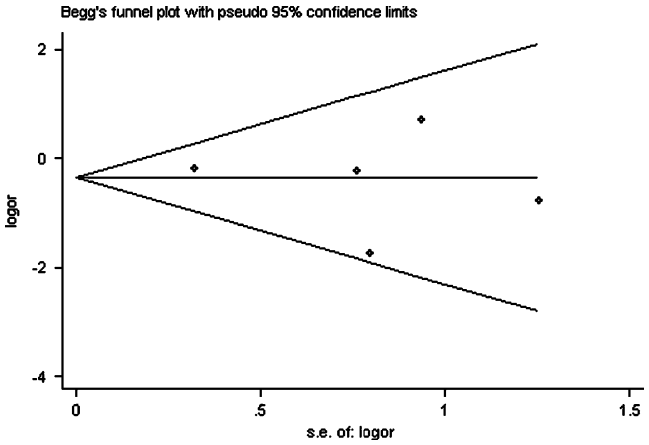

Figure 1 Begg's funnel plot assessing publication bias. *s.e. of logor* represents standard error of log odds ratio; *logor* stands for log odds ratio. The *dashed lines* are pseudo 95% CI. A symmetric plot distribution suggests that there is no evidence of publication bias.

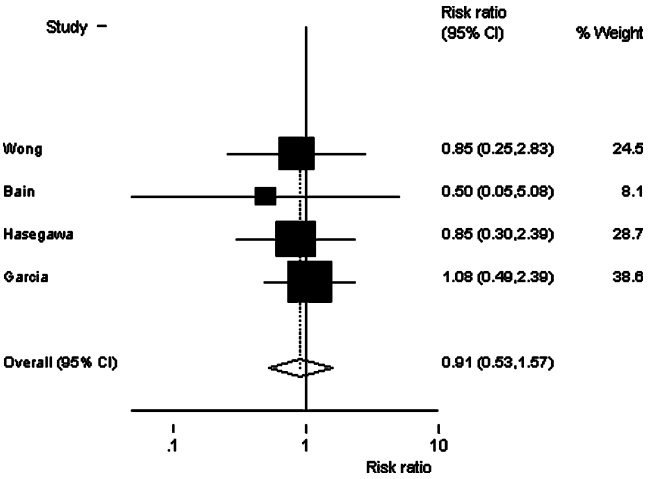

Figure 3 Risk ratio of wound infection after stapled versus handsewn loop ileostomy closures. The *solid central line* represents no difference in infection rate between the two groups. *Values greater than 1* represent an increased infection rate in the stapled group, expressed as the risk ratio. The combined risk ratio is demonstrated on the *bottom*, with its width indicating 95% CI.

loop closures, representing 21.3% of the study weight. The overall combined relative risk (RR) of SBO was 0.67 (95% confidence interval [CI] 0.43 to 1.05), with no statistically significant difference between the two groups.

A fixed-effects model depicting the rates of wound infection is shown in Fig. 3. Four of the six studies reported wound infection rates. None of these studies demonstrated an increased risk of wound infections in either group. There was no statistically significant difference between the groups, with an overall combined RR of 0.91 (95% CI 0.53 to 1.57).

A fixed-effects model depicting the rates of anastomotic septic complication is shown in Fig. 4. Four of the six studies reported on these complications. None of the studies demonstrated an increased risk of anastomotic complications in the either group. The overall combined RR was 0.75 (95% CI 0.33 to 1.67), which is not statistically significant.

Tables 3 and 4 show LOS and OR time data, respectively. A statistical model could not be applied to these because the data required for the necessary calculations were unavailable, as previously discussed. Consequently, LOS and OR times are reported as mean differences. Three of the six studies report LOS data,[2–4] and three studies report OR time.[1,2,4] Two of these studies, representing 25.6% of study weight, reported a longer OR time with sutured closures (Table 3). The difference in LOS

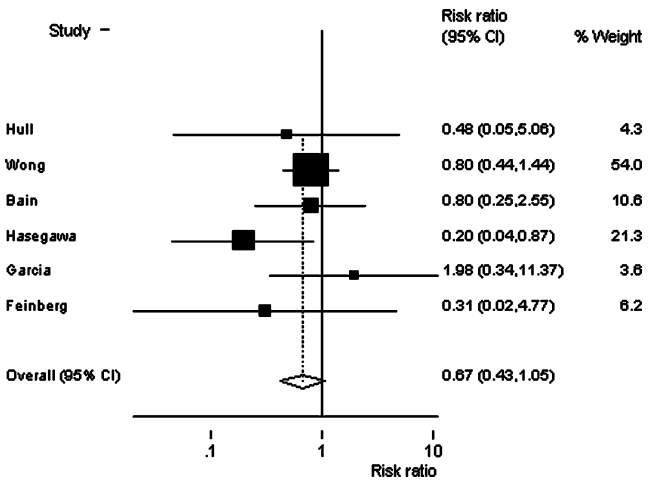

Figure 2 Risk ratio of SBO after stapled versus handsewn loop ileostomy closures. The *solid central line* represents no difference in SBO rate between the two groups. *Values greater than 1* represent an increased SBO rate in the stapled group, expressed as the risk ratio. The combined risk ratio is demonstrated on the *bottom*, with its width indicating 95% CI.

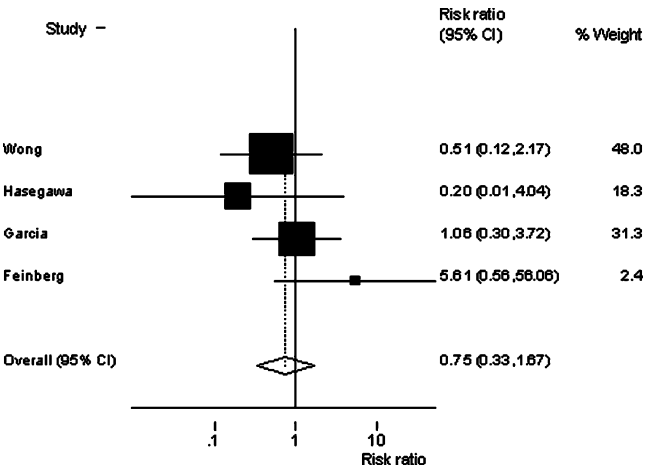

Figure 4 Risk ratio of anastomotic complications after stapled versus handsewn loop ileostomy closures. The *solid central line* represents no difference in complication rate between the two groups. *Values greater than 1* represent an increased complication rate in the stapled group, expressed as the risk ratio. The combined risk ratio is demonstrated on the *bottom*, with its width indicating 95% CI.

Table 2 Perioperative Complications

Study	SBO rate (%)		Wound infection rate (%)		Anastomotic septic complication rate (%)	
	Stapled	Sewn	Stapled	Sewn	Stapled	Sewn
Hull[1]	3.2	6.7	–	–	–	–
Wong[2]	5.3	6.7	1.3	1.6	0.9	1.7
Bain[3]	20	25	5	10	–	–
Hasegawa[4]	2.8	14.3	8.5	10	0	2.9
Garcia[5]	6.4	3.2	19.1	17.7	8.5	8.1
Feinberg[6]	0	15.8	–	–	11.1	3.0

was not statistically significant in any of the studies (Table 4).

Discussion

The temporary loop ileostomy is a frequently constructed stoma used in a variety of situations. It is generally felt to be simple to construct and easy to close, with low perioperative morbidity and mortality. The two principal anastomotic techniques are end-to-end sutured and functional end-to-end stapled anastomoses. Although many surgeons have a preference, the superior technique remains unclear.

This meta-analysis attempts to demonstrate whether any significant difference exists in the short-term outcomes between stapled versus handsewn loop ileostomy closures. However, the studies were difficult to compare because of their significant differences in study design, follow-up period, and even primary outcomes. Two RCTs, three prospective nonrandomized audits, and one retrospective study were analyzed in this paper. In general, the studies were of poor methodologic quality.

One RCT was designed to show faster recovery with stapled anastomoses and, hence, shorter hospital stays,[1] but did not address specific complications of loop closures. The other RCT[4] was intended to demonstrate that both techniques were equivalent. Neither of these studies described their randomization or blinding techniques. Both studies showed similar complication rates between the two surgical techniques, but both were underpowered to show any statistically significant difference.

Two studies were from the same center and cover the same time period.[1,2] One was a large retrospective study[2] that may have included data from the other, much smaller RCT.[1] We contacted the corresponding author in the initial study,[1] but we were not able to determine whether the subsequent study included any of the patients in the first. Because the earlier RCT looked at different outcomes that in fact were not duplicated in the subsequent retrospective study, we elected to include both in this meta-analysis. Although this might skew the results in favor of stapled anastomoses, the numbers in the former study were so small that duplication would be unlikely to have made a significant difference.

SBO in association with loop ileostomies is surprisingly common and can occur while the loop ileostomy is in place or after its closure.[9–11] It is felt that the two most common reasons for SBO in this regard are adhesions and anastomotic strictures. Although it is unlikely that the method of anastomosis will significantly affect adhesion formation, it is possible that the risk of strictures could be different. In the handsewn technique, one is generally anastomosing to a fairly small caliber distal limb, and thus perioperative edema might compromise the luminal diameter enough to cause an early obstruction. Furthermore, later scar formation could be more likely to cause a clinically significant stricture. On the other hand, stapled

Table 3 Mean Difference in Operative Time Between Stapled and Handsewn Loop Closures

Study	Stapled		Sewn		MD (min)
	N	OR Time (min)	*N*	OR Time (min)	
Hull[1]	31	60.0	30	74.7	+14.7*
Bain[2]	20	35	20	37	+2
Hasegawa[4]	71	38	70	42	+4*

N Number of patients; *OR Time* operative time, in minutes; *MD* mean difference, in minutes
*$p<0.05$

Table 4 Mean Difference in Length of Stay Between Stapled and Handsewn Loop Closures

Study	Stapled		Sewn		MD (days)
	N	LOS (days)	*N*	LOS (days)	
Wong[2]	226	3	1278	4	+1
Bain[3]	20	7	20	8	+1
Hasegawa[4]	71	8	70	10	+2

N Number of patients; *LOS* length of stay, in days; *MD* mean difference, in days

anastomoses are, in general, of greater caliber and, thus, may have a lower risk of luminal narrowing.

SBOs were more common in the handsewn group in five of the six trials. This difference was statistically significant in only one of the studies. The combined data showed a relative risk of SBO of 0.67 in the stapled group, which was not statistically significant. However, it may be clinically meaningful and, in view of the poor methodology of the published data, may warrant further study. In addition, it is important to note that these studies looked primarily at early postoperative SBO and not late SBO. Most of the follow-ups were very short and, clearly, only addressed perioperative complications. Thus, the question of whether one technique is superior to the other in terms of late SBO remains unclear.

The risk of wound infections was also addressed by this study. Intuitively, it would seem that the method of handling the wound would have more of an impact on wound infection risk than the type of anastomosis performed. Traditionally, it is believed that open versus closed skin wounds confer a different risk in skin infection, with the latter having a higher risk.[12] However, some believe that there is no such difference between open and closed wounds and that closing a wound avoids the associated long healing times.[13] Although Hasegawa et al., Bain et al., and Garcia-Botello et al. all closed their skin wounds, Hull et al. left the wound open and Wong et al. reported both. In spite of this, all the groups reported no statistically significant differences in wound infection. This is possibly because of random distribution of wound handling techniques such that both groups have a similar number of each, assuming the technique of skin closure actually influences infection rates.

There have been numerous studies comparing the integrity of handsewn versus stapled bowel anastomoses, and it is generally felt that their complication rates (namely, leak and fistula) are similar.[10,14] Not surprisingly, our study showed that anastomotic complication rates are not statistically different between the two groups. It appears that both methods of loop ileostomy closure are similar in regard to anastomotic complications, and as such, there is no single superior method.

We were unable to statistically compare LOS and OR time because the data required for the calculations were unavailable. We contacted the individual authors, who no longer had that data on hand. Despite this, we found that LOS was similar between the two groups, although there was a trend favoring stapled anastomoses in regard to shorter OR times. It is not surprising that LOS is not significantly different between the two groups across the studies. As the perioperative complication rates are comparable, it is reasonable that the LOS would be similar as well.

It was clear that OR time was shorter in two of the three studies, reaching statistical significance. Hull et al.[1] described a lower associated cost with stapled over handsewn anastomoses because of shorter OR times. As such, one could argue that the increased costs of a bowel stapler can be offset by the decreased costs of shorter operative times, resulting in overall savings. However, because OR time and associated costs may be an institution- and an operator-dependent phenomenon, generalization of these results would be difficult.

Conclusion

This study failed to demonstrate a clearly superior anastomotic technique for closing loop ileostomies. There were trends toward superiority of the stapled technique in terms of lower SBO rates and shorter operative time. Further studies are required to definitively address these issues.

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Effect of Laparoscopic Mini-Gastric Bypass for Type 2 Diabetes Mellitus: Comparison of BMI >35 and <35 kg/m^2

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Abstract

Background Laparoscopic gastric bypass resulted in significant weight loss and resolution of type 2 diabetes mellitus (T2DM). The current indication for bariatric surgery is mainly applied for patients with body mass index (BMI) >35 kg/m^2 with comorbidity status. However, little is known concerning T2DM patients with BMI <35 kg/m^2. Recent studies have suggested that T2DM patients with BMI <35 kg/m^2 might benefit from gastric bypass surgery.

Methods From Jan 2002 to Dec 2006, 820 patients who underwent laparoscopic mini-gastric bypass were enrolled in a surgically supervised weight loss program. We identified 201 (24.5%) patients who had impaired fasting glucose or T2DM. All the clinical data were prospectively collected and stored. Patients with BMI <35 kg/m^2 were compared with those of BMI >35 kg/m^2. Successful treatment of T2DM was defined by HbA1C <7.0%, LDL <100 mg/dl, and triglyceride <150 mg/dl.

Results Among the 201 patients, 44 (21.9%) had BMI <35 kg/m^2, and 114 (56.7%) had BMI between 35and 45, 43 (21.4%) had BMI >45 kg/m^2. Patients with BMI <35 kg/m^2 are significantly older, female predominant, had lower liver enzyme and C-peptide levels than those with BMI >35 kg/m^2. The mean total weight loss for the population was 32.1, 33.4, 31.9, and 32.8% (at 1, 2, 3, 5 years after surgery), and percentage to change in BMI was 31.9, 34.2, 32.2, and 29.5% at 1, 2, 3, and 5 years. One year after surgery, fasting plasma glucose returned to normal in 89.5% of BMI <35 kg/m^2 T2DM and 98.5% of BMI >35 kg/m^2 patients (p=0.087). The treatment goal of T2DM (HbA1C <7.0%, LDL <150 mg/dl and triglyceride <150 mg/dl) was met in 76.5% of BMI <35 kg/m^2 and 92.4% of BMI >350 kg/m^2 (p=0.059).

Conclusion Laparoscopic gastric bypass resulted in significant and sustained weight loss with successful treatment of T2DM up to 87.1%. Despite a slightly lower response rate of T2DM treatment, patients with BMI <35 still had an acceptable DM resolution, and this treatment option can be offered to this group of patients.

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Keywords Type 2 DM · Bariatric surgery · BMI <35

Introduction

Obesity and T2DM are of the most common chronic debilitating diseases of the western country today. In the USA, about 30% of the adult population is obese, and 8% have T2DM (mostly obesity-related).[1,2] Both diseases are closely related and very difficult to be controlled by current medical treatment including diet, drug therapy, and behavioral modification.[3–5] There are strong evidences that bariatric surgeries can cure most of the associated T2DM in morbidly obese patients.[6–9] Recently, laparoscopic gastric bypass has also been shown to result in significant weight loss and resolution (83%) of T2DM in morbid obese

Table 1 Patient Characteristics of Study Population by Level of Fasting Plasma Glucose

	Normal	IFG and T2DM	*P* value
N	619	201	
Age (years)	30.7±8.6	34.3±9.7	<0.001*
Sex (female/male)	480/139	143/58	0.065
BMI (kg/m^2)	39.3±8.0	40.7±7.5	0.033*
Waist (cm)	113.2±17.6	118.9±17.7	<0.001*
Glucose (mg/dl)	92.2±8.6	158.9±64.2	<0.001*
T-cholesterol (mg/dl)	195.0±35.5	200.6±40.2	0.062
HDL-C (mg/dl)	46.7±13.0	43.4±17.1	0.011*
LDL (mg/dl)	134.6±32.2	142.6±37.1	0.008*
Triglyceride (mg/dl)	146.4±86.1	248.4±239.4	<0.001*
Insulin (pmol/l)	19.6±20.1	42.7±59.9	<0.001*
C-peptide (mmol/l)	4.2±6.5	6.0±6.9	0.005*
HbA1C (IU/l)	5.9±4.3	7.2±1.9	<0.001*
Metabolic syndrome	19.7%	54.2%	<0.001*

BMI Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high density lipoprotein cholesterol, *MCV* mean cellular volume of red blood cell
*$P<0.05$

patients.[10] However, the current consensus for bariatric surgery is set at body mass index (BMI) >35 kg/m^2 with comorbidities. Although some reports have suggested the criteria can be lowered to BMI >30 kg/m^2, more data are required before a conclusion can be made.[11,12]

The aim of this was to evaluate the effect of laparoscopic gastric bypass on morbidly obese patients with T2DM. We specifically investigated the safety and efficacy in those with a BMI <35 kg/m^2 and compared it with those with >35 kg/m^2.

Materials and Methods

The study group consisted of all patients with T2DM who had undergone laparoscopic mini-gastric bypass from Jan 2002 to Dec 2006 at our department. A comprehensive, multidisciplinary, bariatric management program was in place for the preoperative preparation and postoperative management of patients. The program included support groups and ancillary personnel to provide nutritional, exercise, and psychological care. Nurse specialists for medical and psychiatric management were part of the team. Inclusion/exclusion criteria followed the Asia-Pacific Bariatric guidelines: more than 18 years old, BMI >32 with diabetes or other important comorbidities, no alcohol abuse and concurrent psychiatric illness.[13] However, patients with uncontrollable T2DM were included under a specific phase II clinical trial in our hospital. Written informed consent was obtained from each individual, and the study was reviewed and approved by the institutional Review Board of the Min-Sheng General Hospital.

Diagnosis and classification of T2DMI was based on fasting plasma glucose (FPG) concentrations according to criteria established by the American Diabetes Association (ADA).[14] The categories of FPG include (1) normal fasting glucose defined as FPG <110 mg/dl, (2) impaired fasting glucose (IFG) defined as FPG >110 and <126 mg/dl, and (3) clinical diabetes defined as FPG >126 mg/dl. IFG refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes, now referred to as pre-diabetes. Patients were stratified into groups based on BMI <35, 35–45, and >45 kg/m^2.

Table 2 Patient Characteristics of T2DM Population by Level of BMI

	BMI <35	BMI 35–45	BMI >45	*P* value
N	44	114	43	
Age (years)	39.0±8.9	34.8±9.2	28.2±8.7	<0.001*
Sex (female/male)	38/6	81/33	24/19	<0.001*
BMI (kg/m^2)	31.7±2.7	40.0±2.8	51.4±6.0	<0.001*
Waist (cm)	103.4±7.1	117.6±14.7	137.8±15.3	<0.001*
Glucose (mg/dl)	168.7±70.6	156.3±60.6	156.0±67.1	0.525
T-cholesterol (mg/dl)	205.5±35.4	203.0±44.3	189.3±31.1	0.106
HDL-C (mg/dl)	47.8±13.5	42.4±19.8	42.1±10.4	0.267
LDL (mg/dl)	137.1±32.0	136.8±35.7	134.4±28.7	0.756
Triglyceride (mg/dl)	275.7±244.4	274.3±290.9	178.98±83.1	0.088
Insulin (pmol/l)	23.8±21.9	40.8±56.5	65.0±82.9	0.019*
C-peptide (mmol/l)	3.9±2.3	5.5±3.3	9.0±12.9	0.010*
HbA1C (IU/l)	7.3±2.2	7.3±1.9	6.6±1.2	0.122
Metabolic syndrome	48.6%	69.1%	64.9%	0.563

BMI Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high density lipoprotein cholesterol, *MCV* mean cellular volume of red blood cell
*$P<0.05$

Table 3 Perioperative Outcomes Among Patients with Different Level of Fasting Plasma Glucose

	Normal (n=619)	T2DM (n=201)	P value
Operation time (min)	111.1±36.4	116.3±40.9	0.090
Estimated blood loss (ml)	34.2±27.9	34.3±33.2	0.966
Morbidity (major)	11 (1.8%)	7 (3.5%)	0.152
Mortality	0 (0%)	1 (0.5%)	0.079
Mean length stay (days)	6.1±5.2	6.6±5.8	0.239

One dose of analgesia equals to 50 mg merperidine hydrochloride.
*p<0.05

The surgical technique of laparoscopic mini-gastric bypass was described elsewhere.[15–17] To describe briefly, patients received a long sleeve gastric tube and a single gastrojejunal anastomosis using a linear stapler technique. This procedure was proven to be a simpler procedure than Roux-en-Y bypass with similar efficacy.[16] Bypass limb varied in length according to preoperative BMI (100 cm for BMI <35, 200 cm for BMI 35–50, 300 cm for BMI >50). Patient data were collected prospectively and registered into the database of our bariatric center. Parameters included patient demographics, BMI, waist width, comorbidity, length of hospital stay, complications, weight loss, and change in comorbidity. Complication was defined as a major when any interventional procedure was required to resolve the complication. Patient follow-up was scheduled for the 1, 3, 6 and 12 postoperative months in the first year, then once per year with laboratory evaluation. The successful treatment of T2DM was defined as those who meet the ADA targets for treatment (HbA1C <7.0%, LDL <100 mg/dl, and triglyceride <150 mg/dl).[18]

Descriptive data are expressed as mean value±SD. Group characteristics were compared by paired t tests, and differences between proportions were tested by chi-square tests. The statistical analysis was performed using SPSS release 11.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance was inferred at a two-tailed p value of less than 0.05.

Results

From Jan 2002 to Dec 2006, 820 patients underwent laparoscopic mini-gastric bypass at the Ming-Sheng General hospital, and of these, 117 (14.3%) met diagnostic criteria of T2DM and 84 patients (10.2%) for IFG. Preoperative demographics, operative and clinical data for IFG and T2DM versus normal fasting glucose population are listed in Table 1. Among all the patients, patients who had IFG or T2DM were significant older and had higher BMI, waist circumference, blood pressure, glucose, triglyceride, AST, ALT, GGT, ALP, insulin, C-peptide, HbA1c, ratio of metabolic syndrome, and lower in HDL than those who had normal FPG (Table 1). To brief, patients with IFG or DM are significantly older, more centrally obese with higher triglyceride, liver enzymes, insulin resistance, and poorer in HbA1C level than those with normal fasting glucose.

Characters of Lower BMI Patients

Table 2 showed the preoperative characteristics of study population by BMI levels. Among the 201 patients, 44 (21.9%) had BMI <35 kg/m^2, and 114 (56.7%) had BMI between 35 and 45, 43 (21.4%) had BMI >45 kg/m^2. Patients with BMI <35 kg/m^2 are significantly older, more female predominant, had lower waist, SBP, liver enzymes, and C-peptide than those with BMI >35 kg/m^2. Although

Table 4 Perioperative Outcomes Among T2DM Patients with Different Level of BMI

	BMI <35 (n=44)	BMI 35–45 (n=11)	BMI >45 (n=43)	P value
Operation time (min)	113.0±44.6	116.0±38.5	120.7±43.4	0.672
Estimated blood loss (ml)	33.6±22.9	33.8±36.9	36.2±33.4	0.915
Morbidity (major)	2 (4.5%)	3 (2.6%)	2 (4.7%)	0.753
Mortality	0 (0%)	0 (0%)	1 (2.3%)	0.158
Mean length stay (days)	6.4±7.4	6.4±5.2	7.1±5.5	0.806

One dose of analgesia equals to 50 mg merperidine hydrochloride.
*p<0.05

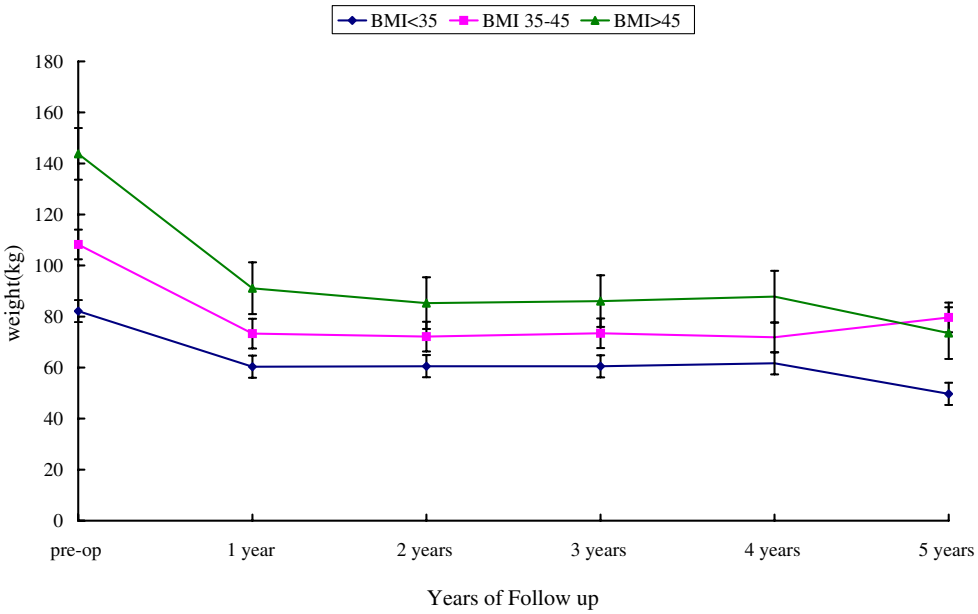

Figure 1 Weight changes among different BMI levels.

lower BMI patients had a trend of lower insulin level and higher HbA1C, it was statistically insignificant.

Operative Outcomes

There were 18 early major complications (2.2%) and one (0.12%) resulted mortality of the whole series. Minor early complications happened in 51 (6.2%) patients. The perioperative data for total population and subgroups are listed in Tables 3 and 4. There was only one mortality that occurred in a T2DM patient with higher BMI group. There was no difference in the perioperative parameters between T2DM and total population, neither in different BMI groups. Bariatric surgery can be performed safely in morbidly obese T2DM patients.

Weight Loss and Comorbidity Assessment

The mean weight loss for the whole group was 32.1% 1 year after surgery; the following weight loss was 33.4, 31.9, and 31.2% (at 2, 3, and 5 years after surgery). The changes in weight among the subjects with different BMI levels are shown in Fig. 1. The weight reducing curves were similar between the groups. The preoperative mean BMI was 39.7 kg/m^2 and decreased to 27.0, 26.1, 26.9, and 28.0 kg/m^2 at 1, 2, 3, and 5 years after surgery, with percentage to changes in BMI of 31.9, 34.2, 32.2, and 29.5% at 1, 2, 3, and 5 years. For different BMI groups, the mean body weight loss 1 year after surgery was 30% for BMI <35 kg/m^2, 32% for BMI 35–45 kg/m^2, and 35% for BMI >45 kg/m^2. The mean BMI reduction was 8.5 (26.8%) in those

Table 5 Change of Clinical data in T2DM Population 1 Year after Surgery by Level of BMI

	BMI <35	BMI 35–45	BMI >45	*P* value
BMI (kg/m^2)	8.5±2.2(26.8%)	12.4±3.2(31.0%)	17.9±5.8(34.8%)	<0.001*
BW (kg)	23.1±6.7(30%)	33.2±8.9(32%)	47.6±14.5(35%)	<0.001*
Waist (cm)	21.5±9.8	27.4±11.2	35.2±15.3	0.002*
Glucose (mg/dl)	80.1±56.2	66.5±74.1	93.8±83.9	0.360
T-chole (mg/dl)	52.2±31.1	52.2±35.5	41.3±24.8	0.408
HDL-C (mg/dl)	8.3±11.2	2.6±30.8	6.2±9.8	0.742
LDL (mg/dl)	53.8±29.0	42.5±7.0	20.5±5.1	0.551
Triglyceride (mg/dl)	147.4±150.4	206.1±282.7	120.3±105.5	0.310
Insulin (pmol/l)	20.6±27.1	38.7±58.7	72.7±107.9	0.134
C-peptide (mmol/l)	2.6±2.3	4.4±4.0	5.2±3.6	0.187
HbA1C (IU/l)	1.7±2.3	1.6±1.4	1.5±1.7	0.943
Metabolic syndrome	42.7%	66.8%	55.8%	0.003*

BMI Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high density lipoprotein cholesterol, *MCV* mean cellular volume of red blood cell
*P<0.05

with BMI <35 kg/m^2, 12.4 (31.0%) in BMI 35–45 kg/m^2, and 17.9 (34.8%) in BMI >45 kg/m^2 1 year after surgery.

Table 5 shows the absolute change of clinical data in T2DM patients with different BMI level groups. Although lower BMI group (<35) had less BMI loss compared to higher BMI groups, the improvement of blood lipid, glucose level, and HbA1C is compatible between groups.

Impact on T2DM Patients with BMI <35

T2DM groups with different BMI levels had sharp reduction of FPG and HbA1C immediately after surgery and maintained during follow-up (Figs. 2 and 3). One year after surgery, fasting plasma glucose returned to normal in 89.5% of BMI <35 kg/m^2 T2DM and 98.5% of BMI >350kg/m^2 patients (p=0.087). Before surgery, the mean HbA1C was 7.3 for T2DM group with BMI <35 kg/m^2 and reduced to 5.6 1 year after surgery. The successful rate for T2DM patients to meet the ADA targets for treatment (HbA1C <7.0%, LDL <100 mg/dl, and triglyceride <150 mg/dl) 1 year after surgery was 76.5% in BMI <35 kg/m^2, 88.9% in BMI 35–45 kg/m^2, and 100% in BMI >45 kg/m^2. Although there was a trend of less success in T2DM treatment for lower BMI patients, there was no significant difference in the successful rate between BMI <35 kg/m^2 and BMI >350 kg/m^2 (76.5 vs 92.4%; p=0.059).

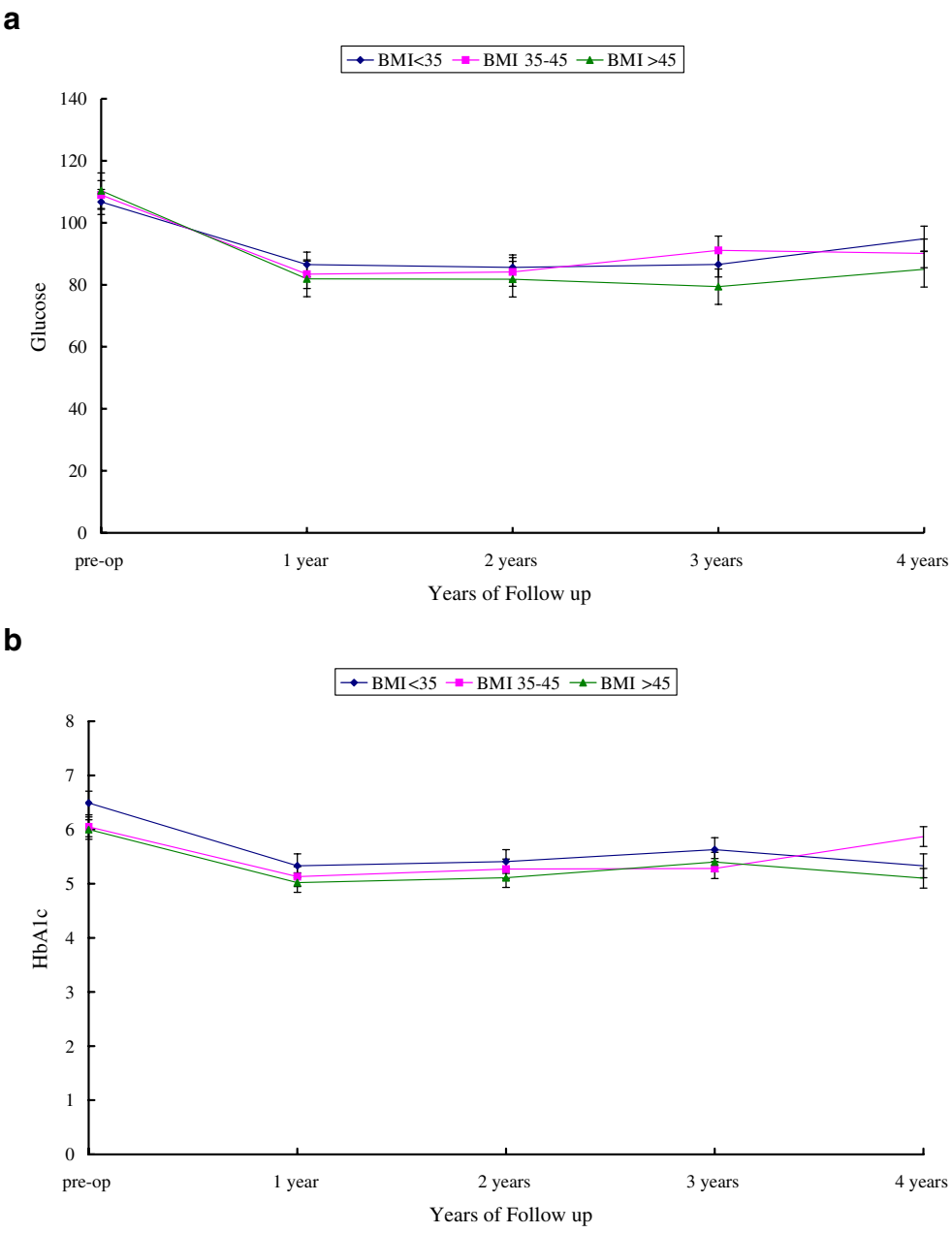

Figure 2 Change in fasting plasma glucose level (**a**) and HbA1C (**b**) after surgery in different BMI levels.

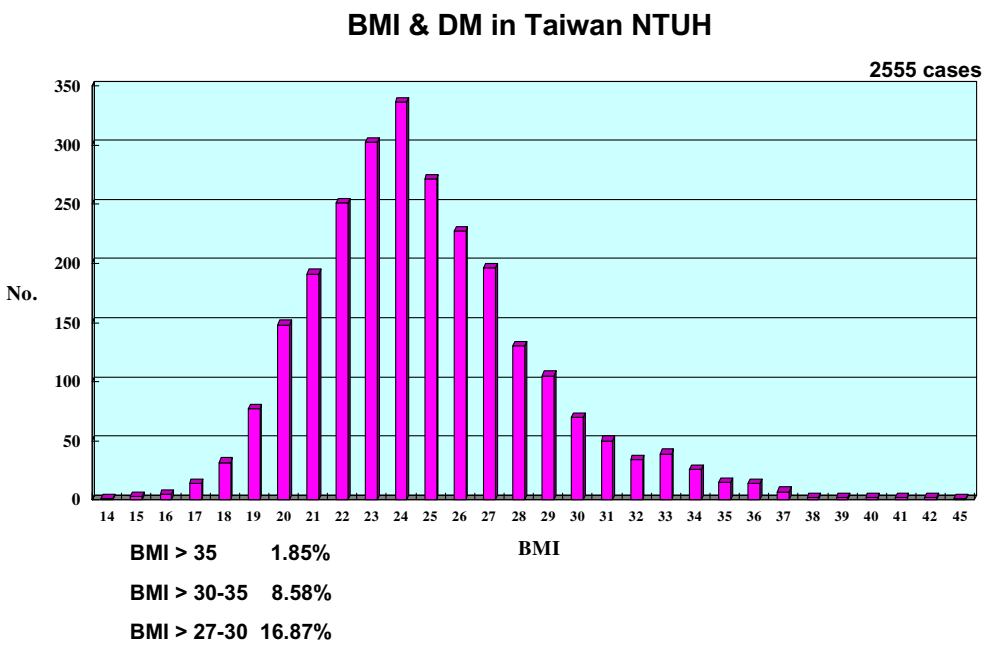

Figure 3 BMI reduction after surgery and during follow-up.

Table 6 specifically examined 14 patients, with their preoperative HbA1C >7.0% out of 44 patients with BMI <35 kg/m^2 T2DM. Among the 14 patients, 11 (78.5%) had met the treatment goal of T2DM after surgery; the other three also had significant improvement of their T2DM. Mean HbA1C decreased from 9.3 to 5.8%, which was much higher than the 7.3 to 5.6% of the whole group. Laparoscopic gastric bypass was especially worthy in this specific group of patients.

Discussion

In this study of 44 patients with T2DM and BMI <35 kg/m^2, we demonstrated that during the 5-year period, laparoscopic gastric bypass resulted in the reduction of FPG (168.7 mg/dl preoperatively and 80.1 mg/dl postoperatively; $P<0.001$) and mean HbA1C (preoperatively 7.3 to 5.6%; $P<0.001$). The efficacy of laparoscopic gastric bypass for T2DM in patients with BMI <35 kg/m^2 is similar to those with BMI above 35 kg/m^2. Among these patients, 76.5% can meet the ADA targets for treatment of T2DM 1 year after surgery, whereas it was estimated that only 7.3% of individuals with T2DM receiving current medical treatment can meet the ADA targets for treatment of HbA1C <7%, LDL <100 mg/dl, and triglycerides <150 mg/dl. This result, combined with the previous reports, support more freely the use of gastric bypass surgery in poorly controllable obese T2DM patients.[6–12]

Table 6 Change of Clinical Data in T2DM Population with BMI <35 and HbA1C >7.0%

	Before Surgery	After Surgery
BMI (kg/m^2)	31.2	24.1
Glucose (mg/dl)	221.5	96.9
LDL (mg/dl)	134.6	90.0
Triglyceride (mg/dl)	267.6	97.4
HbA1C (%)	9.3	5.8

Fourteen patients, 13 women and 1 man, mean age 38.8 years old, mean follow-up 6.4 months

Type 2 (T2DM) is an epidemic health problem worldwide affecting more than 150 million peoples and expected to be doubled by the year 2025.[1,2] However, it was found that although Americans had the highest rates of obesity, they had the lowest levels of diabetes. It was estimated that India, with 31.7 million diabetes patients and China with 20.8 million diabetes patients, had a much higher number of diabetes patients than the 17.7 million patients in the USA.[1] Numerous studies have demonstrated the high levels of metabolic risk factors at relatively low levels of BMI among Asian population because of more proneness to have central obesity.[19] A study in China found a 9.8% prevalence of T2DM in a population with only 4.3% obesity.[20] There is an urgent need for prevention and treatment of T2DM in this region as well as in western countries. It is why Asia-Pacific Bariatric Society has modified the indication for bariatric surgery to BMI >32 kg/m^2 with T2DM.[13] However, even in these criteria, only a few T2DM patients are actually indicated for gastric bypass surgery. The patient data of Diabetes Center in our hospital showed that only 1.8% of the total 2,555 T2DM patients have their BMI >35 kg/m^2, and 10% are >30 (Fig. 3). If we can lower the indication to BMI 27 kg/m^2,

which is the cut-point of obesity in Taiwan, still, only about 25% of the patients are indicated. Further clinical trials are indicated to decide for those mild to moderate obese patients with uncontrollable T2DM as to what extent the indication for bariatric surgery can be.

The understanding of obesity as an important etiology in T2DM is well accepted, and bariatric surgery has been shown to provide good weight loss and significant resolution of obesity-related T2DM.[6–9] However, recent studies have suggested that proximal gut may play an important role in the pathogenesis of T2DM, and bypass of duodenum and jejunum may directly control T2DM without significant weight loss.[21–25] In this study, a longer bypass limb bypass was adopted for higher BMI patients to increase body weight loss. The mean BMI reduction, therefore, was 8.5 in those with BMI <35 kg/m^2, 12.4 in BMI 35–45 kg/m^2, and 17.9 in BMI >45 kg/m^2 1 year after surgery. Although absolute BMI decrease in lower BMI group was less than that of the higher BMI groups, the efficacy of T2DM treatment is similar, which supports the previous theory. If the foregut hypothesis is correct, a larger gastric pouch, wider anastomosis, and shorter bypass limb may be adopted for lower BMI T2DM patients. Still, more clinical trials are required before any conclusion will be made.

Another issue must be addressed before applying gastric bypass widely to treat T2DM, that is, the safety of gastric bypass surgery. In the Swedish obese subjects (SOS) study, the survival advantage of bariatric surgery is dependent on the extremely low surgical morbidity, 2.2% major complication rate and 0.2% mortality.[7] Multivariate analysis has shown that gastric bypass carried a 0.5% mortality rate, but most of the data are from expert hands. Some national wide survey have disclosed high morbidity and mortality up to 2–4% after gastric bypass.[26,27] Therefore, the complication rate and long-term squeal of gastric bypass may cause a tremendous health burden when gastric bypass surgery was applied widely on a national base. A simplified gastric bypass method, mini-gastric bypass, was adopted in this study. In our previous study, we found that laparoscopic R-Y gastric bypass is even much difficult in technique and carried more than three times the risk of major complication than laparoscopic mini-gastric bypass.[16] The overall morbidity rate was 2.6%, and mortality rate was 0.12% in this study, which were compatible with the SOS study and data from center of excellence.[7,28]

State-of-the-art treatment for T2DM is comprised of intensive lifestyle modification along with pharmacologic management of glucose and comorbidities, especially dyslipidemia and hypertension.[3–5,29–33] A recent study has shown that prescribing lipid-lowering agents to individuals with T2DM with elevated lipids can reduce cardiovascular mortality.[34] ADA, therefore, recommended physicians to seek a 30% reduction in LDL levels by treating diabetic patients with statins, regardless of initial lipid levels.[33] The current treatment goals recommended by the American Diabetic Association are HbA1C <7%, LDL <100 mg/dl, and triglyceride <150 mg/dl.[18,33] However, it has been estimated that majority (92.7%) of individuals with T2DM fail to meet the targets.[18] In this study, most of the patients with T2DM can successfully meet the targets 1 year after surgery. For T2DM patients with BMI <35 kg/m^2 and HbA1C >7.0%, the successful rate was 78.5% in this study. This again proves that gastric bypass is not only a weight-reducing surgery but a metabolic surgery which can cure most of the metabolic syndrome.[35]

In summary, our study has demonstrated significant improvement in T2DM and IPG of morbidly obese patients after gastric bypass surgery. Currently, bariatric surgery is indicated in morbidly obese patients with BMI >35 kg/m^2 or >32 kg/m^2 in Asian population. This study supported more free use of gastric bypass in poor control T2DM patients with mild to moderate obese. Further clinical trials are indicated to evaluate the long-term benefit.

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Complications of PTFE Mesh at the Diaphragmatic Hiatus

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Abstract Paraesophageal hernia repair has been associated with a recurrence rate of up to 42%. Thus, in the last decade, there has been increasing interest in the use of mesh reinforcement of the hiatal repair. Polytetrafluoroethylene (PTFE) is one of the materials that have been used for this purpose, as it is thought to induce minimal tissue reaction. We report two cases in which complications specific to the use of PTFE mesh in this location developed over time. In the first patient, a gastrectomy was required to remove a large PTFE mesh which had eroded into the esophagogastric junction and gastric cardia. The second patient experienced severe dysphagia resulting from a stricture caused by the implant, requiring removal of the mesh. Although such complications have only rarely been reported, the severity and consequences of these incidents, as reported in the literature and in light of our observations, suggest that an alternative to PTFE should be considered for crural reinforcement during paraesophageal hernia repair.

Keywords Paraesophageal hernia · Surgical mesh · PTFE · Visceral erosion · Dysphagia

Introduction

The introduction of laparoscopy for the treatment of paraesophageal hernias was introduced in the mid-1990s shortly after surgeons had discovered the benefits of this approach to performing antireflux surgery.[1,2] However, soon after the turn of the century, some studies suggested that the laparoscopic approach yielded a higher recurrence rate, reaching 42% in the report by Hashemi et al.[3] Since then, efforts have focused on the reduction of this significant recurrence rate and the idea of using mesh reinforcement of the hiatal repair was revived given that the use of mesh in other hernias (incisional and inguinal) in the previous decade led to substantial reductions in recurrence rates.[4,5] Although there is no consensus on the best prosthetic material to use in the hiatus,[6] based on the experience with abdominal wall hernias, many authors suggest that the material used should be nonresorbable, given that resorbable material loses its mechanical properties as it is resorbed.[7] Most authors also agree that the ideal prosthetic material would be inexpensive, malleable, and transparent and carry a low risk of adhesion formation. Polypropylene meets most of these requirements and is a commonly utilized prosthetic material in the hiatus. A principal concern with placing any prosthetic material near the esophagus is the potential for erosion into the esophagus or stomach.[8,9] Polypropylene does have the propensity to form visceral adhesions and carries some risk of erosion.[10]

Several types of polytetrafluoroethylene (PTFE) and PTFE composite materials are currently in use in hiatal repair. PTFE is opaque, which can make accurate stapling and suture fixation difficult.[10] However, it is durable and is thought to induce minimal tissue reaction;[11,12] thus, its use has been advocated in the repair of large hiatal hernias. While seldom reported, many esophageal surgeons have encountered complications associated with mesh in this position.[9,13–15] However, reports of these complications probably suffer from the natural publication/reporting bias

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against poor outcomes. Here, we discuss two incidences from our experience in which PTFE mesh used for repair of paraesophageal hiatal hernias has led to nonfatal adverse outcomes.

Case Reports

Patient 1

A 62-year-old patient underwent open paraesophageal hiatus hernia repair with primary crural closure. Seven years later, he experienced hernia recurrence, and a 10 cm by 15 cm PTFE mesh was placed at the hiatus and around the esophagogastric junction during a second open repair with Nissen fundoplication and gastrostomy. Three years later, he began to experience increasing epigastric pain, together with episodes of dysphagia and regurgitation. An endoscopy demonstrated a foreign body in the proximal stomach, consistent in appearance with the mesh, which was not resectable endoscopically (Fig. 1). He was subsequently taken to the operating room for exploration. After a very difficult gastric mobilization, the mesh was palpable within the gastric lumen, and no part of it was visible external to the stomach or esophagus. Because of the location of the mesh at the esophagogastric junction and gastric cardia, a total gastrectomy and a esophagojejunostomy were performed. The specimen revealed an intact PTFE mesh, which had completely eroded through the gastric wall. A tract of granulation tissue had formed around one edge of the mesh, through which it was looped and thus fixed to the cardia, explaining why it was not possible to mobilize this with an endoscope (Fig. 2). The patient recovered without incident and experienced no further pain, dysphagia, or regurgitation.

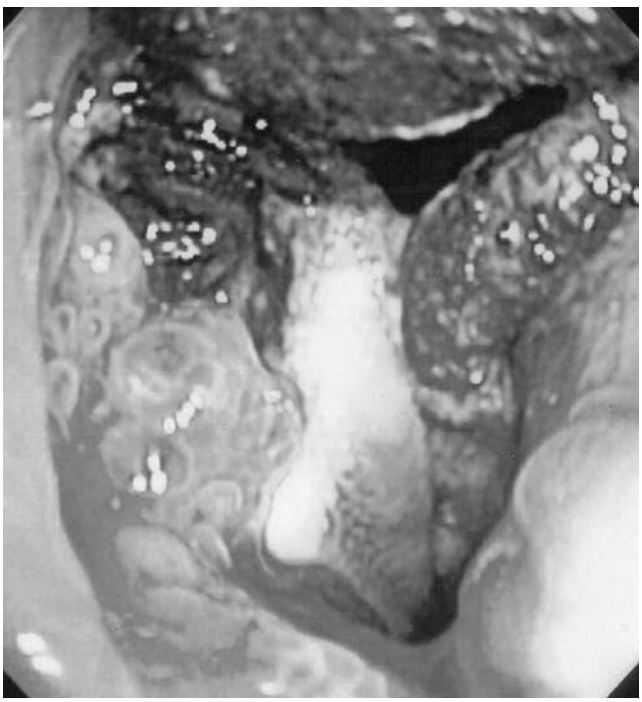

Figure 1 Endoscopic appearance of intragastric PTFE mesh in patient 1. The edges of the mesh are clearly visible.

Patient 2

A 65-year-old patient with Barrett's esophagus and a large type III paraesophageal hiatus hernia as well as an incisional hernia resulting from a total abdominal hysterectomy presented with intermittent abdominal pain and typical reflux symptoms including heartburn. The anatomical defect was evident on a computed tomography (CT) scan, and esophageal manometry demonstrated a hypotensive lower esophageal sphincter (7.5 mmHg) with normal relaxation located between 31 and 34 cm from the nares and normal peristalsis of the esophageal body. She underwent simultaneous laparoscopic incisional hernia repair and paraesophageal hiatus hernia repair with Nissen fundoplication. The diaphragmatic crura were repaired primarily with interrupted non-absorbable sutures. A preshaped 11 cm two-layered PTFE mesh was used to reinforce the crural repair posteriorly and bilaterally; the esophagus was not encircled by the mesh. The patient was discharged on the first postoperative day, and at 2-week follow-up was doing well with only minimal dysphagia. Approximately 1 month later, however, she began to have progressively worsening dysphagia, ultimately limiting her to a liquid diet. An esophagram performed at that time demonstrated a dilated esophagus and a tapered "bird's beak" distal esophageal stricture, an intact fundoplication, and no evidence of re-herniation (Fig. 3). Manometry at this time demonstrated a resting lower esophageal sphincter

Figure 2 Opened gastrectomy specimen from patient 1, demonstrating mesh at esophagogastric junction and gastric cardia incorporated into granulation tract.

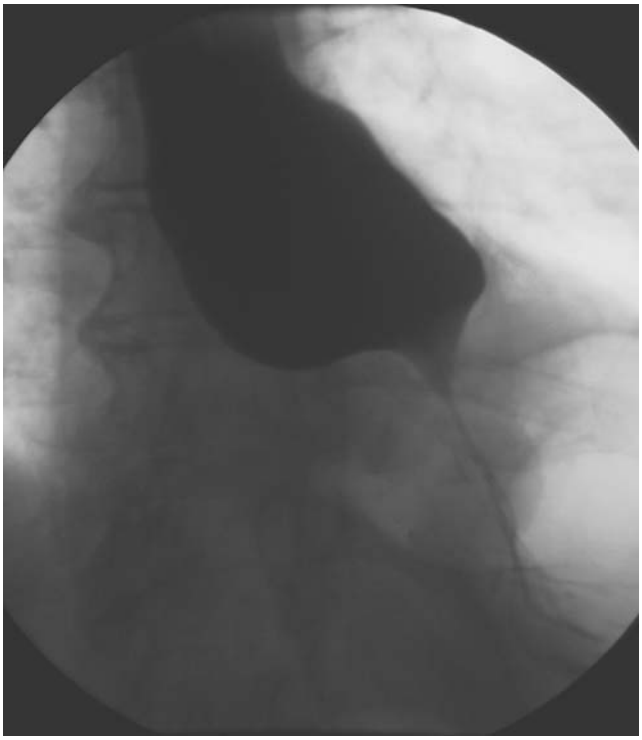

Figure 3 Barium esophagram of patient 2, performed 2 months after laparoscopic paraesophageal hernia repair with PTFE mesh, demonstrating a dilated esophagus and tapered distal esophageal stricture.

(LES) pressure of 18 mmHg with impaired relaxation (72%), while the peristalsis observed in the preoperative studies had been replaced by simultaneous contractions in the distal esophagus. She underwent serial endoscopic esophageal balloon dilations up to 30 mm, each of which provided only temporary and partial relief of her dysphagia. After 7 months of repeated dilations, she was taken back to the operating room. The PTFE mesh was seen to have caused a circumferential stricture about the distal esophagus, with dense adhesions to the stomach and fundoplication. The crural repair remained intact. The mesh was completely removed, and the Nissen fundoplication was taken down and recreated as a Toupet partial posterior fundoplication.

Discussion

Complications directly associated with the use of prosthetic materials in large hiatal hernia repair are rarely cited events in the literature. Those that have been reported involve erosion of the mesh into the digestive lumen[8,9,15] or local fibrosis caused by the mesh with resultant dysphagia.[16,17] There are also reports of injury from staples or tacks used for mesh fixation causing injury to the vital structures surrounding the hiatus.[13] In our own experience with over 2,000 hiatal hernia repairs, synthetic mesh has only been used in seven patients. The fact that both of the cases detailed above come from this relatively small subset suggests that perhaps such complications are not as uncommon as they would appear from evaluation of the available literature.

The benefits of mesh in preventing hernia recurrence are undisputable. While there are no long-term studies confirming the durable efficacy of hiatal hernia repair with mesh, it seems reasonable to assume that overall, placement of mesh at the hiatus would confer similar benefits to the use of mesh for other types of hernias. In fact, there are two randomized trials supporting the use of mesh in hiatal closure. Using a polypropylene onlay and comparing this to suture closure of the crura alone, Granderath et al.[18] demonstrated a significantly lower incidence of intrathoracic wrap migration at 1 year in 50 patients with mesh compared to 50 for whom it was not used (8 vs 28%). Frantzides et al. compared primary suture closure of large hiatal defects (>8 cm) to closure with a PTFE onlay in 72 patients. With a mean follow-up of 3 years, no patient in the PTFE group experienced hernia recurrence, compared to 22% of patients in the primary closure group.[19] No mesh-related complications were observed in either of these trials, but the follow-up periods were relatively short (1–3 years).

Despite the decrease in recurrence when mesh is used in various types of hernia repair, complications such as those reported here point out some of the potential drawbacks. In addition, mesh placement generally requires more operative time, increases cost, and increases the difficulty of the procedure. The most commonly employed synthetic meshes in hiatal hernia repair include polypropylene and PTFE. PTFE is thought by many to induce fewer adhesions and thus pose less of a threat of visceral erosion than polypropylene when exposed to the peritoneal contents.[11,20] A comparison of adhesion formation with intraperitoneal mesh placement between PTFE and polypropylene in rabbits demonstrated significantly fewer adhesions to PTFE at 16 weeks after implantation (30 vs 55%).[11] A more recent study examining the biomechanical properties of implanted intraperitoneal mesh demonstrated an up to 40% adhesion rate to PTFE-containing mesh products after 1 year compared to 80% for bare polypropylene.[20] Thus, it seems reasonable to assume that of these two products, PTFE would be less likely to result in morbidity when used to reinforce the hiatus.

Erosion

Most of the reported complications from the use of mesh at the hiatus involve erosion. The propensity for erosion into the digestive lumen by non-reabsorbable foreign objects placed in or around the hiatus has been known for over two decades. For example, the event was reported with some

frequency after the Angelchik prosthesis became popular some 30 years ago.[21–24] Even Teflon pledgets have been reported to cause similar complications such as erosion into the fundus and the induction of fibrous retraction and dysphagia.[7]

To date, there have been three erosive complications reported in association with the use of PTFE as a prosthesis for crural closure. In one case, a patient developed a delayed esophageal perforation postoperatively requiring reoperation and patch removal. The leak was thought to be related to esophageal ischemia resulting from extensive dissection required to clear dense adhesions, rather than from any specific property of the mesh.[25] In another case, similar to one of our two patients, a PTFE mesh migrated into the gastric lumen at the cardia, leading to reoperation. This was treated by distal esophageal resection and removal of the mesh.[9] A nearly identical case is reported by Hergueta-Delgado et al., although no mention is made of the outcome.[14]

In some cases in which polypropylene mesh has eroded into the esophagus, management short of esophagectomy or gastrectomy has been possible. In a recently reported case by Gajbhiye et al., a polypropylene mesh used to reinforce a repair of an esophageal perforation eroded into the esophageal lumen resulting in dysphagia 2 years after mesh placement. Removal of the mesh was successfully accomplished by endoscopy. Notably, however, this patient subsequently developed a stricture, 6 years later, which ultimately required esophageal resection.[26] In the series of 44 paraesophageal hernia repairs reported by Carlson et al. in 1998, one patient was noted to have a partial erosion of the polypropylene mesh used to reinforce the hiatal repair which was asymptomatic. No intervention was undertaken.[15] In the case reported here, however, the patient had developed severe dysphagia and epigastric pain, and the mesh was firmly fixed to the gastric cardia. Endoscopic removal was not possible, and the patient's symptoms dictated more invasive management, in this case, total gastrectomy.

Although not a true erosion, there has been a report of a fatal complication related to mesh placement in which a patient developed cardiac tamponade caused by a stapler laceration of a coronary vein.[13] This represents a problem of fixation, however, rather than the choice of a particular material used in the repair. Such complications could likely be avoided by suturing the mesh, rather than using a stapling or tacking device.

Dysphagia and Stricture

The occurrence of postoperative dysphagia secondary to stricture formation, resulting in pseudoachalasia as reported here, has not been described elsewhere in the literature in association with PTFE. In a randomized clinical trial reported recently by Granderath et al., dysphagia rates were higher at 3 months after surgery in the group of patients in which a polypropylene mesh onlay was performed compared with those undergoing primary suture closure alone. However, at 1 year, the incidence of dysphagia was identical in both groups (5%). No strictures were observed.[27] It is likely that in the case presented here, in which a stricture developed very early postoperatively, the patient had a particularly vigorous and disproportionate reaction to the mesh material. This is supported by the observation during reoperation that in addition to the fibrosis observed in the region of the hiatus, dense adhesions were noted to have occurred between the peritoneal contents, and a separate PTFE mesh used to simultaneously repair an incisional hernia. Predicting which patients may be susceptible to such a tissue response is not possible at this time.

Alternatives to Synthetic Mesh

It is difficult for surgeons to decide whether the risk of complications is worth the benefits of avoiding recurrences, especially when many recurrences are small and asymptomatic. For this reason, many have sought alternatives to primary repair and the use of synthetic mesh. These include the use of autologous tissue or a relatively new class of biologic mesh materials, in hopes of augmenting the hiatal repair while avoiding any risk of mesh-related esophageal or gastric injury. For example, Varga et al. described the use of ligamentum teres for reinforcement of the hiatal crura in four patients with a hiatal hernia diameter greater than 6 cm. No recurrences were noted after 3 months.[28] This is a potentially useful technique; however, it does involve additional dissection, and the small numbers and short follow-up reported make it difficult to recommend as a strong alternative at this point. There are a host of mesh biomaterials that have come on the market in the last few years. Each purports to act as an extracellular matrix scaffold to augment native tissue healing and regeneration. By nature, they are pliable and temporary, so they should not have the associated risks of the synthetic mesh materials.

There is already good evidence for their use in hiatal hernia repair. For example, Oelschlager et al. described the use of one such material, porcine small intestine submucosa (SIS) (Surgisis; Cook Biotech Incorporated, West Lafayette, Ind) in nine patients undergoing laparoscopic paraesophageal hernia repair.[29] More recently, a prospective randomized trial comparing SIS mesh repair to primary suture repair in 108 patients has been published. The use of SIS was associated with a significantly lower recurrence rate compared with primary repair (9 vs 24%) at 6-month follow-up, as determined by radiologic assessment.[30] Based upon these results, it is now the practice in our institution to

routinely use biomaterial mesh reinforcement for all laparoscopic paraesophageal hernia repairs.

Conclusion

The two cases presented here illustrate some of the possible adverse outcomes associated with the use of PTFE mesh. Although uncommon, these complications can result in severe morbidity for the patient and necessitate significant surgical intervention. Therefore, although use of mesh at the hiatus appears to reduce the recurrence rate seen in the repair of large hiatal hernias, caution must be advised when choosing a particular mesh for this purpose. Because any mesh used in hiatal closure will be in close contact with the esophagus, stomach, and esophagogastric junction, erosive and adhesive complications are theoretically possible with virtually any synthetic material. The use of a biomaterial appears to be a safe and effective alternative to the use of synthetic mesh in the repair of large hiatal hernias.

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The Loop Stoma Bridge—A New Technique

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Abstract
Background Conventionally, supporting rods made of glass, plastic, or similar material have been used for 1 week to 10 days for loop stomas to prevent retraction. However, this is associated with difficulty in applying the stomal appliance till removal of the rod resulting in leakage of fecal matter.
Methods A closed suction drain tube of 16 or 18 F placed in the subcutaneous tissue with the help of a trocar is used as a bridge. The points of entry and exit of the tube are just beyond the circumference of the flange.
Results Apart from discomfort and pain in 5 patients, no major complications were encountered in the 33 patients studied.
Conclusion The method described is safe, cheap, and easily performed by junior surgical resident with low morbidity. The colostomy flange can be applied immediately without leakage.

Keywords Loop colostomy · Loop ileostomy · Bridge

Introduction

Loop colostomy is commonly used in the management of obstructed left colonic or rectal cancer, anastomotic diversion, severe anorectal trauma and perianal sepsis.[1,2] Conventionally, supporting rods made of glass, plastic, or similar material have been used for 1 week to 10 days for loop stomas to prevent retraction. However, these are associated with infection and difficulty in applying the stomal appliance. On many occasions, the discharge of the patient is delayed because of this. In addition, the patient's confidence level would be low if the intestinal contents start leaking underneath the appliance because of presence of the bridge. To overcome this, many techniques of 'stomal bridge' have been described. A technique, which addresses most of the shortcomings in earlier ones, is described.

Methods/Technique

The basic principle is that the function of the bridge should not be compromised but at the same time, it should not interfere with fixing of the stomal appliance. A tube used for closed suction drain like Romo vac™ (Romsons, India) 16 or 18 F is used (Fig. 1a). This tube has adequate stiffness, is porous at one end, and is connected to the trocar at the other. Note that about 30 cm or more of the tube does not have pores. The flange used for the stoma is available in different brands and sizes resulting in variations in diameter. As the incision is generally 4 to 5 cm, a 60-mm Coloplast™ (Coloplast A/S, Denmark) flange is preferred (Fig. 1b) and measures 11 cm in diameter.

A suitable site is marked for the ostomy. Under appropriate anesthesia, a transverse incision, measuring 4 to 5 cm, is made deepening it up to the fascia. The fascia is incised, and the bowel is delivered in a standard fashion.[1,3] A small rent is created between the marginal artery and the

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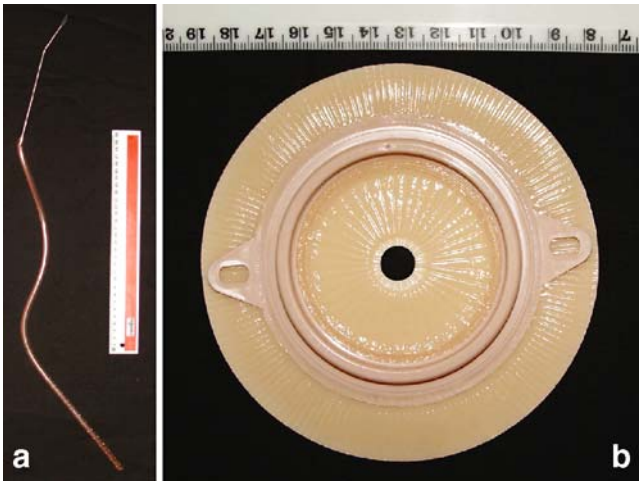

Figure 1 Photograph of the closed suction tube (**a**) and the colostomy flange (**b**).

mesenteric border of the colon in an avascular area. At this stage or immediately after skin incision (Fig. 2a), the entry and exit points of the bridge are marked. Appropriate points of entry and exit should be at least 1 to 2 cm more than the radius of the flange. In this case, it would be 6.5 to 7.5 cm from the incision line. This margin of 1 to 2 cm is required for the application of adhesive plaster over the flange. Entry and exit points at distances lesser than this would prevent the proper application of the flange, whereas greater distances would mean more chances for stomal sagging and retraction. With the help of the trocar, the skin is punctured about 7 cm from the main wound, tunneled in the subcutaneous space immediately below the dermis, and brought out through the main wound (Fig. 2b), dragging the suction tube along with it. A medium-sized artery forceps is then used to bring the tube through the mesocolic rent (Fig. 2c). The tube is then reconnected to the trocar and tunneled in the subcutaneous space above with a skin exit at a similar 7 cm from the wound edge. The rest of the procedure involving the closure of fascia and fixing of the colon to the fascia is completed.[1,3] After ensuring that no porous part of the tubing is used for the bridge, the tube is held taut by pulling both ends and anchoring to the skin (Fig. 2d). The stoma is matured in the standard method and the flange is applied (Fig. 3). The adhesive plaster, bag, and clip are then placed appropriately. The entry and exit points of the tubing may be smeared with a little povidone iodine ointment and left open. The bridge is removed between 7 and 10 days without disturbing the flange.

Results

Over the last 7 years, this technique has been followed for 33 patients undergoing loop transverse or loop sigmoid colostomy. This bridge was used in only one patient who underwent loop ileostomy as there were adhesions of the small bowel. No major complications have been encountered. No retraction of stoma was observed. Complications because of the passage of intestinal contents into the distal loop were not encountered. Four patients complained of discomfort and two of them also complained of pain. They

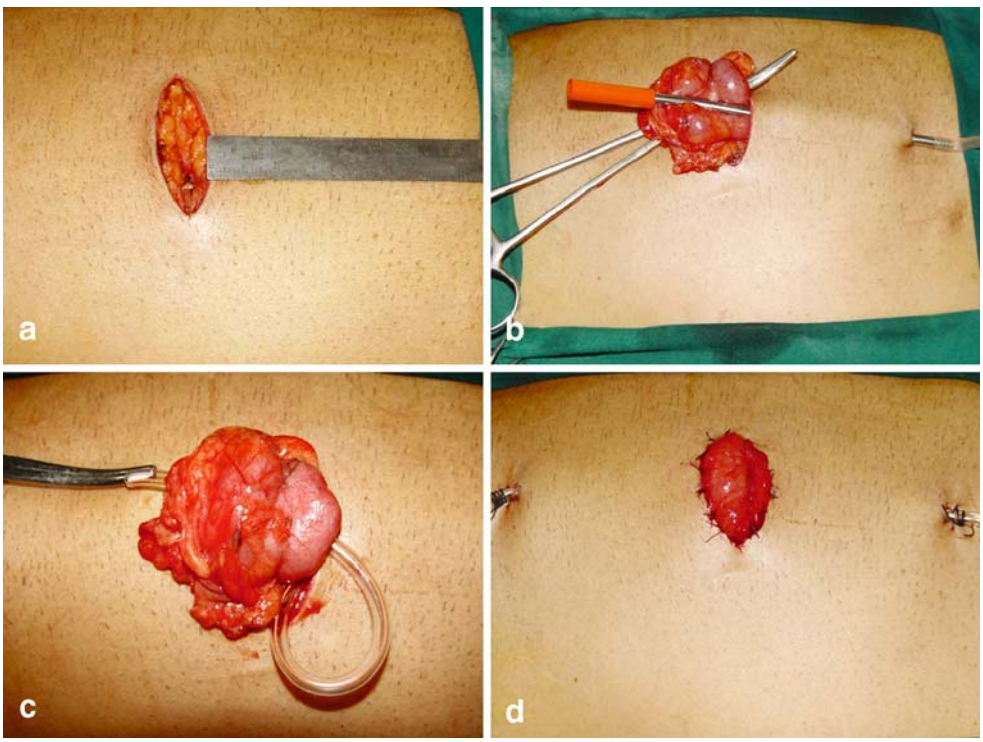

Figure 2 **a** Photograph showing the skin incision with a scale used to mark the entry point of the trocar. **b** The loop of colon is delivered. The artery forceps is placed between the marginal artery and the colon. The trocar has made a tunnel in the subcutaneous plane. **c** The artery forceps has delivered the closed suction tube beneath the colon. **d** The final placement of the tube bridge and maturation of the stoma.

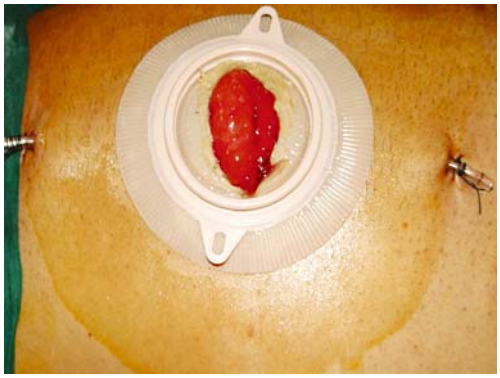

Figure 3 The flange is applied. The area between the points of entry/exit of the tube and the flange is for the application of adhesive plaster.

resolved with removal of the bridge. Three patients had redness and signs of inflammation at bridge entry and exit points by the 5th or 6th day. They were self-contained and subsided with removal of the bridge. None of the patients developed infections spreading along the subcutaneous tube tract.

Discussion

Total diversion of intestinal contents can be achieved only by complete transection. However, a well-constructed loop ileostomy or loop transverse/sigmoid colostomy provides near complete fecal diversion.[1] Hence, diversion colostomies are performed for various reasons ranging from decompression to temporary diversion for the protection of a complicated distal anastomosis. Despite various new techniques like loop-end colostomy,[4] the conventional loop ostomies still need to be performed for various reasons. A bridge is used for all the loop ostomies. There is a view that loop ileostomies do not require a bridge,[5] whereas loop colostomies do. However, some loop ileostomies might still require a bridge. The bridge serves two important functions. First, it prevents retraction or 'sinking' of the loop into the wound whereby the intestinal contents could leak back into the tissues with resultant consequences. Second, the elevated bridge provides the desired 'diversion of fecal matter'.

A glass or plastic rod placed underneath the loop between the marginal artery and the mesenteric border of the colon resting on the skin raising the posterior wall of colon to above the skin level is the standard technique described.[1,3] With the availability of good stoma care equipment, there is no role for delaying the maturation of stoma.[3] Hence, it is imperative that stoma care devices are properly applied at the time of loop colostomy to prevent psychological and physical discomfort to the patient. However, with the standard technique of the rod placement, stoma care device application would be difficult during the initial week or till such time the bridge is removed.

This resulted in the exploration of alternative techniques. Two types of bridges have been described. The first is the skin level bridge, which includes the standard glass or plastic rod. Another technique described, which is much similar to 'V–Y plasty', is the skin itself being used as a bridge.[6] One of the techniques that resulted in a lot of debate was a deep tension suture suggested as a cheap and reliable alternative to a proprietary bridge.[7] Alternatively, a loop of nasogastric or rubber tube is passed under the loop of colon, and the shortened ends are joined together above the bowel with a single nylon suture.[8] This technique is however criticized as 'sinking' of the loop could still occur.[9] Other techniques used are sutures themselves as bridge but they can have bowstring effect.[9–11] The second type of bridge described is subcutaneously placed. Both absorbable[12–14] and nonabsorbable bridges have been described.[15] A recently described technique involves use of rectus fascial sling as a bridge.[2] One of the main criticisms of a subcutaneous bridge is that it does not raise the mesenteric wall of the colon to skin level or beyond. This could potentially result in the lack of total diversion of intestinal contents resulting in the failure of one of the main purposes of the ostomy. However, in practice, intestinal contents and flatus would move preferentially toward the low pressure side of any gradient. This would mean that it would flow into the appliance which is at atmospheric pressure than into the distal loop.[1] Therefore, in practice, a bridge placed anterior to skin or in the subcutaneous tissue should not make a difference.

In the technique described, the bridge tube is placed in the subcutaneous tissue right underneath the dermis. Hence, it would not matter whether the individual is obese or thin. On the other hand, when a rectus sheath sling is used,[2] it would matter if the individual is obese. The tube is inserted and stitched on either side before maturation of the stoma. In addition, the colostomy flange and the colostomy bag are applied immediately. Hence, the chances of infection or contamination of the tube tract are minimal. The bridge needs to be nontoxic, soft, and gentle on the bowel, whereas at the same time stiff enough to prevent retraction and 'sinking' of the loop. The suction drain tube 16 or 18 F meets both these requirements. In addition, the tube is cheap and easily available and supplied in sterile packs.

One of the important aspects is that majority of loop colostomies are performed as an emergency or semi-emergency where a senior consultant might not be available. The technique described in this paper does not require great skill. The suction tubing is readily available. Hence, even a junior surgical resident who probably would perform most of such procedures would not find this technique difficult.

In conclusion, the method described is safe, cheap, and easily performed by junior surgical resident with low morbidity. It helps in the immediate placement of the colostomy appliance resulting in no leakage and instills confidence in the patients.

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Retroportal Hepaticojejunostomy for Extended Resection of Hilar Bile Ducts

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Abstract High hepatic duct resection sometimes is unavoidable in achieving curative resection of hilar cholangiocarcinoma, as tumor cells can extend further than expected along the bile ducts from the macroscopically evident cancer. In patients undergoing left hemihepatectomy with caudate lobectomy whose bile duct must be severed at the subsegmental bile duct levels, the orifices of the posterior bile ducts would lie behind the right portal vein. Conventional hepaticojejunostomy would be risky in such cases because an anastomosis performed in the usual manner would be subjected to strain. Instead, between 2002 and 2004, three patients underwent retroportal hepaticojejunostomy using a jejunal limb mobilized and positioned behind the hepatoduodenal ligament. Primary tumors were classified as type IV in the Bismuth–Corlette classification. Tension-free hepaticojejunal anastomosis was performed successfully in all three patients; insufficiency of the hepaticojejunostomy did not develop. Neither early nor late complications directly related to this method occurred. Retroportal hepaticojejunostomy, thus, permits more peripheral resection of the hepatic duct while providing a sufficient operative field for safe, tension-free anastomosis. This technique is very useful for patients undergoing left hemihepatectomy requiring high hilar resection of the bile duct.

Keywords Hepatectomy · Hepaticojejunostomy · Hilar cholangiocarcinoma · Anastomotic leakage · Hilar plate

Introduction

Surgical results in hilar cholangiocarcinoma gradually have improved because of advanced surgical procedures and accumulation of anatomic knowledge concerning the hepatic hilum.[1] As cancer-free margins are considered particularly important for curative resection of hilar cholangiocarcinoma,[2–4] bile ducts should be dissected longitudinally as far from the tumor as possible to ensure curative resection.

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In some cases where high hepatic duct resection is necessary for this reason,[5] bile ducts must be cut at subsegmental level or higher. In left hemihepatectomy with caudate lobectomy, bile duct orifices of the posterior segment lie behind the right portal vein, causing difficulty in performing hepaticojejunostomy by the usual anteportal procedure because of excessive strain at the anastomotic site; both anastomotic leakage and impairment of portal flow resulting from compression would occur. We have mobilized the jejunal limb to pass through the hepatoduodenal ligament to perform successful hepaticojejunal anastomosis behind the portal vein, as described below.

Materials and Methods

Between 2002 and 2004, three patients underwent retroportal hepaticojejunostomy. Extent of the primary tumors was classified as type IV according to the Bismuth–Corlette classification.[6] Left hemihepatectomy with caudate lobectomy was performed in two patients, whereas left trisectionectomy with caudate lobectomy was performed in the other.

Findings at preoperative cholangiography in case 2 are presented in Fig. 1. Three ductal orifices appeared when the bile duct was initially cut (Fig. 2). At that time, traditional ante-portal hepaticojejunostomy could be performed properly. However, intraoperative frozen-section examination disclosed carcinoma at the initial cut end of the bile duct, and so, bile duct resection was extended peripherally. At that point, the cut end of the bile duct showed no tumor, but the bile duct orifice of B6 + 7 was located behind the portal vein (Fig. 3). The traditional ante-portal pattern appeared extremely difficult to achieve, because the jejunal limb itself covered the B6 + 7 orifice. The portal vein and hepatic artery were carefully dissected from Glisson's sheath to obtain margins for anastomosis of about 5 mm. A longer jejunal limb (70 cm) was carefully prepared to avoid the application of any tension to the anterior ductal anastomosis. Then, the jejunal limb was passed through the mesentery of the ascending colon in-between the right colic artery and the middle colic artery. It was passed upward through the hepatoduodenal ligament. Then, an orifice for B6 + 7 was opened in the jejunum face-to-face with the bile duct orifice. Absorbable thread (4–0 or 5–0) was used for anastomosis. During the anastomotic procedure, the portal vein and hepatic artery were retracted gently using a slender retractor. A drainage tube was placed transjejunally into the bile ducts. Four orifices for the anterior subsegmental bile ducts then were opened into the jejunal limb. After all sutures were placed on the posterior side of the anastomosis, these were tied (Fig. 4). Then the anterior wall of the anastomosis was sutured and hepaticojejunostomy was completed (Fig. 5a,b). No anastomotic insufficiency was observed by cholangiography performed on postoperative day 14 (Fig. 6).

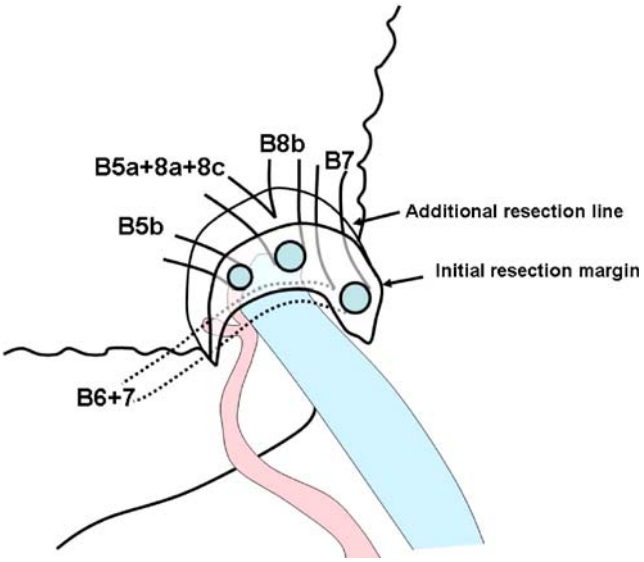

Figure 2 There were three ductal orifices on the initial cut end of the bile duct. At that time, traditional ante-portal hepaticojejunostomy could be performed. Because intraoperative frozen-section examination revealed carcinoma at the initial cut end, bile duct resection was extended peripherally.

Results

Successful tension-free hepaticojejunal anastomosis was performed retroportally in all three patients. Anastomotic insufficiency at the hepaticojejunostomy did not develop in any patient. Neither early nor late complications directly related to this new method occurred. Two patients have no anastomotic insufficiency and no sign of anastomotic stricture. The other patient died 12 months after surgery as a result of metastasis to the spinal cord. The two surviving patients

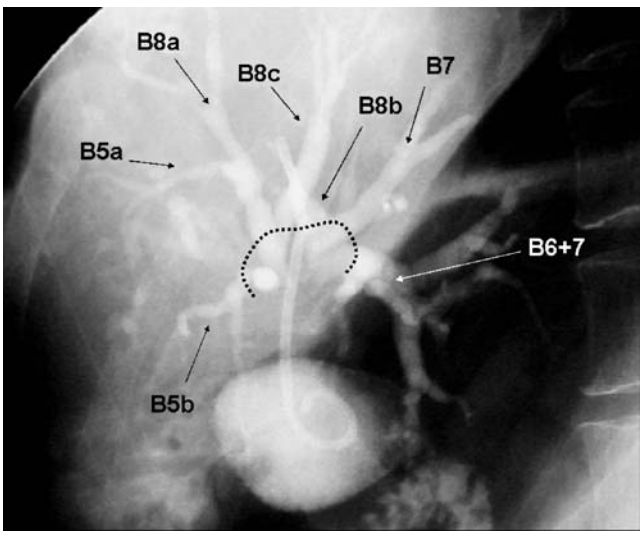

Figure 1 Preoperative cholangiography in right anterior oblique direction. Roots of subsegmental branches of the anterior segment show narrowing. The i*nterrupted line* represents the planned resection line of the bile ducts.

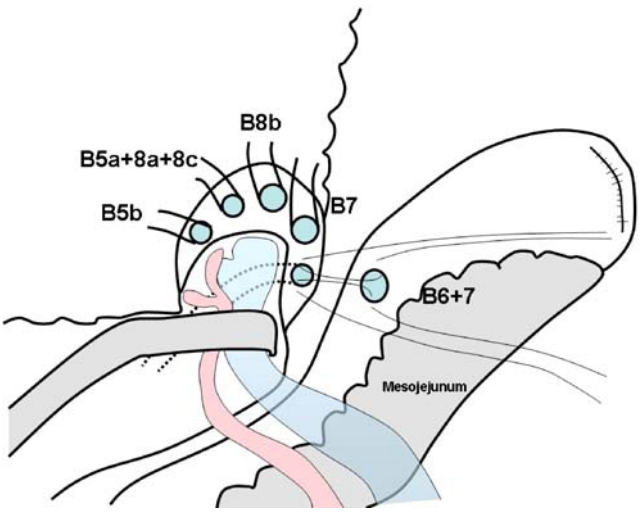

Figure 3 The jejunal limb was mobilized and brought through a defect created in the hepatoduodenal ligament. An anastomotic orifice for B6 + 7 was opened in the jejunum in a position face-to-face with the bile duct orifice.

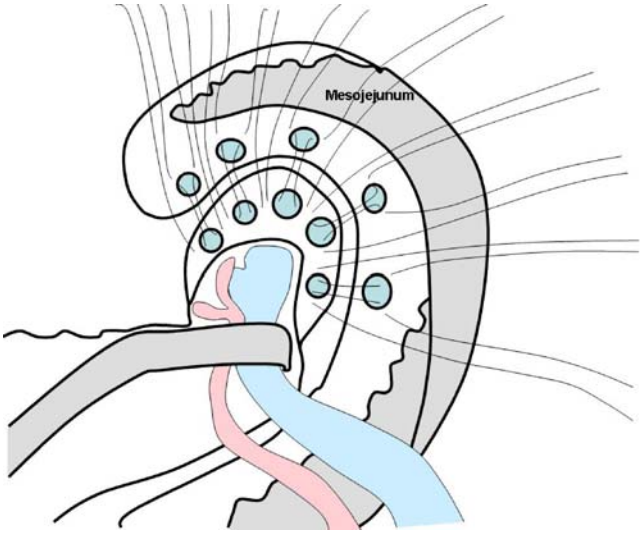

Figure 4 After all sutures were placed at the posterior side of the anastomosis, these were tied.

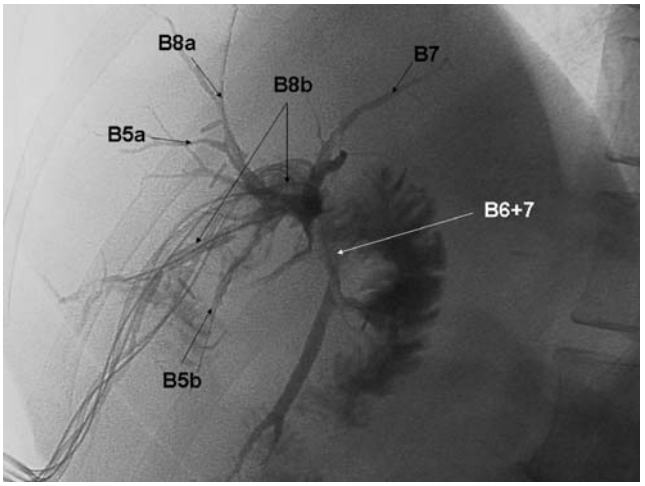

Figure 6 No anastomotic insufficiency was observed by cholangiography performed on postoperative day 14. Anastomotic sites were positioned in a semicircular array.

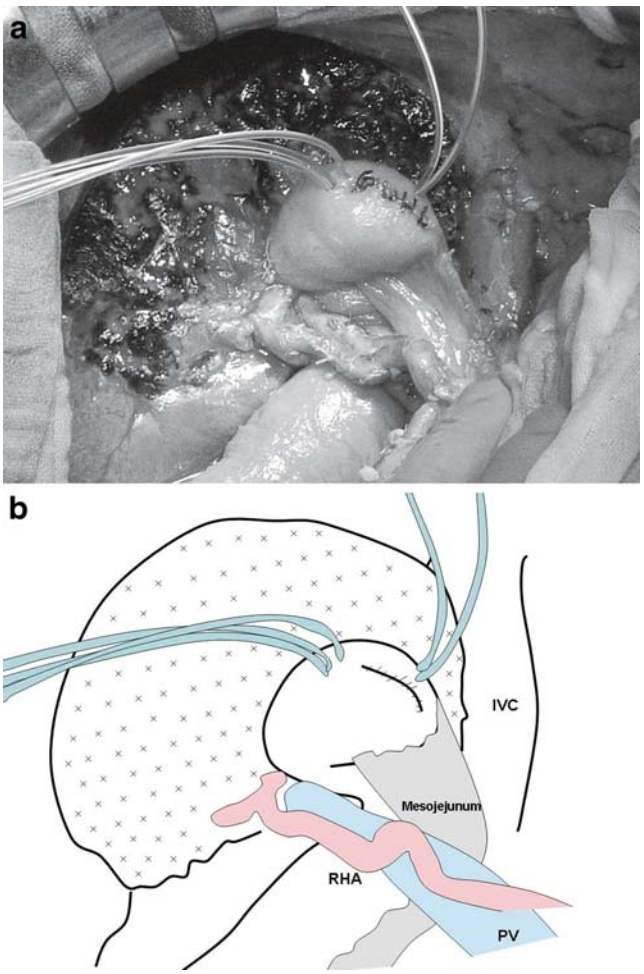

Figure 5 a, **b** Tension-free hepaticojejunostomy was completed. Biliary drainage tubes were inserted in all anastomosed bile duct.

have been free of recurrence and have maintained a good quality of life during follow-up of 19 and 24 months.

Discussion

Prognosis for patients undergoing potentially curative resection for bile duct cancer has gradually improved. Advances in preoperative imaging, such as cholangiography, multidetector-row computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP), now permit more accurate assessment of tumor extent.[7–9] However, a subset of patients prove to have unexpectedly extensive cancer infiltration along the hepatic duct. When an intraoperative frozen section examination of the bile duct stumps shows tumor at the cut end, additional resection of the hepatic duct stump is required for curative resection.

We elevate a Roux-en Y jejunal limb anterior to the right portal vein in most patients whose biliary tree has been divided at the right hepatic duct or at the bifurcation of the anterior and posterior segmental hepatic ducts. However, a small number of patients require interruption at the subsegmental bile duct level, actually, only three cases during 3 years. The orifices of the posterior bile ducts, then, are located behind the right portal vein, making conventional hepaticojejunostomy very difficult, not only because of inadequate operative fields but also because of the excessive stress placed upon the usual anastomosis. Additional resection of the remaining tumor at the cut end of the bile ducts could not be pursued in such cases.

Additional resection of the anterior sector might be another way to resolve this matter. Some surgeons prefer to perform left trisectionectomy for patients with Bismuth type 4 disease.[10] Indeed, trisectionectomy undoubtedly provides a good operative field for bilioenteric reconstruc-

tion. However, extended hepatectomy increases the risk of postoperative liver failure. To ensure safety, extended hepatectomy should be avoided in patients with impaired hepatic functional reserve or advanced age.[11]

In this study, we demonstrated a technique that provided a better operative field for performing hepaticojejunostomy involving the posterior segmental bile ducts as an unavoidable countermeasure for ensuring proper postoperative function. These procedures make anastomotic suture easy to perform even for small, fragile bile ducts. Moreover, the anastomosed region is free from tension because the orifices of the bile duct and jejunum face one another. This procedure appears to be highly useful for patients with longitudinal cancer infiltration along the bile duct because, when needed, it allows the operator to resect the bile duct with a sense of security further toward the hepatic periphery than the usual procedures.

Further investigation is needed to assess aspects of long-term outcome such as avoidance of anastomotic stenosis arising from decreased blood supply to the bile ducts around the anastomotic site, as peribiliary arterial flow can be impaired following procedures separating arteries from bile ducts to ensure tumor-free suture margins. To date, we have not experienced anastomotic leakage, postoperative stenosis, or local recurrence in our two surviving patients following the present procedure.

This procedure has a potential limitation for obese patients with a thick mesentery. In such instances, a jejunal limb with thick mesentery is not likely to be able to pass through the hepatoduodenal ligament. None of the three patients had a thick mesentery.

In conclusion, we successfully performed retroportal hepaticojejunostomy by directing the jejunal limb behind the hepatoduodenal ligament to reestablish biliary continuity in patients undergoing high hilar bile duct resection. This allows more extensive resection of the hepatic duct and provides a good operative field as well as a safe, tension-free anastomosis.

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Liver Regeneration and Tumor Stimulation—A Review of Cytokine and Angiogenic Factors

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Abstract Liver resection for metastatic (colorectal carcinoma) tumors is often followed by a significant incidence of tumor recurrence. Cellular and molecular changes resulting from hepatectomy and the subsequent liver regeneration process may influence the kinetics of tumor growth and contribute to recurrence. Clinical and experimental evidence suggests that factors involved in liver regeneration may also stimulate the growth of occult tumors and the reactivation of dormant micrometastases. An understanding of the underlying changes may enable alternative strategies to minimize tumor recurrence and improve patient survival after hepatectomy.

Keywords Colorectal carcinoma · Liver resection · Liver regeneration · Cytokines · Angiogenesis · Growth factors · Tumor recurrence

Introduction

Long-term survival in patients with secondary liver tumors is achieved in selected patients by hepatic resection. Five-year survival rates in patients undergoing liver resection for colorectal cancer liver metastases range from 20% to 40%.[1] Despite sophisticated staging techniques and adequate surgical clearance, local and systemic recurrences occur in the remaining patients. Recurrent disease in these patients usually appears within the first 12 to 18 months after resection at both hepatic and extrahepatic sites. Approximately 50% of recurrences occur in the liver only, while 15–20% occur in both hepatic and extrahepatic sites. Approximately 25–30%[2] occur in extrahepatic sites only. Timing of the recurrences varies according to the organ involved. In general, extrahepatic recurrences occur later than hepatic recurrences and predominantly in the lung and lymph nodes indicating possible different causative mechanisms. The degree of liver resection is also a significant factor in the patterns of tumor recurrence.

Prognostic factors influencing recurrence after liver resection for colorectal metastases are several. The most significant adverse factors are involved resection margins and the presence of extrahepatic disease. The initial staging of the primary tumor, the number of metastases, timing to recurrence from the primary operation, the degree of differentiation and the presence of specific biological markers are also important prognostic parameters. The presence of angiogenic markers such as a high tumor vessel density and high preoperative serum levels of angiogenic growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), and basic fibroblast growth factor (b-FGF)[3,4] indicate a high propensity to tumor recurrence.

There is now accumulating clinical and experimental evidence that suggests specific factors involved in liver regeneration may influence the growth patterns of residual or dormant micrometastases after resection. The site of these micrometastases and sources of future recurrences remain controversial.

This review will assess evidence on the possible role of cytokine and angiogenic factors involved in liver regeneration on tumor recurrence.

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Evidence for Recurrence of Metastases After Tumor Resection

Clinical evidence suggests that stimulation of tumor growth may occur after resection of liver tumors.[5–7] Surgical strategies such as portal vein embolization and two-stage hepatectomy involving liver regeneration may also be associated with stimulation of tumor growth. Elias et al. performed studies, which assessed liver regeneration after right portal vain embolization of patients who had undergone hepatic resection. The growth rate of liver metastases exceeded that of the normal liver parenchyma by almost eight times, suggesting that the process of regeneration has significant proliferative effect on tumor cells.[8] Kokudo et al. also reported that portal embolization before hepatic resection caused significant enhancement in the growth rate of colorectal cancer (CRC) metastases and poorer disease-free survival in these patients compared to those treated only with hepatic resection.[9] Togo et al.[10] have reported a high incidence of residual liver and lung metastases after two-stage hepatectomy and the need for protective measures such as chemotherapy during the liver regenerative phases. Adam et al.[11] has emphasized the need of adjuvant chemotherapy during portal vein embolization and two-stage hepatectomy to prevent tumor proliferation during the liver regenerative phase. A report by von Schweinitz et al.[12] found accelerated residual tumor growth in children with embryonal hepatoblastoma after liver resection compared to untreated patients. The accelerated growth correlated with increased HGF serum levels.

Animal studies have also confirmed that there is stimulation of tumor growth after liver resection. The degree of liver resection is a significant factor in the degree of tumor stimulation and the development of extrahepatic metastases.[13] De Jong et al.[14] demonstrated that liver regeneration may influence the growth of the remaining micrometastases in the liver by hepatotropic factors. Using rats induced with metastatic colorectal cancer, enhanced growth in the remnant liver after 70% partial hepatectomy was observed. Other studies in hepatectomized rats challenged with tumor cells found that the hepatic metastatic tumors grew faster than in sham hepatectomies.[15] There was no difference in the growth rate of extrahepatic metastases between the two groups, suggesting a local paracrine stimulation by factor(s) related to liver regeneration. In a different study by Schindel and Grosfeld,[6] both hepatic and extrahepatic metastases grew at a faster rate than those in the sham hepatectomized control rats, suggesting that factors induced by hepatectomy influence both local and distal tumor growth. Our studies have confirmed that 70% hepatic resection was associated with increased peritoneal and lung metastases as well as increased growth of intrahepatic metastases. The increase in growth in liver metastases occurred predominantly in the late phase of liver regeneration rather than the early phase.[16] In a study with nude mice, it was found that even minimal liver resection results in a dramatic acceleration of recurring colorectal cancer liver metastases after hepatectomy.[17]

Studies by Ikeda[18] and Slooter et al.[13] suggest that the frequency of metastases after hepatectomy is proportional to the extent of resection. Mueller et al.[19] using a rat model showed that portal branch ligation is associated with increased expression of genes known to promote tumor growth. Kollmar et al.[20] showed that partial hepatectomy significantly increased tumor metastases when compared with nonresected controls or laparoscopy-treated animals and correlated with a significant increase in the expression of the macrophage-inflammatory protein-2 (MIP-2) receptor CXCR-2 on tumor cells and accelerated tumor angiogenesis.

Liver Regeneration After Hepatectomy

Adult hepatocytes are differentiated, metabolically active, and the majority is in the resting (G0) state.[21] During liver regeneration, they undergo a "priming" phase to become "proliferatively competent" and move from G0 to G1. After the priming phase, growth factors and other mitogens stimulate cell proliferation, so that they undergo sufficient rounds of mitosis to restore the original mass of the liver.[22,23] The molecular trigger to liver proliferation appears to be loss of functional hepatic mass. For example, in experimental partial hepatectomy, removal of one third of the liver evokes a poor proliferative response (only isolated hepatocytes proliferate), whereas two-thirds removal provokes 80% to 90% of hepatocytes to undergo coordinated rounds of mitosis.[24] Sensors of such ideal "hepatic functional mass" remain unclear. From gene array and proteomic studies, numerous genes have shown alteration in their expression after hepatectomy.[25–27] Some of the upregulated genes are absolutely necessary for regeneration to occur,[28–30] whereas others show degrees of redundancy.[28,31]

The genes involved in liver regeneration fall into three categories: cytokines, growth factors, and genes with metabolic functions.[32] The trigger of the liver regeneration cascade is thought to be the result of shear stress-induced nitric oxide (NO) and prostaglandins (PGs)[33,34] after the increase in the blood flow-to-liver mass ratio after liver resection. The initiation trigger is followed by an increase in liver cytokines.[35,36] Liver regeneration occurs roughly in three stages (Fig. 1). The first stage is the "priming stage" and occurs during the first few hours after resection. Tumor necrosis factor-alpha (TNF-α) and interleukin- 6 (IL-6) cytokine signaling pathways are the main cytokine activat-

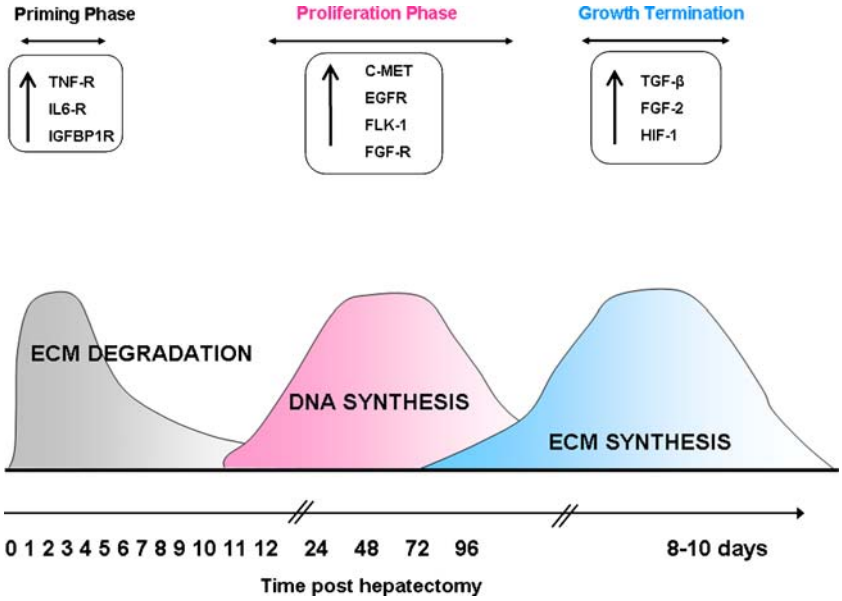

Figure 1 Molecular and ultrastructural changes during liver regeneration. Signaling through the TNFR, IL-6R, and IGFBP1R receptors prime the hepatic cells to enter mitosis. Signaling through c-Met, EGFR, Flk1, and FGFR promote DNA synthesis and drive proliferation during the proliferative phase. TGF-β and b-FGF through their receptor signaling are responsible for growth termination and ECM synthesis. Metalloproteinases play a pivotal role in ECM degradation, the generation of active growth factors, and signaling molecules from the ECM and cell surfaces. They are also responsible for the degradation or inactivation of these factors when none are required.

ed pathways and their signaling duration is very tightly controlled.[25]

Hepatocytes primed through these pathways become responsive to growth factors and enter into the second stage, the proliferative stage. The growth factors and their receptors that dominate this stage have proliferative and cytoprotective functions. The main factors involved are HGF, EGF receptor ligands such as EGF and TGF-α, heparin-binding EGF like growth factor (HB-EGF), amphiregulin,[37] growth hormone (GH),[38] and insulin growth factor binding protein-1 (IGFBP1).[30] The increased metabolic demand on the remaining liver remnant after resection may be the sensor that dictates the extent of replication and also signal the termination onset. Proliferation inhibiting factors such as the transforming growth factor beta (TGF-β) superfamily, which includes TGF-β1, 2, and 3, activins, and inhibins among others, are involved in the termination stage of liver regeneration.[39–41]

During liver regeneration, there is a breakdown and remodeling of the extracellular matrix (ECM)[40] as illustrated in Fig. 1. This is accomplished by the metalloproteinases (MPPs) secreted by pericytes in response to HGF stimulation.[42] During the proliferation phase, the hepatocytes form avascular clusters. The sinusoids become shorter and more dilated and completely disappear in some areas (Fig. 2b). Stellate and endothelial cells proliferate later than hepatocytes and also form clusters adjacent to the hepatocytes. Some of the stellate cells associated with the hepatocyte clusters become activated and fibroblastic in function (Fig. 2c). In the later stages of regeneration, under the stimulation of TGF-β they secrete ECM components. At this stage, endothelial cells migrate into the hepatocyte clusters initiating the reorganization of the hepatocytes and establishment of microcirculation (Fig. 2c). Angiogenesis during liver regeneration involves ECM remodeling and the upregulation of proangiogenic growth factors such as hypoxia-induced factor-1a (HIF-1α), VEGF, and b-FGF.[43,44] New vessels are formed from proliferation and migration of endothelial cells from neighboring vessels and the mobilization and recruitment of endothelial precursor cells (EPC) from the bone marrow.[45–47] The mobilization of both types of cells is induced by local VEGF production, which is upregulated in liver regeneration.[47]

Factors in Liver Regeneration that May Influence Tumor Growth and Metastasis

Tumor recurrence after hepatectomy may result from circulating tumor cells or dormant micrometastases. The source of these occult metastases is uncertain. Micrometastases are detectable on histological examination in resected specimens. These may reside in the portal vein, central vein, sinusoids, and the bile duct.[48] Minimal residual disease in bone marrow may also be a source of tumor micrometastases[49] A number of publications report positive tumor cell circulation after surgery.[50] It has been shown, in animal models, that approximately 10^6 tumor cells per gram of tumor tissue may be shed daily into the systemic circulation.[51] New metastases establish in selective tissues that express receptors that are able to recognize specific ligands such as integrin $\alpha_v\beta_3$ on the circulating tumor cells.[52] These ligands must be activated for adhesion[53,54] and maybe activated during liver regeneration through proteolytic cleavage of inactive surface ligands by MMPs.

It has been suggested that micrometastases remain dormant because proliferation and apoptosis rates of tumor cells are mutually antagonistic.[55,56] Tumor growth requires

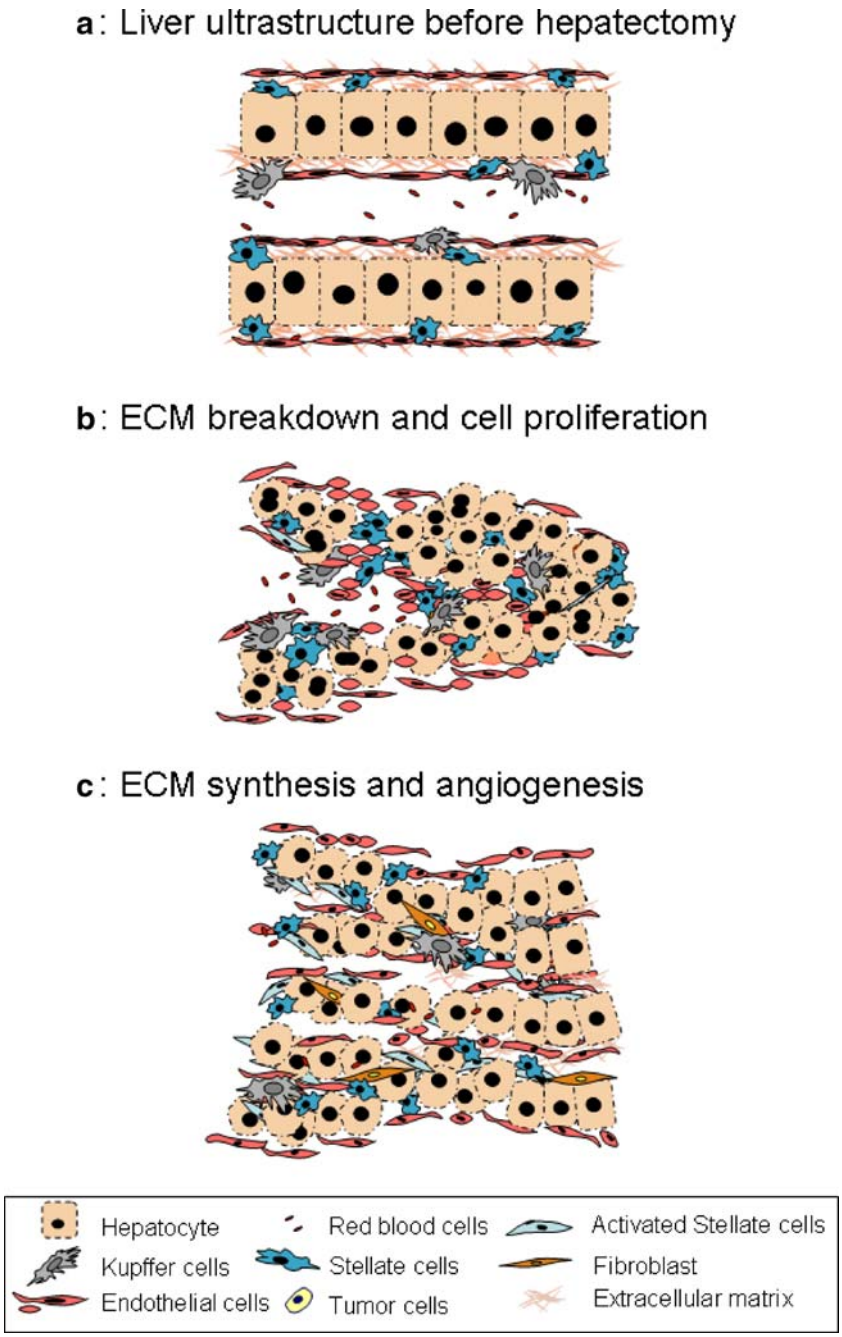

Figure 2 Cellular and ultrastructural changes in liver morphology during liver regeneration. (**a**) Degradation of ECM proteins and collagen. Release and activation of preformed growth factors and other signaling molecules from cell surfaces or the ECM. Cleavage of cell adherence proteins such as cadherins allows cells to move and proliferate. (**b**) Upregulation of growth factors. Hepatocytes undergo DNA synthesis and proliferation forming avascular clusters by 48 hours. Proliferation of non-parenchymal cells by 72 hours. Stellate cells form clusters and are often found within the hepatocyte clusters or near endothelial cells. Sinusoids shorten and become more dilated and cannot be seen in some areas. (**c**) Peak upregulation of pro-angiogenic growth factors VEGF, b-FGF, and TGF β. Synthesis of new ECM components by activated stellate cells. Upregulation of cell adhesion molecules. Adhesion ligands attach to new ECM fibers. Migration of endothelial cells into hepatocyte clusters and reconstruction of new sinusoid vasculature.

the balance of growth factors and cytokines in the microenvironment to favor angiogenesis.[57] Angiogenic inhibitors such as circulating angiostatin, ECM proteins such as thrombospondin,[58] or ECM protein fragments such as endostatin[59] are considered responsible for maintaining the dormant state. Major surgery including hepatectomy results in a major influx of angiogenic factors and cytokines that could alter the microenvironment of distant dormant tumor deposits causing their reactivation. In addition, the activation of the coagulation cascade,[60] the temporary local and systemic immunosuppression after surgery,[61] and the mobilization of EPC and other hematogenic cells have also been shown to enhance tumor metastases.[62]

The liver ECM breakdown and rebuilding during liver regeneration may be a major source of tumor metastasis, both hepatic and extrahepatic. Tumor cells in micrometastases may become detached and find their way to other hepatic sites or into the blood and lymphatic circulation (Fig. 3).

ECM breakdown and remodeling at a smaller scale occurs also at the tumor interface. The factors involved (urokinase-type plasminogen activator (uPA), MMPs, HIF-

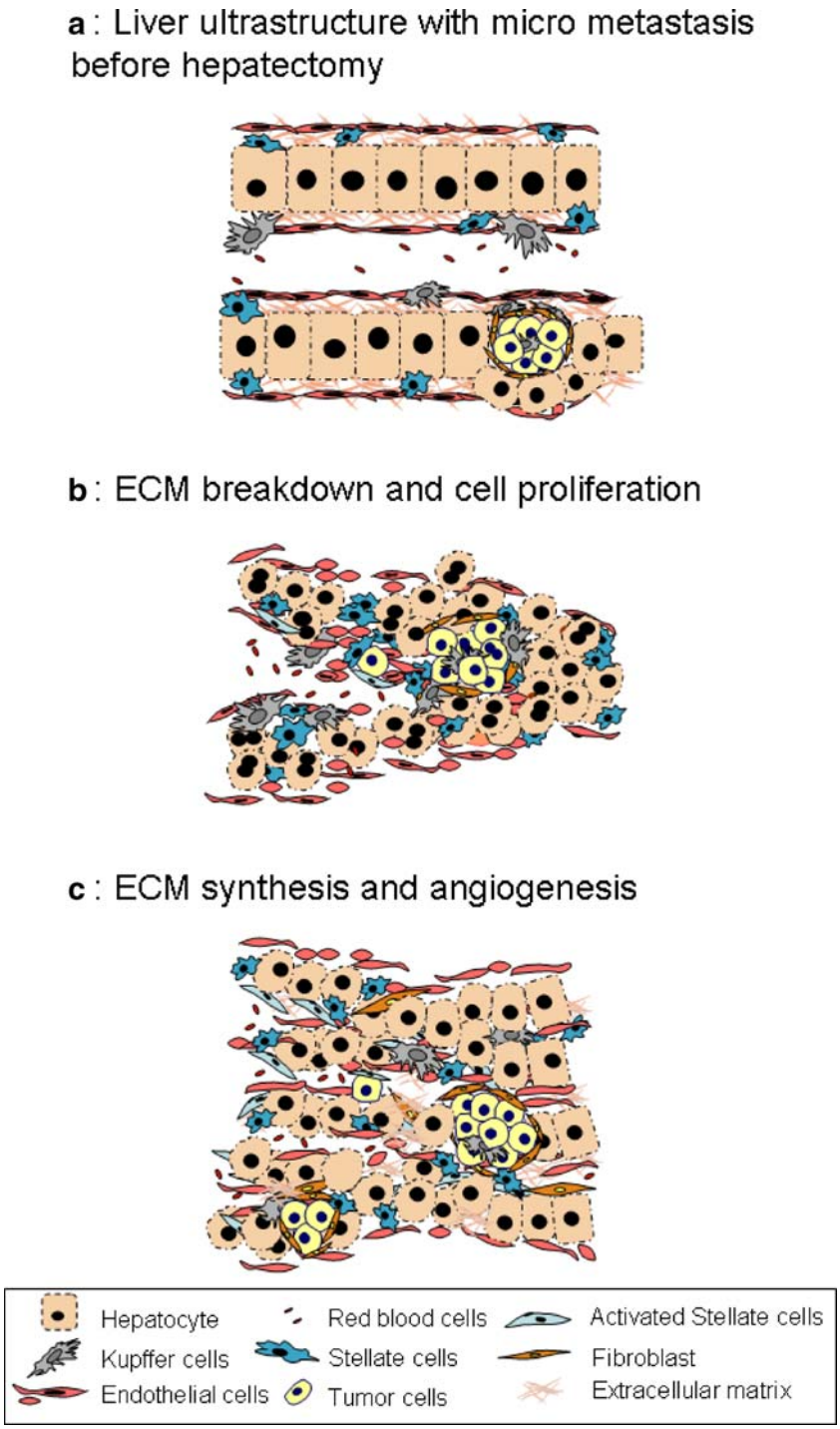

Figure 3 Molecular and ultrastructural changes during liver regeneration could promote tumor recurrence. **a**: Tumor ECM breakdown. Cleaving of cell-cell attachments, activation of cell surface ligands and shedding of cell surface ligands. **b**: Growth factor signalling may stimulate proliferation in tumor cells. Free tumor cells may escape into new sites or into the circulation. **c**: Upregulation of VEGF, b-FGF and TGF-β may induce EMT transition in tumor cells. Upregulation of adhesion molecules on tumor cell surface may aid their migration into new intrahepatic sites or into new vessels and the systemic circulation.

1α, VEGF) are common to those of the liver ECM remodeling during liver regeneration. It has been shown that metastatic epithelial tumors undergo an epithelial to mesenchymal transition (EMT) to become invasive.[63] Various stimuli within the tumor microenvironment also promote EMT transition of carcinoma cells. These include growth factors that bind to tyrosine-kinase receptors (TKR), such as b-FGF, EGF, and HGF, members of the TGF-β superfamily and ECM constituents including MPPs.[64] These factors are upregulated by hepatectomy and in ECM remodeling and may account for increased metastases after liver resection (Fig. 3).

Growth factors such HGF, EGF, TGF-α, TGF-β, HIF-1α, VEGF, and MPPs have been shown in numerous studies (outlined in detail in the following sections) to be associated with tumor aggressiveness and metastasis. Therefore, additional upregulation of these factors during liver regeneration may enhance the metastatic process.

HGF

Hepatocyte growth factor (HGF) is one of the most important growth factors upregulated during liver regeneration. Expression of HGF increases 6 to 8 hours after partial hepatectomy. It is produced and secreted by stellate cells, sinusoidal endothelial cells, and Kupffer cells and acts in a paracrine manner.[65,66] Studies using liver specific HGF receptor (c-Met) knockout mice showed that HGF/c-Met signaling is essential for liver regeneration after hepatectomy.[67,68] HGF is a multifunctional factor. In cell culture, it induces strong mitogenic stimulation on hepatocytes and other cell types[69,70] and exerts morphogenic, mitogenic, and proangiogenic effects on normal and neoplastic epithelial cells.[71–73] It has functional roles in angiogenesis, wound healing, and carcinogenesis.[74] Tamatani et al.[75] reported that addition of exogenous HGF accelerated tumor migration and infiltration and increased MMP activity, suggesting an important role in tumor invasion and progression. HGF stimulates cell motility and the secretion of proteinases, which lyse the tumor basement membrane promoting metastasis.[76,77] HGF is occasionally secreted by tumors, stimulating tumor growth in an autocrine manner.[78]

The HGF receptor belongs to the family of receptors of tyrosine kinases and is encoded by the c-Met protooncogene.[79–81] HGF through c-Met and Mitogen-activated protein kinase (MAPK) signaling was shown to induce growth, invasion, and metastasis in hepatocellular carcinoma (HCC) tumors,[82] and to be involved with high-grade invasive bladder cancer.[75] The HGF/c-Met have also been implicated in CRC pathogenesis.[83] HGF also cooperates with other receptors such as the insulin growth factor receptor (IGFR) in promoting tumor growth.[84]

EGFR and its Ligands

The EGFR, a tyrosine kinase receptor of the ErbB family, comprises the second major signaling system, after the HGF/c-Met, in liver regeneration.[37] The EGFR belongs to a family of four closely related receptors: EGFR (ErbB-1), HER-2/neu (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4). Ligand binding on the EGFR results in the activation of its tyrosine kinase (TK) activity. It initiates receptor-mediated signal transduction, cell mitogenesis, and cell transformation. EGFR ligands include EGF, TGF-α, amphiregulin, HB-EGF, epiregulin, and cellulin. The binding of these ligands to the receptor results in different function modulation for each of them, ranging from cell motility and proliferation to growth inhibition.[37] A number of the EGFR ligands have been shown to be upregulated during liver regeneration (EGF, TGF-α, amphiregulin, and HB-EGF).

The activity of EGFR is abnormally elevated in most human solid tumors[85] including CRC[86] and human HCC.[87–89] EGFR overexpression correlates with early tumor recurrence[90] and extrahepatic metastasis. The EGFR signaling also induces VEGF upregulation and the induction of angiogenesis.[91–93] Cetuximab or gefitinib therapy (EGFR inhibitors), in a colon carcinoma model, results in a decrease of VEGF, b-FGF, and TGF-α expression and a reduction in microvessel count.[94,95] Another EGFR family ligand upregulated in liver regeneration, HB-EGF, binds to ErbB1 and ErbB2 receptors. It plays a major role in angiogenesis by stimulating ErbB receptor phosphorylation and migration of smooth muscle cells (SMCs).[96,97] TGF-α, another EGFR ligand is also upregulated in liver regeneration and is associated with adverse predictors of survival when upregulated in tumor.[98]

VEGF

Angiogenic growth factors such as VEGF that promote new vasculature formation from preexisting blood vessels are increased during liver regeneration. Most solid tumors overexpress and secrete VEGF.[99] It is also secreted by infiltrating immune cells such as monocytes.[100,101] Solid tumors are generally hypoxic, resulting in HIF-1α upregulation, which in turn induces angiogenic factors such as VEGF production.[102] VEGF is also induced through EGFR and c-Met signaling.[97,103] VEGF also plays a role in vasculogenesis by recruiting endothelial progenitor cells from the bone marrow for endothelial vessel formation. Tumors producing high levels of VEGF are associated with increased tumor vascularity, metastasis, chemoresistance, and poor prognosis.[104]

VEGF has several other associated actions, which enhance tumor angiogenesis and metastatic potential, including the upregulation of the VEGF receptor FLK-1 in tumor cells.[105] VEGF also induces the synthesis of a stroma-derived factor (SDF-1) that recruits circulating cells from the periphery to the tumor site where they differentiate into cancer-associated fibroblasts (CAFs). These produce b-FGF and many other factors associated with ECM remodeling, angiogenesis, and cancer-cell EMT.[64] Basic FGF induces endothelial cell proliferation, migration, and capillary tube formation.[106]

TGF-β

Transforming growth factor beta (TGF-β), upregulated in liver regeneration, enhances angiogenesis and metastases by promoting accumulation of ECM glycoproteins and adhesion proteins.[107] Serum TGF-β levels correlate with

the development of liver metastasis after potentially curative hepatic resection.[4,108] Changes in expression and mutations in the genes for TGF-β, the TGF-β receptors, and the SMAD proteins also correlate with metastatic cancers of the colon, liver, and pancreas.[107] Loss of the TGF-β receptors, TGFβR2 and TGFβR1, occurs often in human liver cancer, disrupting the TGF-β signaling pathway.[109,110] Similar loss of these receptors has been reported in preneoplastic and malignant cells from rats, mice, and humans, indicating that loss of the antiproliferative TGF-β signaling results in tumorogenesis.[111]

IGF-I and IGFR

Insulin growth factor I (IGF-I) has not been shown to be upregulated during hepatectomy by gene arrays,[25] and no function has been attributed to it in the regeneration process. However, liver regeneration after hepatectomy is disrupted in male mice that do not express the IGFR in the liver.[112] It is possible that IGF-I is modulated as a byproduct of growth hormone upregulation.[38] GH is upregulated during liver regeneration and it has been shown to be important for the regeneration process. It is the primary regulator of IGF-I synthesis and secretion in hepatocytes. IGF-I in turn regulates GH secretion through a negative feedback loop.[113] IGF-I levels in circulation are modulated by the IGF-binding proteins (IGFBPs) and only 5% of IGF-I circulates unbound.[114,115] The majority of IGF-I in the body is manufactured by the liver[116]. Although it is not clear if IGF-I has a role in liver regeneration, there is able evidence that IGF-I and its tyrosine kinase receptor play important roles in the development and progression of a variety of human cancers including CRC.[117] IGF-I induces CRC proliferation, and high IGF-R expressing tumors colonize the liver more readily than low IGF-IR expressing tumors.[118] This may be the reason that the majority of CRC metastases are found in the liver. Epidemiological studies have established a correlation between circulating levels of IGF-I and IGFBP-3 and the relative risk for developing colon, breast, prostate, and lung cancer.[119,120] High levels of IGF-I and low levels of IGFBP-3 are independently associated with an increased risk of colorectal cancer. Warren et al.[121] showed that IGF-I induces VEGF expression in cultured colorectal carcinoma cells. Wu et al.[117] also demonstrated VEGF upregulation in tumors by IGF-I addition. Similar to HGF/c-Met, IGF-I/IGFR signaling is known to induce tumor cell migration, invasion, and angiogenesis by stimulating endothelial cell VEGF expression[122] and promoting endothelial cell migration.[123] Using plasmid-mediated IGF-I therapy, Rabinovsky et al.[124] demonstrated increased expression of VEGF and activation of the VEGF receptors FLK-1 (VEGFR-2) and FLT-1 (VEGFR-1). FLK-1 receptor signaling induces endothelial cell proliferation and increases permeability, whereas FLT-1 receptor is implicated in vascular remodeling.[125]

IGF-I and HGF have been shown to function as co-mitogens in a rat hepatoma cell line[126]. In addition, Bauer et al.[84] demonstrated a tyrosine kinase receptor cooperation between IGFR and c-Met in human CRC. IGF-I appears to be an upstream regulator of the angiogenic cascade. Even if there is no increase in IGF-I growth factor during liver regeneration, the increase of many other tumor promoting factors that have been shown to cooperate in IGF-I/IGFR signaling suggests that IGF-I is an important contributor to accelerated tumor growth and metastatic activity associated with hepatectomy.

MMPs

The role of MMPs is to maintain homeostasis in the extracellular environment. In liver regeneration, they play central roles in promoting growth factor upregulation or activation, and in the breakdown and remodeling of the ECM.[40] There are several classes of MMPs, and the biological roles of the majority have not been fully elucidated. MMPs are part of an extensive "protease web" where individual members may also be substrates of other proteases, releasing activated ligands or inhibitors in many signaling pathways.[127] Several studies have linked MMPs with numerous types and stages of cancer. They have been implicated in the base membrane alterations leading to tumor metastasis.[128,129] Overexpression of particular MMPs has been correlated with tumor progression, and mouse transgenic models overexpressing MMPs support this finding.[130] In addition to ECM degradation, MMPs promote tumor progression by modulating the generation and active states of key molecules in various signaling pathways including growth factors and chemokines.[127]

Clinical Perspectives

Over 50% of patients who undergo resection for colorectal cancer liver metastases will ultimately have recurrent disease in the liver and/or extrahepatic sites. The major adjunct to surgery has been systemic chemotherapy in the neoadjuvant or postoperative situation. Several studies have now confirmed that conventional combination systemic chemotherapy associated with potential curative liver resection has been associated with increased survival rates.[131,132] The major areas of concern with the use of chemotherapy have been compromised liver function (steatohepatitis, sinusoidal obstructive syndromes), coagulation disorders, and impaired wound healing. In addition, the regenerative ability of the

Table 1 Cancer Therapies Targeting Angiogenesis and Metastasis Promoting Factors

Target	Inhibitor	Reported Clinical Effects	Clinical Stage	Reference
VEGF-A	mAb Bevacizumab (Avastin)	Survival benefit, disease stabilization, partial regression	FDA approval for metastatic CRC in combination with CT	137
	mAb HuMV833	Some clinical activity	Phase I	140
VEGF-A, PDGF	VEGF trap (soluble hybrid VEGFR-1–2 decoy)	Significant radiographic improvement in one patient	Phase I/ II	141
VEGFR-2	mAb 2C3	Inhibits tumor growth and lymphangiogenesis,	Preclinical	142,143
VEGFR-1, -2	SM TKI AZD2171	Partial regression	Phase I	144
VEGFR-1, -2, -3	SM TKI GW786034	Partial regression, disease stabilization	Phase II	145
	SM TKI vatalinib PTK787	Significant clinical effect in a subgroup of patients with high LDH levels	Phase III	137,146
VEGFR-1, -2, PDGFR	SM TKI SU11248 (sunitunib)	Partial regression, complete response Some problems with bleeding	FDA approval for metastatic RCC and GIST	144
VEGFR-1, -2, bFGFR	SM TKI CP-547632	No additional clinical benefit in combination with CT	Phase I/ II	147
VEGFR-1, -2, -3, PDGFR, c-kit, Raf	SM TKI Bay 43-9006 sorafenib	Prolongs progression-free survival	FDA approved monotherapy metastatic RCC	148
PDGFR,c-kit, Abl	SM TKI Imatinib (STI-571)	Significant improvement in survival	FDA approval for treatment of CML and GIST.	149,150
VEGFR-1, -2, -3, EGFR	SM TKI ZD6474	Prologed progression-free survival	Phase II	151
	SM TKI AEE788	Significant reduction of tumor growth and metastasis	Preclinical	
EGFR, bFGFR, FGFR	SM TKI SU6668	Not effective	Phase I	152
EGFR	SM TKI AG1478	Inhibits EGFR activity	preclinical	153
	SM erlotinib (OSI-774)	Significant improvement in median survivalnon-small cell lung cancer.	FDA approval for metastatic lung and pancreatic cancers	154
	SM Gefitinib	Significant improvement in median survival in non-small cell lung cancer: selected patients	Phase I/II	155
	MAb Cetuximab	Promising as monotherapy or in combination with cytotoxic treatment for CRC	FDA approval for metastatic CRC	156
	MAb panitumumab	Improved progression free survival	FDA approval for metastatic CRC	157
ErB2	SM TKI AG879	Inhibits tumor in combination with AG1478	Preclinical	158
EGFR, ErB2	SM TKI GW572016	Inhibits tumor xenografts	Preclinical	159
IGF-R	SM NVP-AEW541	Suppression of tumor growth and metastasis	Preclinical	160
IGF-I, IGF-II	Neutralizing mAbs	Significant tumor growth inhibition and longer survival.	Preclinical	161
MMP-2, 3, 9	SM Tanomastat (BAY 12-9566)	No clinical benefit	Phase III	162
MMP-1, 2, 8, 9, 13	Metastat (CMT-3,Col-3)	No clinical benefit	Phase II/III	163
MMP-2, 3, 9, 13, 14 collagenase III	Prinomastat (AG3340)	Discontinued because of adverse complications	Phase II	164
MMP-1, 2, 3, 7, 9, 12	Marimastat (BB-2516)	No benefit	Phase III	165
Broad spectrum MMPs	Rebimastat (BMS-275291)	No improvement, toxic	Phase II/III	166
Angiogenesis	Endostatin combined with radiotherapy	Blocks tumor revascularization in mouse xenografts. No significant tumor regression in cancer patients	Preclinical, Phase II	167,168
	Angiostatin	High disease control	Phase II	169

Endothelial cells	EMD-121974 Blocks an endothelial integrin	Tumor and endothelial cell apoptosis not reach significance	Phase II	170
	TNP-470 Fumagillin analogue inhibits endothelial cell proliferation	Some clinical benefit. Not effective in colonic carcinoma	Phase I, Preclinical	171,172
$\alpha_v\beta_3$ integrin	MAb Vitaxin MEDI-523	Limited efficacy	Phase I/II	173
	MAb Abergrin MEDI-522	Well tolerated, some clinical activity	Phase I/II	174
$\alpha_v\beta_3$ and $\alpha_v\beta_5$integrin	Cilengitide (EMD 121974)	Well tolerated. Tumor and endothelial cell apoptosis did not reach significance	Phase I/II	170
TGF-β	Neutralizing pan-TGF-β mAb	Inhibits metastases when used with other anticancer treatments	Preclinical	175
	TGF-β1, TGFβ2 antisense oligonucleotides	Increased progression free time	Phase I/II	176,177
TGF-βRII	Dominant negative receptor (DNRII)	Inhibits tumor. Prolongs survival	Preclinical	178
	Soluble domain of TGF-b	Inhibits tumor growth	Preclinical	179
TGF-βRI	SM drugs : SB-505124, SD-208, LY580276	Inhibits tumor growth	Phase I	180
COX-2	SM drug Rofecoxib	Increases levels of endostatin	Phase II/III	181
MIF	Antisense-MIF	Inhibition of tumor growth and metastasis	Preclinical	182
UPAR	uPA peptide antagonist	Clinical activity	Phase I	183
	Mabs	Inhibition of tumor xenografts	Preclinical	184
HIF-1α	Antisense HIF-1a oligonucleotide	Significant tumor growth delays or total tumor suppression	Preclinical	185
	SM inhibitor PX-478	Significant antitumor activity tumor xenografts	Preclinical	186
HGF	Anti-HGF mAbs	Inhibition of tumor xenografts	Preclinical	184
	NK4 (HGF-antagonist)	Inhibits tumor growth, invasion, metastasis and angiogenesis.	Preclinical	187
c-met	c-*met* small-interfering RNA adenovirus	Downregulation of c-Met. Inhibition of tumor in mouse model	Preclinical	188

mAb=monoclonal antibody, TKI=tyrosine kinase inhibitor, GIST Gastrointestinal stromal tumor, CT=chemotherapy, LDH=lactate dehydrogenase, MIF=macrophage migration inhibitory factor, SM=small molecule, CML=chronic myeloid leukemia, PDGF(R)=platelet-derived growth factor receptor, RCC=renal cell carcinoma

liver may be compromised, leading to limited surgical options.[133] Portal vein embolization and two-stage hepatectomy are used in these situations.

There is now accumulating evidence and strong theoretical considerations that the process of liver regeneration after liver resection stimulates tumor recurrence. The specific pathways, including upregulated growth factors and signaling molecules responsible for tumor stimulation and recurrence, remain undefined. Our own evidence suggests that the late phase of liver regeneration is the key process where this occurs. This would suggest that growth factors and cytokines involved in angiogenesis and ECM remodeling are the key processes in liver regeneration involved in tumor growth and metastases.

Selective targeting of these processes in the late phase of liver regeneration may be beneficial in reducing tumor recurrence, without compromising the early phase of liver regeneration.

There are now several trials at various stages of completion, with therapeutic agents targeting these processes. (Table 1 includes a representative list of such studies.)

A number of monoclonal antibodies such as bevacizumab, cetuximab, panitumumab, trastuzumab, and small-molecule tyrosine kinase inhibitors, ZD-1839, OSI-774/CP358774, Sorafenib (Bay 439006) Sunitinib (SU11248), STI-571, have FDA approval for cancer treatments, including CRC (Table 1). Angiogenesis has been specifically targeted through VEGF and its receptors. This treatment is thought to be tumor specific as angiogenesis does not occur in adult tissues with the exception of wound healing, ischemia, menstruation, and pregnancy.[134] Recent studies, however, indicate that inhibition of VEGF signaling could lead to vascular disturbances in normal tissues and even regression of *normal* blood vessels.[135] Wound healing complications increased from 3.4% to 13% in patients receiving bevacizumab when surgery was performed within 60 days after the last treatment.[136] As bevacizumab has a relatively long half life, hepatectomy for tumor downstaging should not be performed for at least 28 days.[136] In advanced CRC disease, bevacizumab in combination with other chemotherapies[137] has shown significant improvement in overall survival.[138] Antiangiogenic drugs in general, however, including bevacizumab, have not proven beneficial as monotherapies in the clinical situation. In advanced tumors, angiogenesis is under the influence of several factors in addition to VEGF,[139] which may account for the limited efficacy of anti-VEGF treatments.

Antiangiogenic treatment to prevent recurrence after potentially curative hepatectomy requires further evaluation. A multitargeting inhibitor such as Sorafenib, administered orally, in combination with conventional chemotherapy, may prove to be the most efficacious. The timing of administration of these agents is uncertain and needs investigation.

Conclusion

Tumor recurrence after hepatectomy for liver tumors is a significant clinical problem resulting in long-term mortality. Strategies for the removal of liver tumors have focused on aggressive surgical resection to achieve clear margins, including techniques such as portal vein embolization and two-stage hepatectomy. Accumulating clinical and experimental evidence suggests that factors involved in liver regeneration may stimulate residual micrometastases. A clear understanding of the underlying processes may allow adjuvant therapies to be used at specific time points after resection to minimize the risk of recurrent disease.

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Isolated Splenic Metastasis from Colorectal Cancer: Report of a Case

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Abstract The authors report a case of a patient with splenic metastasis with previous history of colorectal cancer. A 69-year-old woman underwent a left hemicolectomy for sigmoid colon cancer. The tumor was staged T3N0M0. Two years after the operation, there was an elevation of CEA and computed tomography (CT) scan revealed a mass in the spleen, considered as an isolated metastasis. The patient underwent splenectomy. Histological diagnosis confirmed a metastatic adenocarcinoma from colorectal carcinoma. Patient was alive without neoplasic recurrence 5 years after splenectomy. Generally, splenic metastasis is uncommon. However, with the case of colorectal cancers, metastasis to the spleen is particularly rare. As with splenic metastasis of all primary tumors, the literature recommends that the treatment, where possible, is surgical.

Keywords Splenic metastasis · Colorectal cancer · Splenectomy

Introduction

Splenic metastasis are secondary lesions, generally being found in patients with other metastases, particularly in the liver. All carcinomas can metastasise to the spleen. However, isolated splenic metastases from colorectal cancer are very rare. The authors report a case of splenic metastasis from colorectal cancer treated by splenectomy with a long survival.

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Case Presentation

A woman, aged 69, presented with bloody stools and episodes of diarrhoea was admitted to the surgical department. A colonoscopy with biopsy gave evidence of an adenocarcinoma of the sigmoid colon. The biochemical investigations were within the normal limits, except of a carcinoembryonic antigen (CEA) of 10 ng/ml (normal <5 ml). A computed tomography (CT) scan did not show any metastases. A left hemi-colectomy with a colorectal anastamosis was undertaken. The histological investigations of the excised portion confirmed the existence of a well-differentiated adenocarinoma. The staging of the lesion was $T_3N_0M_0$. Chemotherapy was not carried out. The concentration of CEA, postoperatively, was normal.

Two years after, there was an elevation of CEA recorded at 20 ng/ml. The CT scan showed a mass occupying the inferior third of the spleen (Fig. 1). There were no other secondary localisations. During surgery, it was found to be a spleen tumour, 4 cm in diameter, and a splenectomy was performed (Fig. 2). The histological investigations confirmed a well-differentiated spleen metastasis without lymph nodes involvement.

She is being followed up and has had no relapse (normal CEA and CT findings) after 5 years.

Discussion

Spleen localizations can be revealed by an isolated rise of tumor markers (e.g., CEA), the clinical findings of splenomegaly, left hypochondric pain, haematological disorders with hypersplenism or spontaneous ruptures.[1,2] CT and ultrasound scans can show well-circumscribed spleen lesions. Positron emission tomography (PET) CT scanning can confirm the presence of the metastases—and fluorodeoxyglucose PET (FDG-PET) shows an isolated hypermetabolic state in the spleen.[1]

If the clinical history is enough to diagnose secondary lesions, a certain number of cases could remain unexplained. In these cases, a transcutaneous biopsy or a selective spleen arteriography was possible in the absence of haemostatic disorders.[3,4]

Spleen metastases from colorectal cancer have low incidence rates, the reason for which has formulated many theories. It should be difficult for colorectal cancer cells to reach the spleen through the usual portal venous system from the spleen to the liver. The sharp angulations of the spleen artery with its origin on the celiac trunk and the rhythmic contraction of the spleen have been speculated as two limiting factors of spleen metastasis, perhaps due to a decreased ability for the tumor embolus to implant in the organ.[2] The spleen is the part of the reticuloendothelial system; meaning, the concentrated biological factors

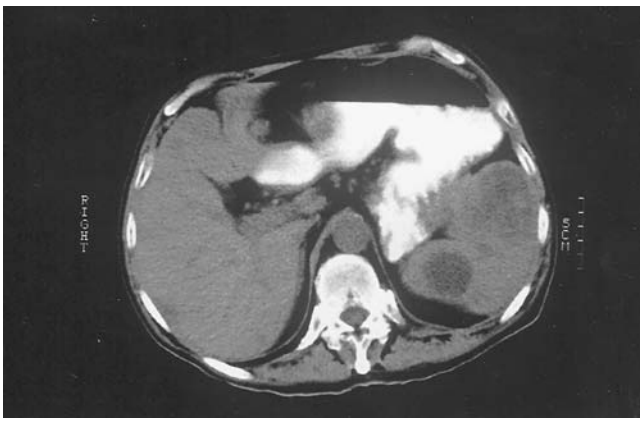

Figure 1 CT scan showed a solid mass occupying the inferior third of the spleen.

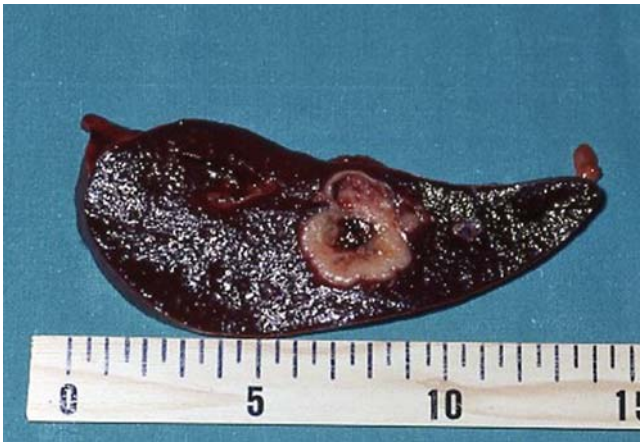

Figure 2 The macroscopic view of the splenectomy specimen with a 4 cm in diameter metastasis.

appears to potently inhibit tumor cell proliferation. Another proposal is the absence of directly related afferent lymphatic to the spleen.[5]

Survival rate after splenectomy in patients with solitary metastasis from colorectal cancer is still unknown; the reported data in the literature indicated that they may survive up to 7 years.[2,6]

Conclusion

Spleen metastasis in colorectal cancer is rare, a chance finding on follow-up radiological imaging in asymptomatic patients, and long-term survival can be achieved with splenectomy in the case of isolated spleen metastasis.

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Small Bowel Obstruction Secondary to Intragastric Erosion and Migration of A Gastric Band

D. M. Egbeare · A. F. Myers · R. J. Lawrance

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Abstract We describe what we believe to be the first reported case of intragastric erosion and migration to the jejenum of a laparoscopically inserted gastric band, 3 months after the original bariatric surgery was performed. This had caused ulceration and necrosis of the small bowel as the tension in the port tubing had caused the bowel to become concertinaed over it and resulted in a cheese-wire effect through the jejunal convolutions. As bariatric surgery becomes more common, patients with complications of their procedure may present to the general surgeon as an emergency. We recommend early intervention in patients with gastric erosion.

Keywords Laparoscopic gastric band · Bariatric surgery · Surgical complication · Small bowel obstruction

A 49-year-old man presented to our emergency take with a 3-day history of upper abdominal pain and bilious vomiting. Three months previously, he had a Swedish adjustable gastric band (Obtech©) inserted laparoscopically. The original surgery was reported to have gone straightforwardly with no immediate complications and he had reattended 6 weeks postoperatively to have the band inflated. He had lost 20 kg since the procedure.

Two weeks before admission, the patient declared he could suddenly eat normally. He had not brought this up with his bariatric surgeon or his GP and had suffered no ill effects until 3 days before admission.

His plain radiology demonstrated the gastric band lying in the central abdomen. (Fig. 1). The CT subsequently arranged showed that the band was lying within abnormal jejunum.

The patient was taken to theatre and at laparotomy the gastric band was felt in the distal jejunum, which had become concertinaed over the tubing running from the port used to inflate the band. The tension created within the port tubing had resulted in a cheese-wire effect through the

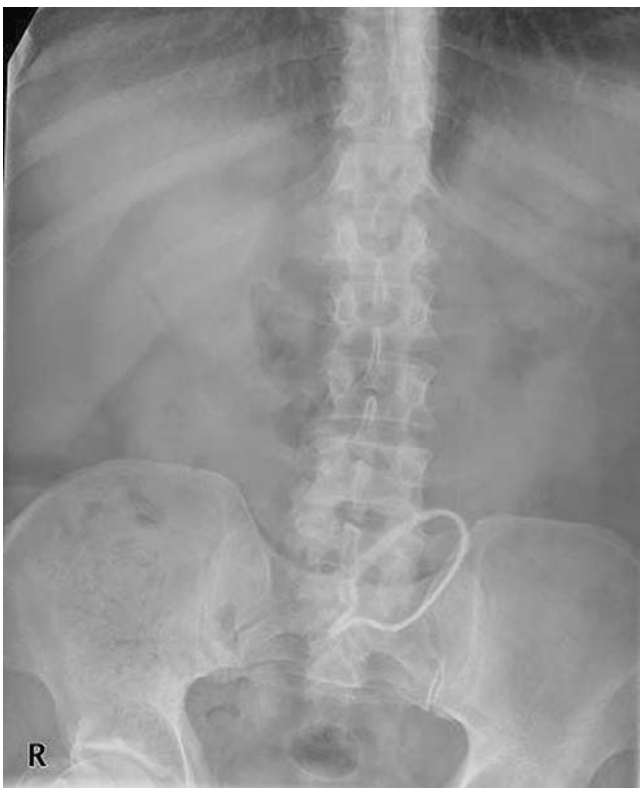

Figure 1 Plain abdominal film.

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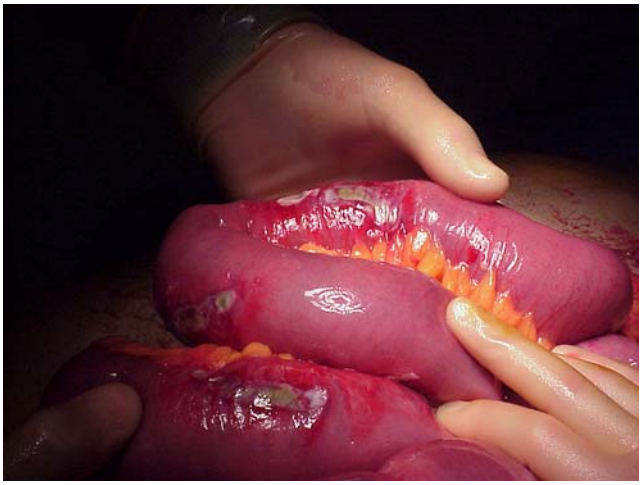

Figure 2 Intraoperative findings.

jejunal convolutions with ulceration and necrosis of the jejunal serosa (Fig. 2).

The band was retrieved retrogradely and removed through the antrum of the stomach. The most distal area of ulceration was subsequently measured as 130 cm from the duodenojejunal (DJ) flexure. The necrosis was more severe distally and 70 cm of distal jejunum was resected. The body and fundus of the stomach were enveloped in inflammatory adhesions and no attempt was made to explore this area. The reservoir port was also removed. The device had port tubing of 60 cm in length.

The patient made an uneventful postoperative recovery, was commenced on a proton pump inhibitor and was discharged home on day 8.

Discussion

Gastric banding is a popular treatment for morbid obesity. Gastric erosion leading to intraluminal migration or intrusion is one of the complications. Several series have reported gastric erosion of different devices and the incidence of reported gastric erosion ranges from 1 to 11%.[1,2] However, we believe this is the first reported case of the band migrating into the jejunum.

Gastric erosion as a complication seems to occur several months after the initial surgery, with some reports of it occurring years after the band insertion.[3] Early erosion is generally thought to be a result of a technical problem: unrecognized gastric perforation, problem with sutures, or early infection. The theories of late erosion range from gastric wall ischemia secondary to a tight band or extensive dissection,[3] chronic infection,[4] or exaggerated stress on the upper gastric pouch (by forced endoscopy or excessive vomiting).[1]

Recommendations

When patients present to a general surgical take with complications of bariatric surgery, there is often a delay in deciding how best to manage them. Early intervention is recommended in patients who present with gastric erosion after gastric banding. These patients need to have the band removed and this can be done endoscopically if the band is still in the stomach. However, if there is evidence that the band has migrated more distally, then early open surgery is recommended to prevent the complications as discussed in this case.

Competing Interests None declared.

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Acute Gastric Dilatation, Necrosis and Perforation Complicating Restrictive-Type Anorexia Nervosa

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Introduction

Hospitalization is occasionally required in anorexia nervosa patients to avoid the life-threatening complications of extreme malnutrition. However, refeeding is not a risk-free process. A constellation of metabolic disturbances can occur as a result of reinstitution of nutrition to patients who are starved or severely malnourished. Patients can develop fluid and electrolyte disorders, especially hypophosphatemia, along with neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications. We present an extremely rare complication that relates to this phenomenon, describing an acute gastric dilatation that led to gastric necrosis and perforation through an unusual mechanism, in an extremely anorectic teenager during hospitalization for refeeding.

Case History

A 16.5-year-old girl was admitted to the Child Psychiatry Department for severe malnutrition. Personal history revealed that she has been weight conscious since the age of 13, when she was 161 cm tall and weighed 50 kg. From then on, she gradually lost weight. During the last month before admission, she lost 12 kg. Recently, she consumed 1,000 kcal per day. On arrival, her weight was 29 kg (body mass index [BMI]=11.3). Extreme emaciation, general weakness, and edema of the lower limbs were apparent. Laboratory results were within normal limits. Echocardiography revealed a small amount of pericardial fluid. During hospitalization, her initial diet regiment included small amounts of solid food along with liquids. She suffered from watery diarrhea and vomiting of small gastric contents. Her general condition deteriorated even further, and she became extremely weak and developed hypothermia (35.1°C). At that time, she was transferred to the Pediatric Intensive Care unit. Her skin was pale, with low turgor pressure. Neurological exam revealed general weakness and decreased deep tendon reflexes and muscle strength. She began receiving peripheral parenteral nutrition (PPN). Next morning, physical exam revealed abdominal distension, diffuse tenderness, and absence of bowel sounds, without signs of peritonitis. Urine output was low, and the patient became even weaker. The blood pH was 7.23, potassium level 3.3 mEq/l, phosphorus 2.9 to 3.9 mg%, magnesium 1.9 mg%, calcium 6.4 to 7.7 mg%, albumin 2.9, total proteins 4.5 g%, and bicarbonate 20 mg%. The abdominal X-ray revealed a huge stomach, with intestinal loops pressed toward the pelvis (Fig. 1). Although slight improvement was noticed after the insertion of the nasogastric tube, deterioration persisted on the next day. Phosphorus levels were reduced gradually to 2.4 mg%. Urgent abdominal computed tomography (CT) scan was performed, demonstrating significant gastric distension, with air in the gastric wall. The stomach was full with content, although the nasogastric tube was correctly placed. Furthermore, there was free air and fluid in the peritoneal cavity (Fig. 2). An emergent operation was conducted, revealing a large amount of clear intraperitoneal fluid and a much distended stomach filled with large amounts of mostly solid content. The entire gastric wall was necrotic, with perforation in the cardia of the stomach. A

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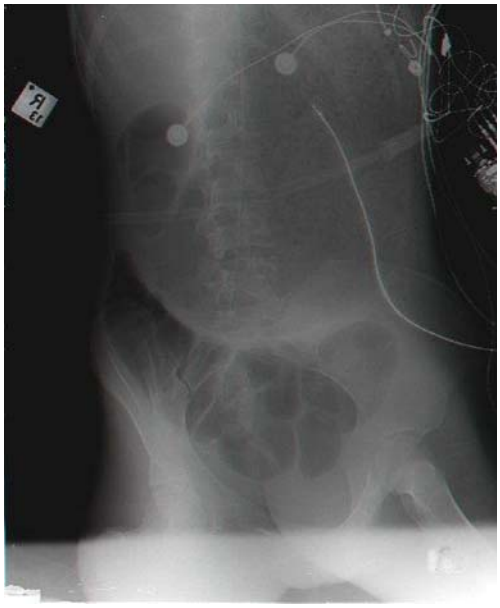

Figure 1 A Plain abdominal X-ray revealing substantial enlargement of the stomach and pressed-down intestinal loops (taken 1 day before the operation).

total gastrectomy was conducted, followed by roux-en-y esophagojejunostomy. A feeding jejunostomy was inserted. Histopathologic examination revealed extensive gastric necrosis involving mucosa and submucosa. In some areas of the stomach, there was transmural necrosis, in accordance with the gross appearance. After the operation, the patient was hypothermic (34.6°C) but hemodynamically stable with fair urine output and oxygenation. In the first 3 days postoperatively, she remained ventilated and received 1,200–1,400 kcal through PPN, followed by gradually increased oral diet. She slowly gained weight (BMI up to 17), and 6.5 month after surgery, she was discharged and returned home, supported by psychological therapy in her community.

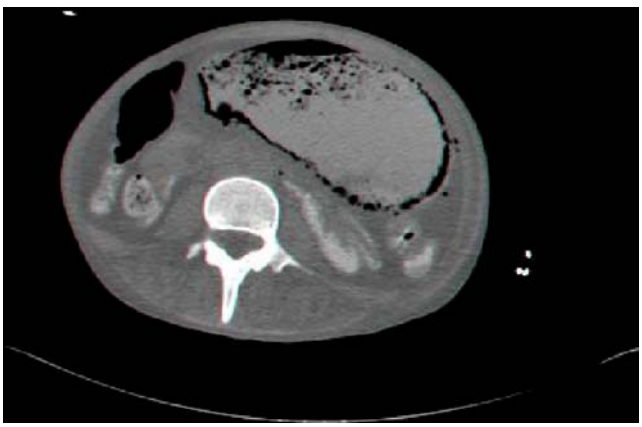

Figure 2 An abdominal CT scan taken several hours before the operation, revealing marked gastric dilatation with a large volume of food inside the stomach. Air in the gastric wall can be seen, as well as free air in the abdomen.

Discussion

The phenomenon presented here is an extremely rare case of acute gastric dilatation, which led to gastric necrosis and perforation during the refeeding phase of treatment in a severely malnourished anorectic patient. Anorexia nervosa, as other eating disorders, is an ever-increasing threat in Western culture, in which thinness is an ideal of beauty. Among patients with anorexia nervosa, 47% have a history of bulimic episodes (known as "binge eating").[1] This type of disease is often referred to as "binge-type anorexia."[2,3] Anorexia without binge eating is referred to as "restrictive-type anorexia."[2] Patients with severe restrictive anorexia can deteriorate into extreme malnutrition and require hospitalization for refeeding, as was the case in our patient. Acute gastric dilatation is a relatively rare but well-documented complication of anorexia nervosa.[4–6] In restrictive-type anorexia (in contrary to the binge type), acute gastric dilatation may occur with the ingestion of small amounts of food, usually during the "refeeding period"—the first 2–4 weeks of the treatment.[5,7]

The pathophysiology of acute gastric dilatation in malnourished anorectic patients during the refeeding period is associated with a long emptying time of the stomach. Hence, food, air, and secretions accumulate within the stomach, causing it to dilate. In manometric testing of cachectic patients, the peristaltic movements of the gastric antrum and the duodenum are weaker then in the normal population.[7–9] This may arise from impaired action of the intrinsic enteric nervous system.[7–9] The atonicity of the proximal gastrointestinal tract is also attributed to electrolyte imbalance common in anorexia, such as severe hypokalemia and hypophosphatemia, which were not recorded in the present case. In comparison to the normal population, anorectic patients have significantly long gastric-emptying time for solid food but not for liquids.[10] This is in accordance with the present case, as the patient received solid food in the days preceding her deterioration. Moreover, the gastric content seen during gastrectomy was mostly solid. The risk for developing serious complications ensues from the combination of two factors. First, as discussed above, there is a perturbation in the normal function of the gastrointestinal tract. Second, any acute gastrointestinal complication that may develop is obscured by a variety of nonspecific gastrointestinal symptoms that are common in anorexia patients, particularly during the refeeding period, as was evident in our patient.[2] As gastric dilation progresses, it may lead to increased intra-abdominal pressure, which in turn may interfere with normal blood flow

and even can cause severe hemodynamic instability.[4] When preventive measurements and conservative treatment fail, intragastric pressure mounts and exceeds gastric venous pressure, resulting in ischemia and infarction of the gastric wall, which eventually leads to gastric perforation.[4,11] The abdominal CT in our case was diagnostic, showing air in the gastric wall as well as free air in the abdomen that was not detected by the abdominal X-ray.

The attitude toward gastric dilatation must include appropriate preventive measurements during the refeeding period, including limitation of initial caloric intake together with careful electrolyte and metabolic monitoring. In extremely cachectic patients, it is recommended to start with total parenteral nutrition and gradually add oral intake, thus enabling the stomach to "relearn" how to digest food. To that, we add the recommendation that the oral food intake in the first days of refeeding should be limited entirely to liquids and that solid food should be added gradually. Sixty cases of spontaneous gastric rupture have appeared in the literature since 1928, where only five of which occurred in anorectic patients.[2,5] Of these five cases, only one occurred during the refeeding period of a restrictive-type anorexia nervosa patient.[5] Gastric perforation is a surgical emergency with a mortality rate of 50 to 73%.[4] Early diagnosis is critical because delayed treatment carries an extremely low survival rate. Surgical options include total gastrectomy with esophagojejunostomy if the patient's condition allows or esophagostomy if peritonitis is present. In any case, feeding jejunostomy should be performed.

In conclusion, this report redirects physicians' and caregivers' attention toward a rare possibility of acute gastric dilatation and perforation during the refeeding of malnourished anorectic patients. It stresses the importance of avoiding solid diet as part of the nutritional regimen, early in this period, to reduce the occurrence of such complication.

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Fewer Infectious Manifestations are Induced By Bacteria Entrapped in Cholesterol Stones Than By Bacteria in Brown Pigment Gallstone

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To the Editor.

"Fewer infectious manifestations are induced by bacteria entrapped in cholesterol stones than by bacteria in brown pigment gallstones" comment concerning the articles by Stewart, et al: "Gallstones containing bacteria are biofilms. Bacterial slime production and ability to form pigment solids determines infection severity and bacteremia" J Gastrointest. Surg. 2007;11:977–984 and "Bacteria entombed in the center of cholesterol gallstones induce fewer infectious manifestations than bacteria in the matrix of pigment stone" J Gastrointest Surg; 2007;11:1298–308.

We agree with many statements and conclusions of the papers by Stewart, et al. However, we would like to make some remarks and comments.

In addition to outline that our comprehensive study (1,000 consecutive patients studied in 1991, more than 2,000 today) showed for the first time bacterial microcolonies in brown stones by SEM, we would stress the importance of considering brown stones, and only pure and entirely brown stones, as a different disease from other types of gallstones.

In fact, only in these stones infection plays a basic role in stone formation from the beginning, being responsible for the precipitation of all stone components.

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Pure brown stones are mainly found as recurrent common duct stones after sphincterotomy and biliary-enteric anastomosis. Nowadays, these stones are usually removed by repeat endoscopic sphincterotomy.

Therefore, pure brown stones are today seldom removed by surgery and are very rare in a consecutive surgical series of 250–350 patients.

On the contrary, in our study dating back to 1970s and recruiting more than 2,000 consecutive patients, we could observe a lot of these stones showing bacteria both in the stone center and periphery. They were always associated with positive bileculture and frequently with severe infectious clinically evident complications. These stones must be classified as a different disease. Bacteria, or bacterial DNA can be found in bile and stones, and is increasingly detectable with improvement of diagnostic tools.

However, these cholesterol, black, mixed or combination stones have a different pathogenesis from brown stones. Obviously, the more abundant the brown material, (which can precipitate in the periphery of a previous cholesterol stones or as entirely brown concrements associated with cholesterol or mixed stones in the same patient), the more severe are infectious complications.

Stewart, et al. suggest that infectious complications are more related with phospholipase-beta glucuronidase activity and inversely related with slime production.

This is a logical thing, which further improves our knowledge. But the better knowledge of these details, together with the improvement of diagnostic tools, cannot change our basic knowledge that only brown stones are "bacterial" stones, whereas all other stones form because of mechanisms different from infection. We would like to stress that diagnostic refinement and improvement of pathophysiological mechanisms should go to the right direction, i.e. not to change long established classification

of gallstones. If we maintain the stone classification that we have suggested, based on "stone type", more than on cholesterol content or bacterial contamination, the spectrum of infectious manifestations logically goes from 100% in pure recurrent brown stones to 0% in pure cholesterol stones. A wide range of manifestations are detectable in between, grossly suggested by the presence of brown pigment material, i.e. bilirubinate, that is produced by beta glucuronidase and palmitate, which is produced by phospholipase. This is what we stated since 1986, by measuring directly both beta glucuronidase and phospholipase in the bile and in gallstones. This is what Stewart, et al. finally suggest in 2007, indirectly estimating phospholipase activity on the basis of calcium palmitate content in gallstones.

The paper by Stewart, et al[1] shows that some properties of the gallstone biofilm determine the severity of the associated illness. In particular, they showed that severe infections correlated directly with β-glucuronidase/phospholipase activity (55% with, vs 13% without; $P<0.0001$), but inversely with slime production. In fact, abundant slime production, while facilitating colonization, inhibited detachment and cholangiovenous reflux.[1] Therefore, no bacteria with slime >75 demostrated bacteremia. In addition, cholesterol stone bacteria caused more severe infections (19%) than sterile stones (0%), but less than pigment stone bacteria (57%; $p<0.0001$).[2]

Our remarks concerning these interesting papers are the following. First of all, Stewart, et al. stated in the introduction that their group was the first to identify bacterial microcolonies in pigment stones.[1] Actually, the presence of bacterial microcolonies was first documented by SEM, both in the center and in the periphery of brown stones, in our paper[3] 1 year before their paper on microcolonies.[4] In addition, we would like to stress, on the basis of our prospective study on 2,000 consecutive patients with gallstones[5] and who had systematic analysis of bile and stones, that even if bacterial microcolonies could be sometimes present in other types of stones, it is important to consider cholesterol or mixed stones from one hand, and entirely brown stones on the other hand, as two distinct entities for both epidemiological/pathophysiological and clinical purposes.

In non-brown stones, bacteria, as well as foreign bodies, or mucus can play a role in the occurrence of some gallstones components, facilitating the precipitation of the central nucleus, or of the pigmented periphery.[5] However, in these stones, bacteria do not play the basic role of being the main responsible from the beginning for the pathogenesis of all stone components, including calcium bilirubinate and palmitate. In our series,[5] cholesterol stones or mixed stones with cholesterol as the main component were 60%. In particular, less than 5% of patients had "pure" cholesterol stones, which usually were unique and smaller than 0.8 cm. Twenty-five percent of patients had ovoidal cholesterol stones, while 35% had faceted mixed, spherical, or mulberry cholesterol stones. Black pigment stones occurred as unique stones in 8.5%, whereas only brown pigment stones were found in 6.5% of cases. On the contrary, in 21% of patients, we have found different stone populations within the same gallbladder. We classified these subjects as having "composite stones", i.e. a different situation from "mixed faceted stones", which consisted of cholesterol, bilirubinate and carbonate and had a levigated surface, and from combination stones, in which a cholesterol nucleus with radial structure was usually surrounded by a pigmented periphery, with alternate tan and light layers. Composite stones may include a combination of cholesterol and black intraparietal stones, i.e. stones initially formed within the Rokitansky-Aschoff sinuses of patients with diffuse or partial adenomyomatosis of the gallbladder, or more frequently, a mixture of a large combination stone, together with mixed faceted stones and/or aggregates of brown mud within the same gallbladder, suggesting that different pathogenetic mechanisms were responsible for the various stone populations.

In most of these stones, some bacteria could be found, but their role was different from being the main determinant of stone formation.

On the contrary, we have shown that patients with previous cholesterol or mixed stones in the gallbladder or common duct associated with negative biliculture after the onset of self-maintaining infection (that was facilitated by sphincterotomy or biliary enteric anastomosis or peri Vaterian duodenal diverticula), invariably only brown stones developed, showing alternating light and tan layers containing calcium palmitate and bilirubinate, respectively, both in the stone center and periphery.[3]

The presence of bacteria was subsequently detected by SEM not only in brown stones, but also in the pigment center and in the periphery of cholesterol or composite stones.[6,7] With the advent of PCR, bacteria or DNA were increasingly recovered by various groups. In particular, it has been suggested that they could play a role in the pathogenesis of all types of gallstones, including cholesterol.[6,7] We showed that most Helicobacter pylori-infected patients had specific antibodies, and some also have H. pylori antigens, and genomic material in bile. This could represent an increased risk of gallstones formation, in particular for mixed or composite stones.[8] However, bacteria never had a role similar to that observed in brown pigment stones.

After more than two decades, we welcome these interesting papers by Stewart, et al. which, in our opinion, go in the right direction. In fact, Stewart, et al. recognize that (1) bacteria microcolonies are much more prevalent in PS, and (2) bacteria entombed or sequestered in cholesterol stones may cause infectious manifestations, which are more

frequent or more severe (19%) than in sterile stones. However, infectious manifestations are less than those determined by pigment stone bacteria (57%; $p<0.0001$) and further less than in brown recurrent common duct stones, in which clinically evident infectious manifestations were present in 100% of cases.[3,5] In all of these stones, bacteria were always cultured from both bile and stones[3,5,6] and alternating layers of calcium bilirubinate and palmitate were found both in the stone center and periphery. In particular, whereas Stewart, et al. estimated phospholipases indirectly on the basis of calcium palmitate in gallstones,[1], we measured directly phospholipase in the bile surrounding calcium palmitate rich gallstones.[11]

Therefore, on the basis of the last papers by Stewart, et al., which substantially confirm our previous findings, we suggest a word of caution before trying to classify gallstones, from which bacteria can be retrieved by whatever method, as "bacterial" stones,[6,7] leaving the term of "bacterial" stones only to brown pigment stones. These stones form primarily in the common duct, usually after sphincterotomy[3,9] or biliary enteric-anostomosis, but can also be found in very old patients, both in the gallbladder and in the common duct.[5] This pathological condition can be considered a true infectious disease even if not contagious. Brown stones are completely different from other types of gallstones, in which other factors, (metabolic imbalance, cholesterol supersaturation, homologous or heterologous—foreign body, suture material, intraluminal metallic clip – nucleation, etc.) play a major role.

Because every type of stone classification should have epidemiological, pathogenetic, and clinical relevance, we suggest to classify gallstones on the basis of "stone type" on cross-section as follows: cholesterol (or pure cholesterol) with radial structure; mixed, usually faceted, with pigment center, (bacteria possibly found); combination (bacteria possibly found in the periphery); black pigment stones, which consist of polymers of bilirubin (related to hemolysis, but also to local stasis within the Rokitansky-Aschoff's sinuses)[10] and are seldom associated with bacteria; and brown pigment stones, in which bacteria are always founds both in the stone center and periphery and which are more frequently responsible for severe infection and bacteremia.[3,5,9]

Other types of gallstone classification (based on the cholesterol content in gallstones) or bacterial contamination (usually in modest amounts), which could be detected in every type of stones while adding little to a better knowledge of their pathogenesis, may be of minor interest or misleading.

On the contrary, it is of paramount importance to state that brown stones are different from other stones because only in them infection plays a major role from the beginning. Only brown stones can be then considered a true "infectious" disease, and clinically relevant complications are in accordance with this statement.

This is also in accordance with previous data by Stewart, et al., showing that acute cholangitis was diagnosed in 52% of patient with infectious stones, mainly consisting of brown pigment, and in 18% of patients with non infectious stones.[4,12]

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