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Clinicopathologic and Immunohistochemistry Characterization of Synchronous Multiple Primary Gastric Adenocarcinoma

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Abstract The aim of this investigation was to evaluate clinicopathologic and immunohistochemical characteristics of synchronous primary gastric adenocarcinomas. Immunohistochemistry for p53 (suppressor pathway) and for hMLH1, hMSH2, and hMSH6 (mutator pathway) was performed using ABC-technique amplification by biotinylated tyramide. Synchronous primary gastric adenocarcinomas were detected in 19/553 (3.43%) of the patients. The tumors were localized in distal stomach in 22, body in 14, and proximal in five. There was a predominance of intestinal type in the group of synchronic tumors compared to the solitary lesions, 73.2 vs 37.3%, $p=0.001$. Synchronous neoplasias were diagnosed in earlier stage than solitary neoplasias, T1–T2=60.9% vs T1–T2=28.4%, $p=0.0001$; and N0=68.4% vs N0=26.2%, $p=0.001$. p53 was detected in 52.6% of the patients with synchronous tumors. Altered hMLH1 immunoexpression occurred in 26.3% of the patients and hMSH6 in 5.3%. hMSH2 immunoreactivity was positive in all tumors. p53 was solely detected in 17 tumors, while hMLH1 was altered in 10/24 negative p53 tumors, $p=0.01$. Synchronous gastric adenocarcinomas presented higher frequency of intestinal type and early gastric cancer in comparison to solitary gastric cancer. Two routes of carcinogenesis, mutator, and suppressor appear to be involved independently in the development of synchronous tumors.

Keywords Synchronous primary gastric adenocarcinoma · Immunohistochemistry · p53 · hMLH1 · hMSH2 · hMSH6

Introduction

Gastric carcinoma is the fourth most common carcinoma and the second leading cause of cancer death worldwide.[1] The prevalence of multiple independent primary gastric adenocarcinoma is high in Japan, ranging from 4 to 10%[2–4]; however, in Western patients, the occurrence of these tumors are largely unknown.[3,5] Synchronous primary gastric adenocarcinomas (SPGA) are significantly more often associated with adenomas, atrophic gastritis, or intestinal metaplasia than solitary carcinomas, suggesting that multiple primary carcinomas more frequently occur when associated with precancerous conditions.[5,6] It has also been reported that secondary cancers occur more frequently in patients with multiple primary gastric cancers than in those with a single gastric cancer.[7] These data may imply that patient with multiple primary gastric cancers may have a genetic predisposition to the development of cancer.

Tumor multiplicity is widely accepted as an indicator of the genetic predisposition for developing a neoplasm.[8] On the other hand, the routes of carcinogenesis have not been clearly clarified in these multiple gastric tumors: the mutator pathway due to defects in DNA mismatch repair genes, and the suppressor pathway due to defects in tumor suppressor genes.[9]

Moreover, the presence of SPGA in the same stomach at the time of resection may alter the extension of surgical treatment. It is noteworthy to investigate the background of

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synchronous primary carcinomas because this may influence the surgical resection management process.[2] Nowadays, wedge resection by laparotomy or laparoscopy and endoscopic mucosal resection are performed for well-differentiated lesions of small diameter that are confined to the gastric mucosa. Thus, it is essential to determine that no other malignancy exist in the stomach of a patient who will undergo such a limited procedure.

Thus, the aim of this investigation was to evaluate clinicopathological characteristics of SPGA compared to the solitary adenocarcinomas, and to verify specific immunohistochemical alterations in the SPGA. We performed immunohistochemical analysis on 41 tumors from 19 synchronous gastric cancer patients. We examined hMLH1, hMSH2, and hMSH6 immunohistochemistry, which are representative of the mutator phenotype and p53 immunoexpression for the suppressor pathway.

Material and Methods

This study was approved by the Hospital Ethics Committee of the University of São Paulo School of Medicine, São Paulo, Brazil. Hospital records from 1995 to 2003 of the gastric cancer patients regarding the presence of SPGA were retrospectively reviewed, and compared with patients who had solitary adenocarcinomas in the same period. During the studied period, 553 patients were submitted to gastric resections and SPGA were detected in 19 patients (3.43%).

Synchronous primary gastric adenocarcinoma was defined as secondary gastric cancer found simultaneously or within 1 year after the detection of the initial gastric cancer. The diagnosis criteria for multiple gastric cancers were the same as those of Moertel et al.[10]: (a) each lesion must be of pathologically proven malignancy; (b) the tumors must be separated by each other by intervals of microscopically normal gastric wall; and (c) the possibility that one of the lesions represents a local extension or a metastatic tumor must be ruled out.

None of the patients with synchronous gastric cancers included in the present series had a family history suggestive of gastric cancer or hereditary colorectal cancer.

Histopathologic and Immunohistochemical Evaluation

Histologic slides were reviewed to confirm the histopathologic diagnosis of SPGA by H&E, and corresponding formalin-fixed paraffin-embedded tissue blocks were sectioned for immunohistochemical analysis. Five to six unstained 4 μm blank histologic sections were cut from each designated block. One blank was used for p53 immunostaining (suppressor pathway) (p53-NCL p53-DO7, Novocastra, Newcastle, UK) and the others for hMLH1, hMSH2, and hMSH6 (mutator pathway) (hMLH1-clone G168-728, Pharmigen, San Diego, CA, EUA; hMSH2-clone G219-1129, Pharmigen, San Diego, CA, EUA; and hMSH6-Pharmigen, San Diego, CA, EUA), using the ABC-immunohistochemistry technique and amplification by biotinylated tyramide (Dako Cytomation CSA II, Carpinteria, CA, EUA). The microwave oven heating technique for antigen retrieval and immunodetection method has been previously described.[11,12] Briefly, immunodetection involved the use of 4 μm thick formalin-fixed paraffin-embedded tissues, treated with 4% hydrogen peroxidase (H_2O_2) in methanol for 35 minutes to eliminate endogenous peroxidase activity. The sections were placed in the microwave oven for 10 minutes for antigen retrieval, rinsed in phosphate-buffered saline (PBS), and incubated with 10% normal horse serum to block nonspecific binding. Upon removal of the serum, the primary monoclonal antibody was applied at room temperature. After further washing with PBS, sections were incubated with biotinylated anti-mouse immunoglobulin for 30 minutes. After washing twice with PBS, the sections were treated with Vectastain Elite horseradish peroxidase complex (Vector Laboratory, Burlingame, CA, USA) for 30 minutes. After another rinse with PBS, the sections were incubated with diaminobenzidine 0.05 and 0.04% H_2O_2 for 20 minutes. After a final wash with distilled water, the sections were counterstained with Harris Alum Hematoxylin, dehydrated through graded alcohols to xylene, and coverslipped. Sections of gastric adenocarcinoma and primary antibody replaced by PBS were used as positive and negative controls, respectively. Specific nuclear immunoreactivity for p53 protein was scored semiquantitatively on a graded scale of 0 through 4 for both intensity and distribution by three investigators in a blinded analysis. p53 was classified solely as positive immunostaining when greater than 2.

hMLH1, hMSH2, and hMSH6 were considered altered when there was a decreased immunoexpression or complete absence of the staining. Lymphocytes and normal adjacent epithelium exhibit strong nuclear staining for hMSH2, hMLH1, and hMSH6 and served as positive internal controls for staining these proteins.

Statistical Analysis

Clinicopathological characteristics of the two groups of tumors and immunohistochemical alterations were compared using Fishers' exact probability test and Pearson chi-square test for qualitative data, and Student's t test for quantitative data, with two-tailed p value at the 5% level considered significant.

Table 1 Clinicopathological Comparisons Between Solitary and Multiple Primary Gastric Adenocarcinomas

	Solitary Tumors	Percentage	Multiple Primary Tumors	Percentage	*P* Value
Number of patients	553		19		
Mean age	61.2 SD=13.8	–	66.8 SD=15.2	–	0.85[a]
Gender					
Men	350	63.3	13	68.4	0.60[b]
Women	203	36.7	6	31.6	
Site of tumor					
Upper third	90	16.3	5	12.2	0.77[b]
Medium third	110	19.9	14	34.1	
Lower third	337	60.9	22	53.7	
Entire	16	2.9	–	–	
Lauren's classification					
Intestinal	206	37.3	30	73.2	0.001[b]
Diffuse	307	55.5	11	26.8	
Undifferentiated (mixed)	40	7.2	–	–	
pT (patients)					
T1–T2	167	31.5	9	47.4	0.04[b]
T3–T4	379	68.5	10	52.6	
pT (tumors)					
T1	66	11.9	24	58.5	0.0001[b]
T2	91	16.5	1	2.4	
T3	349	63.1	15	36.6	
T4	47	8.5	1	2.4	
pN (patients)					
N0	145	26.2	13	68.4	0.0002[b]
N1–2	408	73.8	6	31.6	

[a] Student's *t* test
[b] Pearson Chi-square test

Results

The clinicopathological characteristics of the SPGA patients compared to the patients with solitary lesions are presented in Table 1. Thirteen patients (68.4%) were men and the mean age was 66.8 (range=15–81 years old) for SPGA, while there were 350 (63.3%) men and the mean age was 61.2 (SD=13.8) for the solitary adenocarcinoma. Sixteen patients had two separated tumors and three patients had three tumors in the SPGA group. The tumors were located at the upper gastric third in five (12.2%) and 90 (16.3%), medium third in 14 (34.1) and 110 (19.9%), and in the lower third in 22 (52.7) and 337 (60.9%) of the SPGA and solitary tumors, respectively. Figure 1 demonstrates the presence of SPGA in the resected specimen of a patient who underwent total gastrectomy.

In 14 patients, the lesions of SPGA were close to each other (less than 3 cm), while in five patients, the neoplasias were distant in another portion of the stomach (Table 2). SPGA tumors were diagnosed preoperatively by upper endoscopic examination in 38/41 (92.7%); however, in three cases, the second primary was only noted at the pathological examination.

There was no statistical difference between age, gender, and tumor location when a comparison with the solitary lesions was performed (Table 1).

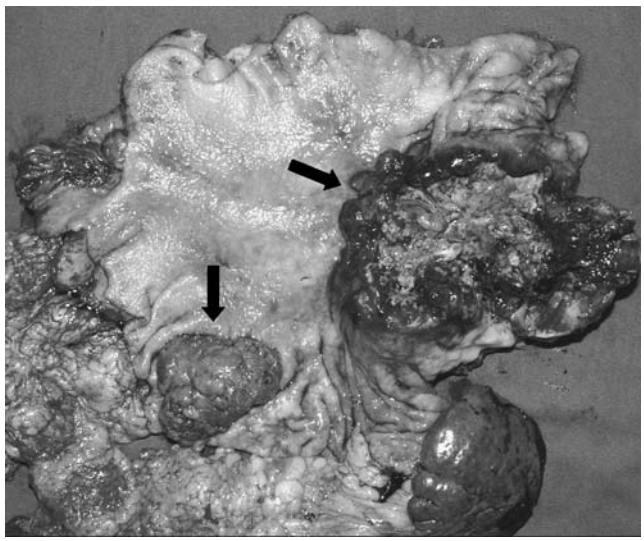

Figure 1 Synchronous primary gastric adenocarcinomas are shown in the resected specimen (arrows).

Table 2 Distribution of 19 Patients with Multiple Primary Gastric Adenocarcinomas According to Clinicopathological Characteristics

Patient	Gender	Age	Laurén			Degree of Differentiation			Site of Tumor			TNM Staging	
			1°	2°	3°	1°	2°	3°	1°	2°	3°	pT	pN
1	F	74	Intes.	Intes.	–	Mod.	Mod.	–	Cardia	Body	–	1	0
2	F	56	Intes.	Intes.	–	Well	Well	–	Antrum	Antrum	–	1	0
3	M	60	Diffuse	Diffuse	–	Poorly	Poorly	–	Antrum	Antrum	–	3	2
4	M	53	Intes.	Diffuse	–	Mod.	Poorly	–	Body	Body	–	4	2
5	M	67	Intes.	Intes.	–	Mod.	Mod.	–	Body	Body	–	3	2
6	F	77	Diffuse	Diffuse	–	Poorly	Poorly	–	Antrum	Antrum	–	3	1
7	M	81	Intes.	Intes.	Intes.	Mod.	Mod.	Mod.	Antrum	Body	Body	3	0
8	F	15	Intes.	Intes.	–	Mod.	Mod.	–	Antrum	Antrum	–	1	0
9	M	52	Intes.	Intes.	Intes.	Mod.	Mod.	Mod.	Antrum	Body	Antrum	3	0
10	M	81	Intes.	Diffuse	–	Poorly	Poorly	–	Antrum	Cardia	–	3	2
11	M	72	Intes.	Intes.	–	Mod.	Mod.	–	Body	Body	–	1	0
12	M	71	Intes.	Intes.	–	Well	Mod.	–	Antrum	Antrum	–	1	0
13	F	74	Intes.	Intes.	–	Mod.	Well	–	Body	Body	–	1	0
14	M	83	Diffuse	Intes.	–	Poorly	Mod.	–	Cardia	Antrum	–	3	0
15	F	74	Intes.	Intes.	–	Well	Well	–	Cardia	Antrum	–	1	0
16	M	61	Intes.	Intes.	–	Mod.	Mod.	–	Antrum	Antrum	–	1	0
17	M	68	Diffuse	Diffuse	–	Poorly	Poorly	–	Antrum	Antrum	–	2	0
18	M	65	Intes.	Intes.	Intes.	Poorly	Poorly	–	Body	Body		3	0
19	M	68	Diffuse	Diffuse	–	Poorly	Poorly	–	Cardia	Antrum	Antrum	3	2

F Female, *M* male, *Intes.* intestinal, *Mod.* moderately

There was a predominance of intestinal type tumors in the group of synchronous tumors compared to the solitary lesions, 73.2 vs 37.3%, $p=0.001$ (Table 1).

Synchronous neoplasias were diagnosed at an earlier stage compared to the solitary neoplasias, so, T1–T2=25 (60.9%) vs T1–T2=157 (28.4%), $p=0.0001$, and N0=13 (68.4%) and 145 (26.2%) vs N1–N2=6 (31.6%) and 408 (73.8%), respectively, $p=0.0002$. The distribution of the clinicopathological characteristics of 19 SPGA are shown in Table 2.

Immunohistochemistry

Nuclear immunoreactivity for p53 was detected in 17 (41.5%) of the SPGA from 10 (52.6%) patients (Fig. 2). In three patients, there was a discordance in the p53 immunoexpression, i.e., one tumor was immunoreactive and the other negative in the same stomach.

Negative hMLH1 immunoexpression was noted in 10 (24.4%) tumors from five (26.3%) patients (Fig. 3). There was a concurrence in hMLH1 immunoexpression in different tumors from the same patient.

Altered hMSH6 immunoexpression was observed in one patient (5.3%) (Fig. 4). Immunostaining for hMSH2 was positive in all SPGA, indicating absence of alterations of this repair gene marker (Fig. 5).

There was an inverse association between immunoexpression of hMLH1 and p53 in the diverse tumors from different patients. p53 was solely detected in 17 tumors, while hMLH1 was altered in 10/24 negative p53 tumors, $p=0.01$. Moreover, patients who had positive tumors for p53 did not have any alteration of hMLH1, while patients with hMLH1 alterations did not present any p53 immunoexpression.

Discussion

Synchronous primary gastric adenocarcinomas may originate from the same genetic background and similar

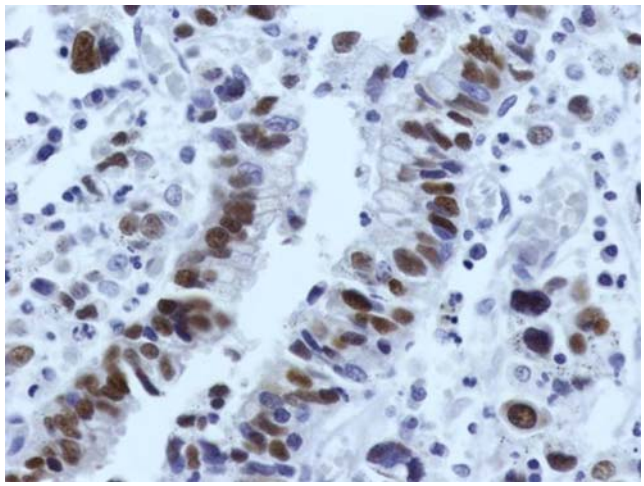

Figure 2 Immunohistochemistry for p53 showing nuclear immunoreactivity in a SPGA (×400).

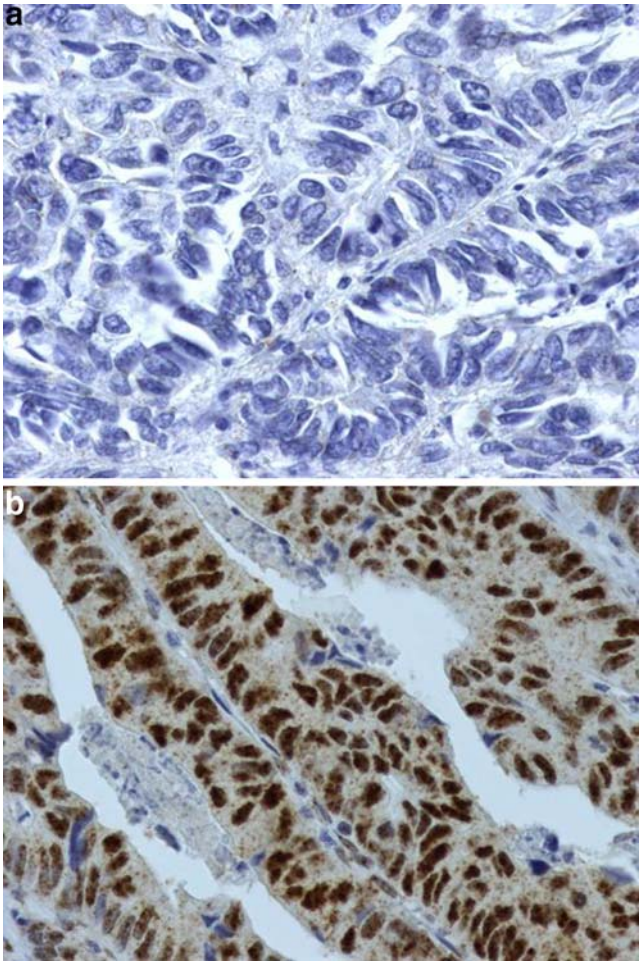

Figure 3 Immunohistochemistry for hMSH1 in SPGA group. **A** Absence of immunoexpression in altered tumor; and **B** normal tumoral immunoexpression (×400).

microenvironment in the stomach.[2,5] Thus, it might be beneficial to investigate cases of synchronous multiple gastric cancer when considering the mechanisms for carcinogenesis.

Analysis of our data has shown that SPGA occur with similarities regarding age onset, gender, and location of the tumor in the stomach. On the other hand, intestinal type tumors were more frequent in SPGA than in solitary tumors, and the tumors were less invasive, with increased presence of early gastric cancer and N0 tumors in the SPGA group.

In 26% of the cases, the tumors were distant of each other, so the gastric resections have to be enlarged to be effective as R0 resection. Cautious upper endoscopic examination should be performed in all cases of gastric cancer to diagnose secondary lesions, which may affect the surgical management, prognosis, and survival of these patients.

Thus far, no molecular markers have been shown to be clinically useful for predicting which patient will or will not

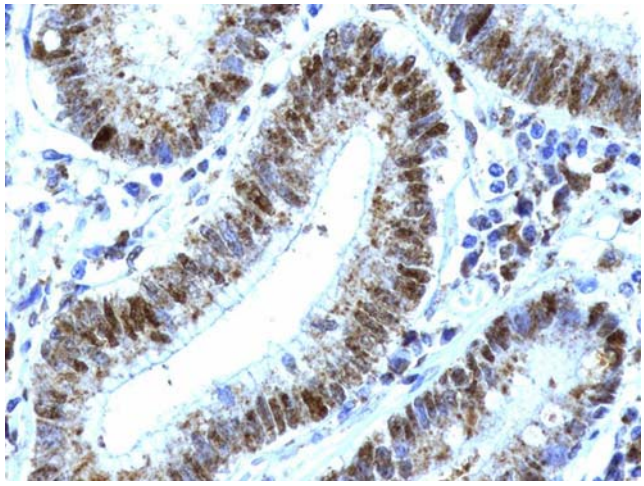

Figure 4 Normal immunohistochemistry for hMSH6 in SPGA (×400).

have multiple gastric cancers. In this investigation, we explored the two major routes of gastric carcinogenesis, mutator, and suppressor routes in the SPGA to detect alterations that could lead to better knowledge about the carcinogenetic process.

We have used immunohistochemical detection of protein products as an alternative to PCR-based mutational studies, based on the information that: (a) loss of gene expression through epigenetic mechanisms (hMLH1, p16, p21), in the absence of mutations, represents an alternative to germline or somatic mutations in the inactivation of the gene and (b) p53 protein accumulation correlates well with mutational analysis of the gene.[13]

The genetic instability caused by aberrations in mismatch repair genes, including hMSH2, hMLH1, hMSH6, hPMS1, or hPMS2, is characteristic of colorectal carcinomas in Hereditary Nonpolyposis Colorectal Cancer fami-

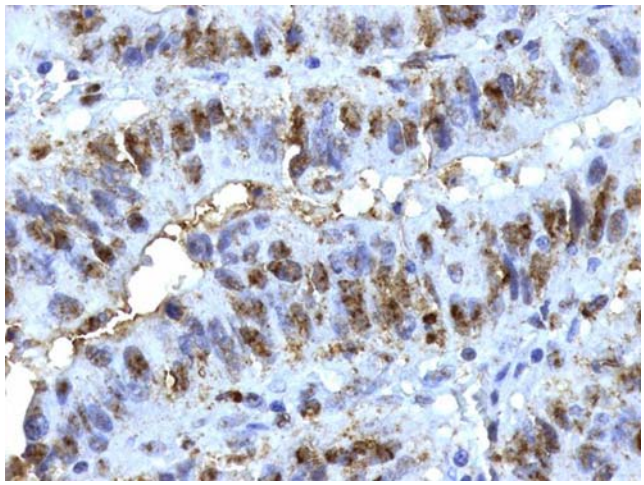

Figure 5 Immunostaining for hMSH2 showing positive nuclei in SPGA, indicating absence of alterations of this repair gene marker (×400).

lies, but is also found in sporadic forms of colorectal carcinomas and other carcinomas including stomach.[14,15]

In gastric cancer, the incidence of MSI varies from 15 to 39%[16–19]; however, there are few reports on MSI in multiple gastric cancers.[6,20–23] MSI rate in synchronous gastric cancers was higher than that in solitary gastric carcinomas.[20,22,23]

Although mutations of the hMLH1 or hMHS2 or hMSH6 are rare in gastric cancers; hypermethylation of the promoter region of hMLH1 is the major causative event in the development of human cancers with MSI phenotype.[12,24] Methylation of the hMLH1 promoter is a frequent event in gastric cancers with MSI-high, both in solitary or multiple primary gastric neoplasias, and the methylation status correlates well with hMLH1 protein expression.[25–28] Consequently, hMLH1 immunohistochemistry may be used as a marker of MSI-high.

Although there are no researches on methylation of the hMSH6 promoter region in gastric cancers, hypermethylation of the hMSH6 promoter region might also be associated with multiple gastric cancers.

The suppressor pathway has been investigated mainly by p53 immunohistochemical analysis. p53 was positive in 33% of the SPGA.[5] Kang et al.[29] reported that 43% of synchronous gastric carcinomas demonstrated p53 mutations and that most cases showed discordant patterns of mutations in individual cancers.

Our results demonstrate that all patients had concordant immunohistochemistry for hMSH1 (MSI phenotype) and 70% of concordance for p53 immunostaining in cancers of the same individual. These results might be associated with observations that synchronous colorectal cancers showed concordant MSI status.[30] There was a concordant protein expression status in the same individual, suggesting a common background of genetic or epigenetic changes of a mismatch repair gene in these cases. Lee et al.[6] also reported that gastric adenomas and carcinomas in the same individual had the tendency of showing concordant MSI phenotype. Multiple carcinomas and precancerous conditions with MSI phenotype occurred in the same early genetic background. However, the concordant MSI phenotype did not imply a clonal origin because MSI results in multiple cancers showed different patterns.[6]

It is possible that exposure to carcinogens in the same environmental background, rather than genetic factors, is responsible for the development of SPGA. Our data corroborates the hypothesis that multiple gastric cancer is an example of "field cancerization", i.e., the repeated carcinogenic exposure of an entire field of tissue, which predisposes the field to the development of multiple cancers.[29]

Previous reports on advanced cancers showed no evidence for the independence of the suppressor pathway, mainly representative of p53 mutations, and the mutator pathway displaying MSI.[31] In the present investigation, no cancers displayed p53 or MSI at the same tumor. These data may indicate that the two major pathways are independent of each other, at least in the early stage of multiple gastric cancer development.[32–34]

Therefore, SPGA presented higher frequency of intestinal type gastric cancer and were diagnosed at lesser advanced stage in comparison to solitary gastric cancer. Careful endoscopic examination of the whole stomach should be performed in patients with gastric cancer, specially for intestinal adenocarcinoma to avoid missed lesions. Two major routes of carcinogenesis, the mutator pathway and the suppressor pathway, appear to be involved independently in the development of SPGA.

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Effectiveness of Diagnostic Paracentesis and Ascites Analysis for Suspected Strangulation Obstruction

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Abstract Strangulation obstruction is a surgical emergency, but its accurate diagnosis and timely surgical treatment are still matters of debate. We conducted a prospective observational study. We performed diagnostic paracentesis preoperatively for patients with suspected strangulation obstruction or, if that was impossible, we obtained ascites at the time of laparotomy. We examined each specimen to see whether ascites color and laboratory parameters could be reliable indicators of strangulation obstruction. During 18 months, 32 patients had suspected strangulation obstruction. At laparotomy, we confirmed strangulation obstruction in 21 patients, simple obstruction in two patients, and pseudo-obstruction in one patient. We treated eight patients conservatively, including one patient with a complication. We identified ascites red blood cell count, hematocrit, and lactic acid as indicators for strangulation obstruction by univariate analysis. An ascites red blood cell count was statistically high in cases with strangulation obstruction by multivariate analysis. Ascites red blood cell count above 20,000/mm^3 had a positive predictive value for strangulation obstruction of 100%, and above 40,000/mm^3, bowel resection was highly necessary. Diagnostic paracentesis and ascites analysis are useful methods for diagnosis of strangulation obstruction. Diagnostic paracentesis and ascites analysis should be combined with careful clinical exams for diagnosis of strangulation obstruction.

Keywords Strangulation · Obstruction · Ascites · Paracentesis · Ultrasound

Introduction

Many surgeons have the regrettable experience of performing a laparotomy only to find dead gut. Bowel necrosis has considerable morbidity and mortality. Strangulation obstruction (SGO), which is a mechanical blockage of bowel lumen with compromised vascular supply, is one of the surgical emergencies that can cause bowel necrosis and complications.[1] Early diagnosis of SGO is crucial to avoid bowel necrosis.

Relationships between clinical parameters and SGO have been sought, but no single factor has been identified that is sufficient to establish or exclude SGO.[2–5] SGO is often diagnosed by clinical gestalt and relies heavily on diagnostic impressions. However, when patients cannot provide reliable history and physical findings, it is so difficult to suspect SGO that the bowel is often necrotic at laparotomy.[1] Even the judgments of experienced senior surgeons are only 48% sensitive and 83% specific.[4] Consequently, delay in diagnosis carries significant morbidity and mortality.[6] Diagnostic imaging methods such as computed tomography and ultrasound are effective for the diagnosis,[7,8] but they identify only irreversible changes due to intestinal necrosis and are unfortunately unable to detect SGO to avoid bowel resection.[9]

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From our unfortunate experiences of finding bowel necrosis, we have known that bowel necrosis is almost always accompanied by bloody or at least serosanguineous ascites. The pathology of the strangulated necrotic intestine shows transmural hemorrhage.[10] We have suspected that serosanguineous ascites could be a reliable sign of bowel ischemia and that it might be utilized for the diagnosis of SGO. For many years, we have performed diagnostic paracentesis (DPC) to see whether ascites was serosanguineous, and it has worked well in diagnosing SGO. We hypothesized that DPC and ascites analysis would be effective for the diagnosis of SGO and have evaluated this hypothesis in the present study.

Methods

The prospective study was conducted at the Okinawa Chubu Hospital, Okinawa, Japan, from August 2003 through January 2005. The study included 32 consecutive patients with suspected SGO. The inclusion criterion was SGO that was suspected preoperatively by conventional means, including history, physical exams, and imaging studies (plain roentgenogram, ultrasound, or CT), irrespective of age or etiology. The exclusion criteria were simple small bowel obstruction, colonic obstruction, and obstruction due to peritonitis carcinomatosa. Pregnant patients and those with anticoagulation therapy were also excluded because paracentesis might be a great risk for those patients. SGO was defined as a small bowel obstruction with intestinal vascular compromise that was confirmed intraoperatively.

We did thorough ultrasound examination of the 32 patients to search for ascites accumulation. We performed DPC under ultrasound guidance if they had enough ascites (Fig. 1). DPC was done by surgical residents in their second, third, or fourth postgraduate year. The site of puncture was usually in the flank abdomen, where sufficient ascites was identified by ultrasound. We aspirated ascites through a 21-gauge needle and syringe under ultrasound guidance after antiseptic preparation of the skin. If ascites could not be aspirated, we gently inserted an 18- or 21-gauge needle until a free-flowing sample of peritoneal fluid was obtained. We classified ascites color by gross appearance as serous or serosanguineous. We defined serosanguineous fluid as that having an appearance darker than a normal human blood specimen that was 1,000-fold diluted. If aspirated ascites was not homogenous and if it contained streak of blood, we considered it to indicate traumatic paracentesis and we repeated the paracentesis at a different site. Our treatment algorithm of suspected SGO is described in Fig. 2. If the ascites looked serosanguineous, we diagnosed the patients as SGO and proceeded to laparotomy. If the ascites was serous, or if we could not perform paracentesis because enough ascites had not developed, we managed the patients conservatively unless they later developed serosanguineous ascites at repeat paracentesis or if clinical signs such as diffuse intense abdominal tenderness, distention, peritonitis, and oliguria strongly suggested strangulation. We obtained intraperitoneal fluid at the time of incision as well. We paid great attention to avoid blood contamination with ascites at the time of incision.

Ascites specimens that were obtained by paracentesis or at laparotomy were sent to the laboratory for analysis, and the ascites color, red blood cell (RBC) count, hematocrit (Hct), white blood cell (WBC) count, lactic acid, pH, base excess (BE), alkaline phosphatase (ALP), amylase (Amy), lactic dehydrogenase (LDH), and direct bilirubin (D-Bil) were evaluated. Ascites RBC count and Hct were analyzed by Sysmex SF-3000 (Sysmex Co. Ltd., Kobe, Japan), and lactic acid, ALP, Amy, LDH, and D-Bil were analyzed by

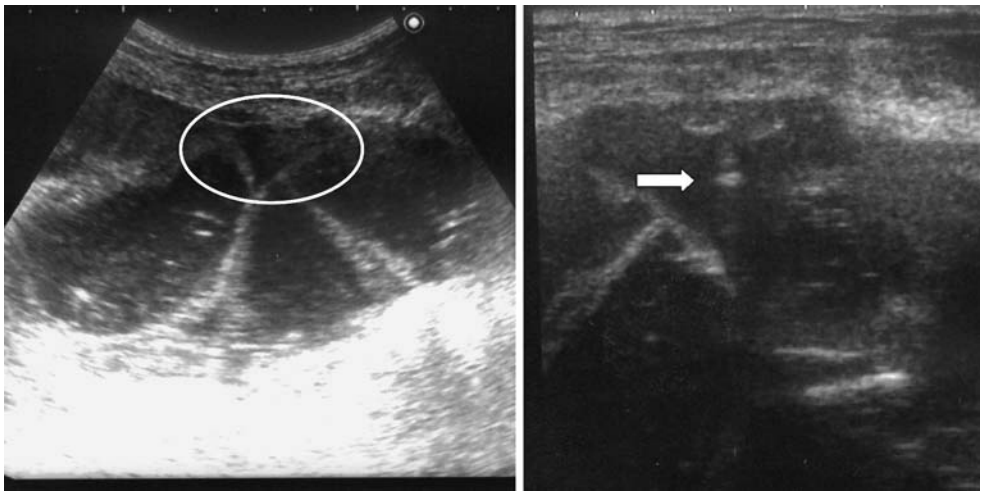
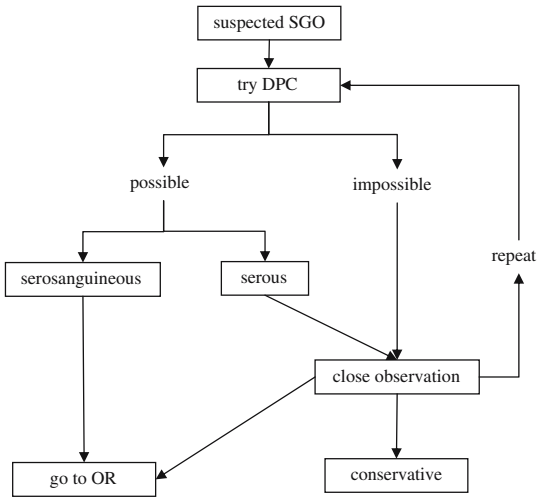


Figure 1 There was small amount of ascites (◇) among dilated small bowel loops in the left picture. The ascites was aspirated through a 21 gauge needle. The tip of a 21 gauge needle (⇨) was identified in the right picture.



SGO; strangulation obstruction DPC;diagnostic paracentesis OR; operation room

Figure 2 Treatment protocol of suspected strangulation obstruction.

Dimension RXM (Dade Behring Co. Ltd., Deerfield, IL, USA). Ascites pH and BE were analyzed by Radiometer ABL835 FLEX, Radiometer Co. Ltd., Copenhagen, Denmark. We compared ascites laboratory data between patients with SGO and those without it. Ascites data by DPC was used for patients who did not have surgeries, and that of laparotomy was used for patients who underwent surgery with a diagnosis of suspected SGO.

All data were compiled in a database for analysis (Microsoft Excel and SPSS 11.0 J for Windows). Differences between numerical variables were tested with Student's *t* test, and those between categorical variables were tested with chi-square statistics. A *p* value of less than 0.05 was deemed significant. The study protocol was approved by the institutional review board of the Okinawa Chubu Hospital and the Department of Surgery. Written informed consent was obtained from each patient.

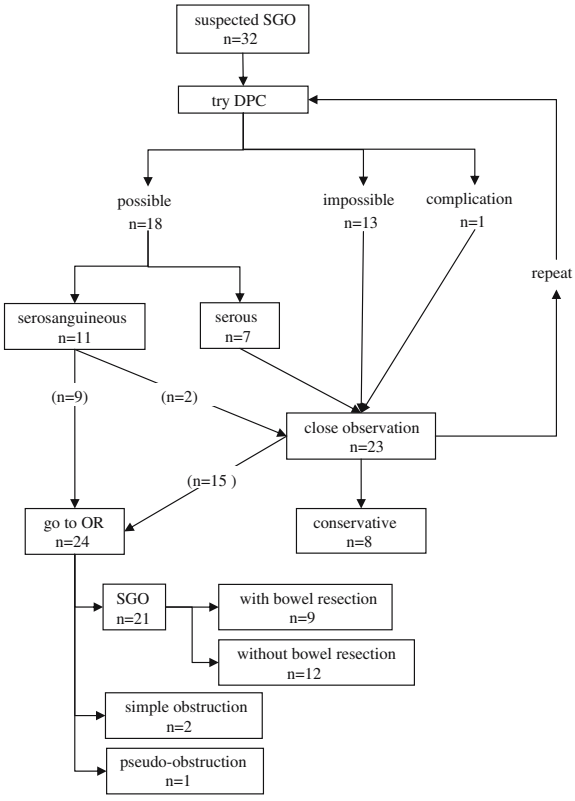
Results

During the 18-month study period, there were 32 consecutive patients with suspected SGO who entered the study. During the same period, there were 151 patients with bowel obstruction who were suspected of simple obstruction, colonic obstruction, obstruction with carcinomatosa peritonitis, etc. Patient characteristics of the 32 patients are listed in Table 1. The clinical course of the 32 patients is summarized in Fig. 3. These 32 patients were basically followed up according to our diagnostic algorithm in Fig. 2. However, there were two patients with serosanguineous ascites by DPC who did not give consent to laparotomy. These two patients were followed up conservatively with great attention and were discharged home without any complications. Among the 23 patients who were closely observed, 15 patients, including all of the 13 patients for whom DPC was impossible and two of the seven patients whose ascites were serous by DPC, eventually went to the operating room (OR). Two of the 15 patients went to the OR on the basis of computed tomography findings, whereas the rest of them went to the OR due to worsened physical findings. Eight of the 15 patients had serosanguineous ascites at laparotomy. Thirteen of the 15 patients were found to have SGO at laparotomy, whereas the rest of the 15 were negative for SGO (one case was simple obstruction, and the other was pseudo-obstruction). The duration of close observation varied with each case. The shortest was less than 1 h, whereas the longest one was more than 2 days. All patients with bowel resection went to the OR within 5 h except one case who needed 13 h. This patient was bed-ridden for Alzheimer's disease and showed only equivocal physical findings. Although we could not find ascites at first because of hypovolemia, she developed ascites with fluid resuscitation 12 h later. She went to OR immediately after we drew serosanguineous ascites by DPC and had bowel resection for incarcerated internal hernia. This difficult case with prolonged observation might be the only delay in our algorithm. There were no other delays in diagnosis. The causes of 21 cases with SGO were adhesional band (14 patients), internal hernia (5 patients), and volvulus (2 patients). There was no mortality, but there were some morbidities: short bowel syndrome and enterocutaneous fistula (one patient), early postoperative small bowel obstruction (one patient), prolonged postoperative ileus (one patient), atrial fibrillation (one patient), pneumonia (one patient), and wound infection (one patient). All patients were discharged home.

The sensitivity and specificity of serosanguineous ascites for SGO were 76 and 78%, respectively. The positive and negative predictive values were 89 and 58%, respectively. Serosanguineous ascites was significantly likely for SGO (p=0.01). Correlation between SGO and ascites laboratory

Table 1 Patient Characteristics of 32 Patients

Demographics	
Men: women	16: 16
Mean age (SD)	54.7 (27.7)
0–15	3
15–70	17
>70	12
Past medical history	
Prior abdominal surgery	18
Prior small bowel obstruction	9
Dementia	5
Cerebrovascular accident	5
Psychiatric illness	6



SGO; strangulation obstruction DPC; diagnostic paracentesis OR; operation room

Figure 3 Clinical course of 32 patients.

data is shown in Table 2. Ascites RBC count, Hct, and lactic acid were significantly higher in cases of SGO (p=0.008, 0.003, and 0.01, respectively; Fig. 4), but other laboratory parameters were unremarkable. Ascites RBC count was correlated to the degree of strangulation (Fig. 5). Plotting a receiver-operating curve, we identified cutoff points for RBC count and lactic acid. If the ascites RBC count was above 20,000/mm^3, the case was significantly likely to be an SGO (p=0.001). The sensitivity and specificity were 70 and 100%, respectively, and the positive and negative predictive values were 100 and 60%, respectively. The ascites RBC count was also significantly higher in patients with bowel resection (p=0.002). Ascites RBC above 40,000/mm^3 had a sensitivity of 89% and a specificity of 80% for bowel resection. The positive and negative predictive values were 66 and 94%, respectively. The sensitivity and specificity of ascites lactic acid more than 1.75 mmol/L were 76 and 66%, respectively. The positive and negative predictive values were 84 and 55%, respectively. We found, by multivariate analysis, ascites RBC count to be statistically significantly higher in cases with SGO.

Discussion

Paracentesis was first introduced by Salmon in 1906 and has been modified by many physicians for trauma and acute abdomen.[11–14] To our knowledge, it has never been used for the diagnosis of SGO. Our prospective pilot study is the first to examine the effectiveness of paracentesis for SGO.

We have defined serosanguineous ascites as that having an appearance darker than that of a normal human blood specimen that was diluted 1,000-fold. The mean RBC count of serosanguineous ascites was 85,000/mm^3. SGO is caused by venous occlusion through compression of mesentery, which causes congestion, edema, mucosal hemorrhage, and finally transmural hemorrhage.[15] In our cases, ascites in non-SGO contained small numbers of RBCs, whereas the ascites RBC counts in SGO increased according to the degree of strangulation (Fig. 5). The pathology of the

Table 2 Correlation Between Laboratory Parameters and Strangulation Obstruction

Parameter	SGO (n=21) Mean±SD	Non-SGO (n=10) Mean±SD	p value*
RBC (×10^3/mm^3)	124±163	10±8.7	0.008
Hct (%)	1.1±1.4	0.08±0.07	0.003
WBC (×10^3/mm^3)	1.84±3.63	2.90±7.56	0.30
Lactic acid (mmol/L)	4.26±3.88	1.73±0.91	0.01
pH	7.39±0.32	7.42±0.12	0.43
BE (mEq/L)	1.02±8.24	3.60±3.15	0.28
ALP (IU/L)	265±285	169±185	0.17
LDH (IU/L)	773±1060	439±633	0.18
Amylase (IU/L)	83±182	49±32	0.28
D-Bil (IU/L)	0.2±0.1	0.1±0.05	0.14

*p value was calculated by unpaired t test.
SGO=strangulation obstruction, RBC=red blood cells, Hct=hematocrit, WBC=white blood cells, BE=base excess, ALP=alkali phosphatase, LDH=lactate dehydrogenase, D-Bil=direct bilirubin
The number of samples was 31 excluding one case with complication.

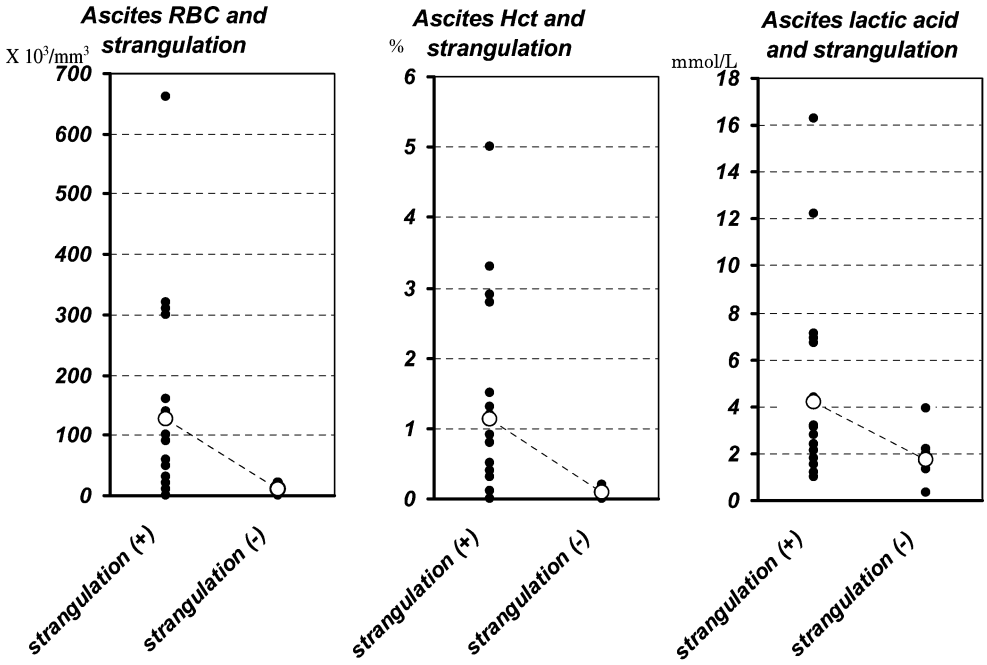
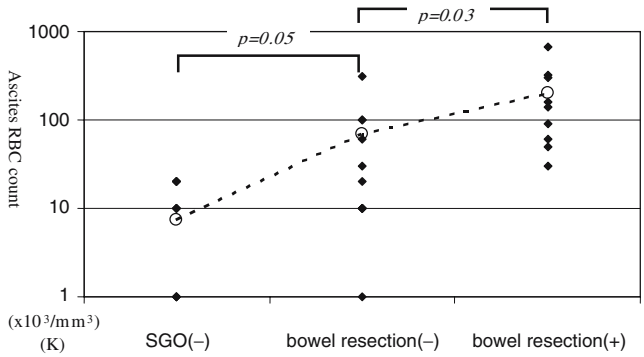


Figure 4 Correlation between strangulation obstruction and ascites red blood cell count, hematocrit, and lactic acid.

RBC: red blood cell, Hct; hematocrit,

○: mean

darkest-colored part of resected intestine in SGO showed transmural hemorrhage, whereas viable pink-colored margins showed only mucosal hemorrhage. Animal models of SGO confirmed these pathologic changes.[10] Those hemorrhagic changes of strangulated intestine seem to cause serosanguineous ascites. We established an ascites RBC count criterion of more than 20,000/mm^3 for the diagnosis of SGO and another criterion of more than 40,000/mm^3 for the necessity of bowel resection. The positive predictive value of ascites RBC count above 20,000/mm^3 was 100%, and the negative predictive value of ascites RBC count above 40,000/mm^3 was 94%. Laparotomy for suspected SGO should definitely be done when the ascites RBC count is above 20,000/mm^3. The surgical goal of SGO can be summarized as early diagnosis before the ascites RBC count exceeds 40,000/mm^3.



SGO: strangulation obstruction

○: mean

Figure 5 Correlation between ascites RBC count and the degree of strangulation obstruction.

Lactic acid is a product of the anaerobic metabolism of glucose, and its arterial level is a good indicator of the severity of metabolic acidosis secondary to tissue hypoperfusion. The time to its normalization reflects survival rate.[16–18] Because SGO is caused by vessel occulusion,[15] we hypothesized that intestinal hypoperfusion and subsequent gangrene must produce tissue lactic acid and cause high levels of lactic acid in ascites before systemic acidosis. Lactic acid was high in SGO, and at the same time, lactic acid was also high in cases of serosanguineous ascites ($p = 0.01$). Because ascites lactic acid correlated with RBC count, lactic acid was not an independent factor predicting SGO by multivariate analysis. Lactic acid in ascites might have been mostly caused by anaerobic RBC. However, among six cases that were false negatives according to the RBC count criteria, three were true positives according to the lactic acid criteria. Tissue hypoperfusion might play some part in raising lactic acid levels, independent of ascites RBC. Combining the RBC count criteria and lactic acid criteria, sensitivity rises to 81%, which is valuable clinically. Differences in other laboratory parameters such as pH, BE, ALP, LDH, Amy, and D-Bil were not statistically significant and thus did not allow us to differentiate SGO.

The 23 patients who were closely observed were a challenge for our treatment algorithm (Fig. 3). Thirteen patients among the 23 patients were eventually found to have SGO. DPC was not enough to exclude SGO. If physical findings are equivocal, patients should be closely observed with careful physical exams and repeated ultrasound every 1 or 2 h. Once ascites develops, DPC should be done. In our experience, even when ascites was serous, it also could not rule out SGO as long as physical findings remained equivocal. Multiple attempts of DPC are necessary in such cases.

There was one procedure-related complication. It was judged to be a complication because the ascites amylase level of the specimen was unexceptionally high (13,970 IU/L) in the absence of peritoneal irritation, and the patient was managed conservatively. Intestinal puncture is the most common complication of paracentesis, and its incidence was 4% in blind paracentesis.[19] Ultrasound guidance can safely avoid such complications most of the time. Even if the intestine is injured, intestinal puncture causes no leakage under normal physiologic circumstances.[20] Ascites amylase level was not effective in differentiating SGO (p=0.28), but it might be useful in identifying intestinal puncture.

Our study has several limitations. First, it was a single-center study. If DPC is performed in other facilities, complications might increase due to physician inexperience or to fatty habitus that precludes ultrasound guidance. Second, the number of samples was small. If the sample number were increased, lactic acid might be an independent predictor of SGO, and other laboratory parameters such as ALP, LDH, and amylase might reach statistical significance. Third, it was an observational study. A randomized study is necessary to prove that DPC and ascites analysis are effective for the early diagnosis and treatment of SGO. Finally, we examined ascites samples by DPC and at laparotomy together. Ascites at laparotomy might be affected by anesthesia, tissue damage at incision, and longer period of bowel ischemia, and its laboratory data might differ from those obtained after DPC. If that's the case, then RBC count criteria established in this study might need to be adjusted slightly.

Conclusion

DPC and ascites analysis are useful methods for the diagnosis of SGO. An ascites RBC count above 20,000/mm^3 is highly predictive of SGO, and an ascites RBC count above 40,000/mm^3 is predictive of bowel resection. DPC and ascites analysis for the diagnosis of SGO should be combined with conventional diagnostic exams, especially when they are equivocal. A randomized study is needed to prove the effectiveness of DPC and ascites analysis for the early diagnosis of SGO.

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The Effect of L-arginine and Aprotinin on Intestinal Ischemia–reperfusion Injury

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Abstract
Background Intestinal ischemia/reperfusion (I/R) results in local mucosal injury, systemic injuries, and organ dysfunction. These injuries are characterized by altered microvascular and epithelial permeability and villous damage. Activation of neutrophils, platelets, and endothelial factors are known to be involved in this process. Cytokines such as TNF-α, IL-1, IL-6, and oxygen-derived free radicals are believed to be important pathogenic mediators. Capillary no-reflow is also known to play a role in I/R. The aim of our study was to examine the role of L-arginine, a known nitric oxide (NO) donor, and aprotinin, a protease inhibitor with multiple effects, on intestinal I/R.
Methods Pigs weighing 20–25 kg were used. Ischemia was established by clamping the superior mesenteric artery (SMA) at its origin and was sustained for 2 hours. Duration of reperfusion was 2 hours. The animals were divided into four groups: group A, the control group, which was submitted to I/R injury only; group B, in which L-arginine was administered at a rate of 5 mg/kg/min during ischemia and continuing throughout reperfusion; group C, in which aprotinin was administered with an initial bolus dose of 20,000 U/kg during ischemia followed by a continuous dose at 50 U/hour throughout reperfusion; and group D in which both substances were administered. In all groups TNF-α, IL-1, and IL-6 levels were measured using ELISA at baseline, 2 hours of ischemia, and 1 hour and 2 hours of reperfusion. SMA blood flow was measured with a

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Doppler probe at baseline, 10 min, 1 hour, and 2 hours of reperfusion. Histological changes of the intestinal mucosa were examined and graded on a five-point scale in all groups.
Results In the control group, levels of TNF-α, IL-1, and IL-6 were significantly increased during reperfusion ($p<0.05$) compared to baseline. Administration of L-arginine and aprotinin led to suppression of the release of TNF-α, IL-1, and IL-6 during reperfusion in a statistically significant manner (all $p<0.05$). A synergistic or additive effect of L-arginine and aprotinin was not observed. SMA blood flow in the control group was decreased ($p>0.05$) during reperfusion compared to baseline. In animals treated with L-arginine and aprotinin, SMA blood flow during reperfusion was significantly increased ($p<0.05$) compared to the control group. Histologic examination of the intestinal mucosa was characterized by flattening of the villi and necrosis in the control group. In the treated animals, less severe histological changes were noted.
Conclusions Administration of L-arginine and aprotinin may lead to amelioration of intestinal I/R injury. We did not note a synergistic or additive effect of these two substances. These findings warrant further studies in clinical settings for future treatment efforts.

Keywords L-arginine · Aprotinine · Ischemia–reperfusion · Cytokine

Introduction

Intestinal ischemia/reperfusion (I/R) injury is associated with serious clinical conditions in adults and infants. Examples of such disorders include mesenteric vascular ischemia, intestinal obstruction with strangulation, hemodynamic shock, sepsis, and necrotizing enterocolitis.[1] Intestinal reperfusion induces inflammation and tissue injury through the endogenous production of oxygen-derived free radicals, and proinflammatory cytokines, such as TNFα, IL-1, and IL-6.[2,3,22] The end result is local intestinal mucosal tissue damage and systemic injury in distant organs systems, which may lead to multiorgan disorder syndrome (MODS).[2,3,5] Bacterial translocation in the intestine also takes place as a result of mucosal injury, thus exposing the circulation to pathogens contributing to adverse systemic effects.[13,14] Blood flow in the microvasculature is impaired during reperfusion, leading to the "no-reflow" phenomenon, which contributes to I/R injury in a significant manner.[4]

L-arginine and aprotinin are substances known to inhibit elements of the mechanisms responsible for I/R injury.[6,7,11,15–17,20–22] Using a porcine model, we induced intestinal I/R injury by clamping the superior mesenteric artery. Cytokine levels, mesenteric blood flow, and intestinal histologic injury were examined as a reflection of I/R injury.

The objective of this study was to investigate the effects of L-arginine and aprotinin on cytokine release, mesenteric blood flow, and intestinal histological changes after intestinal I/R.

Methods

This study was performed in accordance with the guidelines provided by the Medical Experimentation Ethics Committee of the Aristotelian University, Thessaloniki, Greece.

Animals

Twenty healthy male pigs weighing between 20 and 25 kg were used. All animals were approximately 6 months of age. They were kept under standardized conditions for food, water, light, and temperature. Food was withheld 18 hours before the experiment, and water was given ad libitum.

Surgical Procedure

Induction of anesthesia was performed by administration of thiopental (10 mg/kg body weight), fentanyl (5 μg/kg body weight), and vecuronium (0.3 μg/kg body weight) intravenously. A tracheostomy was done and a 6-mm cuffed tracheostomy tube was placed. Anesthesia was maintained with halothane and oxygen, provided via a mechanical ventilator (Ceasar, Milan, Italy). Tidal volumes were maintained at 10–12 ml/kg of body weight. An arterial catheter was placed in the right femoral artery using a cut-down technique. A pulmonary artery catheter was placed via the left jugular vein. A suprapubic catheter was inserted into the urinary bladder with an open technique for continuous monitoring of urine output.

A midline laparotomy was performed. We initially identified the portal vein. A double-lumen catheter was inserted in the vein for collection of blood samples, and secured with a purse-string suture using 4-0 polypropylene. A left medial visceral rotation was then performed by incising Toldt's fascia in the left paracolic gutter. This maneuver exposed the superior mesenteric artery (SMA) at its origin from the aorta. Intestinal ischemia was caused by occluding the SMA at its origin with a bulldog vascular clamp. A total ischemia time of 2 hours and a reperfusion time of 2 hours (after release of the clamp) were used during the experiments. At the end of the experiment, terminal ileum (2 cm in length adjacent to the ileocecal valve) was removed and fixed in formalin for histological evaluation. Finally, animals were sacrificed by KCl injection.

Experimental Groups

The animals were randomly assigned to experimental groups. Each group comprised of four animals.

Group A was the control group. These animals were subjected to mesenteric ischemia and reperfusion without administration of drugs.

In group B, animals were treated with L-arginine infusion (5 mg/kg/min, i.v.) starting at 30 minutes of ischemia and continuing throughout the duration of the experiment.

In group C, animals were treated with aprotinin (20,000 U bolus, i.v, followed by infusion of 50/U/hour, i.v.) starting at 30 minutes of ischemia and continuing throughout the duration of the experiment.

In group D, animals were treated with both drugs at the same dosages mentioned previously, starting at 30 minutes of ischemia and continuing throughout the duration of the experiment.

A final group of sham animals, which did not undergo ischemia/reperfusion injury and drug treatment, were used for histological examination of their terminal ileum. The tissue samples from the sham animals were used as histological controls.

Measurement of Cytokine Levels

Samples of portal venous blood were collected in all animal groups before SMA occlusion, at 2 hours of ischemia and at 1 and 2 hours of reperfusion. The blood samples were immediately centrifuged at 1,000 rpm and stored at −80°C until they could be assayed. Commercially available ELISA kits were used for determination of serum TNFα, IL-1, and IL-6 levels (R&D Systems, Minneapolis, MN, USA). Cytokine levels before SMA occlusion were designated as baseline.

Measurement of Mesenteric Blood Flow

Blood flow was measured at the SMA using a hand-held 5-mm ultrasonic-Doppler probe (Medistim-Quickfit, Oslo, Norway). This probe measures the difference in transit time between pulses in a vessel and displays blood flow on a computer screen. Blood flow was measured in milliliter per minute. Baseline blood flow measurements were taken immediately before SMA clamping. Blood flow during reperfusion was measured 10 minutes and 2 hours after SMA clamp release.

Histopathological Examination

In all animals subjected to intestinal ischemia/reperfusion injury, segments of terminal ileum were obtained at the end of the 2-hour reperfusion period, immediately before sacrifice. In the sham animals, tissue was obtained after laparotomy. The segments of terminal ileum were embedded in paraffin and cut into 5-μm sections. Paraffin sections were then stained with hematoxylin and eosin (HE). Histopathologic specimens were examined under light microscopy. Histologic injury of the ileal mucosa was graded utilizing scale according to Chiu et al:[12] grade 0 represents normal mucosa; grade 1 demonstrates moderate epithelial cell lifting from the lamina propria; grade 2 is characterized by significant epithelial lifting along the villi with few denuded tips; grade 3 demonstrates denuded villi with exposed lamina propria and dilated capillaries; grade 4 shows disintegration of the lamina propria, hemorrhage, and ulceration. All histological examinations were done in a blinded fashion to avoid bias.

Statistical Analysis

All data are expressed as mean and SD. Continuous variables were tested with the Student's *t* test. In all instances, $P<0.05$ was regarded as significant.

Results

Serum Cytokine Levels

TNFα In the control group (group A), there was a significant increase in serum TNFα levels during intestinal ischemia compared to baseline. Reperfusion led to an additional significant increase in serum TNFα (Table 1). Animals treated with L-arginine (group B) displayed

Table 1 Serum Levels of TNFα After Mesenteric Ischemia and Reperfusion With or Without Administration of L-Arginine and Aprotinin*

TNFα levels (pg/ml)				
	Control	L-Arg†	Apr‡	L-Arg + Apr§
Baseline	15±2	19±7	20±8	17±6
2-h ischemia	93±16‖	29±7¶	27±2¶	19±3¶
1-h reperfusion	279±21‖	62±41¶	44±4¶	47±11¶
2-h reperfusion	387±28‖	62±33¶	58±5¶	65±16¶

*Blood samples were obtained from the portal vein before SMA occlusion (baseline), at 2 hours of ischemia and at 1 and 2 hours of reperfusion. Control animals underwent ischemia–reperfusion injury only. Values are presented as mean ± standard error of mean of four animals per group

†L-Arg, animals receiving L-arginine

‡Apr, animals receiving aprotinin

§L-Arg + Apr, animals receiving both L-arginine and aprotinin

‖$P<0.05$ versus baseline.

¶$P<0.05$ versus control.

significantly lower serum TNFα levels compared to controls during both ischemia and reperfusion (Table 1). Similar results were obtained in animals treated with aprotinin (group C) and animals treated with both substances (group D) (Table 1). There was no significant difference in TNFα levels among groups B, C, and D during ischemia and reperfusion.

IL-1 In group A, there was a significant increase in serum IL-1 levels during intestinal ischemia as compared to baseline. Reperfusion led to an additional significant increase in serum IL-1 (Table 2). Animals in group B displayed significantly lower serum IL-1 levels compared to controls during both ischemia and reperfusion (Table 2). Similar results were obtained in groups C and D (Table 2). There was no significant difference in IL-1 levels among groups B, C, and D during ischemia and reperfusion.

IL-6 In group A, there was a significant increase in serum IL-6 levels during intestinal ischemia compared to baseline. Reperfusion led to an additional significant increase in serum IL-6 (Table 3). Animals in group B displayed significantly lower serum IL-6 levels compared to controls during both ischemia and reperfusion (Table 3). Similar results were obtained in groups C and D (Table 3). There was no significant difference in IL-6 levels among groups B, C, and D during ischemia and reperfusion.

Mesenteric Blood Flow

Baseline blood flow was measured in all four animal groups. The difference in blood flow among the four groups at baseline was not significant (Fig. 1). In the control group, a slight but not significant decrease in SMA blood flow was observed at 10 minutes and 2 hours of reperfusion, compared to baseline (Fig. 1). Treatment with L-arginine significantly increased SMA blood flow during reperfusion. Similarly, treatment with aprotinin caused a significant increase in blood flow during reperfusion. The combined administration of L-arginine and aprotinin produced similar results (Fig. 1). There was no significant difference in SMA blood flow among groups B, C, and D.

Table 2 Serum Levels of IL-1 After Mesenteric Ischemia and Reperfusion With or Without Administration of L-Arginine and Aprotinin*

IL-1 levels (pg/ml)				
	Control	L-Arg†	Apr‡	L-Arg + Apr§
Baseline	53±6	58±4	54±7	67±5
2-h ischemia	86±6‖	85±13	53±23	74±19
1-h reperfusion	372±82‖	119±63	69±25¶	78±9¶
2-h reperfusion	483±32‖	157±45¶	85±12¶	94±7¶

*Blood samples were obtained from the portal vein before SMA occlusion (baseline), at 2 hours of ischemia and at 1 and 2 hours of reperfusion. Control animals underwent ischemia–reperfusion injury only. Values are presented as mean ± standard error of mean of four animals per group.
†L-Arg, animals receiving L-arginine
‡Apr, animals receiving aprotinin
§L-Arg+Apr, animals receiving both L-arginine and aprotinin
‖$P<0.05$ versus baseline.
¶$P<0.05$ versus control.

Table 3 Serum Levels of IL-6 After Mesenteric Ischemia and Reperfusion With or Without Administration of L-Arginine and Aprotinin*

IL-6 levels (pg/ml)				
	Control	L-Arg†	Apr‡	L-Arg+Apr§
Baseline	53±9	72±11	54±7	65±16
2-h ischemia	107±34‖	80±23	53±23	72±9
1-h reperfusion	380±74‖	114±43¶	68±25¶	88±8¶
2-h reperfusion	434±46‖	112±38¶	91±2¶	92±8¶

*Blood samples were obtained from the portal vein before SMA occlusion (baseline), at 2 hours of ischemia and at 1 and 2 hours of reperfusion. Control animals underwent ischemia–reperfusion injury only. Values are presented as mean±standard error of mean of four animals per group.
†L-Arg, animals receiving L-arginine
‡Apr, animals receiving aprotinin
§L-Arg+Apr, animals receiving both L-arginine and aprotinin
‖$P<0.05$ versus baseline.
¶$P<0.05$ versus control.

Histopathology

In control animals, mucosal injury was significant and demonstrated loss of villi, hemorrhage, ulceration, and loss of glandular architecture (grade 4 injury). Treatment with L-arginine resulted in significant reduction of mucosal injury, characterized by mild denudation of villous tips and preservation of glandular architecture (grade 2 injury). Treatment with aprotinin resulted in a slightly more congested mucosa than the previous group with preservation of glandular architecture (grade 3 injury), and animals treated with both substances demonstrated grade 2 injury. Representative histological samples from all animal groups are shown in Fig. 2. Table 4 depicts the grade of histologic injury in each animal of the study.

Discussion

Intestinal Ischemia/reperfusion injury is associated with a number of serious clinical conditions such as mesenteric ischemic disease, intestinal obstruction with strangulation,

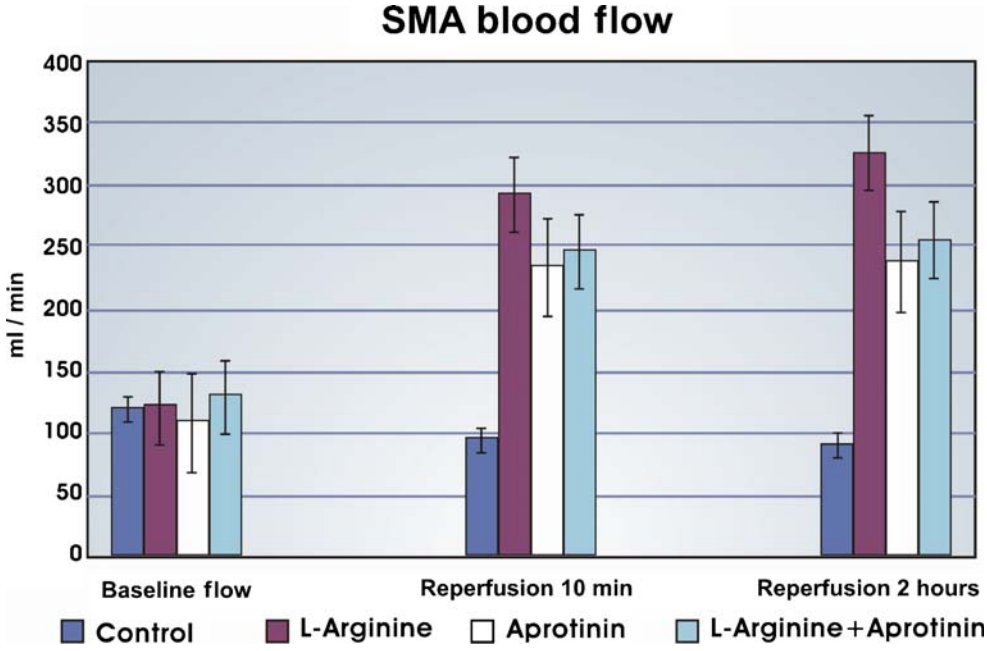

Figure 1 Superior mesenteric blood flow among the four experimental groups. Blood flow measurements (ml/min) were performed with a hand-held ultrasonic probe at origin of SMA. Depicted is mean ± standard error of mean of four animals for each time point. Baseline measurements of blood flow were done before SMA clamping, and at 10 minutes and 2 hours of reperfusion. *$P<0.05$ compared with controls.

trauma, sepsis, surgery for abdominal aortic aneurysm repair, and necrotizing enterocolitis in children.[1] This condition not only causes local mucosal injury, but may lead to distant organ injury and multiorgan dysfunction syndome (MODS).[2,3,5] Most clinical conditions associated with I/R injury are characterized by increased morbidity and mortality.[1–3,5] The key to this phenomenon lies in the intense inflammatory response triggered by the return of blood supply to ischemic tissues.

During I/R injury, several events take place. Oxygen-derived free radicals are formed. These are capable of damaging amino acids, membrane transport proteins and nucleic acids.[2] Proinflammatory cytokines such as TNFα, IL-1, IL-6, and PAF are released by macrophages.[2,19,22] These promote the upregulation of adhesion molecules (ICAM, VCAM) on the surface of vascular endothelial cells, as well as the release of other cytokines and chemokines.[2,3,7,11] Leukocytes are also activated in this process. Specifically, polymorphonuclear leukocytes (PMNs), aggregate in tissues and β2-integrins (CD11a, CD11b, and CD11c/CD18) located on their surface bind to endothelial cell adhesion molecules.[2,7] Interaction between these molecules leads to an ordered process; namely, leukocyte rolling, firm adhesion to the endothelial surface, and diapedesis through the vascular wall and into target tissues.[2,7] PMNs secrete proteolytic enzymes and free radicals, and cause physical obstruction of capillaries producing impairment of the microcirculation, and further extension of ischemia.[1,2,7,11,15,19] NF-kB, a nuclear transcription factor expressed during reperfusion, also induces the rapid expression of cytokines, chemokines, and endothelial adhesion molecules, thus amplifying the inflammatory process.[1,2,7,11]

Several studies have shown that I/R injury results in local activation of the complement system.[18] This system has long been recognized as an important mediator of innate immune defense and inflammation. Activation of complement occurs early in I/R and leads to the release of anaphylatoxins, complement factor 3a (C3a) and 5a and the membrane attack complement complex C5b-9 (MAC).[10,18] This can lead to local and systemic tissue injury.[10]

During I/R injury a reduction in the release of nitric oxide (NO) from the affected vascular epithelium occurs.[2,11] NO can act in a protective manner in tissues through the physiologic regulation of vascular tone, inhibition of platelet aggregation, attenuation of leukocyte adherence to the endothelium, scavenging of free radicals, maintenance of normal vascular permeability, inhibition of smooth muscle proliferation, and stimulation of endothelial cell regeneration.[2,6] The decrease in NO during reperfusion may therefore favor vasoconstriction, leukocyte adherence, and platelet aggregation, as well as accumulation of oxygen-derived free radicals, leading to tissue damage.[2]

The no-reflow phenomenon plays an important role in I/R injury, especially during reperfusion.[4,23] It is known that reperfusion of an ischemic organ is never associated with the complete and immediate reconstitution of blood flow to preischemic levels.[4,23] In several tissue beds, ischemia is followed by compensatory vasodilation during reperfusion of the tissue bed, thus leading to increased blood flow.[23] However, when ischemia time exceeds 2 h, blood flow during reperfusion is always lower than preischemic blood flow. No-reflow takes place in the microvasculature and is associated with narrowing of the capillaries as a result of endothelial cell edema, external compression of capillaries

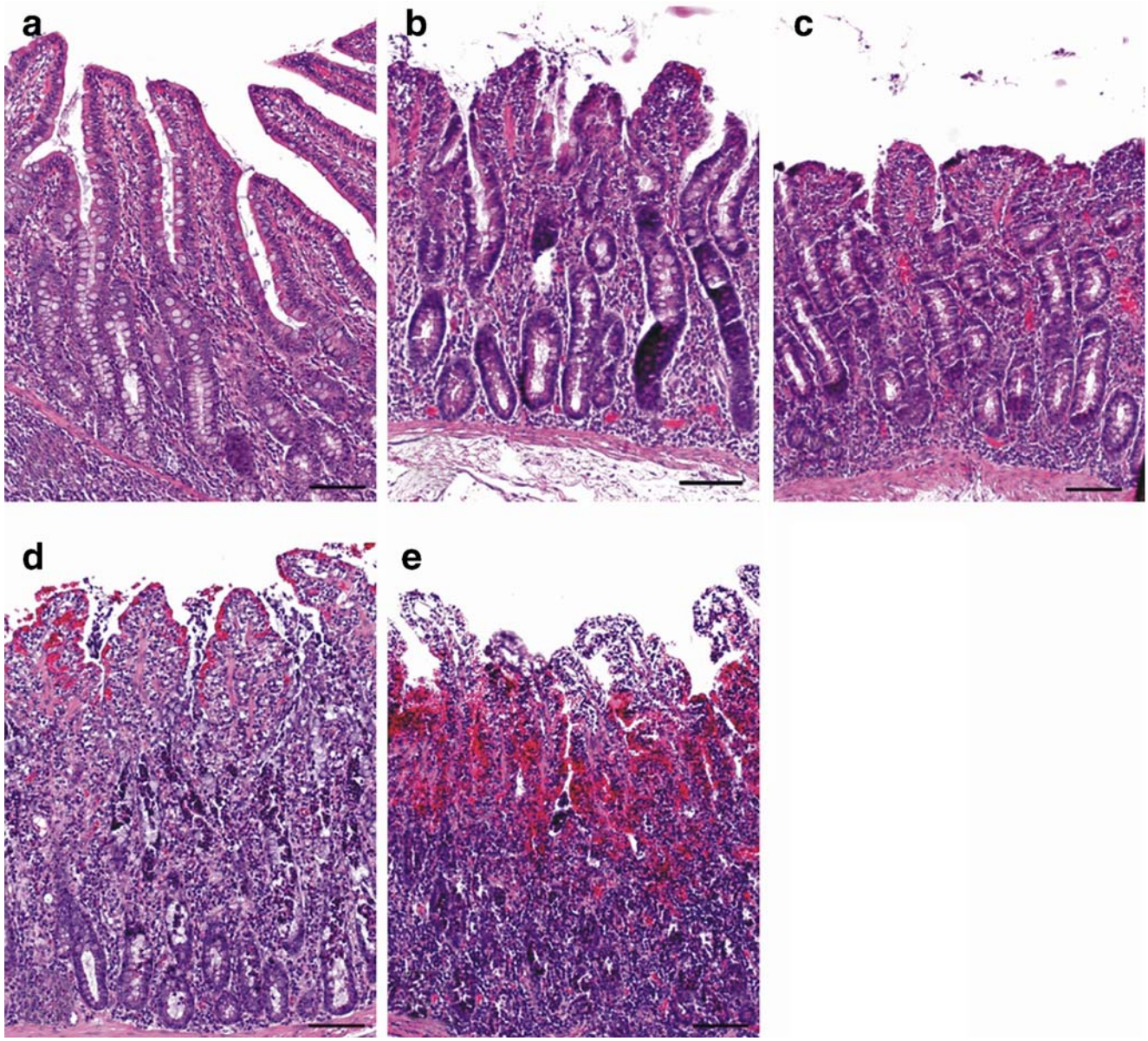

Figure 2 Histopathology of terminal ileum specimens with representation from each experimental group. (a) Sham animal. Villous architecture is preserved and no vascular congestion is present, depicting grade 0 injury. (b) Animal treated with L-arginine. Villous tips are mildly denuded, and there is epithelial lifting, depicting grade 2 injury. (c) Animal treated with aprotinin. Mucosa is congested, capillaries are dilated, and there is significant denudation of the villous tips, depicting grade 3 injury. (d) Animal treated with both substances. Histologic changes consistent with grade 2 injury. (e) Control animal. There is total loss of glandular architecture, disintegration of lamina propria, hemorrhage, and ulceration, representing grade 4 injury.

from interstitial edema, and capillary obstruction from activated leukocytes and aggregated platelets. Another mechanism by which blood flow may be reduced during reperfusion is the loss of vasodilatory autoregulation.[23] The reduction of NO during reperfusion may contribute to this phenomenon, leading to decreased capillary vasodilatory capability. Increased TNFα and PAF production causes vasoconstriction and augmentation of the no-reflow effect.[4,23]

Basic strategies to prevent IR injury, or ameliorate its effect, have focused on nitric oxide supplementation, administration of antioxidants and neutrophil-endothelial cell blockade strategies.[2]

L-arginine is the precursor of NO. A family of enzymes termed NO synthases (NOS) catalyzes the synthesis of NO from its precursor. Several studies have demonstrated that NO supplementation may lead to reversal of I/R injury. NO in gaseous form given at low concentrations leads to

Table 4 Pathologic Evaluation of Terminal Ileum Segments in each Pig After 2 Hours of Reperfusion

Histologic Grade					
Animal	Sham	Control	L-Arg†	Apr‡	L-Arg + Apr§
1	0	4	2	2	2
2	0	4	2	3	2
3	0	4	2	3	2
4	0	4	2	2	2

*A five-point scale of histologic injury was used (grade 0=normal; grade 1=moderate epithelial cell lifting from the lamina propria; grade 2=significant epithelial lifting along the villi with few denuded tips; grade 3=denuded villi with exposed lamina propria and dilated capillaries; grade 4=disintegration of the lamina propria, hemorrhage, and ulceration).
Sham animals not subjected to ischemia–reperfusion injury.
†L-Arg, animals receiving L-arginine
‡Apr, animals receiving aprotinin
§L-Arg+Apr, animals receiving both L-arginine and aprotinin

diminished I/R injury and attenuation of leukocyte–endothelial adhesion and platelet aggregation.[15] L-arginine reverses the deleterious effects of NOS inhibition on mucosal barrier function during I/R. L-Arginine infusion has been shown to be effective in I/R of rabbit skeletal muscle, rat skin, and rat liver.[2] In addition, the blockade of NOS activity with NOS inhibitors has been shown to aggravate reperfusion injury. In gene-knockout animals for eNOS (a NOS isoform), reperfusion injury was similarly augmented. However, there have been studies demonstrating that NO can exert a detrimental effect on I/R injury.[17] This may be associated with the combination of endothelial derived NO with superoxide derived from activated neutrophils, which produces peroxynitrite, a powerful oxidant that causes local intestinal mucosal injury.[2,15] In addition, NO-associated injury may be related to the increased activity of the iNOS relative to cNOS, and the timing of NO supplementation during I/R injury.[15]

Aprotinin is a naturally occurring serine protease inhibitor.[16] It forms a reversible enzyme inhibition complex with serine proteases by binding to the proteases in a dose-dependent manner. Examples of such proteases are plasmin, trypsin, chymotrypsin, kallikrein, thrombin, activated protein C, elastase, and tissue plasmin activator. Aprotinin is an antifibrinolytic modulator of the coagulation cascade, a modulator of inflammation, and a platelet protectant. It has been extensively used in cardiac surgery, where it has demonstrated improved hemostasis, reduction in transfusion requirements, and efficacy in reducing postcardiopulmonary bypass systemic inflammation.[16]

Beneficial effects of aprotinin include reduction in cytokine-induced bronchial inflammation and attenuation of lung reperfusion injury during lung transplantation. Studies have also demonstrated improved vascular endothelial cell relaxation, decreased leukocyte adhesion to the endothelium, and decreased transmigration of neutrophils through the vessel wall.[16]

In high doses of aprotinin administration, neutrophils display reduced expression of the membrane attack complex as complement activation is reduced. In addition, reduced levels of TNFα, IL-1, IL-6, IL-8, and elastase have been observed.[20] In rats, I/R-induced CD11/CD18 and ICAM upregulation is decreased during aprotinin administration, thereby limiting neutrophil adhesion and transmigration through vascular endothelial cells.[16,20,21]

In the present study, we examined the effect L-arginine and aprotinin administration, either separately or in combination, on inflammatory mediators, SMA blood flow, and intestinal mucosal injury during intestinal ischemia and reperfusion. As predicted, intestinal I/R caused a significant increase in the proinflammatory cytokines IL-1 and TNFa. This increase was markedly significant during reperfusion. Both of these cytokines have been shown to increase in several models of I/R. We also studied levels of IL-6, a multifunctional cytokine that modulates both local and systemic inflammation and immunity. Clinical studies suggest that elevated serum IL-6 may be predictive of acute intestinal ischemia and the need for surgical intervention.[8,9] In our study, IL-6 was also significantly increased during I/R. Cytokine levels were measured to demonstrate both local intestinal I/R injury and the potential for systemic I/R injury, as these substances exert their effects in distant organ systems.[19]

Treatment with L-arginine significantly reduced levels of all three cytokine during both ischemia and reperfusion, thus demonstrating the protective effects of NO supplementation on I/R injury in our model. It is important to note that L-arginine infusion started during ischemia; studies have shown that timing of L-arginine administration may determine the beneficial or other effect of the substance on I/R injury. Ward et al. showed that pretreatment with L-arginine before ischemia had a protective effect on I/R, whereas L-arginine infusion initiated during reperfusion did not.[15]

Aprotinin also decreased the levels of inflammatory cytokines significantly, reflecting its complexity of action at several levels of the inflammatory cascade.

The combined administration of L-arginine and aprotinin did not demonstrate additive or synergistic effects on cytokine release.

During reperfusion, we observed a slight decrease in SMA blood flow in comparison to baseline levels. The decrease was in the order of 10 percent and was not statistically significant. We believe that this decrease was consistent with the no-reflow phenomenon. Compensatory vasodilation and, therefore, increased blood flow relative to baseline was not observed, possibly secondary to ischemia time of 2 hours and concomitant loss of intestinal vascular

autoregulatory systems. Although flow measurements were performed at the SMA, these possibly reflected the pathophysiology at the microvascular level. Administration of L-arginine significantly increased SMA blood flow, possibly as a result of the vasodilatory effects of NO, inhibition of leukocyte and platelet aggregation. Aprotinin also caused significant increase in SMA blood flow, also reflecting its inhibitory effects on neutrophil and platelet aggregation and activation, thus decreasing endothelial and interstitial edema, capillary narrowing. These effects lead to attenuation of the no-reflow phenomenon.

Intestinal mucosal injury was significant in our I/R model. We observed attenuation of mucosal injury with the administration of L-arginine. Mucosal injury was slightly increased in several animals treated with aprotinin in comparison to L-arginine-treated animals. We are unable to provide an explanation for this observation with our current knowledge of aprotinin action. Treatment with both substances resulted in an injury grade similar to the L-arginine-treated group. In conclusion, both substances demonstrated local mucosal protective effects.

Several limitations of the study can be mentioned. The number of animals studied can be considered small.

In addition, the selection of timing of administration of the two substances in the study probably does not correlate with a realistic clinical situation, as diagnosis of mesenteric ischemia is rarely made in only 30 min from the inciting event. In future experiments, different starting times of substance administration relative to the onset of ischemia should be studied. Nevertheless, these relatively simple experiments led to interesting results.

Instestinal I/R remains an interesting phenomenon. Despite advances in the understanding of the pathophysiology of this condition and experimental trials of pharmacological substances for reversal of I/R injury, advances in the clinical application of such manipulations has been minimal. Mesenteric ischemia, a condition encountered by the majority of general surgeons, is a clinical entity that is difficult to diagnose, with a relatively high morbidity and mortality. Early detection and early intervention is the only known treatment, and no adjunctive measures have been shown to improve clinical results.

Conclusions

In summary, we have shown that the administration of L-arginine and aprotinin demonstrates a reduction in local tissue injury and potentially in systemic injury after intestinal I/R injury in a porcine model. Elevation of proinflammatory cytokines, intestinal mucosal injury, and the presence of the no-reflow effect were found to be consistent with I/R injury. Decreased cytokine levels, attenuation of mucosal injury, and increased SMA blood flow after administration of these substances, alone or in combination, were believed to be a sign of reduction of I/R injury. Any results extrapolated from this study must first be validated in further well-designed trials. Further elucidation of the biology of ischemia/reperfusion injury is required, with the purpose of finding clinical adjuncts to improve outcomes in patients in which this injury is encountered.

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Rates and Patterns of Recurrence for Percutaneous Radiofrequency Ablation and Open Wedge Resection for Solitary Colorectal Liver Metastasis

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Abstract
Introduction The purpose of this study was to compare rates and patterns of disease progression following percutaneous, image-guided radiofrequency ablation (RFA) and nonanatomic wedge resection for solitary colorectal liver metastases.
Methods We identified 30 patients who underwent nonanatomic wedge resection for solitary liver metastases and 22 patients who underwent percutaneous RFA because of prior major hepatectomy (50%), major medical comorbidities (41%), or relative unresectability (9%). Serial imaging studies were retrospectively reviewed for evidence of local tumor progression.
Results Patients in the RFA group were more likely to have undergone prior liver resection, to have a disease-free interval greater than 1 year, and to have had an abnormal carcinoembryonic antigen (CEA) level before treatment. Two-year local tumor progression-free survival (PFS) was 88% in the Wedge group and 41% in the RFA group. Two patients in the RFA group underwent re-ablation, and two patients underwent resection to improve the 2-year local tumor disease-free survival to 55%. Approximately 30% of patients in each group presented with distant metastasis as a component of their first recurrence. Median overall survival from the time of resection was 80 months in the Wedge group vs 31 months in the RFA group. However, overall survival from the time of treatment of the colorectal primary was not significantly different between the two groups.
Conclusions Local tumor progression is common after percutaneous RFA. Surgical resection remains the gold standard treatment for patients who are candidates for resection. For patients who are poor candidates for resection, RFA may help to manage local disease, but close follow-up and retreatment are necessary to achieve optimal results.

Keywords Liver resection · Colorectal liver metastases · Radiofrequency ablation

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Introduction

Despite improvements in systemic chemotherapy, surgical resection remains the most effective treatment for colorectal metastases confined to the liver. Complete surgical resection was associated with 5 and 10 year survival rates of 27–58% and 20–27%, respectively, whereas long-term survivors with chemotherapy alone are rare[1–4]. Often, however, patients with liver metastases are not candidates for resection because of the extent or distribution of their

disease, comorbid conditions, or a combination of these factors. Various local and regional ablative approaches have been applied to liver metastases as either adjuncts or alternatives to resection. Radiofrequency ablation (RFA) is one of the most widely utilized modalities, with numerous studies demonstrating safety and radiographic response after tumor ablation in small tumors[5–11]. At least two studies have demonstrated that radiographic response correlated with pathologic evidence of coagulation necrosis in lesions that were resected after ablation[12,13].

RFA has been performed using open surgical, laparoscopic, and percutaneous approaches. In general, the effectiveness of RFA by any approach appears to be limited in large tumors and in tumors with proximity to major vessels because of "heat sink" effect[7,8,14–16]. An additional limitation of the image-guided, percutaneous approach includes the potential understaging of up to 40% of patients with unsuspected additional liver metastases or extrahepatic disease[17–19]. However, obvious advantages of the percutaneous approach are that it is less invasive and that it can be easily repeated. These are important benefits in patients with colorectal liver metastases, most of whom have undergone prior colorectal surgery, and not infrequently, prior liver resection. This appeal and the widespread availability of percutaneous RFA have led to a dramatic increase in the application of this modality to colorectal liver metastases, even as a proposed alternative to resection for patients with resectable disease[11,20]. However, there are no randomized prospective studies demonstrating an effect of RFA on survival at all, much less studies demonstrating equivalency to resection.

The purpose of this study was to examine rates and patterns of recurrence after percutaneous RFA for solitary colorectal liver metastasis. The authors' preferred approach for management of colorectal liver metastases is resection with at least a 1-cm margin and anatomically based whenever feasible. RFA is reserved for patients with contraindications to resection. To compare this local ablative procedure to a truly local resection, we also examined rates and patterns of recurrence in patients who underwent nonanatomic wedge resection of a solitary liver metastasis.

Methods

Patients

A prospectively maintained surgical database was searched for patients who underwent nonanatomic wedge resection of a solitary colorectal liver metastasis. Patients who underwent concurrent placement of a hepatic arterial infusion pump were excluded. A prospectively maintained interventional radiology database was searched for patients who underwent percutaneous RFA of a solitary colorectal liver metastasis rather than resection.

RFA Technique

Procedure planning Diagnostic work-up included contrast enhanced abdominal computed tomography (CT) examination. Treatment decision was based on biopsy proven metastases or image evidence of growing masses in patients with known metastatic disease from colorectal cancer. The procedures were performed while the patients were monitored by an anesthesiologist under either conscious sedation or general anesthesia.

Targeting A limited non-contrast CT was always performed to localize the lesion. RFA was performed using the Radiotherapeutics (Boston Scientific), RITA (RITA Medical), or Radionics (Tyco Healthcare) device. This decision was made by the interventional radiologist based on the location, size, and shape of the tumor. Accurate needle and tine position was confirmed with CT imaging before the initiation of RFA. Treatment was performed with the intent to complete a radius of ablation 5–10 mm larger than the largest lesion diameter to achieve necrosis with a clear ablative margin around the tumor. In all cases, grounding was achieved with the appropriate pads for each device and RFA protocol was completed according to the manufacturer's instructions. Tract ablation was performed routinely. A limited non-contrast CT was obtained through the lesion post-ablation to evaluate for bleeding at the treatment site. No contrast was administered and no immediate re-ablations were performed.

Follow-up

An early baseline CT was performed within 6 weeks after RFA to assess treatment response. No standardized follow-up was enforced, but most patients in both groups underwent repeat imaging at 3 or 6 month intervals for the first 2–3 years after ablation/resection. Serial imaging studies were retrospectively reviewed by a single radiologist (CTS) for evidence of local tumor progression. Persistent or recurrent tumor at or adjacent to the ablation site or resection margin was categorized as "true" local liver tumor progression, whereas progression at other sites in the liver was categorized as "other" liver recurrence.

Survival estimates were calculated using the Kaplan–Meier method and compared using the log-rank test. Comparisons between the RFA and Wedge group were performed using the Chi-squared test for dichotomous

variables, the Student's *T* test for continuous variables, and the Mann–Whitney *U* test for nonparametric variables.

Results

Patient Characteristics and Short-Term Outcomes

From 1992–2002, 1,144 patients underwent liver resection for metastatic colorectal cancer; 580 of these patients had solitary liver metastases. Only 30 patients (2.6% of total) were identified who underwent nonanatomic wedge resection of a solitary liver metastasis. All were resected with negative margins. We identified 22 patients who underwent percutaneous RFA of a solitary liver metastasis from 2000 to 2004. The indications for percutaneous RFA were prior major hepatectomy in 11 patients (50%), major medical comorbidities in 9 patients (41%), and relative unresectability in 2 patients with deeply situated tumors that would have necessitated an excessive sacrifice of normal parenchyma for resection.

The characteristics of patients in the two groups are shown in Table 1. The groups were similar in age, but patients in the RFA group were more likely to be female and were treated more recently. The groups were similar with respect to preoperative comorbidities, as measured by the Charlson index[21]. Patients in the RFA group were more likely to have undergone prior liver resection and were more likely to have a disease-free interval (DFI) of greater than 1 year both from their primary colorectal tumor resection and their last resection, whether primary or recurrence ("true" DFI). Patients in the Wedge group were more likely to have extrahepatic disease other than their primary disease. One patient in the RFA group had stable small lung lesions; four patients in the Wedge group underwent prior or concurrent resections of extrahepatic lesions (two lung, one ovary, one adrenal). Patients in the RFA group were more likely to have an elevated CEA level

Table 1 Characteristics of Patients Undergoing Wedge Resection or RFA for Solitary Colorectal Liver Metastasis

Characteristic		Wedge (*N*=30)	RFA (*N*=22)	*P*
Age	Mean (±SD)	63 (±9.6) years	62 (±7.5) years	NS
	Median (range)	62 (42–81) years	62 (48–77) years	NS
Gender	Female	10 (33%)	14 (64%)	0.02
	Male	20 (67%)	8 (36%)	
Charlson index	Median (range)	6 (6–8)	6 (6–9)	NS
Year of treatment	Median (range)	1996 (1992–2002)	2003 (2000–2005)	<0.01
Prior liver resection	Yes	7 (23%)	12 (55%)	<0.01
Number of prior liver resections	0	23 (77%)	10 (45%)	0.03
	1	5 (17%)	11 (50%)	
	2	2 (6%)	1 (5%)	
DFI from resection of primary	Median (range)	6 (0–79) months	23 (7–83) months	0.01
	<1 year	17 (57%)	5 (23%)	0.01
	>1 year	13 (43%)	17 (77%)	
DFI from most recent resection (primary or recurrence)	Median (range)	6 (0–62) months	17 (7–63) months	0.01
	<1 year	17 (57%)	6 (27%)	0.03
	>1 year	13 (43%)	15 (73%)	
Extrahepatic disease	Yes	4 (13%)	1 (5%)	0.02
Tumor diameter	Mean (±SD)	2.7 (±1.1) cm	2.4 (±1.0) cm	NS
	Median (range)	2.5 (1.0–5.0) cm	2.0 (1.0–5.0) cm	NS
Node-positive primary	Yes	15 (56%)	12 (50%)	NS
Pre-treatment CEA level	Normal	13 (43%)	3 (14%)	<0.01
	>5–200 ng/ml	8 (27%)	15 (68%)	
	>200 ng/ml	0	1 (5%)	
	Not available	9 (30%)	3 (14%)	
Clinical risk score[a]	0	3 (10%)	8 (36%)	NS
	1	14 (47%)	8 (36%)	
	2	4 (13%)	3 (14%)	
	Not available	9 (30%)	3 (14%)	

SD Standard deviation, *DFI* disease-free interval, *NS* not significant

[a] One point for each of the following: tumor diameter greater than 5 cm, node-positive primary, DFI less than 1 year, more than one tumor, and CEA level greater than 200 ng/ml

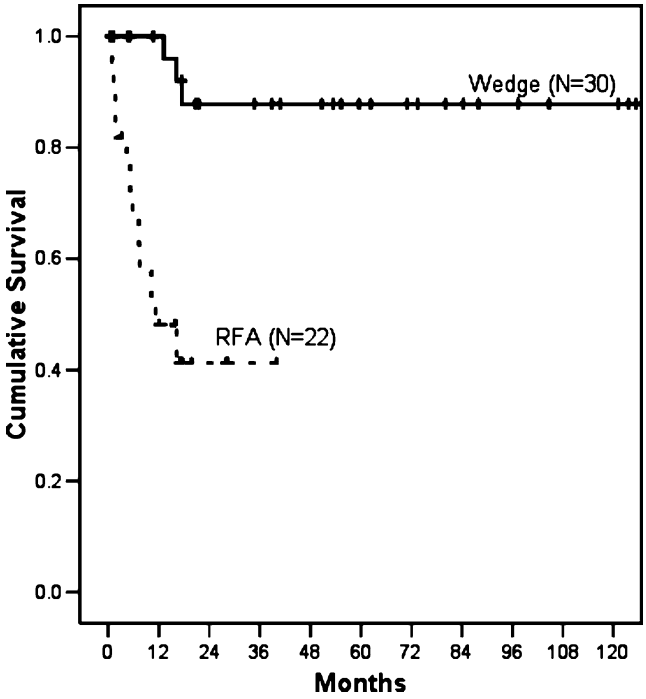

Figure 1 True local tumor progression-free survival in patients who underwent wedge resection or percutaneous RFA for solitary colorectal liver metastases.

before treatment, but the groups were similar with respect to tumor diameter, lymph node status of the primary, and Clinical Risk Score as described by Fong et al.[2]

RFA was associated with a lower incidence of major complications (4 vs 14%, $P<0.01$) and shorter hospital stays (1.3 vs 8.1 days, $P<0.01$). There were no deaths within 30 days in either group. Over two-thirds of patients in the Wedge group received first-line "adjuvant" systemic chemotherapy with 5-fluorouracil (5-FU) and leucovorin after resection, with the addition of either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) since 2000. The majority of patients in the RFA group had previously received first-line systemic chemotherapy; approximately half were observed immediately after ablation, and half were treated with second-line or investigational chemotherapy regimens.

Progression and Recurrence

True local tumor progression-free survival (PFS) at the ablation/resection site at 1 year was 96% in the Wedge group and 48% in the RFA group ($P<0.01$; Fig. 1 after a median follow-up, 68 and 17 months in surviving patients, respectively. Two-year true local tumor PFS was 88% in the Wedge group and 41% in the RFA group. There were no significant differences in local tumor progression based on tumor size, DFI, pretreatment CEA, or primary nodal status. Although follow-up is relatively immature in the RFA group, there were no patients identified with true local tumor progression identified beyond 2 years.

Two patients in the RFA group underwent re-ablation, and two patients underwent resection to improve "assisted" true local tumor disease-free survival (DFS) to 62% at 1 year and 55% at 2 years. Two patients were re-ablated at 8 and 11 months after RFA and are free of local disease at 9 and 15 months from re-ablation, respectively. One patient underwent resection 3 months after RFA and survived more than 3 years without local disease progression. Another patient underwent resection 7 months after RFA and recurred at the resection margin 3 months later. A fifth patient with cirrhosis has undergone re-ablation twice with persistent hypermetabolic activity on positron emission tomography (PET) scan and was not considered to have been rendered disease-free by re-ablation.

Overall liver PFS rates at 2 years were 66 and 37% ($P<0.01$; Fig. 2). Long-term liver PFS was 50% in the Wedge group, with the curve reaching a plateau at approximately 5 years. Of the 12 patients in the RFA group with true local tumor progression, 3 had progression at other sites in the liver before or concurrent with local tumor progression, and one had concurrent extrahepatic recurrence. Only one patient in the RFA group had an isolated progression at another site in the liver.

Median overall PFS was 48 months in the Wedge group and 7 months in the RFA group ($P<0.01$; Fig. 3). Unlike true local tumor progression and overall liver progression,

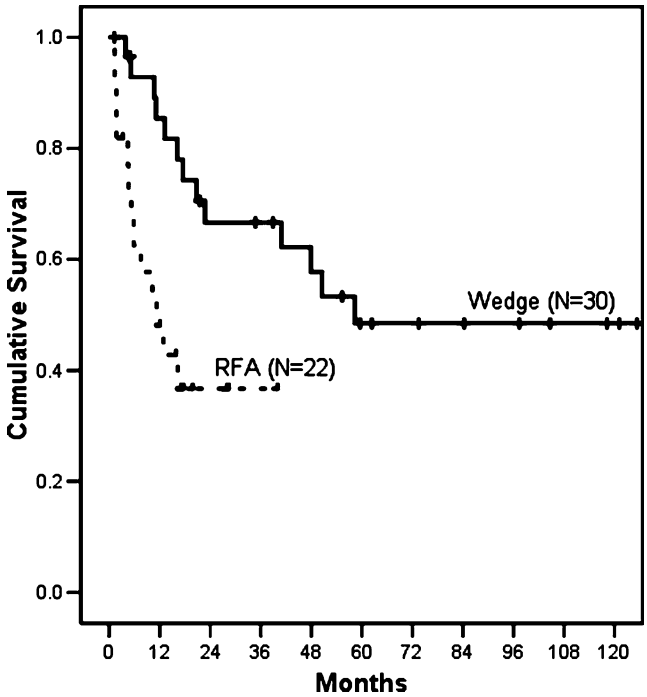

Figure 2 Overall liver progression-free survival in patients who underwent wedge resection or percutaneous RFA for solitary colorectal liver metastases.

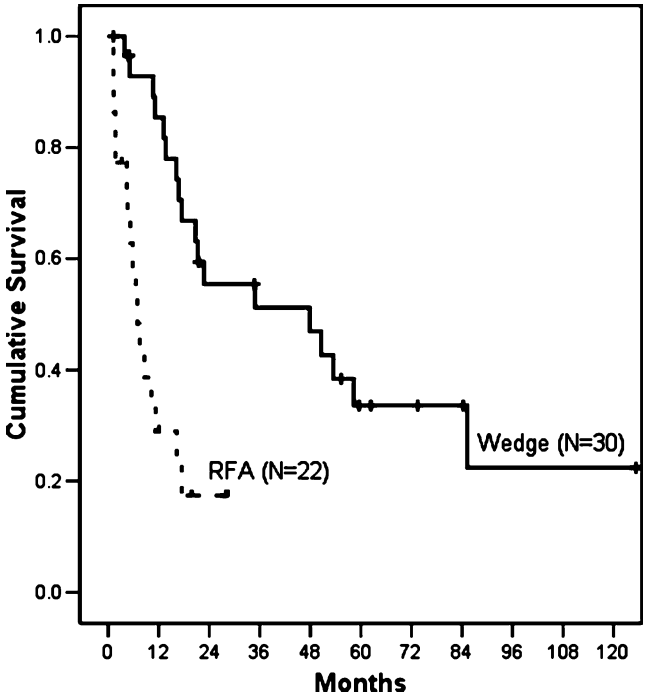

Figure 3 Overall progression-free survival in patients who underwent wedge resection or percutaneous RFA for solitary colorectal liver metastases.

extrahepatic recurrences continued to occur beyond 5 years, with the latest being a lung metastasis at 7 years after Wedge resection.

The first sites of disease progression are listed in Table 2. Approximately 30% of patients in each group presented with distant metastasis as a component of their first recurrence. A third of patients in the RFA group had isolated local tumor progression as their first site of progression, and an additional 15% had first sites of progression at other sites in the liver with or without local tumor progression. In contrast, no patient in the Wedge group had isolated local tumor progression, although 30% had first sites of progression elsewhere in the liver with or without local tumor progression. Four patients in the RFA group are alive with no evidence of disease at 3, 12, 20, and 28 months of follow-up.

Median overall survival from the time of resection in the Wedge group was 80 months with 40% 10 year survival. Despite the high rates of local tumor progression, median overall survival from the time of ablation in the RFA group was 31 months (Fig. 4). However, overall survival from the treatment of the primary colorectal tumor was not significantly different between the two groups (Fig. 5).

Discussion

A limited number of studies have specifically examined RFA for potentially resectable disease, as summarized in Table 3. In a bi-institutional nonrandomized prospective trial reported by Livraghi et al., percutaneous RFA was performed on patients who were "potential candidates" for resection with no more than three lesions and a maximum diameter of 4 cm[11]. Complete ablation was achieved in one session in only 37 (42%) and two sessions in 16 (18%) of the total 88 patients. Twenty of the 35 patients with persistent local disease underwent resection, and no patient became unresectable because of the growth of the ablated lesion, only because of the development of new lesions or extrahepatic disease. A British study by Oshowo et al. retrospectively compared percutaneous RFA to resection for solitary liver metastases. No data on true local disease progression were provided, but overall survival rates were comparable at 3 years in this small study[20]. A recent study from M.D. Anderson Cancer Center (MDACC) by Aloia et al. retrospectively compared RFA, performed using a predominantly open approach, to predominantly anatomic resection for solitary liver metastases[22]. In contrast to the British study, significantly better local disease-free, overall disease-free, and overall survival rates were seen in the resection group.

In the current study, true local liver disease progression after percutaneous RFA was common. Tumor-dependent factors, which were associated with local disease progression have included size and proximity to major blood vessels[7,8,15,16]. These factors do not account for the higher

Table 2 Sites of First Disease Progression for Patients Undergoing Wedge Resection or RFA for Solitary Colorectal Liver Metastasis

Sites of first disease progression		Wedge (N=30)	RFA (N=22)
Liver only	True local liver only	0	8 (36%)
	Other liver only	8 (27%)	1 (5%)
	Local + other liver	1 (3%)	2 (9%)
Extrahepatic	Any liver + extrahepatic	4 (13%)	1 (5%)
	Extrahepatic only	5 (17%)	5 (23%)
None		9 (30%)	4 (18%)
Unknown		3 (10%)	1 (5%)
Median follow-up		68 months	17 months

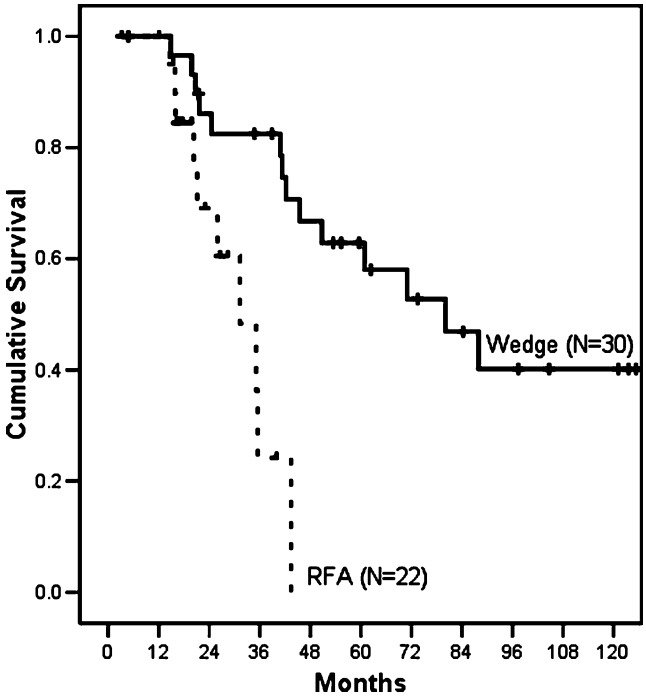

Figure 4 Overall survival in patients who underwent wedge resection or percutaneous RFA for solitary colorectal liver metastases.

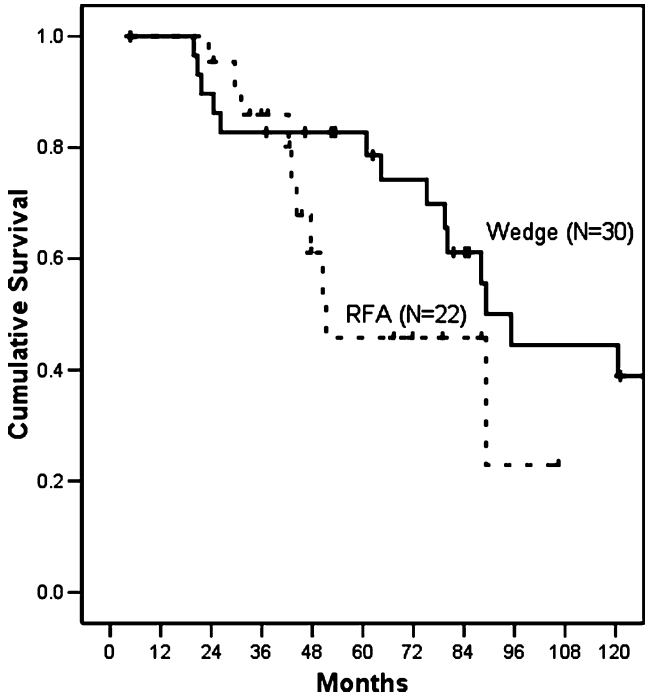

Figure 5 Overall survival from the treatment of the primary colorectal tumor in patients who underwent wedge resection or percutaneous RFA for solitary colorectal liver metastases.

rate of local disease progression in this study, as all patients had relatively small tumors (median 2 cm, maximum 5 cm), and only one patient had proximity to a major blood vessel. It has been proposed that probe positioning may be less accurate with percutaneous than intraoperative RFA, which allows mobilization of the liver and better access to lesions high in the liver[14,15]. In a recent meta-analysis of over 5,000 patients in 95 studies of RFA, local disease progression rates were significantly higher with the percutaneous approach, independent of tumor size[14]. However, the local disease progression rate in the current study is higher than those reported in other recent studies of percutaneous RFA, which have ranged from 9 to 47%[8,10,11,15,16,23]. In the early experience reported in this study, only limited non-contrast CT imaging was performed post-ablation to evaluate for bleeding. No contrast was administered, and no immediate treatment was undertaken based on imaging findings consistent with incomplete ablation. This may partially explain the high rate of local disease progression that was observed in this series. We have changed our protocol and currently perform immediate post-ablation contrast CT imaging and re-ablate margins as needed. However, patient-dependent factors probably contributed the most to this high rate of local disease progression. Nonrandomized comparisons between surgical and nonsurgical patients are inherently limited by numerous selection biases. The authors take an aggressive approach to resection (and

Table 3 Studies of RFA for Potentially Resectable Colorectal Liver Metastases

Author (year)	Technique	Median follow-up	Local disease progression	Overall survival	Inclusion criteria
Livraghi[11]	88 percutaneous RFA	33 months	40%	NR	≤3 lesions and ≤4 cm
Oshowo[20]	25 percutaneous RFA	Not reported	Not reported	53% at 3 years	Solitary
	20 anatomic resection	Not reported	Not reported	55% at 3 years	
Aloia[22]	27 open RFA 3 percutaneous RFA	31 months[a]	39%	27% at 5 years	Solitary
	147 anatomic resection		5%	71% at 5 years	
	13 wedge resection				
Current study	22 percutaneous RFA	17 months	55%	Median 31 months	Solitary
	30 wedge resection	68 months	12%	58% at 5 years	

re-resection) of colorectal liver metastases[24], and patients with solitary metastases who are not considered candidates for resection are a highly selected group and either have a high risk for recurrence or are medically unfit. This is perhaps best evidenced by the fact that over half of the patients in the RFA group had undergone prior liver resection. In contrast, the MDACC study did not include patients who had undergone prior liver-directed therapy (resection or ablation)[22], and no information regarding prior liver-directed therapy was provided in the British study[20].

Progression at other sites in the liver was also common after percutaneous RFA in this study, although not commonly as a first site of progression. At surgical exploration, recent studies have demonstrated that up to 40% of patients have unsuspected additional liver metastases, which would not be treated with percutaneous RFA[17–19]. These numbers will likely decrease as imaging continues to improve. However, this is an obvious disadvantage of percutaneous RFA compared to surgical approaches but one that may be outweighed by the advantage of being minimally invasive and easily repeatable.

Unlike the British study, in both the current study and the MDACC study, the differences in local disease-free survival appeared to translate to differences in overall survival from the time of treatment. A central question in the treatment of liver metastases is how much local control of hepatic disease impacts on a systemic disease. Although the impressive long-term survival rates seen after complete resection suggest that a local treatment can impact overall survival, it is unlikely that the dramatic difference in overall survival between the Wedge and RFA group in our study can be entirely attributed to local control. By selecting patients who underwent wedge resection rather than anatomic resection, we were attempting to minimize the disparities between the groups and to compare a local ablative therapy to a truly local resection. However, patients who underwent RFA were more likely to have undergone prior liver resection and to have an abnormal CEA. The similarity in overall survival between the two groups *from the treatment of the colorectal primary* also suggests that patients in the RFA group, who had a longer DFI from their primary and were more likely to have undergone prior liver resection, were being treated at a time point further along in the course of their disease.

Currently, there are insufficient data to support RFA as an *alternative* to resection in patients with resectable disease. A more appropriate question is whether RFA is beneficial as an *adjunct* to chemotherapy in unresectable patients or in resectable patients as part of a neoadjuvant approach. Several nonrandomized studies have suggested that survival rates in patients undergoing RFA are better than those historically reported patients for receiving chemotherapy alone[7,23,25]. In retrospective series from MDACC, patients undergoing open RFA for unresectable disease had better survival than a contemporary control group of patients with surgically staged liver-only unresectable disease who received chemotherapy only[26]. The Chemotherapy plus Local Ablation versus Chemotherapy (CLOCC) trial is a randomized phase II study being conducted by the European Organization for Research and Treatment of Cancer (EORTC) to help answer this question.

For patients with resectable disease, there are several rationales for neoadjuvant therapy before resection. In addition to potentially improving resectability, this approach provides a biological "test of time" for patients with adverse risk factors for recurrence such as multiplicity, short disease-free interval, and extrahepatic disease[27,28]. Particularly in this era of more effective chemotherapy, patients who actually progress on chemotherapy have a very poor prognosis, even after resection[29]. In the present study and the trial by Livraghi et al., the site of first tumor recurrence after treatment was extrahepatic in approximately 30% of patients[11]. Theoretically, these patients were spared the morbidity of a nontherapeutic liver resection. With vigilant follow-up, re-ablation, and/or resection to treat radiographically evident tumor progression, patients should not miss an opportunity for resection because of local disease progression. Disadvantages of this approach are that radiographic response to RFA obscures the response of the tumor to chemotherapy and that inflammatory response to RFA may make subsequent resection more difficult.

In conclusion, only a small percentage of patients with colorectal liver metastases are even candidates for RFA because of the number, size, or location of their tumors. For patients with resectable disease, surgical resection remains the gold standard treatment. For patients who are poor candidates for resection because of medical comorbidities, tumor location, or prior liver resection, RFA and other ablative therapies may help to manage local disease, but their value in addition to chemotherapy alone for these patients has not yet been proven. Percutaneous RFA was associated with a high rate of local disease progression; careful patient selection and close follow-up with aggressive re-ablation or resection are necessary to achieve optimal results.

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Hepatic Artery Chemoembolization in 122 Patients with Metastatic Carcinoid Tumor: Lessons Learned

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Abstract
Background Hepatic artery chemoembolization (HACE) is a treatment option in the management of metastatic carcinoid. We reviewed our experience to identify potential factors that influence survival.
Methods The records of 122 patients with metastatic carcinoid tumor undergoing HACE were reviewed. Log-rank analysis and Cox proportional hazards were applied to identify factors predictive of decreased survival.
Results Median follow-up after HACE was 21.5 months. Complications occurred in 23% with periprocedural mortality of 5%. Radiographic tumor regression was seen in 82%, with stabilization of disease in 12%. Median duration of CT response was 19 months. Improvement in symptoms occurred in 92% for median duration of 13 months. HACE resulted in complete normalization of serum pancreastatin in 14%, with greater than 20% reduction in another 66%. Median overall survival was 33.3 months after HACE. Only pancreastatin level ≥5,000 pg/ml was associated with decreased survival by multivariate analysis.
Conclusion HACE offers symptom palliation and long-term survival in patients with incurable carcinoid metastases. Although safe, it should be approached cautiously in patients with significant tumor burden as evidenced by pancreastatin levels ≥5,000 pg/ml. We do not recommend whole-liver embolization in these patients but prefer a staged approach to each lobe of the liver.

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Introduction

Carcinoid is an indolent form of malignancy with a predilection for hepatic metastases.[1,2] When present, metastatic disease is rarely resectable for cure. This, coupled with the innate resistance to cytotoxic agents of carcinoid tumors, has led to the routine application of liver-directed embolic therapy to control tumor progression and palliate the symptoms of carcinoid syndrome (e.g., diarrhea, flushing, night sweats, wheezing, and right heart damage).[3–6] Hepatic artery embolization (HAE) and chemoembolization (HACE) have become the mainstay of regional therapy for patients with advanced carcinoid.[7,8] Whereas the two approaches have not been prospectively compared head-to-head, each has proven efficacy.

Our experience with percutaneous HACE for metastatic carcinoid began in earnest in 1992. We currently utilize this technique in patients who have symptoms that are difficult to control with octreotide therapy, radiographic evidence of progressive disease, or have a large tumor burden such that any progression may compromise hepatic function. We undertook this review of our experience to evaluate outcomes after HACE for metastatic carcinoid and to identify factors that might predict poor response to therapy and/or decreased survival.

Methods

Patients

From January 1992 through December 2004, 122 patients with inoperable hepatic carcinoid metastases underwent HACE for palliation of symptoms related to carcinoid syndrome or in attempts to slow tumor progression in the face of large tumor burden. Approval was obtained for this retrospective review from the Institutional Review Board of the Ohio State University.

Embolization Procedure

The decision for HACE was made based on two general criteria: the inability to control symptoms with octreotide therapy or high-volume/progressive hepatic tumor burden regardless of symptoms. Symptoms were typical of metastatic carcinoid and included diarrhea, flushing, palpitations, night sweats, wheezing, pain, and fatigue. HACE was considered in asymptomatic patients or those with well-controlled symptoms if there was radiographic evidence of tumor progression in the liver or if tumor burden was extensive enough that any progression would jeopardize hepatic function, thus making HACE contraindicated in the future.

Minimal eligibility criteria included tissue diagnosis of well- or moderately differentiated neuroendocrine carcinoma (carcinoid tumor), preserved hepatic (serum bilirubin levels <2 mg/dL) and renal function (serum creatinine <2 mg/dL), normal coagulation profile, and adequate hematologic profile (leukocyte count >2,000/ml and platelet count >100,000/ml). Patients with portal vein occlusion and absent hepatopetal flow were not offered HACE, but the presence of extrahepatic disease was not considered a contraindication. When possible, the entire liver was treated in one setting unless large tumor volume was noted. If a staged embolization procedure was planned, the lobe of the liver containing the *greater* tumor burden was addressed first. The timing of the subsequent HACE was dictated by the patient's symptoms, response, and toleration of the previous treatment. All treatment decisions were discussed in a multidisciplinary setting with the treating surgeons, medical oncologists, and interventional radiologists.

Patients were admitted in the morning of the procedure. Upon admission, all patients were started on a continuous intravenous infusion of octreotide at 35 μg/hour, which continued for 24 hours after the HACE. Prophylactic broad-spectrum antibiotics were routinely used. All procedures were performed by interventional radiologists in the angiography suite. Conscious sedation was utilized along with local anesthesia. A diagnostic angiogram was first completed via a femoral approach to review the anatomy and confirm the patency of the portal vein. Generally, a microcatheter was advanced through a five-french sheath via the common femoral artery into the hepatic artery of interest. After completion of the diagnostic digital subtraction angiogram, the chemoembolic agents (doxorubicin 30 mg, mitomycin 30 mg, cisplatin 50 mg, ioxaglate sodium, and ethiodized oil 37%) were injected. Additional embolic material (gelfoam, polyvinyl alcohol particles, or Embospheres [Biosphere Medical, Inc., Rokland, MA, USA]) were injected until flow in the hepatic artery ceased. Patients remained hospitalized for 3 to 5 days as their clinical recovery dictated.

Response Assessment

Radiographic, clinical, and biochemical responses to HACE were determined. Computed tomography (CT) was generally utilized to assess radiographic response to HACE. Radiographic response to therapy was determined as reduction in size and/or number of hepatic lesions as well as development of significant calcifications in the lesions. Any increase in size or number of lesions was considered progressive disease at any point during follow-up. Subjective symptom responses were obtained from the clinic chart based on patient and physician assessment. Worsening of symptoms or the requirement of higher doses of octreotide to control symptoms was considered progression of disease. Finally, serum pancreastatin levels were utilized to determine biochemical response to therapy. Complete response was considered as normalization (i.e., <135 pg/ml) of serum pancreastatin in a patient who had an elevated pancreastatin before HACE. A reduction of pancreastatin by 20% or more was considered a partial response,[9] whereas an initial increase by 20% or more was considered a progression. Stable disease was defined as an increase or decrease in pancreastatin by less than 20%. Any increase in pancreastatin after a nadir had been reached was considered as disease progression.

Statistics

Overall and progression-free survival curves were constructed using the Kaplan–Meier method and comparisons made using log-rank analysis. Overall survival was determined from the time of first HACE until death from any cause. Progression-free survival was calculated from the time of the first HACE until any progression event (i.e., radiographic, symptomatic, or serologic). Categorical data were compared by Fisher's exact test and continuous data were compared by Mann–Whitney *U* test. Logistic regression analysis was undertaken to identify predictors of response to therapy, whereas Cox Proportional Hazards analysis was used to determine prognostic variables. All statistical analyses were completed using SPSS v14.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Patients

Between 1992 and 2004, 122 patients with hepatic carcinoid metastases underwent HACE at The Ohio State University. The patients ranged from the very young to the very old, with a near-equal gender distribution (Table 1). Commensurate with their age, significant comorbidities including hypertension, diabetes, coronary artery disease, and chronic obstructive pulmonary disease were present in nearly half. The vast majority of carcinoids were gastrointestinal in origin, with 14% having no known primary. The majority originated in the small bowel or pancreas. The primary carcinoid was ultimately resected in 73, six of which underwent HACE first.

Most patients presented with symptoms of carcinoid syndrome, although some were asymptomatic at the time of diagnosis (Table 1). At the time of HACE, nearly all patients had radiographic evidence of bilobar hepatic disease, with over one quarter having evidence of extrahepatic disease as well. Pre-HACE serum pancreastatin levels were available in 101 patients, 98 of which were abnormally elevated (normal <135 pg/ml), yielding a sensitivity of 97%.

Table 1 Baseline Clinical Characteristics of 122 Patients

Clinical characteristics	Number
Total number of patients	122
Gender	60M/62F
Median age (yr)	54 (range, 16–87)
Comorbidities	65 (53%)
Location of primary*	
Small bowel	57 (47%)
Pancreas	26 (21%)
Lung	10 (8%)
Rectum	5 (4%)
Colon	4 (3%)
Stomach	3 (2%)
Unknown	17 (14%)
Resection of primary tumor	73 (60%)
Symptoms	
None	16 (13%)
Pain	4 (3%)
Fatigue	3 (2%)
Carcinoid syndrome	99 (81%)
Distribution of metastases	
Left lobe only	2 (2%)
Right lobe only	2 (2%)
Bilobar	118 (96%)
Extrahepatic	34 (28%)
Median pancreastatin level (pg/ml)†‡	2,120 (range, 20–249,000)

*Total does not equal 100% due to rounding.
†Normal pancreastatin <135 pg/ml.
‡Pre-HACE pancreastatin levels available for 101 patients

Table 2 Periprocedural Data for 122 Patients Who Underwent Hepatic Artery Chemoembolization

Data	Number
Total HACE procedures	156
Laterality of HACE	
Bilateral	92 (75%)
Right only	25 (21%)
Left only	5 (4%)
Complications	28 (23%)
Deaths	6 (5%)

Treatment Administered

A total of 156 HACE procedures were completed in our 122 study patients, with a mean of 1.3 per patient (Table 2). Thirty-three patients underwent at least two HACE procedures, with two patients having a third. Nine repeat HACE procedures were planned second-stage procedures, whereas the remainder was for recurrent/progressive disease. In most instances, the entire liver was embolized at one time.

Adverse Events

Twenty-nine complications occurred in 28 patients resulting in six deaths. The deaths were the result of multisystem organ failure (MSOF) in three, complications of gangrenous cholecystitis in one, myocardial infarction in one, and carcinoid crisis in one. The last patient underwent unilateral HACE of the right lobe after presenting with extensive bilobar and extrahepatic disease, rapid disease progression, poorly controlled symptoms on octreotide therapy, and a pre-HACE pancreastatin level of 249,000. Mortality was similar between patients who had bilateral and unilateral

HACE (4% vs. 7%, respectively, $p=0.64$). Patients with pre-HACE pancreastatin ≥5,000 pg/ml had higher periprocedural mortality (10% vs. 2%), but this did not reach statistical significance ($p=0.07$). Cardiac dysrhythmia was the most common complication occurring in five patients, whereas MSOF and transient encephalopathy occurred in four patients each. Carcinoid crisis occurred in three patients and was treated with continuous intravenous octreotide infusion. Intrahepatic abscess requiring percutaneous drainage occurred in two patients and transient renal insufficiency caused by acute tubular necrosis occurred without the need for dialysis in two. Two additional patients developed severe hypertension requiring continuous monitoring without long-term sequelae. Finally, congestive heart failure, severe chest pain, transient respiratory distress, severe hyponatremia, and stroke occurred in one patient each. Fatigue, right upper quadrant pain, and fevers after HACE are common and were not considered complications of the procedure. Complication rates were significantly higher after unilateral HACE compared to bilateral (37% vs. 18%, $p=0.048$).

Response to HACE

Median follow-up for all patients still alive after HACE was 21.5 months (Table 3). Post-HACE CT scans were available in 96 patients, 94% of which showed evidence of tumor regression or stabilization of disease. Six patients showed radiographic evidence of tumor progression after HACE. Five of these patients underwent HACE for large tumor burden or rapidly progressive disease and four of the six had unilateral treatment only. The presence of comorbidities was the only significant risk factor for lack of radiographic tumor regression by logistic regression analysis (RR 4.0 [95% CI 1.2–13.3], $p=0.02$). In those with regression or stable disease, the median duration of response was 19 months.

Symptom improvement was reported in 92% of patients and no patients reported worsening of symptoms (Table 3). Of the seven patients reporting no improvement in their symptoms, two underwent unilateral HACE and three had

Table 3 Radiographic, Symptomatic, and Biochemical Responses to Hepatic Artery Chemoembolization. Percentages are Calculated Based on the Number of Patients with Complete Data

Response	Number
Median follow-up (mo)	21.5 (range, 1–127)
CT response*	
Regression	79 (82%)
Stable	11 (12%)
Progression	6 (6%)
Median duration	19 mo
Symptoms†	
Improved	85 (92%)
Unchanged	7 (8%)
Worse	0
Median duration	13 mo
Serum pancreastatin‡§	
Complete response	14 (15%)
Partial response	60 (65%)
Stable	9 (10%)
Progressive	10 (11%)
Median duration	7 mo

Percentages are calculated based upon the number of patients with complete data.
*CT scan data available for 96 patients after HACE
†Does not include 16 patients without symptoms before HACE and 14 patients with incomplete data
‡Pre- and post-HACE pancreastatin levels available for 93 patients
§Total does not equal 100% due to rounding.

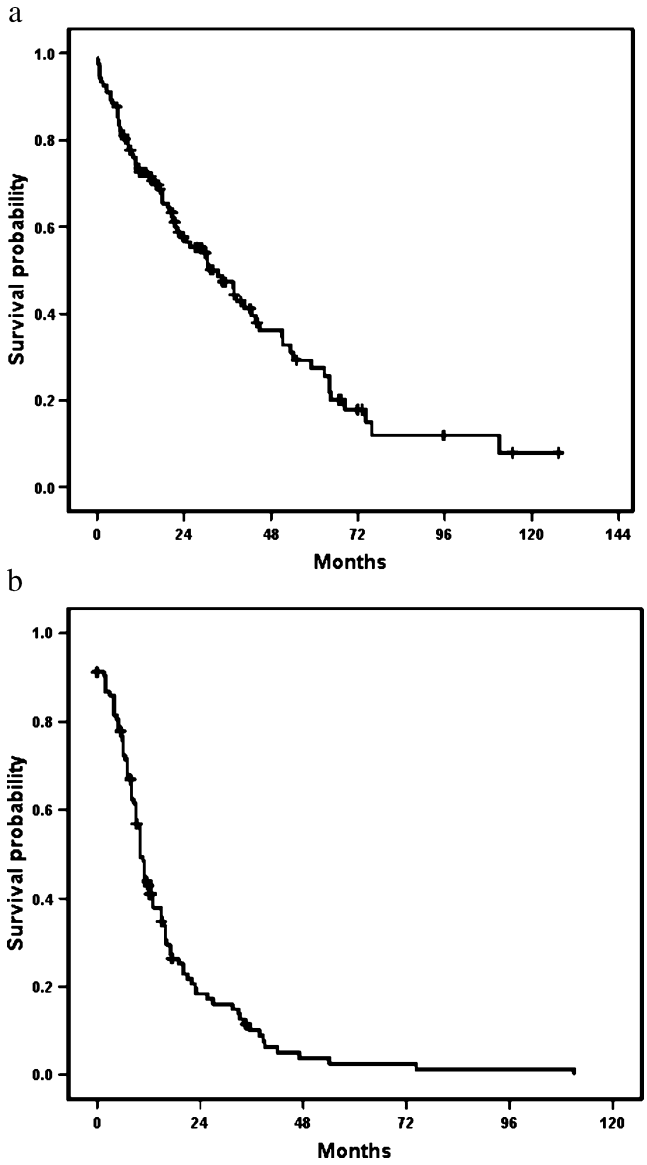

Figure 1 Overall (a) and progression-free (b) survival of 122 patients undergoing HACE for metastatic carcinoid.

Table 4 Evaluation of Pre-HACE Prognostic Factors for Decreased Overall Survival

	Univariate	Multivariate
Pre-HACE variables		
Age ≥50	0.425	0.384
Gender	0.668	0.508
Comorbidities	0.088	0.061
Location of primary	0.088	0.167
Resection of primary	0.067	0.078
Differentiation (well vs. moderate)	0.347	0.146
Extrahepatic disease	0.463	0.942
Carcinoid syndrome	0.405	0.072
HACE indication	0.761	0.484
Pancreastatin ≥5,000 pg/mL	0.019	0.005
HACE-related variables		
Unilateral vs. whole-liver HACE	0.882	0.642
Complications	0.005	0.356
No radiographic tumor regression	0.012	0.636
No symptom improvement	0.0005	0.018
<20% pancreastatin reduction	0.026	0.089

no radiographic evidence of tumor regression. Lack of symptom improvement correlated with lack of tumor regression by CT (Pearson's r=0.247, p=0.024).

Both pre- and post-HACE serum pancreastatin levels were obtained in 93 patients. HACE resulted in significant reduction in pancreastatin levels (median 2,120 pg/ml vs. 606 pg/ml, p=0.0001). In 13 patients with an elevated initial serum pancreastatin level, HACE resulted in a normal level representing a complete response to treatment and an additional 66% of patients had a reduction in pancreastatin by at least 20% (Table 3). Patients with a pre-HACE pancreastatin level less than 5,000 pg/ml were more likely to achieve a complete response than those with levels of 5,000 or more (OR 10.0 [95% CI 1.2–80.2], p=0.03), whereas more patients with a pancreastatin ≥5,000 achieved at least a partial response (94% vs. 71%, p=0.008). In total, 90% of patients had at least stabilization of their pancreastatin (Table 3). Median reduction in pancreastatin levels was 67% (5% to 99%). The average time to achieve this nadir was 3.5 months ± 4.3 and was durable for 10 months (Table 3). At least 20% reduction in pancreastatin levels after HACE significantly correlated with a radiographic reduction in tumor burden (Pearson's r=0.296, p=0.008).

Survival and Prognostic Factors

Kaplan–Meier survival curves for overall and progression-free survival (PFS) are shown in Fig. 1. Median PFS was 10.0 months (95% CI 8.5–11.5) based on clinical follow-up and median overall survival was 33.3 months (95% CI 22.3–44.4) based upon survival data obtained from the Social Security Death Index. The 2-, 5-, and 10-year PFS was 18%, 3%, and 0%, respectively, whereas overall survival was 58%, 28%, and 8%, respectively. Potential variables that may influence survival were divided into pre-HACE and post-HACE factors (Table 4). Before HACE, only pancreastatin levels of 5,000 pg/ml or greater were predictive of decreased survival by univariate and multivariate analysis (RR 2.6 [95% CI 1.3–5.0]). Median survival for patients with pre-HACE pancreastatin level <5,000 pg/ml was 40.7 months (95% CI 22.4–59.0) compared to 22.9 months (95% CI 17.9–27.9) for those with pancreastatin levels ≥5,000 pg/ml (p=0.019; Fig. 2, top panel). After HACE, the occurrence of a complication or lack of radiographic, symptomatic, or biochemical response were associated with decreased overall survival

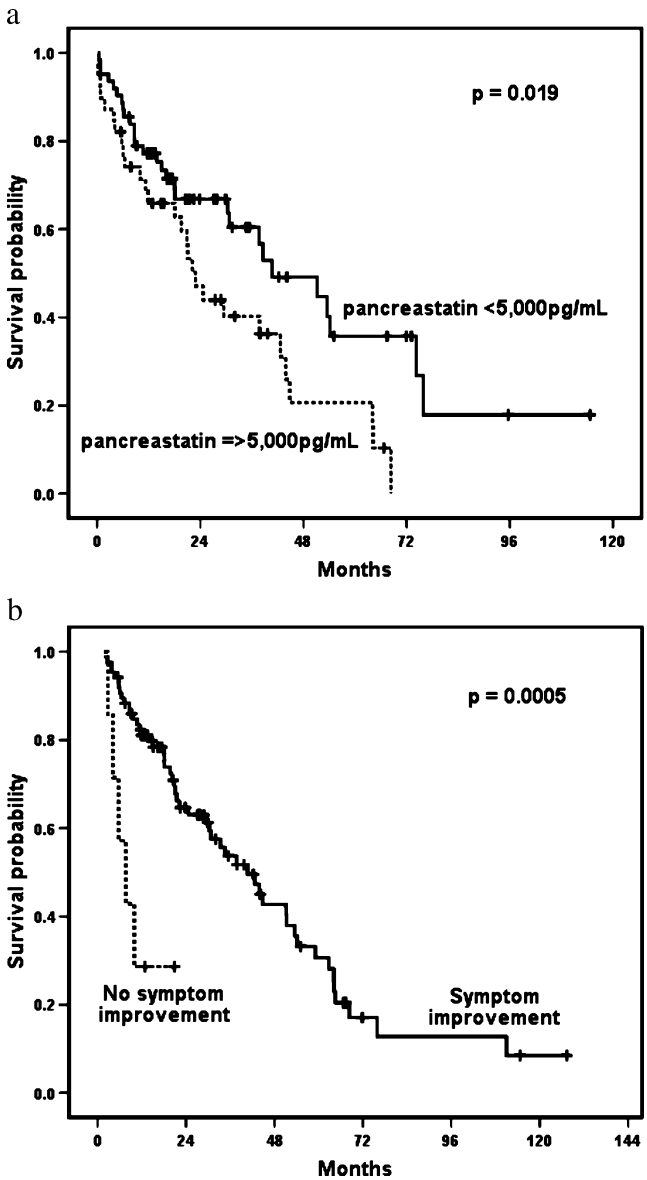

Figure 2 Overall survival following HACE based on preoperative serum pancreastatin levels (a) and symptom response to HACE (b).

(Table 4). Only the lack of symptom improvement was significantly predictive of poor outcome by multivariate analysis (RR 4.6 [95% CI 1.3–16.3]). Patients with improvement in their symptoms after HACE had a median survival of 40.7 months (95% CI 29.6–51.8) compared to 7.6 months (95% CI 2.7–12.6) in those who had no change in their symptoms (p=0.0005; Fig. 2, bottom panel).

Discussion

Although not curable, long-term survival is possible in patients with metastatic carcinoid. Given the predilection for carcinoid to metastasize to the liver whether they arise in the lungs or the gastrointestinal tract and their resistance to systemic chemotherapy, liver-directed therapies such as HAE and HACE are logical treatment modalities. Still, few institutions have amassed a large enough experience to make meaningful conclusions about the efficacy of these approaches. Herein we report the largest experience to date with HACE for metastatic carcinoid.

Our patient population was similar to those that have been reported.[10–12] Patients selected for HACE were not candidates for curative resection or palliative debulking as a result of extensive liver involvement, which would preclude removal of at least 90% of the tumor volume.[13,14] The bulk of the primary tumors were gastrointestinal in nature and, of these, mostly derived from the midgut. The location of the primary, when considered organ by organ or grouped by embryologic origin, did not significantly impact response rates or survival. Whereas others have suggested that the location of the primary may impact survival, these studies do not compare location in the population with known metastatic disease.[1,2,15] In a recent review of the M.D. Anderson experience, Gupta et al. reported a survival disadvantage for islet cell tumors compared to carcinoid after liver-directed therapy.[11] The heterogeneous make-up of the islet cell tumors in that study, however, makes definitive conclusion about the true impact of a pancreatic primary difficult. The impact of resection of the primary lesion is more debatable. Yao et al suggested that, in their population of 45 patients who underwent HACE or resection, resection of the primary was associated with a significant survival advantage, particularly if resected before the need to address hepatic metastases.[16] This finding may be more related to the biology of metachronous vs. synchronous disease, an issue that we did not address in this study. Still, three-quarters of our patients had resection of their primaries at some point before or after HACE, which did not prove to be a predictor of survival. The frequency of resection of primaries is much higher than the 30–50% reported in other studies.[10,12,17] This is likely related to the low incidence of unknown primaries in our study and our aggressive approach to removing gastrointestinal tumors before obstruction.[18]

On average, less than two HACE procedures were completed per patient. This is substantially less than the two to three per patient reported in other series.[10,11,13,16,17] Our approach to whole-liver HACE in one session likely accounts for this difference. The predominant preference for staged HACE relates to the risk of liver failure and prolonged recovery seen after whole-liver therapy. In our series, we did not see an increase in complications or deaths associated with bilobar HACE. In fact, unilateral embolization resulted in twice as many complications as bilateral. However, this likely reflects a selection bias as patients with high-volume disease were more likely to have unilateral therapy. Patients with higher volume of tumor or more hormonally active tumor as indicated by a pre-HACE pancreastatin level ≥5,000 pg/ml showed a trend toward higher peri-procedural mortality.

All-in-all, HACE was safe, but certainly not innocuous, given the 23% complication rate and 5% mortality rate. Postprocedural events such as fevers, pain, and fatigue are common after HACE[19] and, therefore, not considered complications. Whereas cardiac complications were most common, these are difficult to prevent but emphasize the need for in-patient monitoring after HACE. Hepatic insufficiency and/or MSOF are dreaded complications of HACE and are best prevented by patient selection. As such, there has been a trend in our practice toward more staged unilobar or even selective embolization in patients with high tumor burden. Whereas this may simply reflect the evolution of our referral patterns toward more advanced disease, our threshold for staged embolization is lower. Gangrenous cholecystitis is another feared complication that occurred in one of our patients and accounted for one of the deaths. It is our practice to undertake prophylactic cholecystectomy only in coordination with other operations and not as a separate procedure.

The most common indication for HACE was symptom palliation, most commonly related to carcinoid syndrome. Nearly all of our patients (92%) experienced symptom improvement with many decreasing or even discontinuing octreotide usage. This compares favorably to other reports.[10,13,17] There does appear to be a link between symptom response, radiographic response, and biochemical response to HACE in our data set. Interestingly, symptom response is the only post-HACE factor that is predictive of survival as well. The duration of symptom response is even more difficult to quantify. For consistency purposes, we interpreted any increase in octreotide dosage or report of new or worsening symptoms, no matter how minor, as progressive disease. Whereas this may grossly underestimate the true durability of symptom control after HACE, it was the most objective criteria in this retrospective setting.

Our current prospective database more objectively defines symptom progression by having patients rate changes in their symptoms after each therapeutic intervention. Also, application of a neuroendocrine-specific quality of life questionnaire[20] will allow more meaningful conclusions.

Radiographic response to HACE is also difficult and, therefore, often not reported. The application of criteria set forth jointly by the World Health Organization, National Cancer Institute, and the European Organization for Research and Treatment of Cancer addresses changes in up to five target lesions plus nontarget lesions.[21] These "Response Evaluation Criteria in Solid Tumors" (RECIST) rely on clear measurement of target lesions and assume that changes in these target lesions are reflective of changes in all lesions within the entire organ. Whereas this is beneficial when comparing efficacy of systemic therapies, it has inherent flaws when comparing embolic or particle therapy where tumors may receive varying amounts of drug. It is not clear how RECIST should be applied when unilateral HACE results in regression on the treated side, whereas tumor progresses on the untreated side. Even less clear is how to address lesions that have developed calcifications or necrosis after treatment but have not changed in maximum diameter. With these questions in mind, we elected to rely on the overall interpretation of the attending radiologist in each case, which often included RECIST, and simply classify tumors as regressive, stable, or progressive. As such, at least stabilization of disease was seen in 94% of patients, which also correlated with other measures of tumor response. Obviously, this method of assessing response to HACE is potentially biased, again reflecting the retrospective nature of this study. Whereas we have adapted RECIST into our prospective database to maintain a common language, response to therapy and treatment decisions are still inevitably subjective and are therefore best discussed in a multidisciplinary setting.

We have relied on pancreastatin as the biochemical tumor marker of choice to monitor response to therapy for carcinoid. This split product of chromogranin A has been shown to be a sensitive marker in carcinoid and other neuroendocrine tumors.[22–25] Previously, we showed that a 20% reduction in serum pancreastatin correlated with improved outcome after HACE for carcinoid.[9] Using this same cutoff, responses were seen in 80% of patients including complete response in 14%. This response correlated with other measures of response as well as being predictive of improved survival by univariate analysis. Although pancreastatin response was not a significant prognostic factor by multivariate analysis, a pre-HACE pancreastatin level ≥5,000 pg/ml was highly predictive of decreased survival. Also, pancreastatin was highly sensitive for metastatic carcinoid (97%) before HACE in our patients.

Finally, overall and progression-free survival was evaluated. Median PFS was less than 1 year in our series. This is lower than what has been reported.[10,13,17,26] This is likely related to how progression is defined. Most reports define progression by either radiographic progression or symptom progression only. In our study, any increase in size or number of lesions by CT scan, any increase in pancreastatin after a nadir had been reached, any increase in symptoms, or death defined a progression event. Overall survival, on the other had, was similar to or longer than other smaller studies.[10,11,13,17,27–29] Before HACE, only serum pancreastatin ≥5,000 pg/ml was predictive of decreased overall survival. This holds true when those who died as a result of complications related to the procedure are excluded as well. We did not correlate the extent of radiographic tumor burden with serum pancreastatin level but presume that this is the most likely explanation for the differences in survival. Interestingly, although patients with a pancreastatin <5,000 were 10 times more likely to achieve a complete biochemical response after HACE, more patients with pancreastatin ≥5,000 achieved a ≥20% reduction in pancreastatin than those with a pre-HACE pancreastatin <5,000. This reflects significant reduction in tumor burden in these patients with very advanced carcinoid.

Conclusion

HACE is an effective therapy for symptom palliation and tumor control in patients with unresectable hepatic carcinoid metastases. Long-term survival is possible in this group of incurable patients, particularly those with lower tumor volume. In this lower risk group, HACE is quite safe and effective. Patients with high tumor volume as evidenced by serum pancreastatin ≥5,000 pg/ml are at a higher risk for periprocedural mortality and poor long-term outcome. Whereas the risk in these patients is not prohibitive, HACE must be approached carefully with consideration of staged unilateral or segmental HACE. The superiority of HACE over bland embolization and the optimal measure of response to therapy and outcome are issues that still need to be addressed in a prospective setting.

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A 30-Year Analysis of Colorectal Adenocarcinoma in Transplant Recipients and Proposal for Altered Screening

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Abstract
Purpose The risk of malignancy after solid-organ transplantation is well documented. However, the incidence and specific risk for colorectal adenocarcinoma, although previously proposed, has been difficult to calculate. We reviewed the University of Wisconsin transplant database for all cases of colorectal adenocarcinoma to assess the risk of this malignancy, as well as the need for improved screening in this population.
Methods The transplant database was queried using diagnosis codes for colorectal adenocarcinoma to configure a list of eligible patients. Exclusion criteria included: age less than 18 years at the time of transplant, diagnosis of colorectal cancer or patient death less than 12 months posttransplant, and pretransplant history of colorectal cancer or proctocolectomy. Statistical analysis determined overall incidence, age-specific incidence, and survival for this population.
Results A total of 5,603 kidney, liver, or combination transplants were eligible for analysis from 1966 through 2004. The mean follow-up was 9.3 years. We identified 40 cases of colorectal adenocarcinoma. Twenty-five of these cases (62%) occurred in kidney transplant recipients, 13 after liver transplant, and two after kidney–pancreas combination. Twenty-seven patients (68%) diagnosed with cancer have died, 12 of metastatic disease. The median survival postcancer diagnosis was 2.3 years. These results were compared to the National Cancer Institute Survival, Epidemiology, and End Results (SEER) database for colon and rectal cancer. The current age-adjusted annual incidence based on year 2000 census data is 0.053% (52.9/100,000), and the extrapolated 10-year incidence is 0.27%. The 10-year incidence in the transplanted cohort is 0.71% (incidence ratio=2.6). The 5-year survival postcancer diagnosis is 63.5% in the general population (SEER), vs. 30.7% in the transplant cohort. The SEER median age at diagnosis of colorectal adenocarcinoma is 72.0 years. Of the transplant recipients who developed cancer, the median age at diagnosis was 58.7 years (32.4 to 78.2), and 11 patients (27%) were diagnosed at or before age 50. In the U.S. population, the annual incidence of colorectal adenocarcinoma below the age of 50 is 0.0055% (5.52/100,000) and the 10-year extrapolated incidence is 0.11%. The 10-year incidence in the under-50 transplant cohort is 0.33% (incidence ratio=3.0). In this under-50 cohort, median time from transplant to cancer diagnosis was 7.8 years.
Conclusion The incidence of and 5-year survival after diagnosis of colorectal adenocarcinoma in transplant recipients is markedly different than the general population. Patients are often diagnosed at a younger age. With current screening guidelines, over 25% of at-risk patients would not be screened. We propose modifying these guidelines to allow earlier detection of colorectal cancer in this population.

Keywords Colorectal adenocarcinoma · Organ transplantation · Cancer

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Introduction

The solid-organ transplant population has a well-documented risk for certain malignancies. The first reports of soft-tissue and lymphoproliferative malignancy among renal transplant recipients date back to the late 1960s.[1,2] As the variety of transplanted organs has grown and long-term survival is now expected, the range and severity of neoplasms have become a formidable medical challenge. The reported

lifetime incidence of posttransplant malignancy varies, but overall the risk appears to be three to five times that of the general population.[3,4] The majority of these neoplasms are nonmelanoma skin and lymphoproliferative cancers, which differs significantly from the predominant tumors presenting in the general population.[5] However, the incidence of several other neoplasms, excluding cutaneous and lymphoproliferative disease, is also significantly increased.[6,7]

Included in these other neoplasms has been colorectal adenocarcinoma, although the true risk is less well characterized. European data, including Swedish and Danish studies, have documented an increased risk among solid-organ recipients, especially those post-liver transplant.[7,8] Australian and New Zealand transplant registries have confirmed these findings.[9] Interestingly, the data for American patients are less clear, with some studies demonstrating no increased risk.[5] Previous attempts to calculate colorectal cancer risk in the U.S. have utilized databases that include only transplant patients with cancer, and a true incidence therefore cannot be calculated.[5] Because the transplant database at the University of Wisconsin is prospective and includes data from over 5,000 transplant recipients, a more accurate calculation of the incidence, age at presentation, and survival of solid-organ transplant recipients diagnosed with colorectal cancer is possible and is the primary aim of this study. In addition, as a secondary aim, the information gained by this assessment allows further insight to the need for future screening alterations, because current guidelines are the same for transplant recipients and the general population.

Materials and Methods

The University of Wisconsin organ transplantation program has existed since 1966. A prospective database for these patients has evolved significantly since that time. In its current computerized form, it contains pre- and posttransplant information for abdominal solid organ and small bowel transplant recipients, as well as diagnosis codes for all types of secondary diagnoses and related follow-up. Approval for this review was granted by the University of Wisconsin Institution Review Board. The database was queried for all cases of colorectal adenocarcinoma among transplant recipients who were greater than 18 years of age at the time of transplant. The age at diagnosis, time from first transplant to cancer diagnosis, time from cancer diagnosis to death, and cause of death were subsequently identified. These variables were then used to calculate a 10-year colorectal cancer incidence and survival in this patient population.

To properly identify the population at risk, several exclusion criteria were utilized. Patients were excluded from the analysis if they: 1) were under the age of 18 at the time of their transplant, 2) did not have their first transplant at the University of Wisconsin (to properly calculate the length of time from first transplant to cancer diagnosis), 3) were diagnosed with colorectal cancer within the first 12 months of transplant (as this likely represented a pretransplant condition rather than a result of the transplant itself), 4) died within 12 months of transplant, 5) had a known preoperative diagnosis of colorectal cancer, prior adenomatous polyps, inflammatory bowel disease (IBD), and/or prior proctocolectomy, or 6) underwent combined heart or intestine solid-organ transplant.

These results were compared to the most appropriate data available from the National Cancer Institute's Survival, Epidemiology, and End Results (SEER) database. This database is composed of multiple epidemiologic reporting centers throughout the U.S., which were selected based on the region's ability to maintain a high-quality cancer reporting system. The total SEER population consists of approximately 26% of the total U.S. population and is assumed comparable in composition to the U.S. population overall. The database collects information from each reporting center on patient demographics, primary tumor site, stage at diagnosis, and follow-up. It is currently the best estimate of cancer incidence, age, and survival statistics for the U.S. population.

Because the incidence data in the SEER database is reported per year, it is difficult to compare the number of transplant patients who developed cancer during the follow-up period with the incidence in the general population. However, the 10-year risk by age group (decade) is available for the general population.[12] These data were plotted and the specific 10-year incidence was extrapolated from the graph using the mean age at the time of transplant. Similarly, this approach was repeated for comparison between the U.S. population and the transplant cohort under the age of 50. An incidence ratio was calculated as the Kaplan–Meier estimate of the 10-year cancer incidence in the transplant group divided by an estimate of the 10-year incidence from the SEER database.[10,11]

Statistics

All statistics were reviewed by a senior statistician (G.E.L.) Patient survival rates and free-of-colorectal-adenocarcinoma rates were estimated using the methods of Kaplan and Meier. The increase in risk of patient death associated with the posttransplant development of colorectal adenocarcinoma was estimated by employing a Cox proportional hazards model with a time-varying covariate. Continuous variables were summarized by reporting means ± standard deviations and discrete variables were summarized by reporting

percentages. All analyses were performed using SAS statistical software version 6.12, SAS Institute, Inc. (Cary, NC, USA).

Results

The University of Wisconsin transplant database includes 6,771 transplant recipients from 1966 through 2004. This population includes patients whose first recorded transplant was performed at the University of Wisconsin, as well as patients who had a subsequent transplant at UW after receiving their first organ at a different institution. After excluding 253 patients whose first transplant was not performed at the University of Wisconsin, 6,518 patients remained. An additional 26 patients were excluded who received combination heart or intestine solid-organ transplants, leaving 6,492 patients eligible for analysis. An additional 889 patients met our exclusion criteria as described in Materials and Methods (Table 1). These included 396 patients younger than 18 years of age and 477 patients who died within the first year after transplantation. Finally, 14 patients had a known preoperative diagnosis of adenocarcinoma, adenomatous polyps, inflammatory bowel disease (IBD), or prior proctocolectomy. However, the total number of patients in the transplant population who had either IBD or a history of colectomy was 101; all but 14 were previously excluded because of one of the other criteria listed above. Two patients were censored because of a diagnosis of colorectal adenocarcinoma within 12 months of transplant. Therefore, a total of 5,603 patients remained for inclusion in this analysis.

In the transplant recipient population overall, the mean age at transplant was 43.4 years, and the percentage of patients transplanted before age 50 was 67.6%. The mean length of follow-up was 9.3 years. Sixty percent of UW transplant recipients were male. The majority of patients were cadaveric kidney recipients (2,400 patients, 42.8%), with living-related kidney (1,249, 22.3%), living-unrelated kidney (303, 5.4%), kidney–pancreas (798, 14.2%), kidney–liver (17, 0.3%), and liver (836, 14.9%) comprising the remaining transplant types (Table 2). The overall survival for transplant recipients at the University of Wisconsin, including those patients with colorectal cancer, is 87.8% at 5 years and 71.0% at 10 years.

Among the 5,603 patients, a total of 40 cases of colorectal adenocarcinoma were identified. Of those who developed cancer, the median age at diagnosis was 58.7 years. Twenty-five of these cases (62%) occurred in kidney transplant recipients, 13 (32.5%) after liver transplant, and two (5%) after kidney–pancreas combination (Table 2). The median time from transplant to cancer diagnosis was 6.6 years, and 12 patients (30%) were diagnosed less than 5 years post transplant (Fig. 1). In the liver transplant population specifically, 103 patients (out of 836) were transplanted for primary sclerosing cholangitis (PSC); two of these patients were eventually diagnosed with colorectal adenocarcinoma, although they were screened aggressively preoperatively and were not found to have evidence of active ulcerative colitis or polyps. According to the SEER database, in the U.S. general population from 1998 to 2002, the median age at colorectal cancer diagnosis was 72.0 years. The age-adjusted annual incidence for the general population based on year 2000 census data is 0.053% (52.9/100,000). Based on the plot of 10-year risk by decade of life in the U.S. population, the 10-year incidence for a 43-year-old (mean age of transplant) is 0.27%. The 10-year incidence in the transplanted cohort is 0.71%. Therefore, the incidence ratio for cancer diagnosis in this group compared to the general population is 2.6. Twenty-seven patients (68%) diagnosed with cancer have died, 12 of metastatic disease. The median survival after colorectal cancer diagnosis was 2.3 years (Fig. 2). In the UW transplant recipient population overall, the diagnosis of colorectal adenocarcinoma results in a relative risk of death of 6.6 (4.3–9.3). The 5-year survival for all stages of colon cancer is 63.5% in the general population (SEER) compared to 30.7% in the transplant cohort (Table 3).

Considering only those patients under the age of 50, the mean age at transplant was 36.5 years. Among the 40

Table 1 Patient Demographics with Exclusion and Inclusion Criteria

Demographics and criteria	Number
Number of solid organ transplant recipients (1966–2004)	6,771
Non-UW first transplant	253
Combination heart or intestine with solid organ transplant	26
Less than 18 years old at time of transplant	396
Death within 1 year of transplant	477
Prior history of adenomatous polyps, adenocarcinoma, inflammatory bowel disease, or proctocolectomy	14
Diagnosis of adenocarcinoma within 1 year of transplant	2
Total patients remaining	5,603

UW=University of Wisconsin

Table 2 Relative Proportion of Patients by Transplant Type

	No. of patients	Relative proportion , %
Cadaveric renal transplants (n=5,603)	2,400	42.8
Living-related kidney transplants (n=5,603)	1,249	22.3
Living unrelated kidney transplants (n=5,603)	303	5.4
Liver transplants (n=5,603)	836	14.9
Kidney–liver transplants (n=5,603)	17	0.3
Kidney–pancreas transplants (n=5,603)	798	14.2
Kidney recipients with cancer (n=40)	25	62.5
Liver recipients with cancer (n=40)	13	32.5
Kidney–pancreas recipients with cancer (n=40)	2	5

transplant recipients with colorectal adenocarcinoma, 11 patients (27.5%) were 50 years old or younger (Fig. 3). In this subgroup of patients, the median age at cancer diagnosis was 42.4 years. In the U.S. general population (SEER), the age-adjusted annual incidence of colorectal adenocarcinoma in patients under 50 years old is 0.0055% (5.52/100,000). The 10-year risk for a 36-year-old in the general population is 0.11%. The estimated 10-year incidence in this 50-and-under transplanted group is 0.29% (11/3794). Therefore, the incidence ratio for transplant recipients under the age of 50 compared to people under 50 in the general population is 3.0. The median time from transplant to cancer diagnosis in this subgroup was 7.8 years, and the median survival post cancer diagnosis was 2.4 years. In all, 23/40 patients (58%) were either 50 years old or younger at the time of diagnosis, or were diagnosed with cancer within 5 years of their transplant.

Discussion

A significantly higher risk of developing neoplasia is noted in transplant recipients when compared with age-matched controls. The first such report dates back to 1968.[1] Since then numerous studies have documented this correlation, with estimates of three to five times the overall risk for malignancy, and a lifetime incidence of 6%.[3–5,7] Interestingly, most of these neoplasms differ from the predominant tumor types seen in the general population and are comprised mainly of nonmelanoma skin and lymphoproliferative cancers.[5,7,13] However, even after excluding these common posttransplant malignancies, the incidence of other neoplasia is also increased, with an overall relative risk of up to 3.4 times that of the general population.[9]

An increased risk for the development of colorectal cancer after solid organ transplantation has been previously suggested, primarily by European data. The Swedish cancer registry, which followed 5,931 solid organ recipients for an average of 6.8 years, identified 34 cases of colorectal adenocarcinoma.[7] Compared with the Swedish population overall, the incidence of colon and rectal cancer using

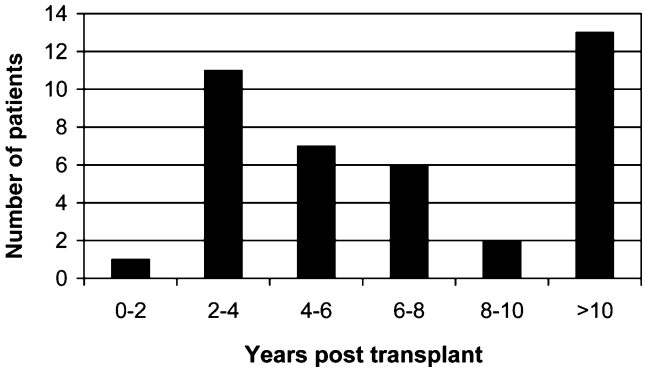

Figure 1 The length of time from transplant to cancer diagnosis was calculated for each of the 40 transplant recipients who developed colorectal adenocarcinoma. This was plotted in years post transplant and grouped into 2-year increments. Patients who developed cancer within 1 year of transplant were excluded from the total eligible patient pool due to the likelihood of a pre-existing condition. A total of 13 patients developed cancer 10 or more years post transplant (range 10.1–33.8).

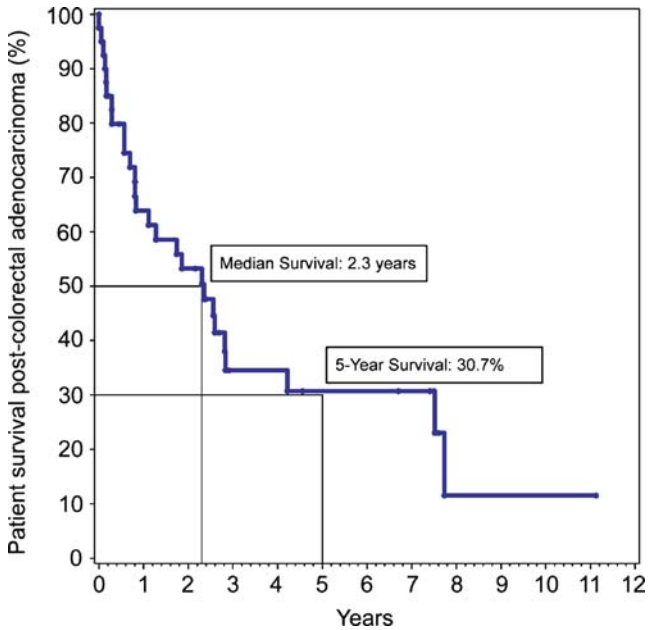

Figure 2 Kaplan–Meier curve depicting survival in the 40 transplant recipients who were diagnosed with colorectal adenocarcinoma. The 5-year survival and median survival are designated on the graph. In all, 27 out of 40 patients are dead, 12 of metastatic disease.

Table 3 University of Wisconsin Transplant Recipients versus US General Population

	Transplant recipients	US general population	Comparison (UW vs. SEER)
10-year overall incidence of colorectal adenocarcinoma	0.71%	0.27%	Ratio 2.6
Median age at cancer diagnosis	58.7 years	72.0 years	
5-year survival post cancer diagnosis	30.7%	63.5%	
10-year incidence in patients aged <50 years	0.33%	0.11%	Ratio 3.0

The SEER database was used for US population statistics
UW=University of Wisconsin; SEER=Survival, Epidemiology, and End Results database of the National Cancer Institute

standardized incidence ratios was approximately twofold higher in the transplanted group. In addition, they noted a predilection for right-sided cancers, with a standardized incidence ratio of 3.3 vs. 1.8 for left-sided colon tumors.[7] Other studies have determined the overall lifetime risk for colon cancer to be two to three times that of the general European population, especially more than 10 years post transplant.[14,15] Similarly, Birkeland et al. reviewed 5,692 renal transplant patients transplanted between 1964 and 1982 in Scandinavia and calculated male and female standardized incidence ratios of 3.2 and 3.9 for colon cancer compared to the general population.[4]

The combined New Zealand and Australian tumor registries also reported an increased risk for posttransplant colon cancer. The authors identified 38 cases of colorectal cancer among 6,641 renal transplant recipients, with a calculated risk ratio of 2.6 compared to the general population.[16,17] In contrast, conflicting evidence for this risk comes from a multinational database including more than 300 transplant centers worldwide. From this Collaborative Transplant Study, over 76,000 patients post heart or kidney transplant have been followed since 1983. In this analysis, a modest but not statistically significant increased incidence in colon cancer was observed.[18]

The incidence of colorectal cancer among transplant recipients within the U.S. is less clear. Previous estimates of this risk have utilized the Israel Penn International Transplant Tumor Registry, which is comprised of solid-organ transplant recipients with a diagnosis of malignancy. Early reports from this database did not specifically address colorectal cancer incidence, although 386 cases of colorectal cancer were identified among 10,667 transplant recipients.[5,19] As this database is comprised exclusively of transplant recipients with malignancy, a true cancer incidence is difficult to calculate. Because the University of Wisconsin transplant database is prospective for transplant recipients overall, a more reliable estimate of the incidence in this population is possible. Although a comparison of this incidence to that of the general population is difficult, our efforts to do so based on SEER database statistics for a similarly matched age group reveal an appreciably higher incidence in the transplanted cohort.

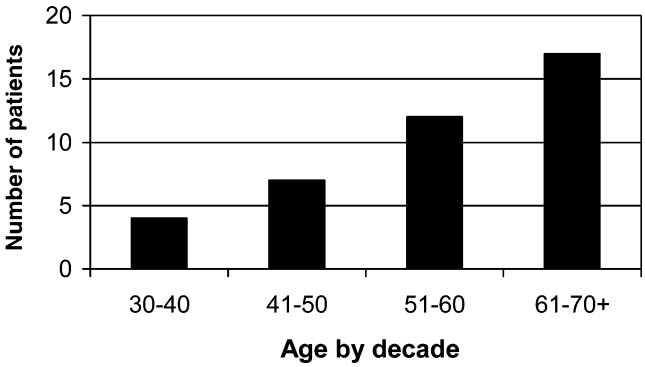

Figure 3 The age of each transplant recipient at the time of cancer diagnosis was determined for each of the 40 patients who developed colorectal adenocarcinoma. Note that 11/40 (27.5%) of patients were age 50 or less at the time of cancer diagnosis and would have been missed by current cancer screening guidelines.

Additional U.S. studies include a work by Agraharkar et al., who compared the risk of colorectal malignancy among 1,739 U.S. renal transplant recipients to the SEER database in a single institution retrospective review. A total of six cases of colorectal cancer were identified, and a standardized incidence ratio (SIR) of 1.5 was calculated.[6] Similarly, a single institution review of 556 U.S. renal transplant recipients identified three cases (0.5%) of colorectal cancer. All cases occurred in male patients over the age 50 without a history of prior screening colonoscopy. The mean time from transplant to cancer diagnosis in this study was 11 years. The authors concluded that there did not appear to be an increased risk of colorectal cancer when compared to the general population, although a more aggressive phenotype was observed.[20]

Regardless of the incidence, the behavior of these neoplasms does appear different in this immunosuppressed population. It has been previously noted in transplant recipients that squamous cell skin cancers act more aggressively and are diagnosed at a younger age.[5,21–26] Similarly, Papaconstantinou et al. found that transplant recipients developed de novo colorectal cancer at a younger age (58 vs. 70 years) and had a worse 5-year survival (43.5% vs. 62.3%), compared with NCI/SEER database statistics.[27] Our data also suggest that the behavior of colorectal cancer is more aggressive in this population. Of

those with cancer, the median age at diagnosis in our population was 58.7 years, compared to 72.0 for the U.S. population in general. The 5-year survival post cancer diagnosis was just 30.7% vs. 63.5% in the SEER database. In addition, more than 25% of transplant recipients diagnosed with colorectal adenocarcinoma in our database were younger than 50 years old. It is unclear whether this apparently more aggressive phenotype is a result of immunosuppression, later stage at diagnosis secondary to screening issues, or a combination of these and other factors.

Several theories have been proposed to explain the association between immunosuppression and malignancy. Immunosuppressive agents themselves have been identified as possible factors. For example, metabolites of azathioprine are known to sensitize the skin to sunlight and may increase the risk of skin cancer, and some agents such as azathioprine, cyclophosphamide, and cyclosporine may directly damage DNA.[5,22] Agents like cyclosporine and T-cell specific inhibitors such as OKT3 and ATG, while rescuing the patient from graft loss also create dysregulation of the body's natural antineoplastic defenses. Although the type or degree of immunosuppression was not the focus of this study, the most likely mechanism relating to the development of colorectal cancer is the body's inability to respond against natural carcinogens.[22] The degree of immunosuppression has been found to be an independent risk factor in the development of carcinoma, and in some cases the reduction in immunosuppression has been utilized as treatment after cancer diagnosis.[5] Similarly, it has been noted that chronic disease states requiring immunosuppression, such as rheumatoid arthritis and systemic lupus erythematosis, have higher rates of malignancy as well.[28]

If indeed immunosuppression is the reason for these findings, one would expect a greater risk in patient cohorts requiring higher doses of antirejection medication. Heart recipients, for example, have generally been maintained on stronger immunosuppressive regimens because allograft loss would result in death and several studies have found a higher cancer incidence in this transplant cohort.[7,29] However, if immunosuppression is the only factor, we would expect the incidence of all cancer types to be equally more common. Clearly, additional risk factors such as genetics, geography, and premalignant conditions are also important considerations. Finally, the time from transplant to diagnosis (duration of immunosuppression) may also be a significant factor. In European studies, the cumulative risk for developing any malignancy posttransplant was recorded as 13.6% at 10 years and 31.8% at 20 years.[7] In 124 cardiac transplant recipients, the cumulative cancer risk was 2.7 % at 1 year and 25.6% at 5 years.[30] In liver transplant patients, the overall risk of de novo malignancy was 6%, 20% and 55% at 5, 10, and 15 years of follow-up, respectively.[8] Although the prevalence of cancer increases with age in the general population as well, the incidence among transplant patients is clearly much higher.

Liver transplant recipients have been previously identified as being at risk for developing colorectal cancer. Proposed mechanisms have included liver dysfunction, which may expose the colon to carcinogens, or premalignant conditions such as ulcerative colitis often noted in patients transplanted for primary sclerosing cholangitis. Haagsma et al. found 21 malignancies among 174 liver transplant recipients, followed for a mean of 5.1 years in the Netherlands. Three cases of colon cancer were found with a calculated relative risk of 12.5 times that of the general Dutch population. Their series included 29 patients transplanted for primary sclerosing cholangitis (PSC) and 18 patients with ulcerative colitis, although a subgroup analysis did not find these patients at increased risk when compared to the remaining liver transplant recipients.[8] A recent review of the Pittsburgh liver transplant registry revealed 50 malignancies among 1,657 patients. Colon adenocarcinoma was identified in 3.1%, although premalignant conditions were not specified.[31] Bleday et al. discovered colon cancer or high-grade dysplasia in 3 of 27 patients who underwent liver transplantation for PSC. These patients all had negative pretransplant colonoscopies and developed neoplasia within 13 months of transplantation.[32] Similar findings were published by Loftus et al., who noted a 1% per person per year incidence of colorectal neoplasia in liver recipients transplanted for PSC.[33] Trotter et al. suggested that aggressive posttransplant surveillance, including annual colonoscopy with biopsy in patients with inflammatory bowel disease, and colonoscopy every 3 years in patients with adenomatous polyps, may improve disease-free survival in liver transplant recipients.[33,34] It seems likely that a correlation between PSC and ulcerative colitis places these patients at increased risk for eventual colorectal cancer development. In our analysis, we specifically excluded patients with known inflammatory bowel disease to more clearly demonstrate the direct association between transplantation and colorectal cancer risk. Even with this exclusion, our liver transplant recipients comprised 32.5% of the patients with cancer, but only 15% of the total transplant population. Out of 103 liver recipients in our series transplanted for PSC, two patients were eventually diagnosed with colorectal adenocarcinoma, although they were screened aggressively pre transplant and were not found to have polyps or active IBD. Therefore, we found no clear association between a history of PSC without IBD and eventual colorectal cancer.

In the present study, we identified a significant cohort of patients diagnosed with colorectal cancer at an age less than 50. Based on the mean age of all transplant recipients under age 50, we extrapolated a 10-year incidence from the SEER database. Upon comparison, transplant recipients under the

age of 50 were found to have a threefold greater risk of developing colorectal cancer. Because the current recommendations for screening transplant recipients does not differ from that of the general population, it is likely that several of these younger patients would be excluded from current colorectal cancer screening guidelines.[34,35] Most transplant centers, including the University of Wisconsin, now administer a preoperative colonoscopy to patients over age 50 and subsequent postoperative surveillance colonoscopy based on standard U.S. screening guidelines.[34,36] Unfortunately, most transplant registries seldom report whether aggressive or standard postoperative surveillance was administered. Similarly, our database does not record which of these patients received screening or surveillance colonoscopy appropriately. On the other hand, some might argue that many of these patients are actually screened more aggressively, and the higher rates of colorectal cancer are the result of selection bias. Current recommendations from the American Society of Transplantation are not different from that of the general population.[35] Therefore, there is little reason to believe that patients without documented prior disease or risk factors such as inflammatory bowel disease are screened differently than the general population.

Conclusion

Our data would suggest that the incidence of and 5-year survival after diagnosis of colorectal adenocarcinoma in transplant patients is markedly different from the general population. Although the median age at cancer diagnosis was 58.7 years of age, there is a significantly higher risk in those less than age 50 as well. In addition, it appears that these malignancies may behave more aggressively. Based on our findings, we would propose the following post-transplantation screening colonoscopy recommendations. Initial screening in existing transplant recipients should be performed within 2 years of the first transplant. For those not yet transplanted and older than age 50, a baseline pretransplant screening colonoscopy should be obtained (if not already done) along with a follow-up surveillance exam 2 years after transplant. In patients not yet transplanted and under the age of 50, a preoperative screening colonoscopy could also be considered, although more importantly, initial screening should begin within 2 years post transplant. Clearly, prospective, multiinstitutional data are needed to further clarify the ideal regimen and better define the time interval after initial screening. However, it seems a relatively short interval between screenings may be necessary. The impact of colorectal screening in the general population has been significant to date, and although this malignancy may present earlier and act more aggressively in transplant recipients, one may be comforted by the fact that more aggressive screening may continue to preserve this most precious gift in an at-risk population.

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Granulocyte Colony-stimulating Factor Supports Liver Regeneration in a Small-for-size Liver Remnant Mouse Model

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Abstract Experimental partial hepatectomy of more than 80% of the liver weight bears an increased mortality in rodents, due to impaired hepatic regeneration in small-for-size liver remnants. Granulocyte colony-stimulating factor (G-CSF) promotes progenitor cell expansion and mobilization and also has immunomodulatory properties. The aim of this study was to determine the effect of systemically administered G-CSF on liver regeneration and animal survival in a small-for-size liver remnant mouse model. Mice were preconditioned daily for 5 days with subcutaneous injections of 5 μg G-CSF or aqua ad injectabile. Subsequently, 83% partial hepatectomy was performed by resecting the median, the left, the caudate, and the right inferior hepatic lobes in all animals. Daily sham or G-CSF injection was continued. Survival was significantly better in G-CSF-treated animals ($P<0.0001$). At 36 and 48 h after microsurgical hepatic resection, markers of hepatic proliferation (Ki67, BrdU) were elevated in G-CSF-treated mice compared to sham injected control animals ($P<0.0001$) and dry liver weight was increased ($P<0.05$). G-CSF conditioning might prove to be useful in patients with small-for-size liver remnants after extended hepatic resections due to primary or secondary liver tumors or in the setting of split liver transplantation.

Keywords Liver regeneration · Granulocyte colony-stimulating factor · *In vivo* study · Rodent

Introduction

Intense regeneration and almost 100% survival follows partial hepatectomy (PH) of 70% of liver mass in rodents.[1–3] More extensive resections of 70 to 85% PH bear increased mortality due to impaired liver regeneration and the development of acute hepatic failure.[4–7]

Similarly, the human liver regenerates after hepatic resection. The size of the remaining liver tissue after resection is crucial for successful restoration of liver mass. In humans, a liver remnant of 45%, corresponding to at least 1.2% of body weight, results in excellent regeneration and uncomplicated recovery.[8] More extensive resections (i.e., 50 to 70% resections) with smaller liver remnants can cause impaired regeneration and subsequent hepatic failure. Therefore, 0.8% of body weight is currently considered the minimal weight of the liver remnant in patients undergoing hepatic resection.[8–11]

While liver regeneration after partial hepatectomy is a well-characterized phenomenon, the reasons for impaired regeneration in small-for-size liver remnants (i.e., <0.8% of body weight) are far from being understood.[3,12,13] Recently identified bone marrow-derived adult liver progenitor cells might play an important role in the pathophysiology of impaired liver regeneration.[14,15]

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Granulocyte colony-stimulating factor (G-CSF) promotes proliferation and mobilization of the bone marrow progenitor cell population.[16–18] Furthermore, G-CSF has antiinflammatory and antiinfectious effects.[16,19] Clinical data in humans indicate that G-CSF administration provides hepatic support during acute liver failure and is also beneficial after major surgical interventions.[19,20]

In rodent models of toxic liver injury, G-CSF accelerated recovery and improved animal survival.[21–23] From a surgical point of view, the support of hepatic recovery after extended liver resection is of crucial importance.[10,24] We hypothesized that G-CSF could provide such support in an experimental setting. Using a microsurgical small-for-size liver remnant mouse model (remnant liver weight below 0.8% of mouse body weight), we determined the effects of G-CSF on animal survival, on the number of nucleated bone marrow cells, and on hepatic regeneration.

Material and Methods

Adult male BalbC mice (n=102, 20–25 g, 6–8 weeks) were kept under standard conditions. All animal experimentation was approved by the local committee for animal welfare in accordance with the European Convention on Animal Care. Surgeries were performed as previously described.[25]

Experimental Groups

Animals were stratified in a G-CSF (n=53) and a sham-conditioned group (n=49). G-CSF animals received a daily subcutaneous injection of 5 μg G-CSF in 100 μl of aqua ad injectabile (Granocyte®, Aventis Pharma AG, Zurich, Switzerland) for 5 days preoperatively and daily after liver resection until the end of the experiment. Sham controls were injected daily with 100 μl of aqua ad injectabile.

Surgical Procedures

From a microsurgical point of view, the mouse liver consists of five lobes. For male adult BalbC mice, the relative weight of each liver lobe as a percent of the whole is known: the left lobe=34%, the median lobe=26%, the right superior lobe=17%, the right inferior lobe=15%, and the caudate lobe=8%.[25] For the 83% PH, the lesser omentum was incised and the caudate lobe resected. After incision of the left triangular and the falciform ligament, the left and the median lobes were resected. The pedicle of the right inferior lobe was exposed by incision of the ligament between the vena cava posterior and the anterior liver capsule. The pedicle of the right inferior lobe was then carefully ligated and the right inferior lobe excised.[7] The resected liver tissue and the entire mouse were weighed. Animals were kept under a warming lamp for 24 h postoperatively. To prevent postoperative hypoglycemia, 1.0 ml of 5% glucose (Bioren SA, Couvet, Switzerland) was injected subcutaneously.[6,26] Daily subcutaneous G-CSF and sham conditioning were continued.

Tissue Harvest

The regenerating liver was examined 36 and 48 h after 83% PH in 20 animals. 5-bromo-2'-deoxyuridine (BrdU, 50 mg/kg body weight, Fluka Biochemica, Buchs, Switzerland) was injected intraperitoneally 2 h before liver harvesting. Under inhalation anesthesia, animals were then killed and the remnant right superior liver lobe excised, weighed, and fixed in 4% formalin (Sigma, Buchs, Switzerland). Dry liver weight was determined 72 h after 65°C heat exposure. Tissue from the duodenum and testis served as positive controls for BrdU incorporation.

Immunohistochemistry (Ki67 Expression, BrdU Incorporation)

To measure hepatic proliferation, the expression of Ki67 and BrdU incorporation were determined in the right superior liver lobe at 36 and 48 h after 83% PH on paraffin-embedded tissue sections as described.[7] Briefly, before Ki67 staining, 2–3 μm paraffin-embedded sections were dewaxed, rehydrated, and pretreated by boiling in 10 mM citrate buffer, pH 6.0, in a pressure cooker. Sections were then washed in Tris-buffered saline (TBS) and incubated with a rat anti-mouse Ki67 antibody (clone TEC-3; Dako, Glostrup, Denmark) diluted 1:200 in TBS with 0.5% casein and 5% normal goat serum for 60 min at room temperature. Next, a 1:300 dilution of a biotinylated goat anti-mouse immunoglobulin antiserum (DakoCytomation, Glostrup, Denmark) was applied for 45 min. Thereafter, sections were incubated with an avidin–biotin-complex/horseradish peroxidase system (1:100 in TBS, Vector, Burlingame CA, USA) for 45 min. Finally, sections were developed in 0.1% 3,3′-diaminobenzidine (Sigma, St. Louis MO, USA) with 0.03% H_2O_2, counterstained with hematoxylin, and mounted. Ki67 positive and negative nuclei were counted in 10 high-power field microscopy images by two independent researchers, and the Ki67 labeling index was calculated from the data obtained.[27]

After BrdU staining,[7] BrdU positive cells in duodenal crypts and testis demonstrated systemic BrdU uptake and nuclear incorporation. Liver samples not treated with the primary anti-BrdU antibody served as negative controls. BrdU positive and negative cells were counted and the BrdU labeling index was calculated as described.[7]

Cell Isolation from the Adult Mouse Bone Marrow and Magnetic Cell Sorting of β_2-Microglobulin Negative/ Thy-1 Positive Progenitor Cells

Femoral bone marrow cells were harvested by aspiration through a 23-gauge needle (Venflon, Becton Dickinson, Fraga, Spain) as described,[28] filtered through a 30 μm filter (Nr. 130-041-407, Myltenyi Biotech, Bergisch Gladbach, Germany), and counted. To determine the amount of adult bone marrow-derived liver progenitor cells, β_2-microglobulin negative/Thy-1 positive cells were isolated according to a recently developed magnetic cell-sorting protocol and counted using a Neubauer counting chamber in a blinded fashion.[15,29]

Statistical Analysis

Results are expressed as mean ± standard deviation. Cumulative survival was analyzed according to Kaplan–Meier and survival curves compared by the use of the log-rank test. For normally distributed data, Student's *t* test was applied (Jandel Scientific 1.0, San Rafael, CA, USA), and for nonnormally distributed data the Mann–Whitney rank sum test was used. The significance level was set at $P<0.05$.

Results

The Small-for-size Liver Remnant Model (83% PH) in the Mouse

The amount of liver tissue resected corresponded to 3.8± 0.4% of mouse body weight in the sham-conditioned group and was not different in the G-CSF-conditioned group (3.9±0.3% of body weight, *t* test: $P=0.54$).

Cumulative Survival

The cumulative survival was determined according to Kaplan–Meier in G-CSF-conditioned ($n=35$) and in sham-conditioned animals ($n=33$). The survival curve is depicted in Fig. 1. By postoperative day 3 all animals of the sham-conditioned group were dead. G-CSF-conditioned animals survived significantly better (25.7% on day 7 and thereafter, log rank test: $P<0.0001$). A total of nine G-CSF-conditioned animals were censored 14 days after 83% PH.

Dry Liver Weight

Dry liver weight was significantly increased in G-CSF-conditioned mice (0.475±0.050% of body weight) when compared to sham-treated control animals (0.325±0.096% of body weight, *t* test: $P<0.05$) 36 h after 83% partial hepatectomy.

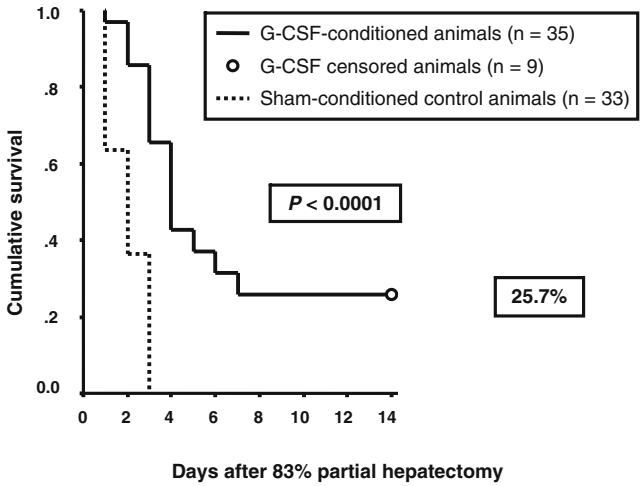

Figure 1 Cumulative survival (according to Kaplan–Meier) in G-CSF-conditioned mice and sham-treated control animals after 83% partial hepatectomy. Survival after extended 83% hepatic resection in mice was significantly better with granulocyte colony stimulating factor (G-CSF) conditioning. No sham-conditioned animals survived longer than 72 h after 83% partial hepatectomy, while 25.7% survival was observed in the G-CSF-conditioned group.

Markers of Liver Regeneration (Ki67 Expression and BrdU Incorporation)

Ki67 expression in hepatocytes was elevated in the G-CSF group at 36 h (2.8±2.6 vs 0.03±0.2%, rank sum test: $P<0.0001$) and at 48 h (45.1±34.6 vs 0.7±1.0%, rank sum test: $P<0.0001$) after 83% PH. BrdU labeling of hepatocytes at 48 h was 0.1±0.3% in the sham and 35.2±34.2% in the G-CSF group (rank sum test: $P<0.0001$; Fig. 2). No zone-specific BrdU-positive cell clusters were seen.

Isolation of Nucleated Cells from the Adult Bone Marrow

The total nucleated cell count of the adult femoral mouse bone marrow was $9.5 \pm 0.8 \times 10^6$ cells ($n=3$ for each experimental group and each time point) in sham-conditioned animals before hepatic resection, and significantly lower at $6.9 \pm 0.1 \times 10^6$ cells 24 h after 83% PH ($P<0.05$).

After 5 days of G-CSF preconditioning, $8.5 \pm 1.7 \times 10^6$ nucleated cells were present in the bone marrow (P=ns when compared to sham-conditioned control animals). At 24 h after 83% resection, the total number of nucleated cells rose significantly during hepatic regeneration in G-CSF-conditioned animals, to $13.4 \pm 1.4 \times 10^6$ cells ($P<0.05$ when compared to preoperative values, and $P<0.05$ when compared to bone marrow cell numbers in sham-conditioned mice 24 h after 83% PH).

Adult liver progenitor cells were purified by β_2-microglobulin negative and Thy-1 positive magnetic cell sorting. In sham-conditioned animals, 6.3±0.8% were identified before and 7.5±5.8% after 83% PH as β_2-microglobulin

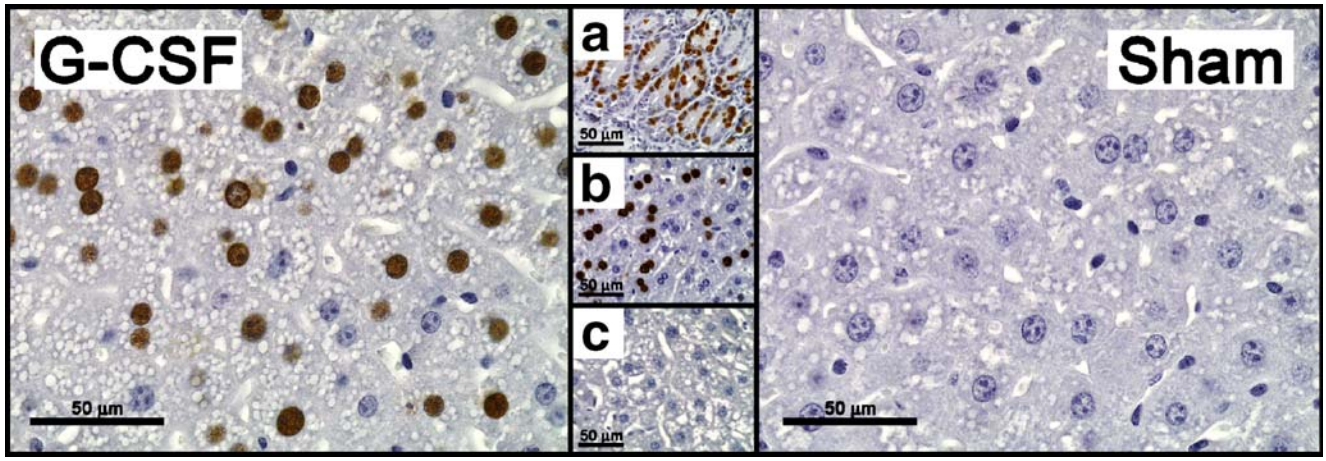

Figure 2 BrdU staining 48 h after 83% partial hepatectomy. While no BrdU positive cells were detectable in the sham-conditioned group, active liver regeneration, and positive BrdU staining were seen in G-CSF-treated animals. Duodenal tissue (a) served as an internal control to ascertain adequate BrdU uptake and incorporation. Liver samples after 70% partial hepatectomy served as positive (b) and negative (no primary antibody, c) controls.

negative/Thy-1 positive (P=ns). In G-CSF-conditioned animals, 5.4±4.3% of bone marrow cells were β_2-microglobulin negative/Thy-1 positive before resection and 5.8±2.1% were β_2-microglobulin negative/Thy-1 positive after 83% PH (P=ns).

Discussion

The microsurgical 83% PH mouse model is suitable for testing hepatic supportive regimens in the experimental setting of small-for-size liver remnants. Control mice showed impaired liver regeneration, hepatic encephalopathy, and consequent death within 3 days after 83% PH, as expected.[6,13,26]

In contrast, 25.7% of G-CSF-conditioned mice survived. Dry liver weight was significantly increased, and expression of the immunohistochemically measured markers of proliferation was significantly higher in the G-CSF group.

For clinical use, the described systemic G-CSF conditioning could under certain conditions allow more radical resections for primary or secondary liver tumors and support the small-for-size liver remnant during hepatic regeneration. This support could also be helpful in the setting of living related liver donation. Currently, a right hemihepatectomy is performed for adult living related liver donation and consequently around 65% of the liver is grafted.[30] The remaining 35% of the left liver should allow safe and uncomplicated hepatic regeneration for the donor. However, due to technical difficulties when performing right hemihepatectomies, including multiple anatomic variants of the portal triad and the hepatic veins or due to impaired hepatic regeneration, a 0.5% mortality is reported after living related liver donation in the donor population.[30] Due to limitations in the ratio of graft liver weight to recipient body weight, living donor liver transplantation of the left lateral segments II and III is so far mainly established in pediatric recipients. From the surgical point of view, this procedure is significantly safer than a right hemihepatectomy for the donor.[31] When the regenerative capacity of small split liver grafts could be augmented (i.e., by the use of G-CSF preconditioning), segmental liver transplantation from both cadaveric and living donors could be safely proposed for adult recipients as well.

On the other hand, the administration of growth factors to patients suffering from carcinomatous disease has to be critically assessed. Fortunately, 15 years of clinical experience have provided no convincing evidence that G-CSF causes malignant transformation or worsens the course of malignant disease.[32,33]

A distinct progenitor cell population was recently successfully isolated from adult rodent bone marrow by our group.[15,28,29] We expected that G-CSF might expand, activate, and mobilize the described β_2-microglobulin negative/Thy-1 positive bone marrow progenitor cells during regeneration of the small-for-size liver remnant. Nucleated bone marrow cells were therefore monitored before and after 83% PH. As expected, the total nucleated cell count was significantly elevated after 6 days of G-CSF conditioning.[18] But to our surprise, no alteration of the β_2-microglobulin negative/Thy-1 positive progenitor cell pool was detectable after 83% PH in either experimental group by the magnetic cell sorting procedure used. Furthermore, a typical pattern of progenitor cell support was not seen in the

G-CSF-conditioned regenerating liver samples and homogeneously distributed BrdU as well as Ki67 positive hepatic nuclei were found in the entire mouse liver lobes.[15,34] It is, however, possible that bone marrow progenitor cells supported liver regeneration by direct fusion, as described.[35] On the other hand, the observed G-CSF effect might be directly related to its recognized immunomodulatory properties and possibly improved neutrophil function,[19,20] thereby preventing typical systemic septic complications during the clinical course after extended liver resection.[8]

Conclusion

G-CSF supports liver regeneration and promotes survival in a small-for-size liver remnant mouse model. Additional human studies might prove that systemic G-CSF conditioning could be clinically valuable for the treatment of patients after major hepatic resections or in the setting of split liver transplantation.

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Gastroesophageal Reflux Disease and Obesity. Pathophysiology and Implications for Treatment

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Abstract Although the etiology of gastroesophageal reflux disease (GERD) is multifactorial, the pathophysiology of the disease in morbidly obese patients remains incompletely understood. The aims of this study were to compare in morbidly obese (body mass index (BMI) ≥35) and nonmorbidly patients (BMI <35) with GERD: (a) lower esophageal sphincter (LES) profile; (b) esophageal body function; and (c) esophageal acid exposure. We reviewed esophageal manometry and ambulatory 24-hour pH monitoring studies of 599 consecutive patients with GERD (DeMeester score >14.7). Patients were divided into two groups according to the BMI: (1) 520 patients (86.8%) with BMI <35 and (2) 79 patients (13.2%) with BMI ≥35. While the DeMeester score was not different between the two groups, morbidly obese patients had higher LES pressure and higher amplitude of peristalsis in the distal esophagus (DEA). Among these patients, LES and DEA pressures were often hypertensive. A linear regression model showed that BMI, LES pressure, LES abdominal length, and DEA were independently associated with the DeMeester score. These data showed that: (a) BMI was independently associated to the severity of GERD; and (b) in most morbidly obese patients with GERD, reflux occurred despite normal or hypertensive esophageal motility. These findings show that the pathophysiology of GERD in morbidly obese patients might differ from that of nonobese patients, suggesting the need for a different therapeutic approach.

Keywords Gastroesophageal reflux disease · Obesity · Esophageal manometry · Ambulatory pH monitoring · Bariatric surgery

Introduction

The prevalence of gastroesophageal reflux disease (GERD) has been increasing in the Western world, and it is presently as high as 20%.[1] At the same time, the prevalence of obesity has reached epidemic proportions, being almost 30% at the end of the last century.[2] Some studies have suggested a possible link between these two occurrences. A high body mass index (BMI) increases the risk of GERD[3–5] and there is a dose–response relationship between increasing BMI and prevalence of GERD and its complications.[4,6]

Although it is known that the etiology of GERD is multifactorial, the pathophysiology of the disease in morbidly obese patients remains incompletely understood.

The aims of this study were to compare in nonmorbidly and morbidly obese patients with GERD: (a) lower esophageal sphincter (LES) profile; (b) esophageal body function; and (c) esophageal acid exposure.

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Patients and Methods

This study is a retrospective review of prospectively collected data of patients referred to the Center for the Study of Gastrointestinal Motility and Secretions between

January 2003 and September 2005. We reviewed esophageal manometry and ambulatory 24-hour pH monitoring studies of 599 consecutive patients with GERD (DeMeester score >14.7). Patients were divided into two groups based on the BMI (kg/m^2): group A, BMI <35 and group B, BMI ≥35.

Patients with previous foregut surgery or named esophageal motility disorders were excluded from the study.

Symptomatic Evaluation

Every patient was questioned regarding the presence and severity of heartburn, regurgitation and dysphagia. Symptoms were scored using a 5-point scale, ranging from 0 (no symptom) to 4 (disabling symptom).

Esophageal Manometry

Patients were studied after an overnight fast as previously described.[7] Medications that might interfere with esophageal motor function (i.e., calcium channel blocking agents, nitrates, and metoclopramide) were discontinued at least 48 hours before the study. Position, pressure, and length of the LES were measured using the station pull-through technique. LES pressure was considered normal between 14–24 mmHg. Esophageal body function was assessed by giving 10 swallows of 5 ml of water at 30-second intervals. Distal esophageal amplitude (DEA) was considered normal when the mean pressure in the distal esophagus (sensors located 3 and 8 cm above the upper border of the LES) was between 60 and 140 mmHg. DEA was considered hypotensive if it was <60 mmHg and hypertensive if it was >140 mmHg.

The data were analyzed using a commercially available software program (Gastrosoft, Medtronics Functional Diagnostic, Shoreview, MN, USA).

Ambulatory 24-Hour Esophageal pH Monitoring

Acid-suppressing medications were discontinued 3 (H2 blocking agents) or 14 days (proton pump inhibitors) before the study. During the study, the patients consumed an unrestricted diet and took no acid reducing medications. Ambulatory pH monitoring was performed by placing a pH probe 5 cm above the upper border of the manometrically determined LES. The data were incorporated into a composite score (i.e., DeMeester score), which takes into account six elements: (a) number of reflux episodes; (b) number of reflux episodes longer than 5 min; (c) duration of the longest reflux episode; (d) percentage of time the pH is less than 4 for the total duration of the study; and (e) in the upright and (f) supine position. A score greater than 14.7 was set as abnormal based upon data obtained from 50 volunteers.[8]

Statistical Analysis

Student's *t* test was used for comparison of continuous variables, Chi-square test for categorical variables, and Mann–Whitney test for scores. We also constructed a linear regression model of the DeMeester score using a backward selection procedure. BMI was the predictor of interest. Covariates of age, gender, LES pressure, LES abdominal length, and DEA were included in the model. The model was checked for interactions between BMI and other covariates. No interactions were found. The model was checked by examination of the residuals and bootstrap analysis.

Values are reported as mean±standard deviation, except for symptom score that is reported as a median. A *p* value of less than 0.05 was considered statistically significant.

Statistical analysis was performed using STATA Statistical Software: Release 9.1 (Stata Corporation, College Station, TX, USA).

Results

Five hundred and ninety-nine patients were divided into two groups according to the BMI: (1) group A, 520 patients (86.8%) with BMI <35 (mean 26.4±3.8, range 15.5 to 34.6); and (2) group B, 79 patients (13.2%) with BMI ≥35 (mean 42.6±6.8, range 35 to 71). Overall, 192 patients (32%) had a BMI <25, 227 patients (38%) had a BMI between 25 and 29, 101 patients had a BMI between 30 and 34 (17%), 35 patients had a BMI between 35 and 40 (6%), and 44 patients had a BMI >40 (7%).

Nonmorbidly obese patients (group A) were more frequently males and older than morbidly obese patients (group B) (Table 1).

The prevalence and severity of symptoms were not different between the two groups (Table 1).

The morbidly obese patients had a higher LES pressure (Table 2). The LES was hypotensive (<14 mmHg) in 54%

Table 1 Demographics and Symptoms

	Group A (BMI <35) *n*=520	Group B (BMI ≥35) *n*=79	*P* Value
Age (yr)	51±13	46±10	0.0007
Males	242 (47%)	17 (22%)	0.0005
Heartburn	235 (45%)	44 (56%)	0.08
Heartburn score	3.0	4.0	0.89
Regurgitation	95 (18%)	13 (16%)	0.70
Regurgitation score	3.0	3.0	0.27
Dysphagia	36 (7%)	6 (8%)	0.83
Dysphagia score	3.0	3.0	0.81

Table 2 Manometric and Reflux Profile

	Group A (BMI <35) n=520	Group B (BMI ≥35) n=79	P Value
LES pressure (mmHg)	14±7.6	17±9.2	0.0015
Hypotensive LES	282 (54%)	30 (38%)	0.007
Hypertensive LES	51 (10%)	18 (23%)	0.001
LES total length (cm)	2.3±0.8	2.3±0.9	0.62
LES abdominal length (cm)	2.0±0.8	2.0±0.9	0.90
DEA (mmHg)	96±54	116±60	0.0028
Hypotensive DEA	136 (26%)	8 (10%)	0.009
Hypertensive DEA	98 (19%)	20 (25%)	0.15
DeMeester score	55±41	58±43	0.57

of group A patients and in 38% of group B patients ($p<0.007$). The LES was more frequently hypertensive (>24 mmHg) among morbidly obese patients ($p<0.001$).

The mean DEA was normal in both groups, even though it was higher among morbidly obese patients ($p<0.0028$). The DEA was more frequently hypotensive in group A patients and hypertensive in group B patients (Table 2).

The DeMeester score was similar in the two groups (Table 2).

The linear regression model showed that BMI, LES pressure, LES abdominal length, and DEA were independently associated with the DeMeester score. After adjustments for these variables, as well as age and gender, BMI remained independently associated with the DeMeester score. For each 5-point increase in BMI, the DeMeester score was expected to increase by three units (Table 3).

Discussion

The results of this study show that: (a) one-third of a large cohort of consecutive patients with GERD were either obese or morbidly obese; (b) BMI was independently associated with the severity of GERD; (c) in most obese patients with GERD, reflux occurred despite the presence of a normal or hypertensive LES, and normal or hypertensive esophageal peristalsis.

Gastroesophageal Reflux Disease and Obesity

We found that among a large cohort of patients referred to our Swallowing Center, 17% were obese and 13% were morbidly obese. Even though these results cannot be extrapolated to the entire population of patients with GERD, they corroborate the findings of other studies which show that the increased prevalence of GERD in the Western world has been paralleled by the epidemic of obesity.[1,2] Today, they both affect between 20 and 30% of the population.

Some studies have suggested a possible link between these two processes, as it has been shown that a high BMI increases the risk of GERD,[3–5] and that there is a dose–response relationship between increasing BMI and prevalence of GERD and its complications.[4,6]

Our data demonstrated that the BMI had an effect on the severity of GERD (based on the DeMeester score) that was independent of LES abdominal length, LES pressure, or amplitude of peristalsis. Because our model was created from patients with GERD, the specific coefficients cannot be applied to all obese people. The association, however, appears robust and we expect it will hold up after examination in a broader cohort of patients with and without a diagnosis of GERD.

Obesity and Physiology of Reflux Control

Approximately 60% of patients with GERD have a mechanically defective LES[9] and about 45 to 60% have abnormal peristalsis, as shown by esophageal manometry.[7,10] In a study of 1,006 consecutive patients with GERD, Diener and colleagues found that esophageal peristalsis was abnormal in 44% of patients. They showed that the more abnormal the esophageal peristalsis (lower amplitude, higher number of nonpropagating waves) the worse the gastroesophageal reflux.[7] Our findings show that the motility profile of morbidly obese patients differs from that of nonmorbidly obese patients. Overall, the LES pressure was higher than in the group of nonmorbidly obese patients, with a hypertensive LES present in 23% of patients. In contrast, in the nonmorbidly obese group the LES was more frequently hypotensive. The finding of a low prevalence of a mechanically defective LES among obese patients has also been documented by others, with a prevalence ranging between 14 and 21%.[11–13]

We also found that the amplitude of peristalsis in the distal esophagus was higher among the morbidly obese patients, with a trend towards a more frequent pattern of hypertensive waves. Only 10% of morbidly obese patients

Table 3 Linear Regression Model

	Rise in DeMeester Score	95% CI	P Value
5-Point BMI increase	2.95	0.6–5.3	0.015
1-mmHg decrease in LES pressure	0.6	0.9–1.0	0.019
1-cm decrease in LES abdominal length	6.7	2.7–10.7	0.001
10-mmHg DEA decrease	0.7	0.04–1.4	0.039
Male gender	5.8	−0.9–12.5	0.088
10-year decrease in age	0.3	−2.8–2.2	0.80

had hypotensive peristalsis. Others have documented a low prevalence of abnormal peristalsis among morbidly obese patients.[11,13] For instance, Weiss and colleagues found impaired peristalsis preoperatively in only 23% of patients undergoing laparoscopic gastric banding.[13]

The meaning of these findings is incompletely understood, but it might reflect a physiologic compensatory response to other factors present in the morbidly obese patients, such as increased intragastric pressure.[14] Our regression model helps explain the finding of a similar DeMeester score between the two groups. The stronger LES and the more vigorous peristalsis among the morbidly obese patients may represent a compensatory mechanism to balance the effect of a higher BMI, thereby limiting the amount of reflux.

Our study has limitations. Because most patients were referred for esophageal manometry and pH monitoring only, we do not have data on the prevalence of hiatal hernia or esophagitis. Patients were evaluated only one time so that the manometric findings are no more than a snapshot in time of an individual esophageal function. In addition, because the esophageal manometry was performed with a water-perfused catheter, we do not know the prevalence of transient LES relaxations, which may cause abnormal reflux in patients who have a normal LES pressure. Finally, we cannot draw conclusions regarding the effect of fat distribution, as it was not assessed.

Even with these limitations, our study provides important information in a large cohort of patients with GERD and various BMIs, showing that the common causes of reflux in nonobese patients (hypotensive LES and abnormal esophageal peristalsis) occur less frequently in the morbidly obese population. These findings should be taken into account when planning surgical therapy for reflux. The effect of a fundoplication is due to its action at the level of the gastroesophageal junction. While some have reported good results independently from the patient's weight,[15,16] others have shown a high recurrence rate of reflux in the obese patients.[17] For instance, Perez and colleagues studied the recurrence rate of reflux among 224 patients who underwent either a transthoracic Belsey Mark IV or a transabdominal Nissen fundoplication.[17] Patients were divided into three groups based on their BMI (<25, 25–29.9, and ≥30). They found a significantly higher recurrence rate among the obese patients, which was independent from the type of operation. The authors suggested that factors such as elevated intraabdominal pressure may overcome the effect of the fundoplication.

On the other hand, a Roux-en-Y gastric bypass might have a more pronounced and durable effect due to the induced weight loss, the minimal number of parietal cells present in the gastric pouch, and the complete elimination of the duodenogastroesophageal reflux.[18–20] Future studies should prospectively compare the efficacy of these procedures in relationship to the presence of morbid obesity.

Conclusions

Our study has shown that a significant proportion of patients with GERD are obese and that among these patients reflux occurs despite the presence of a normal or hypertensive LES and normal or hypertensive esophageal peristalsis. Furthermore, obesity is directly associated with the amount of reflux.

These findings raise concern about the wisdom of performing a fundoplication in morbidly obese patients with GERD. We think that a prospective trial comparing a fundoplication with a Roux-en-Y gastric bypass is indicated to establish the procedure of choice in morbidly obese patients with GERD.

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Internal Hernias: Clinical Findings, Management, and Outcomes in 49 Nonbariatric Cases

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Abstract Internal hernia, the protrusion of a viscus through a peritoneal or mesenteric aperture, is a rare cause of small bowel obstruction. We report the clinical presentation, surgical management, and outcomes of one of the largest series of nonbariatric internal hernias. Ten-year retrospective review of patients at our institution yielded 49 cases of internal hernias. Majority of patients presented with symptoms of acute (75%) or intermittent (22%) small bowel obstruction. While 16% of CT scans were suspicious for internal hernia, in no cases the preoperative diagnosis of internal hernia was made. The most frequent internal hernias were transmesenteric (57.0%) and 34 hernias (69%) were caused by previous surgery. All internal hernias were reduced and the defects were repaired. Compromised bowel was present in 22 cases and 11 patients underwent small bowel resection. The mean postoperative hospitalization was 10.9 days. The overall mortality rate from our series is 2%, and the morbidity rate is 12%. Transmesenteric hernias, as complications of previous surgeries, are the most prevalent internal hernias. Preoperative diagnosis of internal hernia is extremely difficult because of the nonspecific clinical presentation. However, if discovered promptly, internal hernias can be repaired with acceptable morbidity and mortality.

Keywords Internal hernia · Hernia · Intestinal obstruction

Introduction

An internal hernia is an acute or chronic protrusion of a viscus through a mesenteric or peritoneal aperture.[1–4] These mesenteric and visceral peritoneal defects are secondary to congenital mechanisms, surgery, trauma, or inflammatory processes. Internal hernias have an autopsy incidence of 0.2 to 0.9% and are the cause of small-bowel obstruction in 0.6 to 5.8% of cases.[1,2,4–7]

Internal hernias are classified based on the location of the potential defect and are separated into six main groups: paraduodenal hernias, hernias through the foramen of Winslow, transmesenteric hernias including intersigmoid hernias, transomental hernias, pericecal hernias, and paravesical and pelvic hernias.[3–14] Except for internal hernias complicating bariatric surgery, internal hernias are sparsely described. The literature on the subject is comprised of small case series or is concentrated in the radiology literature. We are reporting one of the largest case series of nonbariatric surgery related internal hernias and discuss their incidence, anatomic distribution, clinical presentation, management, and outcomes.

Poster presentation at Digestive Disease Week, May 22, 2006, Los Angeles, California, USA.

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Material and Methods

After approval by the Mount Sinai Medical School Institutional Review Board, a retrospective review of the electronic medical records was performed to identify the diagnosed cases of internal hernia at our institution from 1994 to 2004. Operative records were then examined to confirm the presence and nature of the internal hernia. Patients with history of gastric bypass surgery were excluded because the postoperative occurrence of internal hernias in this patient population has been described extensively. Patients with

intestinal herniation through adhesive bands who were treated by adhesolysis were also excluded from the study. Hospital records of these patients were reviewed for information on incidence, presentation, work-up, management, and outcomes.

Results

Forty-nine patients with surgically proven internal hernias were identified. There were 21 males (43%) and 28 females (57%) with a mean age of 56.4 years (SD 20.2, range 4 months to 93 years). Mean body mass index was 23.2 (SD 5.16, range 12.7–41). Table 1 lists the type and frequency of the internal hernias in our series. As listed, 65% (n=28) of the hernias were transmesenteric. Forty-three percent of these patients (n=12/28) carried a diagnosis of inflammatory bowel disease (IBD) and 14% (n=4) had colorectal cancer. Ninety-three percent of these patients (n=26) underwent a total of 37 abdominal operations.

Table 2 lists the presenting symptoms of the patients in our series. Acute and intermittent obstruction was present in 47 (97%) patients. Associated obstructive symptoms included abdominal pain (n=42), nausea (n=41), vomiting (n=35), constipation (n=17), and obstipation (n=10). The interval between the development of symptoms and hospitalization ranged from several hours to 5 months (median 2 days, mean 11.7 days). The physical exam revealed abdominal tenderness in 44 patients (89%), abdominal distention in 29 patients (59%), and fever and peritonitis in five patients (10%). One patient presented in septic shock requiring ventilatory support and vasopressors, while another patient deteriorated into hemodynamic instability and acidosis several hours after admission to the hospital. Lastly, one case (paraduodenal internal hernia) was discovered incidentally during the surgical resection of a gastrointestinal lymphoma.

Table 1 Type and Characteristic of the Internal Hernias

Type of Internal Hernia	Frequency n (%)	Primary Defect n (%)	Secondary Defect* n (%)
Transmesenteric	28 (57)	2 (7)	26 (93)
Paraduodenal	6 (12)	6 (100)	0 (0)
Transomental	5 (10)	2 (40)	3 (60)
Pericecal	3 (6)	2 (67)	1 (33)
Intersigmoid	3 (6)	1 (33)	2 (67)
Paravesical and pelvic	3 (6)	1 (33)	2 (67)
Foramen of Winslow	1 (2)	1 (100)	0 (0)
Total	49 (100)	15 (31)	34 (69)

*Defects secondary to previous surgery.

Table 2 Presenting Symptoms

Symptoms at Presentation	Number of Patients (%)
Acute bowel obstruction	37 (75)
Intermittent bowel obstruction	11 (22)
Peritonitis	5 (10)
Sepsis	2 (4)
Leukocytosis*	10 (22)
Lactate elevation†	6 (12)

*Mean WBC 15.97×10^3 per μl (range 11.4–22×10^3 per μl).
†Mean 5.42 mg/dl (range 1.7–5.9 mg/dl).

A total of 74 diagnostic tests were performed preoperatively. Eighteen patients underwent both computed tomography (CT) scan and plain abdominal radiography, while five patients had a repeat obstructive series. Evidence of small bowel obstruction was found on two follow-up obstructive series after initial normal studies. Overall, 88% of CT scans (n=22/25) and 80% obstructive series (n=28/35) showed small bowel obstruction. Four out of 25 CT scans (16%) had findings considered suspicious for an internal hernia. Figure 1 illustrates the suspicious CT scan findings in three patients. These findings included matted or twisted small bowel with intervening mesentery, tethering of small bowel with portions of small bowel in unusual location, swirling and stretching of the mesentery, and engorgement and crowding of the mesenteric vessels. Two out of the eight small bowel series (25%) had findings consistent with paraduodenal internal hernia.

The median number of days from admission to surgery was 1 day (mean 1.7, SD 3.69, range 0–18 days). Thirty-eight patients (77.6%) went to surgery within 2 days of admission. Twenty-seven patients (55%), however, were initially managed conservatively with bowel rest, hydration, and nasogastric tube decompression for an average 3.1 days (median 1 day, range 1–18 days). These patients underwent surgery due to the failure of conservative management and worsening symptoms. The duration of symptoms before hospital admission and surgical management ranged from several hours to 5 months (median 3 days). Several patients had experienced intermittent symptoms over several months before presenting to the hospital. The operative management consisted of 31 cases (63%) of exploratory laparotomy, and 18 cases (37%) of diagnostic laparoscopy. Five of the 18 (28%) laparoscopic cases were converted to laparotomy.

Table 3 lists the most common operative findings. All internal hernias consisted of small bowel except for one patient with herniation of terminal ileum and cecum into the foramen of Winslow. The length of the herniated bowel ranged from 10 cm to the entire length of small bowel. In

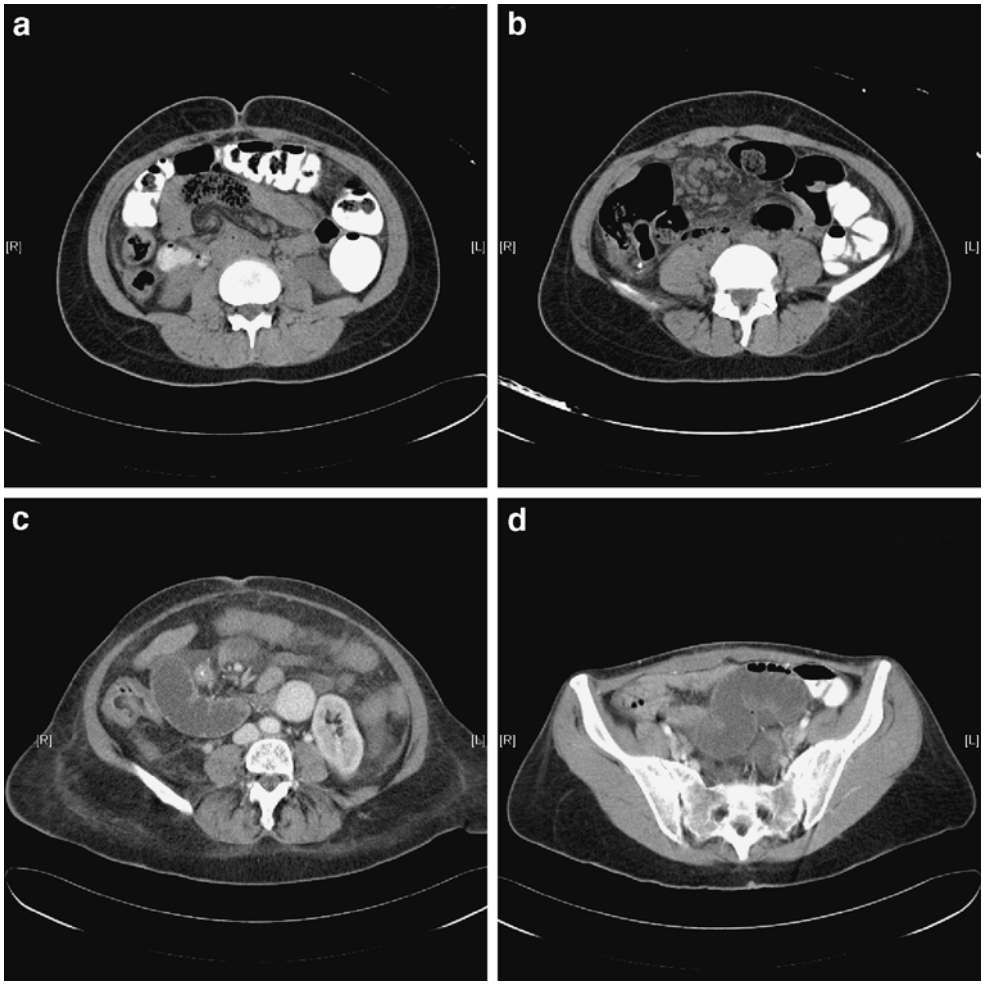

Figure 1 CT scan images of patients with findings suspicious for internal hernias. **(a)** The "swirl sign" of the twisting mesentery. **(b)** The stretching of the mesentery and engorgement and crowding of the mesenteric vessels. **(c)** and **(d)** Dilated loops of small bowel with transition zones.

all cases, the internal hernias were reduced. All mesenteric and peritoneal defects were repaired through suture closure to replicate the normal anatomy. In two cases of transmesenteric hernias and one case of transomental hernia, the hernia orifices had to be extended to allow for the reduction of dilated loops of herniated bowel. While there were cases of necrotic bowel (n=11), there were no perforations. Nine patients (18.4%) required intraoperative manual decompression of distended bowel.

Table 3 Type of Surgery and Operative Findings

Type of Surgery and Operative Findings	Number of Patients (%)
Exploratory laparotomy	31 (63)
Diagnostic laparoscopy	18 (37)
Laparoscopy converted to laparotomy	5 (10)
Ascites (hemorrhagic or turbid)	11 (22.5)
Compromised bowel	
Viable	11 (22.5)
Nonviable	11 (22.5)
Perforated	0 (0)
Total patients with compromised bowel	22 (44.9)

Eleven patients (22.4%) had irreversible changes requiring small bowel resection and primary anastomosis. Defects leading to resection and anastomosis included transmesenteric hernia (n=8), transomental hernia (n=2), and pericecal hernia (n=1). The average length of resected bowel was 20 cm (range 8–120 cm). Eight patients with small bowel resection required intensive care unit (ICU) admission for an average 19.4 days (range 1–60 days).

The mean hospital length of stay for all patients was 12.6 days (range 4–65 days), with median post-operative hospitalization 8 days (mean 10.9, SD 11.92, range 3–65 days). The postoperative mortality rate was 2% (n=1) and the complication rate was 12% (n=6) (Table 4). The patient who ultimately expired (on postoperative day 48) underwent a bowel resection for a gangrenous transmesenteric hernia and developed an intraabdomial abscess. The abscess was treated by open operative drainage on postoperative day 19. One patient returned to the emergency room several days after discharge complaining of abdominal pain. The work-up was normal and patient was discharged from the emergency room after resolution of pain.

Table 4 Complications

Complications	Number of Patients (%)
Mortality	1 (2)
Sepsis	1
Morbidity	6 (12)
Pancreatitis	1
Wound infection	1
Intraabdominal collection	2
DVT	1
Resolved abdominal pain	1
Reoperation	3 (6)
Abdominal washout	3

Discussion

An internal hernia is defined as the protrusion of bowel through a normal or abnormal opening within the boundaries of the peritoneal cavity. The herniation may be through a normal anatomic structure, such as the foramen of Winslow, or through a pathologic defect of congenital or acquired origin.[1–5,10–14] Congenital defects are anomalies of intestinal rotation and mesenteric attachments, while acquired defects are caused by abdominal surgery, trauma, or inflammation. The autopsy incidence of internal hernias has been reported to be 0.2 to 0.9%.[1,2,4–7]

Internal hernias are classified based on their topographic distribution through potential orifices in the peritoneal cavity.[4,5,10–14] Previously, paraduodenal hernias have been considered to be the most common type of internal hernias, reported in 50–55% of cases, followed by pericecal hernias (10–15%) and transmesenteric hernias (8–10%).[1,4,5,7,8–10] Our study reveals that transmesenteric hernias are the most prevalent internal hernias at our institution (57%). Previously, Blachar et al. have also reported the increased frequency of transmesenteric hernias. They attribute the increase to the rise in the number of Roux-en-Y procedures.[15–17] In our study, patients with such operations were excluded. However, 93% of patients with transmesenteric hernias (n=26/28) had undergone a total of 37 abdominal operations. Fifty-seven percent of these cases (n=16) involved small bowel or colon resection for inflammatory bowel disease and colorectal cancer. We propose that mesenteric defects resulting from previous operations are responsible for the development of the majority of transmesenteric hernias at our institution.

The clinical symptoms of internal hernias may range from intermittent mild digestive complaints to acute-onset intestinal obstruction. Patients may be symptom free if the hernia is easily reducible, however, the majority, 97% of cases in the study, present with obstructive symptoms of abdominal pain, nausea, vomiting, constipation, and obstipation. The interval between the development of symptoms and hospitalization ranged from hours to several months. We presume that the spontaneous reduction of internal hernias were responsible for the symptom-free periods in those with chronic intermittent symptoms versus incarceration in those with acute onset symptoms.

Internal hernias are a rare cause of small bowel obstruction (0.6 to 5.8%). This rarity and their nonspecific presentation make the preoperative diagnosis of internal hernias very difficult. In this study, the preoperative diagnosis was made in none of the cases. Computed tomography has been proposed as a diagnostic modality for the preoperative diagnosis of internal hernias.[15–21] Blachar et al. report CT scan sensitivity of 63%, and specificity of 76% in diagnosing transmesenteric hernias.[17] In this study, 16% of CT scans (n= 4/25) were suspicious for internal hernias, while 88% displayed signs of small bowel obstruction. Patients with a history of previous abdominal surgery are prone to develop intestinal adhesions and small bowel obstruction, which may be difficult to differentiate from internal hernias by CT scan.[10,17]

The CT diagnosis of transmesenteric hernias is even more challenging than other subtypes because the lack of a confining sac results in a more variable appearance. However, the CT findings considered to be the predictors of these internal hernias include engorgement of the mesenteric vessels, crowding and stretching of the mesenteric vessels, the whirl sign indicative of small bowel volvulus, right and left displacement of the descending colon, dilatation of the small bowel, presence of a transition zone, and presence of small bowel obstruction.[15,18–20]

A delay in surgery, the definitive treatment, leads to the development of gangrenous bowel in a large portion of patients.[10–12] Newsome has reported the presence of gangrenous bowel at exploration in 64% of cases (n=9/14).[10] In our series, 22% (n=11) required resection secondary to gangrenous incarcerated small bowel. Seventy-three percent of those cases (n=8/11) consisted of transmesenteric hernias. Transmesenteric hernias are more prone to develop volvulus and ischemia than other internal hernias due to the lack of a limiting hernia sac, which allows the herniation of a considerable length of small bowel.[17,22–27] Eleven percent (n=3) with transmesenteric hernias had volvulized necrotic bowel.

Newsome has reported 31% (n=4/13) postoperative mortality rate in the Veteran Administration patients with internal hernias.[10] These patients had presented with sepsis as a result of gangrenous incarcerated bowel. In this study, two patients (4%) presented with peritonitis and sepsis. The lone mortality (2%) in our study was a 74-year-old patient, who presented with peritonitis and sepsis, and underwent laparotomy and resection of a large segment of necrotic bowel in a transmesenteric hernia. The patient was hemodynamically unstable postoperatively and eventually expired

during a long intensive care unit admission. In this study, the postoperative morbidity (12%) consisted of intraabdominal collection (n=2), pancreatitis, deep vein thrombosis, wound infection, and abdominal pain. Six percent (n=3) required reoperation for abdominal washout.

Conclusion

Previously, duodenal hernias have been reported as the most common internal hernia. In our study, transmesenteric hernias, as complications of previous surgeries, are the most prevalent internal hernias. The majority of internal hernias present with signs and symptoms of acute or chronic intermittent small bowel obstruction, which are indistinguishable from other causes of obstruction. Radiographic imaging, including CT scan, lacks sensitivity and specificity for definitive diagnosis of internal hernias. Because of their rarity and the nonspecific clinical presentation, the preoperative diagnosis of internal hernias remains challenging for the clinician. Surgeons should maintain a high index of suspicion for internal hernias in patients with obstructive symptoms and previous abdominal surgery, as a delay in diagnosis can be life threatening. If discovered promptly, internal hernias can be repaired with acceptable morbidity and mortality.

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Long-term Results of a Primary End-to-end Anastomosis in Peroperative Detected Bile Duct Injury

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Abstract The management of a bile duct injury detected during laparoscopic cholecystectomy is still under discussion. An end-to-end anastomosis (with or without T-tube drainage) in peroperative detected bile duct injury has been reported to be associated with stricture formation of the anastomosis area and recurrent jaundice. Between 1991 and 2005, 56 of a total of 500 bile duct injury patients were referred for treating complications after a primary end-to-end anastomosis. After referral, 43 (77%) patients were initially treated endoscopically or by percutaneous transhepatic stent placement (n=3; 5%). After a mean follow-up of 7±3.3 years, 37 patients (66%) were successfully treated with dilatation and endoscopically placed stents. One patient died due to a treatment-related complication. A total of 18 patients (32%) underwent a hepaticojejunostomy. Postoperative complications occurred in three patients (5%) without hospital mortality. These data confirm that end-to-end anastomosis might be considered as a primary treatment for peroperative detected transection of the bile duct without extensive tissue loss. Complications (stricture or leakage) can be adequately managed by endoscopic or percutaneous drainage the majority of patients (66%) and reconstructive surgery after complicated end-to-end anastomosis is a procedure with relative low morbidity and no mortality.

Keywords Cholecystectomy · Bile duct injury · End-to-end anastomosis

Introduction

Bile duct injury (BDI) after laparoscopic cholecystectomy (LC) is still a major problem in current surgical practice. BDI is associated with reduced survival, increased morbidity, and poor long-term quality of life (QoL).[1,2] The incidence of BDI at laparoscopic cholecystectomy has been reported between 0.3 to 1.4%,[3–5] depending on the criteria used to define the injury as well as the study population. Of these injuries, one-third is detected during the procedure.[6] Measures to prevent and recognize BDI are outlined in many publications.[6–8,9–11] The optimal treatment strategy and short- and long-term outcome has been published extensively.[12–14] Controversy exists however about the management of peroperative detected BDI. The most important factor is the extent of tissue loss of the common bile duct, but also severity of inflammation and the size and diameter of the proximal duct. The peroperative management range from simple drainage and referral to a tertiary center to an end-to-end anastomosis (EEA) (duct to duct, with or without T-tube drainage) or a hepaticojejunostomy (HJ).

It has been suggested that EEA is associated with a relative high stricture rate up to 70–80% and consequently a high incidence of secondary repair.[15] Therefore, many tertiary centers prefer to perform a HJ instantly. A secondary repair after EEA should be associated with an increased risk of postoperative complications as the

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formation for strictures and stenosis.[16,17] Others, however, consider EEA as a relative simple definitive repair, and also an optimal initial drainage procedure before reconstructive surgery in a secondary setting.[18] Reports on large consecutive series to analyze the outcome of EEA are scary because this procedure is generally not performed in referral centers. One should realize that patients referred to such a center after previous EEA elsewhere are a negative selection of the EEA population. So far, a systematic analysis of a large group of patients with an EEA has not been performed and therefore this study was conducted.

The aim of the present study was to analyze short- and long-term outcome in patients who are referred after failure of a primary EEA.

Patients and Methods

Patients Cohort and Data Collection

Between January 1991 and January 2006, 500 consecutive patients were referred to the Academic Medical Center (AMC) in Amsterdam for the management of a BDI after cholecystectomy. Patient data was induced in a prospective database. All types of BDI were included, also minor injuries such as leakage from the cystic duct or ducts of Luschka. To define the location of BDI, the Bismuth classification was used.[18] For the present study, the medical charts of all patients who underwent a primary EEA were retrospectively reviewed to analyze the initial operation reports and clinical data.

Data from the referring hospital included: indication for cholecystectomy, type of initial procedure, location of injury, type of repair including the use of a T-tube, the postoperative diagnostic interventions, and the therapeutic interventions before referral. Data from the present center included: symptoms at referral, diagnostic work-up, type of treatment, short-term, and long-term complications.

Endoscopic, Radiological, and Surgical Treatment for complicated EEA

Endoscopic treatment was performed by balloon dilatation or catheter dilatation before stent placement. The biliary stent is placed over the guide wire bridging the stenosis. Two or more stents were inserted if possible. For multiple stent insertion, an endoscopic sphincterotomy was performed to facilitate stent placement. Stents were replaced after 6 weeks and subsequently exchanged every 3 months to avoid cholangitis.

Percutaneous transhepatic catheterization was performed by injecting the contrast medium from the right intercostal approach. A right or left approach for the percutaneous transhepatic biliary drainage was chosen depending on ultrasound images illustrating the biliary anatomy, and the possibility of puncturing a dilated intrahepatic bile duct. Catheterization of intrahepatic bile ducts was performed in standard fashion. A guide wire was advanced through the biliary stricture into the duodenum. When this was achieved, a biliary drainage catheter was inserted. All drainage procedures were performed with the administration of broad-spectrum antibiotics.

In case of a surgical reconstruction, the procedure was performed via a Roux-en-Y hepaticojejunostomy. The stricture in the CBD is transected and the hilar plate is opened. The hepatic ducts of different segmental bile ducts are mobilized and from there opened over the left hepatic duct. Intrahepatic segmental ducts are mobilized and if possible sutured together before one or two jejunal anastomosis are made. A closed suction drain is placed during operation and removed 24–48 hours after surgery. Percutaneous transhepatic drains, when inserted before surgery are left in place and removed after 10 days till 6 weeks, depending on the clinical course, the level of anastomosis and the surgeons' preference.

Outcome

Follow-up data was obtained through outpatient records and the records of the general practitioner. The outcome of treatment was analyzed by the number complications and late restenosis during follow-up. Failure of treatment was defined as recurrent stenosis after stent therapy followed by surgery or recurrent stenosis after surgical reconstruction followed by additional therapy.

Statistical Analysis

Data from patient characteristics, management, and outcome show descriptive statistics in number of patients and percentages. Mean and median values are given with a minimum and maximum. Long-term stricture-free survival was analyzed by Kaplan Meier Survival Analysis. Data analyses were performed using SPSS® software (SPSS, Chicago, Illinois, USA).

Results

Patients' Characteristics at Referral

The referral pattern of BDI patients (n=500) throughout the last 15 years are summarized in Fig. 1. From the total of 500 patients, 56 (11.5%) underwent a primary EEA. Patient characteristics are listed in Table 1. The laparoscopic

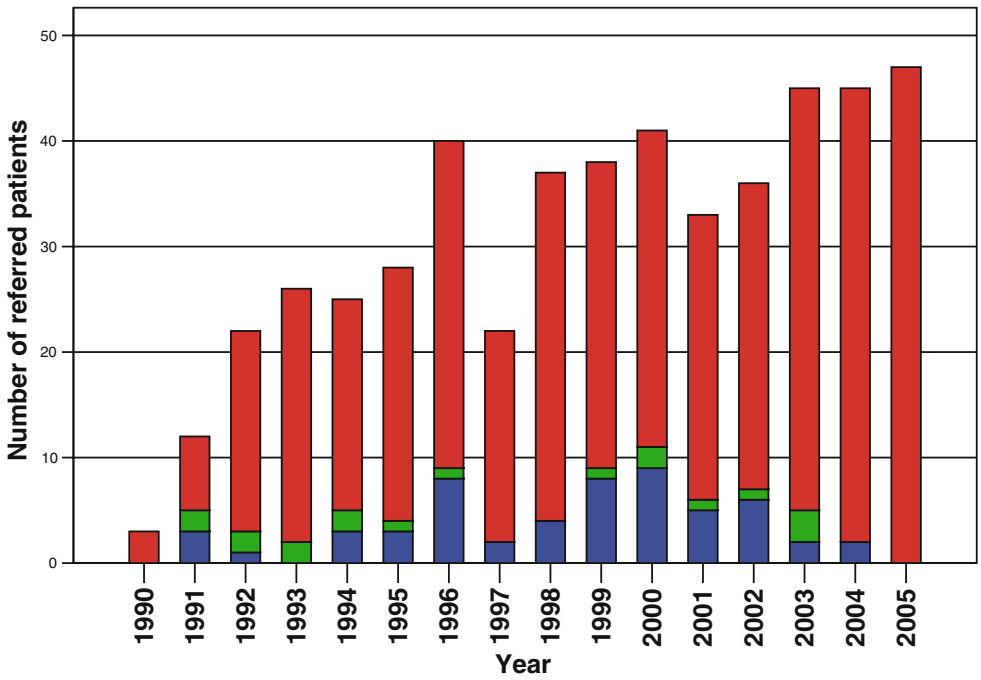

Figure 1 Referred patients for treatment of bile duct injury. Total number of referred patients (red), patients referred after a primary end to end anastomosis (blue), and patients referred after a primary biliodigestive reconstruction (green).

cholecystectomy (n=48, 86%) was converted in all patients. An open cholecystectomy was performed in eight patients (14%). In 49 patients (88%), the anastomosis was made over a T-tube. The tube was removed at the referring hospital or at the AMC after a mean of 52 days (range 2–145 days).

After the primary EEA, 19 patients (34%) underwent other therapeutical interventions before referral (Table 2). These patients underwent a range of one to three procedures before referral (median 2). The interventions included a relaparotomy in two patients (4%), percutaneous drainage of fluid collections in five patients (9%), endoscopically placed stents in 12 patients (21%), a papillotomy in nine patients (16%), and percutaneous transhepatic drainage in two patients (4%). The median interval from the primary EEA to referral was 16 weeks (range 0–141 weeks). At referral, a biliary stricture was diagnosed in 38 patients (68%); in 10 patients (18%), bile leakage was diagnosed and combination of both in eight patients (14%). Symptoms at referral were cholestasis (n=14, 25%), cholangitis (n=10, 18%), and abdominal pain (n=15, 27%). Three patients were referred because of uncontrolled sepsis (n=2) and peritonitis (n=1). According to the Bismuth classification, the majority of injuries (leakage of stricture) (n=47, 84%) was located below the bifurcation. In nine patients (16%), the injury (mostly strictures) involved the bifurcation or the right or left hepatic duct (i.e., Bismuth classification grades IV and V).

Table 1 Patient Characteristics

	Primary EEA	
	n=56	%
Age at cholecystectomy		
Mean (years)	52	
Gender		
Female	43	77
Indication for cholecystectomy		
Symptomatic cholelithiasis	45	80
Cholecystitis	5	9
Cholecystitis a froid	6	1
Type of initial operation		
Open procedure	8	14
Laparoscopic to open procedure	48	86
Anastomosis over T-tube	49	88
Duration of T-tube in situ		
Days, median (range)	42(2–145)	

Management after Referral

Diagnostic work-up was performed by CT-scan (n=9; 16%), endoscopic cholangiography (n=38; 68%), and transhepatic cholangiography (n=9; 16%). The definitive treatment of BDI patients after EEA is shown in the flow diagram (Fig. 3). After work-up, three patients (5.3%) were treated with percutaneous transhepatic cholangiographic drainage (PTCD) and 40 patients (71.4%) were treated endoscopically. Thirteen patients (23%) underwent reconstructive surgery after work-up; eight patients because of a complete stenosis of the CBD, in three patients reconstructive surgery was performed after failure of stent therapy at the referring hospital and in two patients because of a percutaneous fistula and persistent bile leakage.

Table 2 Referral Pattern

	Primary EEA	
	n=56	%
Time interval between injury and referral		
Weeks, median (range)	16 (0–141)	
Intervention after EEA and before referral		
Explorative relaparotomy	2	4
Percutaneous drainage	5	9
Endoscopic stenting	12	21
Endoscopic papillotomy	9	16
PTD[a]	2	4
Symptoms at referral		
Cholestasis	14	25
Cholangitis/fever	10	18
Abdominal pain	15	27
Abces/biloma	4	7
Uncontrolled sepsis/peritonitis	3	5
Diagnosis at referral		
Stenosis	38	68
Leakage	10	18
Combination of stenosis and leakage	8	14
Location of injury at referral[b]		
I	9	16
II	21	38
III	17	30
IV	7	12
V	2	4

[a] Percutaneous transhepatic drainage
[b] According to Bismuth classification

Radiological and Endoscopic Treatment

Three patients were successfully treated by PTCD. In two patients, a stenosis was treated by transhepatic dilatation and in one patient, bile leakage was treated by external transhepatic stent insertion.

Forty patients (71.4%) were treated endoscopically (Fig. 2). In 37 patients (66%), stent insertion was successful and in three patients (5%), adequate drainage succeeded by papillotomy. The median number of stent replacements was five (range 1–15) with a median duration of treatment of 359 days (range 39–1,355). Complications occurred in nine patients (24%). Stent dislodgment (*n*=3), clogging (*n*=2), and cholangitis (*n*=5) were mild complications and were successfully treated by stent exchange or administration of antibiotics. One severe complication occurred in a 75-year-old patient. After 4 years of stent therapy, the stent migrated and perforated the duodenum. Finally, the patient died due to multiple organ failure and sepsis.

Surgical Treatment

After referral and during the follow-up period, a new hepatobiliary anastomosis was performed by hepaticojejunostomy in 13 patients (23.2%). Mean duration of hospital stay was 9.1±3.1 days. Postoperative complications occurred in one patient (7.6%) who underwent a PTC procedure after leakage of the anastomosis. No hospital mortality occurred in patients who underwent a reconstructive procedure after a previous EEA.

Long-term Follow-up

After a mean follow-up of 7.1±3.3 years, seven patients (13%) have died. One endoscopically treated patient died due to a complication of treatment as described above. The other patients died due to malignancy (*n*=4) and myocardial infarct (*n*=2).

The long-term results in patients treated with endoscopic and radiological treatment are as follows: from a total of 43 patients treated with endoscopic or PTCD procedures, 86% (*n*=37) was successful. In three patients (7%), signs of restenosis occurred after stent removal after 2, 3.5, and 4 months. Continued stent therapy was successful in all three patients. Five patients underwent reconstructive

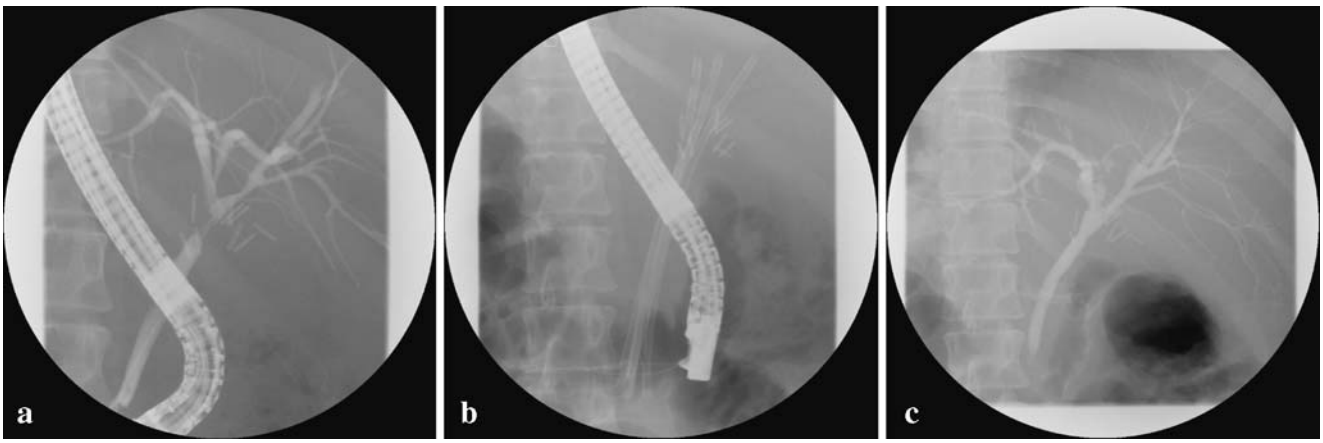

Figure 2 ERCP showing successful (aggressive) stent therapy after primary EEA. a Stenosis of the common bile duct. b Stents in situ. c After stent removal within a year.

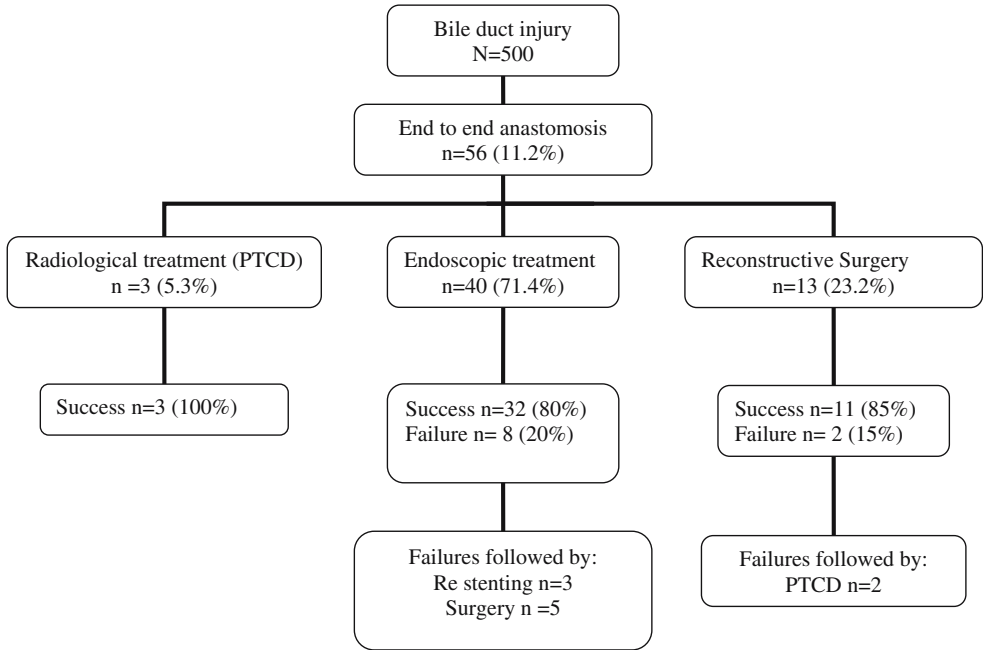

Figure 3 Flow diagram of the success and failure rates after a multidisciplinary treatment of patients who underwent a peroperative end to end anastomosis for bile duct injury. Given percentages are calculated from the number of patients in the previous flow box. *PTCD* Percutaneous transhepatic catheter dilatation.

surgery after prolonged endoscopic stenting. Postoperative complications occurred in two of the five patients and these patients received additional therapy for wound infection (n=1) and postoperative cholangitis (n=1).

The long-term results of surgical treatment after EEA are as follows; from 13 patients who underwent a HJ after work-up, a stenosis of the anastomosis occurred in two patients (15%). Both patients underwent successful percutaneous transhepatic dilatation, respectively 9 and 35 months after surgery.

The overall 5 years stricture free survival in the total cohort (n=56) is 91%, shown by a Kaplan Meier curve in Fig. 4.

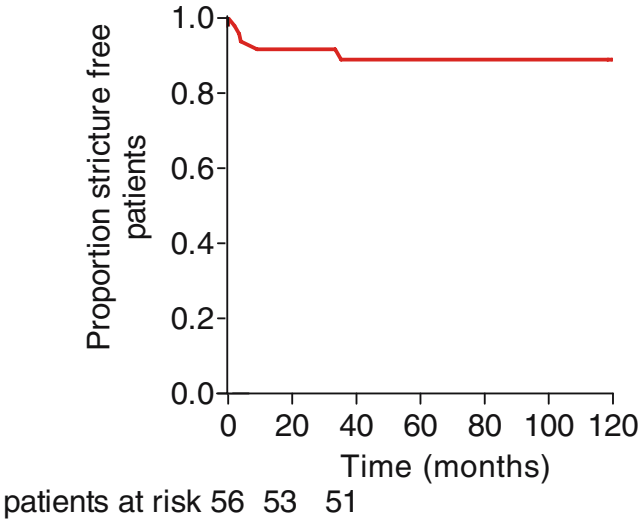

Figure 4 Kaplan–Meier plot showing proportion of patients without restenosis among 56 bile duct injury patients treated for complications after EEA.

Discussion

The present study describes a selected group of BDI patients, who were referred for treatment after a complicated EEA. This group of patients is a negative selection, representing the worst complications of EEA; otherwise, patients were not referred for additional treatment. So, this study does not provide any information about the success rate of EEA. The present study shows a long-term stricture free survival of 91% in EEA patients after treatment in a tertiary center. The analysis showed that even the majority of complications after primary AEE in a general hospital can successfully be treated by endoscopic and radiological interventions. In only one-third of the patients, a secondary surgical repair is necessary. The surgical reconstruction after EEA was associated with acceptable morbidity and without mortality.

Around 40 to 45 patients are referred annually without any sign of decrease over the last years. Considering 15.000 LC's per year in the Netherlands, we still consider 0.4–0.5% mentioned in the reviews as an underestimation of the real incidence of BDI, at least in the Netherlands.[19] In 20% of the patients referred to the AMC, the injury was detected during the initial surgical procedure. This finding is similar to reports in literature.[6,20] From the total of 500 referred BDI patients, 11.2% was referred for the treatment of a complication after peroperative EEA. Because referred patients only represent the complications after EEA, we do not know the real incidence of EEA procedures in BDI.

Peroperative repair in BDI detected during surgery can be performed by EEA (with or without the use of a T-tube) or by a primary HJ. A HJ is a more complex procedure and

one should be very careful not to further extend the injury into the intrahepatic ducts or subsequently damage the arterial supply (bleeding and clipping or ligation of right hepatic artery).[21,22] The present study shows that if complications occur after EEA, these can successfully be treated by percutaneous or endoscopic balloon dilatation and/or stenting in the majority of patients. A HJ in the acute setting without dilated bile ducts is even more difficult and therefore consulting a surgeon with experience in reconstructive hepatobiliary surgery is recommended. In contrast with a primary HJ an EEA is a relatively simple procedure and can also be performed in less experienced hands. The risk to increase damage is smaller in an EEA procedure and with the use of a T tube instant bile drainage is realized. If indicated, reconstructive surgery by means of an elective HJ can be performed. It is strongly advised to perform a HJ after classification the injury and analyzing the biliary anatomy. Preoperative cholangiography (with the use of the T tube) will illustrate the location of the stenosis and the extension of dilation of the proximal bile ducts. A reconstructive procedure for stenosis of EEA has a satisfying outcome, as peroperative conditions are good after the inflammation has subsided and the bile ducts are dilated due to stenosis.

In a situation in which peroperative bile leakage is due to (extensive) tissue loss, in particular, in patients with more proximal lesions at the bifurcation or intrahepatically, no primary repair should be performed. In this situation, adequate drainage of the upper right abdomen is strongly advised and the patient should be referred for elective reconstruction. Referral to tertiary center in this situation has a positive effect on outcome.[2]

End-to-end anastomosis is reported to be associated with a high incidence of recurrent jaundice due to stricture formation of the anastomotic area.[15] Therefore, some authors suggest that EEA is almost never appropriate if the bile duct has been completely transected,[15,23] while others favor this strategy when there is no extensive tissue loss.[18] Stent therapy for iatrogenic bile duct strictures has changed during the last decade and therefore the long-term outcome after stenting has improved.[24] A more aggressive approach with more stents and smaller time intervals between stent changes is favored. With this new approach, 80% of the patients who undergo an ERCP for postoperative bile duct stenosis, have a 10-year stricture-free survival.[25] Although complications occur at a significant rate, these are usually mild. The only severe complication occurred in the present series, due to a migrated stent, was not reported in previous series.[24,25] After stent removal, recurrent stenosis develops in 20% of patients within 2 years of stent removal.[25] Therefore, endoscopic treatment should be the initial management of choice for postoperative bile duct strictures. Without signs of improvement after endoscopic stenting, reconstructive surgery is indicated in otherwise fit patients.

Of interest is the evaluation of the long-term stricture-free survival after treatment for complications after EEA. After a mean follow-up of 7.1 years, restenosis after treatment developed in 9% of the patients. In all patients who underwent initial endoscopic therapy, restenosis occurred a relatively short time after stent removal, diagnosed within 2 to 8 months follow-up. Therefore, endoscopic treatment is not associated with a high rate of long-term restenosis after stent removal. In two patients, a restenosis occurred within 3 years after a hepaticojejunostomy. Symptoms were cholestasis and cholangitis. In both patients, transhepatic dilatation was successful to resolve the stenosis. The long-term stricture-free survival of 91% in the present series provides evidence for a good outcome after treating complicated EEA patients. If BDI is detected during surgery, in particular if there is no extensive tissue loss, the local anatomy is clear and there is no inflammation, EEA could be considered as a sufficient treatment strategy. Patients with postoperative complications (stricture or leakage) should be treated by a multidisciplinary team of gastroenterologists, radiologists, and surgeons. Postoperative complications can adequately be managed by endoscopic or percutaneous drainage in two-third of the patients. Reconstructive surgery after a complicated EEA is associated with low morbidity and no mortality.

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Conflicts of Interest None.

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Roux-en-Y Drainage of the Pancreatic Stump Decreases Pancreatic Fistula After Distal Pancreatic Resection

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Abstract Clinically relevant fistula after distal pancreatic resection occurs in 5–30% of patients, prolonging recovery and considerably increasing in-hospital stay and costs. We tested whether routine drainage of the pancreatic stump into a Roux-en-Y limb after distal pancreatic resection decreased the incidence of fistula. From October 2001, data of all patients undergoing pancreatic distal resection were entered in a prospective database. From June 2003 after resection, the main pancreatic duct and the pancreatic stump were oversewn, and in addition, anastomosed into a jejunal Roux-en-Y limb by a single-layer suture (n=23). A drain was placed near the anastomosis, and all patients received octreotide for 5–7 days postoperatively. The volume of the drained fluid was registered daily, and concentration of amylase was measured and recorded every other day. Patient demographics, hospital stay, pancreatic fistula incidence (≥30 ml amylase-rich fluid/day on/after postoperative day 10), perioperative morbidity, and follow-up after discharge were compared with our initial series of patients (treated October 2001–May 2003) who underwent oversewing only (n=20). Indications, patient demographics, blood loss, and tolerance of an oral diet were similar. There were four (20%) pancreatic fistulas in the "oversewn" group and none in the anastomosis group (p<0.05). Nonsurgical morbidity, in-hospital stay, and follow-up were comparable in both groups.

Keywords Distal pancreatic resection · Pancreatic fistula · Roux-en-Y anastomosis · Morbidity

Introduction

Pancreatic distal resection is a standardized procedure for the resection of lesions localized to the left of the portal vein. Despite advances in surgery during the last two decades, leakage from the pancreatic remnant after distal pancreatectomy presents a persistent problem.[1,2] Thus, the incidence of postoperative pancreatic fistulas varies between 5 and 30% in recent studies.[3–10] Various techniques are used for closure of the pancreatic remnant, such as ligation of the pancreatic duct followed by closure of the pancreatic stump with or without a serosa patch or closure using a stapling device.[6,11–14] Interestingly, even when an identical technique was used, the reported incidence of fistulas varies widely.[15] This variation may be attributable to differences in the definition of "pancreatic fistula" but also to technical variabilities within groups of "identical" stump closure and to the heterogeneity of patient populations.[16]

Importantly, a recent study found that complications derived from pancreatic fistulas after distal pancreatectomy doubled the cost and dramatically increased health-care resource use.[2] Therefore, strategies are urgently needed that aid in reduction of the incidence of postoperative pancreatic fistulas, and thus, may decrease direct treatment costs. A retrospective survey found that draining the pancreatic remnant into an excluded loop of jejunum was only used sporadically.[17,18] We therefore tested the hypothesis that routine drainage of the pancreatic stump into a Roux-en-Y limb may decrease the fistula rate after pancreatic distal resection.

Wagner and Gloor both contributed equally in this work.

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Patients and Methods

From October 2001, all patients undergoing pancreatic surgery were enrolled in a prospective data registry. Patients underwent a standardized preoperative evaluation consisting of contrast-enhanced abdominal computed tomography or magnetic resonance imaging. In selected patients, endoscopic retrograde cholangio- and pancreatography was performed. In patients in whom cancer was suspected, resection was performed in the absence of hematogenous metastases and when no gross retroperitoneal neoplastic or complex vascular infiltration was evident. Surgery consisted of an en-bloc pancreatic left resection, together with the spleen and the adjacent lymphatic tissue in all these patients. The extension of the cancer into the body of the pancreas determined the amount of tissue that was resected. In patients with chronic pancreatitis, the indications for surgery were intractable pain, alteration of the left-sided pancreas (e.g., pseudocysts), duct stenosis, pancreatic stones, or suspicion of cancer. In these patients, the spleen was conserved whenever technically feasible.

From October 2001 to May 2003, stump closure for pancreatic distal resection was accomplished by closing the pancreatic duct with interrupted prolene sutures followed by oversewing the pancreatic stump, cut in a fish-tail-like fashion, with a second layer of interrupted sutures using a resorbable, atraumatic suture material (PDS, Ethicon, Switzerland).

From June 2003, a modification was applied consisting of suturing the pancreatic stump as described above followed by an end-to-side pancreatico-jejunostomy into a retrocolic Roux-en-Y limb with a length of at least 30 cm. The jejunum was opened slightly smaller than the diameter of the pancreas, and the anastomosis was performed in a capsule-to-mucosa fashion using a single layer resorbable, monofilament suture with interrupted stitches (PDS, Ethicon, Switzerland). A drain was placed near the anastomosis in all patients, and octreotide was administered for 5–7 days postoperatively (3×0.2 mg s.c. daily). All patients received, perioperatively, a single-dose antibiotic prophylaxis (amoxicillin and clavulanic acid, GlaxoSmithKline, Switzerland). Empiric antibiotic treatment was continued after surgery in patients with manifest infections until resistance probes were received or the clinical presentation ameliorated.

Postoperatively, patients were cared for in the intensive or intermediate care unit as needed. Fluid was given intravenously, and patients were allowed to drink fluids depending on the operative procedure and clinical presentation. Solid foods were administered according to gastrointestinal (GI) function using a stepwise dietary regimen. Abdominal drainage volume was registered daily, and the amylase concentration of drained fluid was measured and recorded every other day. Patient demographics, duration of hospital stay, incidence of pancreatic fistula, perioperative morbidity, and follow-up after discharge were recorded and compared with our previous series of patients in whom the pancreatic remnant was oversewn only. A pancreatic fistula was defined as secretion of at least 30 ml of amylase-rich fluid (more than 5,000 U/l) per day on or after the tenth postoperative day. Mortality was defined as the total in-hospital death rate. A biliary fistula was diagnosed if bilirubin-rich fluid was drained for more than 5 days. Bleeding was defined as the need for more than two units of packed red blood cells more than 24 h after operation or the need for reoperation for bleeding.

All variables were analyzed using the Fisher's exact test, χ^2 test, and Mann–Whitney U test, where appropriate, using SPSS Statistical Software (Chicago, IL, USA). All quantitative data are reported as median values and ranges. Differences at $P<0.05$ were considered statistically significant.

After discharge, all patients were seen in our outpatient clinic at least once. Thereafter, follow-up was registered using a standardized questionnaire, and patients were contacted by phone.

Results

A total of 44 pancreatic distal resections were performed during the study period. One patient who underwent emergency pancreatic distal resection because of a rupture of the pancreas after blunt abdominal trauma was excluded from the analysis. The remaining 43 patients were included. A total of 23 patients underwent distal resection with a pancreatico-jejunostomy, and 20 patients underwent stump closure by simple suturing of the pancreatic remnant. Demographic characteristics are summarized in Table 1 and were comparable between the two groups. The histologic classification and the range of surgical treatments are shown in Table 2. A neoplasm was found in 74 and 85% of patients, respectively (group "anastomosis" vs "oversewn"). Mean operative time was 345 min after pancreatico-jejunostomy vs 305 min after "oversewing" only; $p=0.329$. Duration until solid food intake was tolerated and duration of hospital stay (group 1: 13 days vs group 2: 16 days; $p=0.325$) was comparable between groups. Drains were removed after a mean duration of 6 days in both groups ($p=0.5$).

Postoperative morbidity is listed in Table 3. After pancreatico-jejunostomy, one patient had to be reoperated because of intra-abdominal bleeding in the region of the gastro-duodenal artery. Subsequently, this patient developed an intra-abdominal abscess caused by a localized necrosis in the pancreatic head and was treated by percutaneous drainage (amylase concentration of the drain fluid<220 U/l).

Table 1 Demographics in Patients Undergoing Pancreatic Distal Resection (n=43)

Clinical Data	Group 1 (n=23) (with Pancreaticojejunostomy)	Group 2 (n=20) (No Anastomosis)	P Value
Age (years)	58 (22–78)	60 (18–84)	0.372
Gender:			
Male	9 (39%)	8 (40%)	0.954
Female	14 (61%)	12 (60%)	
ASA risk classification			
I–II	14 (67%)	14 (74%)	0.736
III–IV	7 (33%)	5 (26%)	
Body weight (%)[a]	97 (80–100)	97 (87–100)	0.417
Duration of symptoms (wk)	44 (1–468)	14 (1–200)	0.037
Diabetes mellitus	2	4 (20%)	0.398
Cardiac disease	7 (30%)	5 (25%)	0.708
COPD	2	1	0.999
Albumin<30 g/l	2	1	0.995
Creatinine>150 mmol/l	5 (22%)	2 (10%)	0.412

Quantitative variables are given as median (range). A Fisher's exact test or a χ^2 test was used for qualitative variables and a Mann–Whitney U test for quantitative variables.
ASA American Society of Anesthesiology, *COPD* chronic obstructive pulmonary disease
[a] Body weight as a percentage of pre-morbid body weight

One patient underwent interventional drainage for a retroperitoneal abscess after distal pancreatectomy with a pancreaticojejunostomy and left nephrectomy. The amylase concentration in the drain fluid measured less than 500 U/l. No pancreatic fistula required an operative intervention; however, all four patients underwent interventional drainage. A 78-year-old female patient died from postoperative sepsis and multi-organ failure caused by an infected central venous line. The autopsy report revealed a vital and completely healed pancreatic anastomosis and no signs suggesting an intra-abdominal cause of sepsis.

Table 2 Histology and Additional Surgical Procedures Performed in 43 Patients Undergoing Pancreatic Distal Resection

Operative Procedure	Group 1 (n=23) (with Pancreaticojejunostomy)	Group 2 (n=20) (No Anastomosis)
Histology		
Pancreatic neoplasms	13 (57%)	14 (70%)
Other neoplasms	4 (17%)	3 (15%)
Chronic pancreatitis	5 (22%)	2 (10%)
Other	1	1
Procedures		
Splenectomy	18 (78%)	18 (90%)
Liver resection	3 (13%)	3 (15%)
Gastric resection	3 (13%)	2 (10%)
Colon resection	3 (13%)	2 (10%)
Nephrectomy	3 (13%)	1
Adrenalectomy	2	2 (10%)
Necrosectomy	1	0

Follow-up was completed in 41 patients (95%). Two patients were lost to emigration. Median follow-up was 20 months (range 1–49), and mean survival was 33 months (95% C.I. 29–43). No readmission occurred as a result of a postoperative pancreatic fistula. Follow-up morbidity was comparable between the two groups. A total of 9 patients (29%) died because of recurrent malignant disease. Six patients were reoperated during follow-up: one patient underwent hepatic resection because of a recurrence of a neuroendocrine neoplasm; one patient required colon resection because of diverticulitis; and another patient underwent incisional hernia repair. The other three patients had extra-abdominal surgery. No patient required recurrent pancreatic surgery, and no patient who underwent pancreaticojejunostomy developed bowel obstruction. Fourteen patients (32%) required insulin after pancreatic resection, and the incidence of pancreatogenic diabetes did not differ between the two groups. Enzyme supplementation was prescribed in 22 patients (51%), and six patients (14%) noted clinical signs of exocrine pancreatic insufficiency despite enzyme supplementation. The majority of patients could work or pursue their daily activities (75 and 66%, respectively, for groups "anastomosis" and "oversewn").

Discussion

A pancreatic fistula according to a recently published classification is any measurable drainage on or after postoperative day 3 with an amylase content of more than

Table 3 Postoperative Outcome (Frequency)

Parameters	Group 1 (n=23) (with Pancreaticojejunostomy)	Group 2 (n=20) (No Anastomosis)	P Value
Surgical morbidity			
Pancreatic fistula	0	4 (20%)	0.039
Bleeding	1	1	0.995
Intra-abdominal abscess	2[a]	1[b]	0.995
Biliary fistula	0	1[c]	0.465
Relaparotomy	1	0	0.995
Nonsurgical morbidity[d]			
Cardiopulmonary	6 (26%)	3 (15%)	0.087
Renal	1	2 (10%)	0.590
Other	4 (13%)	2 (10%)	0.561
Mortality	1	0	0.995

A Fisher's exact test or a χ^2 test was used for qualitative variables and a Mann–Whitney U test for quantitative variables.
[a] Including the one patient requiring reoperation for bleeding in this group
[b] This patient also suffered from a pancreatic fistula
[c] Related to a liver resection that was performed together with the pancreatic left resection
[d] Systemic complications: cardiopulmonary, renal, sepsis, neural, others

three times the upper limit of serum amylase[19]. Three categories were defined: biochemical fistula without clinical sequelae (grade A); fistula requiring any therapeutic intervention (grade B); and fistula with severe clinical sequelae (grade C). Because the current study was begun in October 2001 and data were prospectively entered into a database, we did not use the new classification published in 2005. Retrospectively, all fistulas diagnosed in this paper were either grade B or grade C. The definition used in this study is the same as that used in previous analyses of our patients[20,21] and is in accordance with other published series from high-volume centers[3,22]. Several different techniques were used for the treatment of the pancreatic stump after distal resection[6,11–14,23]. In a large single-center series of 235 pancreatic distal resections performed between 1994 and 1997, the incidence of postoperative pancreatic fistula was 5%[6]. Others have reported a fistula rate of almost 30%.[10] However, assessment of data from different centers is limited because of differences in fistula definition and patient heterogeneity, precluding unbiased comparison of outcomes. We therefore chose to perform a single-center study and compared results with our new technique with those from an earlier group of patients otherwise treated identically but without a pancreaticojejunal anastomosis.

Patient demographics were well comparable in our two groups of patients despite published data from other centers reporting changes in patient characteristics and indications for resection over time (increase in age and more resections for cystic lesions and fewer for chronic pancreatitis)[24]. In an earlier retrospective observational survey of 113 patients, 46 were treated with an additional pancreaticoenteric anastomosis, and no superiority of this technique was found.[17] Adam et al. performed a pancreaticoenteric anastomosis in 27 of 41 patients undergoing distal pancreatic resection between 1994 and 2001. The anastomosis was associated with a leak-rate of 7% (2/27) compared to 29% (4/14) in the control group, but the difference did not reach the level of significance because of small sample size.[18] In a prospective trial, 69 patients were randomly assigned to five treatment groups: suturing of the pancreatic stump, suturing and applying fibrin glue, suturing plus mesh, pancreaticojejunostomy, and stapler closure of the stump. The overall fistula rate was 19%, ranging from 7 to 33%, without a statistical advantage of one technique over the other.[25]

Besides technical reasons, the incidence of postoperative pancreatic fistula may also be influenced by the use of synthetic somatostatin analogues (octreotide, lanreotide, or vapreotide) and the texture of the gland. Three randomized trials evaluated the use of prophylactic octreotide in patients undergoing pancreaticoduodenectomy and found no benefit for the use of octreotide, as did a meta-analysis in 2002.[22,26–28] On the other hand, four randomized, placebo-controlled, multicenter trials reported significant decreases in overall complication rates, and two of the four reported significantly lowered rates of pancreatic fistula in patients receiving prophylactic octreotide. Based on such data, our patients all received octreotide, which is also in accordance with a recent meta-analysis, demonstrating a reduction in the incidence of complications with the use of synthetic somatostatin analogs.[29]

Pancreatic texture and consistency were correlated with a risk of postoperative pancreatic fistula development.[30] Partial resection of a fibrotic pancreas is associated with lower leak rates (0 to 5%) compared to resection of a soft pancreas (20 to 25%), while the incidence of a postoper-

ative fistula in a pancreas with an intermediate consistency is 3 to 5%[22].

Reoperation, septic complications with localized abscesses, and bleeding are other rare but important complications and indicators of surgical quality, having also a major impact on health-care resource consumption and economic outcome.[2,31] In our series, there were three abscesses. However, the amylase concentration reached the level required for a pancreatic fistula only in the abscess in the patient from group 2.

Because of different health-care systems, duration of hospital stay for a given intervention in Switzerland, in general, is greater than those reported in series from the US. Thus, in Switzerland, many complications are diagnosed during the initial hospital stay. Accordingly, there was no early readmission for either postoperative fistula or for abscess or bleeding. This outcome is in contrast to a recent paper from the US reporting on 56 patients with distal pancreatic resection of whom eight developed a pancreatic fistula grade B or C. Six of these eight patients were readmitted.[32]

The duration of hospital stay was similar in both groups in our study, suggesting that not only the presence or absence of a pancreatic fistula but also other factors, such as the cardiopulmonary or renal comorbidity that was evenly present in both groups, had a major impact on the duration of the hospital stay.

The additional operative effort of creating a Roux-en-Y limb and performing an anastomosis increased the duration of the operation only a short time, but did not reach statistical difference most likely because of the small number of patients studied.

Conclusion

This study may serve as an effort to evaluate Roux-en-Y drainage of the pancreatic stump after distal pancreatic resection. Further prospective randomized studies are needed to finally define the role of this technique in routine pancreatic left resection. Based on our results, a randomized trial would need 113 patients in each treatment arm to meet a power of 90% with a 5% two-sided significance level, assuming that a pancreatico-jejunostomy would modify the incidence of postoperative fistula after pancreatic distal resection by 15%.

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Relief of Dysphagia after Laparoscopic Heller Myotomy Improves Long-Term Quality of Life

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Abstract
Background and Objective Quality of life (QoL) is getting more attention in the medical literature. Treatment outcomes are now gauged by their effect on the QoL along with their direct effect on the diseases they are targeting. The aim of the study was to assess the impact of residual dysphagia on QoL after laparoscopic Heller myotomy for achalasia.
Methods QoL was evaluated using the short-form-36 (SF-36) and postoperative dysphagia was assessed using a dysphagia score. The score (range 0–10) was calculated by combining the frequency of dysphagia (0=never, 1=<1 day/wk, 2=1 day/wk, 3=2–3 days/wk, 4=4–6 days/wk, 5=daily) with the severity (0=none, 1=very mild, 2=mild, 3=moderate, 4=moderately severe, 5=severe). Patients were classified in the Nonresponder group when their dysphagia score was in the upper quartile.
Results Questionnaires were mailed to 110 patients. The overall response rate was 91% with 100 patients (54 female) returning the questionnaires. The average follow-up was 3.3 years. There was a significative inverse correlation between dysphagia score and mental component (P=0.0001) and total SF-36 (P=0.001) scores. According to their postoperative dysphagia scores, 77 patients were assigned to the Responder Group and 23 patients to the Nonresponder Group. The two groups were similar in terms of age, gender, rate of fundoplication, and length of follow-up. Mental component and total SF-36 scores were significantly (P<0.05) higher in the Responder group. Successful relief of dysphagia after Heller myotomy was associated with health-related quality of life scores that were 13 higher in Vitality (P<0.05), 11 points higher in mental health (P<0.05), and 12 points higher in General Health (P<0.05). Overall patient satisfaction with surgical outcome was 92%, with only eight patients not satisfied with the surgery.
Conclusion Laparoscopic Heller myotomy offers excellent long-term relief of achalasia-related symptoms, namely dysphagia, and this was projected on a significant improvement in quality of life and patient satisfaction.

Keywords Achalasia · Quality of life · Laparoscopic Heller myotomy · Dysphagia · SF-36

Introduction

Achalasia is a primary motility disorder of the esophagus characterized by loss of peristaltic waveform in the body and failure of the lower sphincter to relax in response to swallowing. The condition is relatively rare, occurring at an incidence of 0.5 to 1.0 in 100,000 of the general population[1], and affects any age group[2]. The etiology of achalasia remains unknown, although in South America many patients have infestation by *Trypanosoma cruzi* as an underlying pathogenesis. The main symptoms are dysphagia and chest pain, although in the late stages regurgitation of swallowed material may occur. Other common symptoms include heartburn and weight loss.

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At present time no treatment can reverse the degeneration of the myenteric plexus and restore normal relaxation of the lower esophageal sphincter (LES) with swallowing[3]. Therefore, the current treatment strategy is aimed to relief the main symptom of achalasia: the dysphagia. Subjective relief of dysphagia and body weight regain have been the most common endpoints used in studies aimed to evaluate the therapeutic outcome of Heller myotomy or endoscopic dilation. However, Quality of life (QoL) is getting more attention in the medical literature[4]. Treatment outcomes are now gauged by their effect on the QoL along with their direct effect on the diseases they are targeting.

We hypothesize that successful relief of achalasia symptoms after laparoscopic Heller myotomy is associated with improved QoL. To test this hypothesis, we assessed how residual dysphagia after laparoscopic Heller myotomy for achalasia affects long-term QoL.

Patients and Methods

Patients who underwent laparoscopic Heller myotomy for achalasia were mailed a follow-up survey under an IRB approved protocol. The survey included: a Short Form-36 (SF-36) health status questionnaire, a follow-up structured dysphagia score questionnaire[5], and a query regarding long-term satisfaction. All patients who did not return the questionnaires received a second mailing or were allowed to answer the survey over the phone.

The SF-36 questionnaire includes 36 questions that yield an eight-scale profile of scores. Scores range from 0–100, with higher scores indicating better QOL. Scoring is designed so that the average American individual would score on average 50 with 10 points standard deviation. The eight scales of the questionnaire include: 1) general health, 2) physical functioning, 3) bodily pain, and 4) role-physical, which all correlate with the physical health summary measure; and 5) mental health, 6) social functioning, 7) vitality, and 8) role-emotional, all of which correlate with the mental health summary measure.

The dysphagia score (range 0–10) was calculated by combining the frequency of dysphagia (0=never, 1=<1 day/wk, 2=1 day/wk, 3=2–3 days/wk, 4=4–6 days/wk, 5=daily) with the severity (0=none, 1=very mild, 2=mild, 3=moderate, 4=moderately severe, 5=severe). The cutoff point used to define successful outcome after laparoscopic Heller myotomy was selected at the 75th percentile (upper quartile) of the entire cohort. Patients with dysphagia score falling above the cutoff point were classified into the unsuccessful outcome group (Nonresponders).

Operative Technique

Our technique for laparoscopic Heller myotomy has been previously described[5]. Briefly, after exposure of the anterior gastroesophageal (GE) junction, the myotomy is created by incising the distal 4–6 cm of esophageal musculature. The myotomy is extended 1–2 cm onto the gastric cardia using cautery scissors or an ultrasonic scalpel. Intraoperative endoscopy is performed before and simultaneously with the myotomy to assess the adequacy of the myotomy.

Statistical Analysis

The data are presented as mean±SD for continuous variables and as counts or proportions (%) for categorical variables. Continuous variable means were compared by appropriate parametric or nonparametric tests. Categorical variables were compared with the Chi-square test. Statistical significance was set at $P<0.05$.

Results

The questionnaires were mailed to 160 patients and successfully received by 110 patients. One hundred patients returned the questionnaires with an overall response rate of 91%. The average postoperative follow-up was 3.3 years (range 12–120 months). The study cohort was constituted by 54 female and 46 male, with a mean age of 53 years. Laparoscopic Heller myotomy alone was performed in 67 patients and Dor fundoplication was added in 33 patients. As shown in Table 1, dysphagia and SF-36 scores were not affected by the addition of a Dor fundoplication.

There was a significant inverse correlation between dysphagia score and mental component (Pearson $r=-0.379$; $P=0.0001$) and total SF-36 (Pearson $r=-0.328$; $P=0.001$) scores.

As shown in Fig. 1, patients were considered to have a successful outcome after laparoscopic Heller myotomy when their postoperative dysphagia score was ≤ 5 (first to 74th percentile). According to this cutoff dysphagia score,

Table 1 Effect of Dor-fundoplication on Dysphagia and SF-36 Scores

Variable	Heller myotomy ($n=67$)	Heller-Dor ($n=33$)	P
Dysphagia score	3.8±2.8	2.9±2.8	NS
Total SF-36	74.7±18.7	73.8±20.8	NS
SF-36 (PCS)	68.1±20.8	70.7±21.8	NS
SF-36 (MCS)	76.5±17.4	72.9±21.1	NS

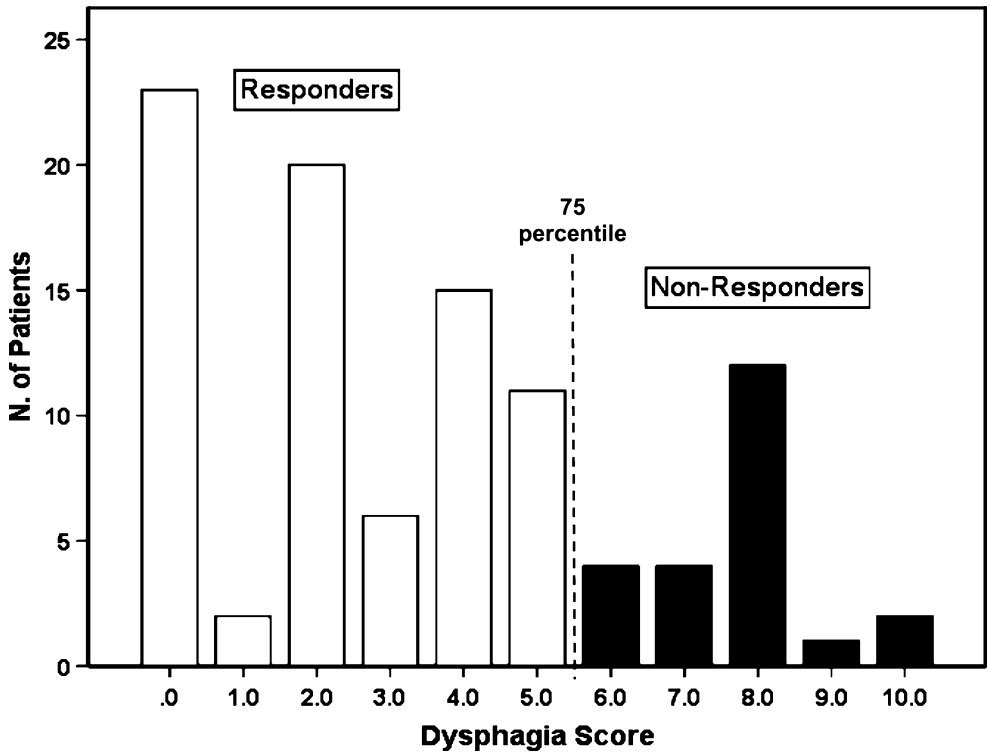

Figure 1 Dysphagia score distribution and according classification of the two groups (white bar: responder; black bar nonresponders).

77 patients were included in the Responder group and 23 patients were classified in the Nonresponder group.

Table 2 illustrates that there were no differences between the two groups in terms of mean age, gender distribution, rate of fundoplication, and length of postoperative follow-up.

As shown in Fig. 2, the Responder group had a significant higher ($P<0.05$) mental component (MCS) and total SF-36 scores than Nonresponder group.

Figure 3 shows the eight domains of the SF-36 score. Successful relief of dysphagia after laparoscopic Heller myotomy was associated with health-related QoL scores that were 13 points higher in Vitality ($P<0.05$), 11 points higher in mental health ($P<0.05$), and 12 points higher in General Health ($P<0.05$).

Overall patient satisfaction with surgical outcome was 92%, with only eight patients not satisfied with the surgery.

Table 2 Demographic and Operative Data of the Two Groups

Variable	Responders ($n=77$)	Nonresponders ($n=23$)	P
Age	54.9±14.9	50.1±13.2	NS
Gender	42 female, 35 male	12 female, 11 male	NS
Fundoplication	27 Dor (35%)	6 Dor (26%)	NS
Follow-up	40±22 months	40±22 months	NS

Discussion

Our study has demonstrated that laparoscopic Heller myotomy offers excellent long-term relief of achalasia-related symptoms resulting in a significant improvement of health-related QoL and patient's perceived satisfaction.

Current treatments for achalasia, whether medical or surgical, cannot restore normal esophageal motility. Therefore, all the therapeutic options, including endoscopic botulinum toxin injection and pneumatic dilation of the LES are aimed to improve subjective symptoms[6,7]. The main drawback of these treatments is their transient effect on dysphagia. Differently, laparoscopic Heller myotomy is a durable and effective treatment for achalasia[8,9].

Patients with achalasia are greatly affected by their disease. They commonly experience loss of physical strength, fatigue, frustration, and even strains in personal relationships. Many studies have showed that QoL and gastrointestinal symptoms related to achalasia improve significantly after laparoscopic Heller myotomy[4,10–14]. However, our study was the first to assess long-term QoL and to correlate better health-related QoL with successful relief of dysphagia.

The present study finds that dysphagia score is inversely correlated with total and mental health SF-36 scores. This finding confirms the observation previously made by Mineo and collaborators[15]. In their study, four-year dysphagia score was inversely correlated with postoperative changes in mental health. A plausible explanation for this

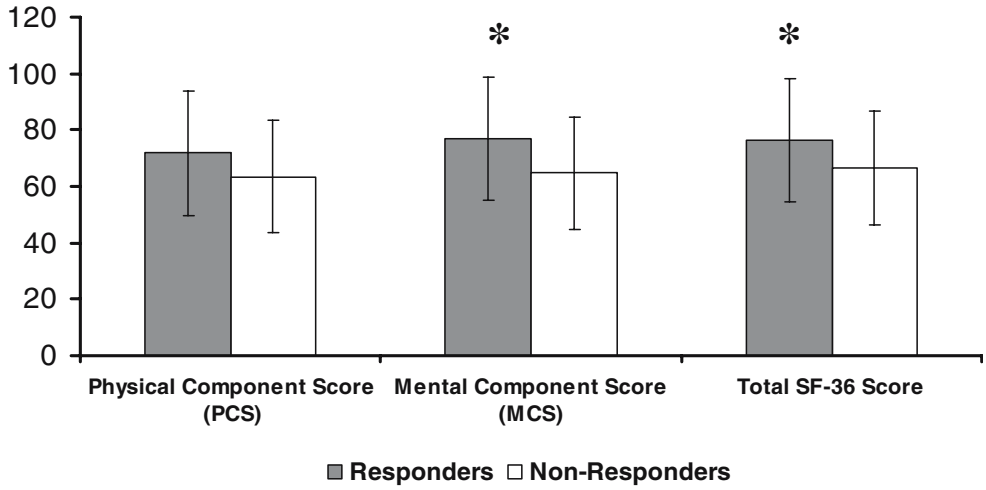

Figure 2 Mean SF-36 scores of the two groups (*$P<0.05$).

observation is that the loss of normal swallowing and diet increases depression-related symptoms that directly affect the mental component of the SF-36 score[16]. Therefore, the finding of higher mean SF-36 mental score in the responder group is not surprising. In this group, the most significant improvements were seen in domains such as mental health and vitality. Similarly, Perrone and collaborators found significant postmyotomy improvements in domains affecting the mental SF-36 score, such as social function, and role limitations due to emotional problems[17].

In patients with achalasia, it is very difficult to objectively assess the results of surgery because of the low incidence of the disease and the cost of the postoperative studies. In addition, patients are reluctant to undergo invasive testing, especially when they are satisfied with the surgical outcome. So we often rely on the patient's assessment of their symptoms in determining the outcome of the surgery. This also has its downside, mainly because patients with achalasia often modify their diet to avoid symptoms of dysphagia, which may overestimate the therapeutic effectiveness of the myotomy. In addition, some studies have found no relationship between objective outcome measures and subjective measures[12,18–20]. Therefore, we need to highlight more the importance of instruments aimed to objectively assess surgical outcome from the patient's perspective. SF-36 is a well-validated instrument that has been already used to evaluate surgical outcome. However, it is desirable to develop a valid and reliable measure of disease-specific health-related QoL. Recently, Urbach et al. developed a 10-item measure of disease-specific health-related QoL that sampled the concepts of food tolerance, dysphagia-related behavior modifications, pain, heartburn, distress, lifestyle limitation, and satisfaction[21].

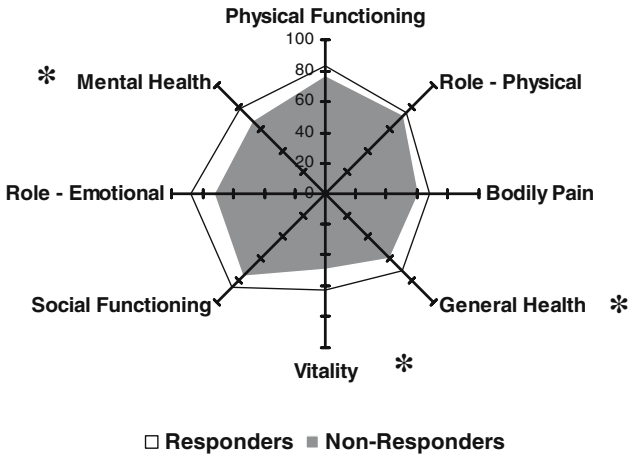

Figure 3 SF-36 domain scores of the two groups (*$P<0.05$).

We were unable to implement this new instrument because our study was already ongoing at the time of the publication. However, future studies will benefit from using this disease-specific QoL instrument.

Our study also inquired about patient's satisfaction. Among the 100 patients enrolled in the study, 92 were satisfied with the surgery and only six will not undergo surgery again. However, only 30 patients think that they were cured by surgery. On the other hand, successful relief of dysphagia, measured by dysphagia score, was observed in 77% of patients. This discrepancy can be explained by the fact that self-perceived outcomes measured by binary endpoints (i.e., yes/not) generally overestimate successful outcome when compared with continuous variable endpoints (i.e., Likert scale).

In conclusion our study demonstrated that successful relief of dysphagia after laparoscopic Heller myotomy for achalasia leads to an overall improvement in health-related QoL.

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Preemptive Total Gastrectomy for Hereditary Gastric Cancer

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Abstract Hereditary gastric cancer is a recently described clinical syndrome, associated with truncating mutation of the E-cadherin gene, named *CDH1*. It is characterized by autosomal dominant transmission, presentation at an early age, and with diffuse type of gastric adenocarcinoma. Clinical management of these patients is challenging and includes intense endoscopic surveillance or prophylactic gastrectomy, which is associated with short- and long-term morbidity. We report four patients submitted to a prophylactic gastrectomy performed in members of three families with hereditary gastric cancer in a tertiary referral center in Mexico City. These are the first Hispanic families with hereditary gastric cancer reported in the literature.

Keywords Hereditary gastric cancer · E-cadherin mutation · Prophylactic gastrectomy

Genetically defined inherited forms of cancer are relatively uncommon, representing 5 to 10% of many types of adult-onset malignancies, although familial clustering of cancer often constitutes another 20% or more of cases. One of the most recently defined inherited cancer syndromes is that predisposing to gastric cancer and, in particular, the pathologically diffuse type of gastric cancer.[1] An increased incidence of familial gastric cancers has been recognized as a component of several inherited cancer syndromes[2,3] like Lynch type II, Li–Fraumeni, familial adenomatous polyposis, and Peutz–Jeghers syndromes, which exhibit elevated rates of gastric cancer compared with the general population. However, several families have been identified that are specifically predisposed to diffuse gastric cancers (DGCs), together with lobular breast cancer, and that share inherited germline mutations in the *CDH1* gene encoding for the E-cadherin protein. Clinical criteria defining hereditary diffuse gastric cancer (HDGC) families include two or more pathologically documented cases of DGC in first- or second-degree relatives, with at least one diagnosed before the age of 50 years, or three or more DGC cases in first- or second-degree relatives diagnosed at any age.[4]

The incidence of HDGC is relatively low compared with the most common inherited cancer syndromes, accounting for 1 to 3% of gastric adenocarcinomas. Gastric cancer presenting in younger patients with familial clustering has been reported in Mexico,[5] but there are no reports of families with HDGC. Management of patients with HDGC is controversial, ranging from endoscopic surveillance[6] to total gastrectomy, with very few cases of the latter approach reported in the literature.[7,8] We reported four cases of prophylactic total gastrectomy performed in patients from three different families with clinical criteria for HDGC in a tertiary referral center in Mexico City.

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Case Reports

Family A

The proband in family 1 (subject III-4; Fig. 1, family a) was a 27-year-old man with strong family history of gastric cancer. The pedigree is shown in Fig. 1, family a. The family was referred to our institution for endoscopic surveillance. Upper endoscopy with chromoendoscopic technique discovered a small lesion in the gastric body in the proband. Biopsy showed diffuse type of gastric cancer. The patient underwent total gastrectomy in February 2003. Pathology report showed multiple foci of signet ring cell adenocarcinoma limited to the mucosal layer in the entire stomach. In March 2003, all of the proband's relatives underwent upper endoscopy with chromoendoscopic technique and magnification with no evidence of disease. One of the proband's brothers, who was 24 years old (subject III-6; Fig. 1, family a), complained of abdominal bloating and discomfort 4 months after a normal upper endoscopy. He was admitted to the hospital 1 month later with massive ascites. Upper endoscopy with chromoendoscopic and magnification techniques was performed with no evidence of abnormality in the stomach. The patient underwent laparoscopy with evidence of diffuse carcinomatosis. Biopsy of peritoneal lesions showed signet ring cell adenocarcinoma. Upper endoscopy was repeated and 27 random biopsies of gastric mucosa were performed; one of them was positive for gastric adenocarcinoma. The patient underwent palliative chemotherapy but died 2 months later because of chemotherapy-related complications.

A DNA sample was obtained from the proband and sent to the Otago University in New Zealand looking for *CDH 1* mutation. No germline mutation inactivating *CDH1* could be detected in this patient. However, a homozygous change in the promoter region (−160C>A) of the gene was reported.

After extensive genetic counseling, two of the proband's brothers underwent elective prophylactic total gastrectomy (subjects III-5 and III-9; Fig. 1, family a). The first surgery was performed in September 2003 on a 25-year-old man (subject III-5; Fig. 1, family a). Extensive pathology sampling was performed with evidence of two microscopic foci of high-grade dysplasia. The patient was asymptomatic during the last clinical consultation, 2-years after surgery. The second prophylactic gastrectomy was performed on a 19-year-old man in June 2004 (subject III-9; Fig. 1, family a). Pathology report showed nodular gastritis in the antrum with no evidence of dysplasia. The patient was in good health during his last follow-up visit, 18 months after prophylactic surgery. Other siblings of the proband (subjects III-1 and III-2; Fig. 1, family a) chose continued endoscopic surveillance.

Family B

The proband in family 2 (subject III-4; Fig. 1, family b) was a 19-year-old man who was diagnosed with DGC at our institution in 1985. He had stage IV disease at presentation and he underwent palliative chemotherapy. He died of DGC

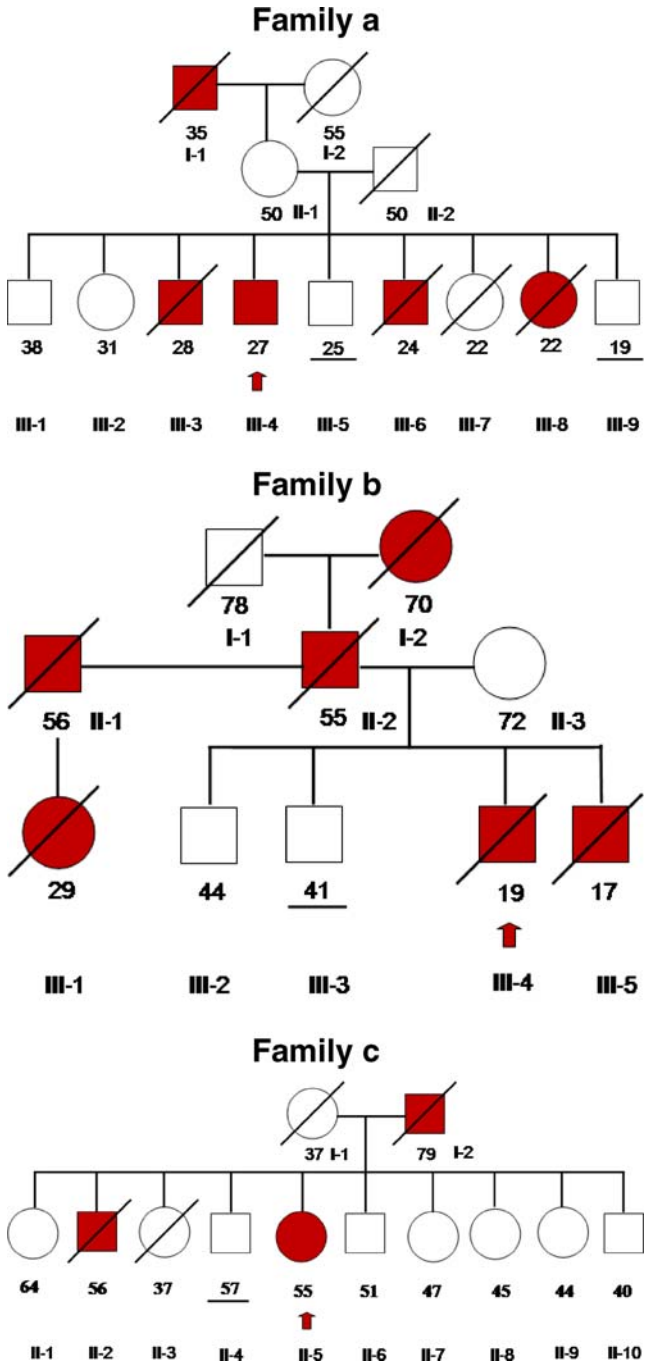

Figure 1 Pedigrees of families **a**, **b**, and **c**. The squares represent male family members and the circles female family members. Open symbols indicate unaffected persons and solid symbols affected persons. A slash over the symbol denotes death, and a line under the symbol prophylactic gastrectomy. Arrow indicates the index case. The age at diagnosis is indicated under each symbol.

6 months after diagnosis. At the time of admission the patient had a family history of DGC. Pedigree is depicted in Fig. 1, family b. The two remaining brothers of the proband have been followed up at our institution since 1986, with endoscopies with gastric biopsies performed every 6–12 months. Since the year 2001 chromoendoscopic exams have been carried out in these patients. In August 2004, subject III-3 (Fig. 1, family b) underwent routine follow-up examination and a small superficial erosion in the greater curvature of the stomach was found. Biopsy showed two isolated signet ring cells not definitive for carcinoma. DNA analysis did not show inactivating mutation of the *CDH1* gene or any other genetic abnormality. After extensive discussion and genetic counseling, the patient was admitted for surgery. He underwent total gastrectomy with Roux-en-Y reconstruction on September 2004. Pathologic examination showed foci of low-grade dysplasia without evidence of carcinoma. During last follow-up in November 2005, the patient was free of malignant disease. The patient's brother (subject III-1) continued with endoscopic surveillance.

Family C

An orthopedic surgeon (subject II-4; Fig. 1, family c) was referred to our institution because of considerable family history of DGC, which is depicted in Fig. 1, family c. The patient began a chromoendoscopic surveillance program in the year 2000. Pathologic diagnosis from biopsies obtained every 6 months showed intestinal metaplasia with low-grade dysplasia. In December 2001 moderate dysplasia was found, but a new endoscopy in March 2002 demonstrated low-grade dysplasia again. The patient continued under surveillance until October 2005, when gastric biopsies showed intermediate-grade dysplasia. DNA was obtained from the proband (subject II-5; Fig. 1, family c) and no genetic abnormality was found. After extensive discussion, the patient elected prophylactic surgery, and in November 2005 he underwent total gastrectomy. Pathologic analysis showed three foci of high-grade dysplasia in the gastric antrum. No invasive neoplasia was identified.

Discussion

Gastric cancer ranks second in terms of global cancer burden worldwide.[9] In Mexico, it is the second most frequent gastrointestinal cancer after colon carcinoma according to the most recent reports. Approximately 10% of cases of gastric cancer, both of the diffuse and intestinal types, show familial clustering.[10] The first clear evidence for a gastric cancer susceptibility genetic locus was the identification, in 1998, of a germline inactivating (truncating) mutation in the gene encoding for E-cadherin, called *CDH1*, in a large Maori family from New Zealand with kindred early-onset DGC.[1] From the original description, several families of diverse ethnic backgrounds have been reported with germline inactivating mutations of E-cadherin.[11–13] To our knowledge there are no previous reports of Hispanic families with HDGC. Pathologically, all the gastric cancers with *CDH1* mutations have shown invasive, poorly differentiated, DGC and display signet ring cells. The estimated cumulative risk for gastric cancer by the age of 80 years in HDGC families is 67% for men and 83% for women.[14] The age of onset shows marked variation between and within families, as what occurred in the families we reported. In addition to gastric cancer, several other cancers seem to occur at somewhat elevated incidence in HDGC families. Most notably, lobular breast cancer has been observed to occur in approximately 20 to 40% of women from families who carry *CDH1* mutations.[14] In our families, only cervical cancer was present in one of the members of family 3 (subject II-3), but this cancer is endemic in our country and has not been associated with HDGC.

The International Gastric Cancer Linkage Consortium has developed the clinical criteria defining HDGC families.[4] The suggested clinical criteria are two or more documented cases of DGC in first- or second-degree relatives, with at least one diagnosed before the age of 50 years (families a and b), or three or more cases of documented DGC in first- or second-degree relatives, independent of the age of onset (family c). The same consortium has established that carriers of the germline mutation in *CDH1* have a high lifetime risk of developing gastric cancer, but penetrance is less than 100%. The cumulative risk for developing gastric cancer increased steadily for each generation in men and women, and for individuals younger than 40 years of age, the relative risk of gastric cancer was several thousand times that of the general population. This phenomenon is well represented in the reported families: In all of them, DGC presented in more individuals and at a younger age in each generation.

Based on the clinical criteria for defining HDGC, approximately 25 to 50% of families meeting one of these criterions have identifiable germline mutations in the *CDH1* gene. The other families may have unidentified mutations in regulatory elements or mutations in unidentified genes that also contribute to HDGC. In family A, no germline mutation inactivating *CDH1* could be detected in the proband; however, there was a homozygous change in the promoter region of this gene (−160C>A). The latter variation may have some influence on DGC risk as it has been shown to reduce *CDH1* transcriptional activity in vitro. Actually, this single nucleotide polymorphism (SNP) has been associated with DGC in Italian,[15] but not in Korean populations.[16] At present, our group is conducting a case control study analyzing this SNP in a Mexican

population. Because this SNP cannot be used as genetic testing in the remaining family members, we must rely on clinical criteria for definition and management of these families. Two other reported families fulfill the criteria for HDGC; however, no genetic abnormality could be detected and the surgical decision was based on endoscopic findings.

Because not all patients with clinical criteria of HDGC have the mutation and between individuals with *CDH1* gene inactivating mutation the penetrance is at most 83% in female patients at the age of 80, clinical management in these patients is very challenging. Diagnosing gastric cancer in its early stages provides the best chance for curative resection but is a difficult task. Symptoms attributable to gastric cancer do not appear until the disease is more advanced and are generally nonspecific. When the diagnosis of gastric carcinoma is established, it is most often locally advanced, and in our country, up to 60% of patients present with stage IV disease.[17] Endoscopy is generally considered to be the best method for gastric cancer screening, but diagnosing diffuse gastric carcinoma is most difficult because these lesions tend not to form a grossly visible exophytic mass but rather spread submucosally as single cells or clustered islands of cells. Emerging new technologies for the diagnosis of early DGC lesions include the use of colored or florescence stains to aid in endoscopic detection.[6] However, as demonstrated in family a, even this approach with the aid of magnification could be misleading. On the other hand, two pathology reports from prophylactic gastrectomies have found foci of carcinoma in surgical specimens.[7,8]

At present, at the very least, regular endoscopic examination with random biopsies of the stomach should be performed every 6 to 12 months, probably starting 10 years earlier than the youngest affected patient in the family or by 25 years of age. Because mucosal abnormalities tend to occur late in DGC and delay the endoscopic diagnosis, prophylactic gastrectomy should be seriously considered as a means to prevent gastric carcinoma, although it clearly comes with morbidity. The decision to perform prophylactic gastrectomy should be balanced with age-based risk, based on age-specific penetrance data and many other personal factors. Therefore, it is essential that patients carrying the gene, but also patients that fulfill clinical criteria for HDGC, have the opportunity for extensive counseling, discussion, and reflection with knowledgeable clinicians, geneticists, and counselors before making the decision to proceed.

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Liver Resection for Primarily Unresectable Colorectal Metastases Downsized by Chemotherapy

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Abstract This study was performed prospectively to assess the effect of systemic chemotherapy (FOLFIRI protocol) in patients with initially unresectable colorectal liver metastases (CRLM) and, after performing liver resection in patients with downsized metastases, to compare the postoperative and long-term results with those of patients with primarily resectable CRLM. Records from a prospective database including all consecutive admissions for CRLM between June 2000 and June 2004 were reviewed. The analysis addressed all patients who underwent hepatectomy for primarily resectable CRLM (Group A), or underwent chemotherapy for primarily unresectable CRLM and among these, particularly the patients who were finally resected after downsizing of CRLM (Group B). There were 60 primarily resected patients (Group A). Forty-two other patients underwent chemotherapy; after an average of nine courses, 18 of them (42.8%) with significantly downsized lesions were explored and 15 (35.7%, Group B) were resected, whereas three had peritoneal metastases. Group B differed from Group A for a significantly higher rate of synchronous CRLM upon diagnosis of colorectal cancer, a larger size of CRLM upon evaluation in our center, and a lower rate of major hepatectomies (20.0% vs. 51.6 %) at surgery. No patient in Group B had positive margins of resection. Operative mortality was nil and morbidity was 20.0% in both groups. In Group B vs. Group A median survival after hepatectomy was 46 vs. 47 months (n.s), 3-year survival rate was 73% vs. 71% (n.s.), disease-free survival rate was 31% vs. 58% ($p=0.04$) and, at a median follow-up of 34 months, tumor recurrence rate was 53.3% vs. 28.3% (n.s.). Four out of the eight Group B patients with recurrence underwent a re-resection, and were alive at 9 to 67 months after the first resection. These results show that in about one-third of the patients with primarily unresectable CRLM, downsizing of the lesions by chemotherapy (FOLFIRI protocol) permitted a subsequent curative resection. In these patients, operative risk and survival did not differ from the figures observed in primarily resectable patients and, in spite of a lower disease-free survival with more frequent recurrence, re-resection still represented a valid option to continue treatment.

Keywords Liver resection · Unresectable colorectal liver metastases · Chemotherapy · "Downstaged" liver metastases · Downsized liver metastases

Introduction

Colorectal cancer is one of the commonest tumors with about 700,000 new cases diagnosed every year throughout the world.[1] About 50% of patients with colorectal cancer will develop liver metastases.[2,3] Hepatic resection is currently the only treatment option that can offer a chance of long-term survival, with 5-year survival rates ranging from 30% to 40%.[4–8] The natural history of untreated patients with colorectal liver metastases (CRLM) demonstrates no spontaneous long-term survival, with a median survival time of 6 to 18 months.[9–12] Chemotherapy can only marginally prolong life expectancy, and the chance of being alive at 5 years, for a patient with unresectable CRLM, even with gold-standard chemotherapy, is less than

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2%.[4,8,13–15] Therefore, surgery should be the first therapeutic option for CRLM. However, resectability is the limiting factor; indeed, it has been estimated that a curative resection can only be performed in 10–20% of all patients presenting with CRLM.[13,16] Until recently, the systemic administration of 5-fluorouracil (5-FU) with folinic acid (FA) has been the gold standard for chemotherapy of CRLM; however, the response rate is only 20–30%.[17–19] An increase in response rate of up to 50%[15] has been obtained by combining 5-FU-FA with irinotecan (FOLFIRI protocol) or oxaliplatin and by modifying delivery regimens.[17,20–25] This improved efficacy has resulted not only in an increased survival for patients treated with palliative intent, but also in the possibility for patients with initially unresectable CRLM to undergo curative surgical resection after downsizing of CLRM by chemotherapy.[13,16,26–28]

The aim of our study was to prospectively investigate the effect of a single line of treatment (FOLFIRI protocol) in patients with initially unresectable CRLM and, after performing liver resection in patients with downsized lesions, to compare the postoperative and long-term results with those of another group of patients with primarily resectable CRLM operated over the same period of time.

Materials and Methods

Patients

Since 1987 a prospective database has been established for all consecutive admissions related to possible liver resection. For this study, the records of all new patients evaluated for CRLM in the last 4 years (June 2000–June 2004) were reviewed. Cases with extrahepatic metastases and cases who had undergone previous treatments for their CRLM (chemotherapy, liver resection, or local ablation techniques such as radiofrequency or cryosurgery) before referral to our center were not considered. Patients involved in other specific strategies to achieve resectability (portal vein embolization, two-stage hepatectomy) and those undergoing intraoperative treatments (radiofrequency) were also excluded. After selection by these criteria, the patients with CRLM were divided into two groups: Group A (primarily resectable patients) and Group B (initially unresectable patients who became resectable after downsizing of CRLM by chemotherapy).

Criteria of Resectability

There were no predefined criteria of resectability with regard to number, size, and ill-location of the metastases, provided that a complete and macroscopically curative resection could be anticipated by leaving a sufficient volume of functional residual liver (at least 30% of nontumoral parenchyma). No patient had liver cirrhosis.

Chemotherapy

Initially unresectable patients underwent chemotherapy according to the FOLFIRI protocol. This line of treatment consisted of a combined regimen of i.v. irinotecan 180 mg/m^2 on day 1, i.v. folinic acid 200 mg/m^2 on day 1 and 2, i.v. 5-FU 400 mg/m^2 boluses on day 1 and 2, and i.v. 5-FU 1,200 mg/m^2 continuous 48-h infusion starting on day 1. The treatment was repeated every 2 weeks. Response to chemotherapy was assessed every 12 weeks (six courses) by a multidisciplinary team of oncologists, surgeons, and radiologists highly specialized in hepatic imaging, until the achievement of surgical resectability, assessed by CT scan of the abdomen, pelvis, and chest; in the presence of a good response, subsequent assessments were performed at closer intervals. The response to chemotherapy was determined by using the World Health Organization (WHO) criteria,[29] and defined as complete (disappearance of the lesion), partial (≥50% reduction in total tumor size) or minor response (<50% reduction in total tumor size). According to our policy, which is consistent with the concept developed by Adam et al.,[28] liver resections were performed as soon as resectability was technically possible, without waiting for a complete response to chemotherapy, and avoiding time intervals >2–3 weeks between the last course of chemotherapy and the operation.

Liver Resection

The operative technique has been described previously.[30,31] A complete exploration of the liver by palpation and intraoperative ultrasound was always carried out before proceeding with the operation. All resections were performed with the intent to remove all the neoplastic tissue (R0 resection) and to provide a tumor-free margin of at least 1 cm whenever possible. When a complete response to FOLFIRI was obtained, the sites of the disappeared metastases were always carefully evaluated to resect all the potentially residual neoplastic tissue. Anatomic liver resections according to the Couinaud classification were usually performed, and were classified as major (removal of ≥3 segments) and minor hepatectomies (removal of <3 segments).

Postoperative Treatment

All the resected patients from both groups were treated postoperatively by the FOLFIRI protocol for at least 6 months. The follow-up included evaluation by the use of tumor markers (CEA and CA 19-9) and hepatic

Table 1 Patient Data

	Group A Primarily Resectable (n=60)	Group B Primarily Unresectable (n=15)	P value
Mean age (range) yr	64 (38–81)	59 (32–75)	ns
Male/female	36/24	10/5	ns
Dukes stage C at diagnosis of colorectal cancer	33 (55.0%)	10 (66.6%)	ns
Liver metastases at diagnosis of colorectal cancer			
Synchronous	19 (31.6%)	12 (80.0%)	0.002
Size >5 cm	11 (18.3%)	7 (46.6%)	0.05
Number >3	6 (10.0%)	3 (20.0%)	ns

ultrasound every 4 months, and abdominal and chest CT scan every 6 months. If a recurrence was found, a new resection was performed whenever it was feasible.

Results

From June 2000 to June 2004, 102 consecutive patients admitted with CRLM and meeting the criteria of inclusion in the study were identified in the prospective database and enrolled in the study.

Sixty patients were primarily resected (Group A). Forty-two patients were initially unresectable and underwent chemotherapy according to the FOLFIRI protocol. After an average number of nine courses of chemotherapy, 18 of these patients (18/42=42.8%) with significantly downsized metastases underwent surgical exploration, and 15 (15/42=35.7%) were resected, whereas three were unresectable because of the presence of multiple peritoneal nodules. The 15 resected patients represent the second group (Group B) in our study. Group A (primarily resected patients) and Group B (patients resected after downsizing of CRLM) were comparable on the basis of all the considered criteria, except for a higher rate of occurrence of synchronous metastases at the time of diagnosis of colorectal cancer, and for a larger size of the metastases in Group B compared to Group A (Table 1).

The causes of primary unresectability in the 18 patients with downsized lesions were: lesions >5 cm in nine cases (two also unresectable after downsizing of lesions, due to peritoneal diffusion), ill-located lesions close to the hilum in four cases (one also unresectable after downsizing of lesions, due to peritoneal diffusion) or close to the caval–hepatic junction in two cases, and multinodularity in three cases.

Response to Chemotherapy

Real downsizing of CRLM after following FOLFIRI protocol, in terms of achievement of liver resectability, was thus observed in 15 out of the 42 treated patients (35.7%), whereas three other patients with an apparently satisfactory response had multiple peritoneal nodules at laparotomy. Most of the responses to chemotherapy in these 15 patients (12/15=80.0%) could be defined as partial response to chemotherapy, that is, ≥50% reduction in total tumor size; one patient (1/15=6.7%) had a complete response, and two patients (2/15=13.3%) a minor response (<50% reduction in total tumor size). The response could be defined as partial also in the three patients who became unresectable due to peritoneal diffusion. With regard to the other 24 primarily unresectable patients, 11 remained with stable disease and 13 had disease progression while undergoing chemotherapy.

Table 2 Liver Resections and Operative Complications

	Group A Primarily Resectable (n=60)	Group B Primarily Unresectable (n=15)	P value
Major hepatectomies	31 (51.6%)	3 (20.0%)	0.05
Resection margins			
Positive	2 (3.3%)	0	ns
<1 cm	21 (35.0%)	7 (46.7%)	ns
≥1 cm	37 (61.7%)	8 (53.3%)	ns
Blood transfusions	7 (11.7%)	2 (13.3%)	ns
Mortality	0	0	
Postoperative complications	12 (20.0%)	3 (20.0%)	ns
Specific	7 (58.3%)	1 (33.3%)	
General	5 (41.7%)	2 (66.7%)	

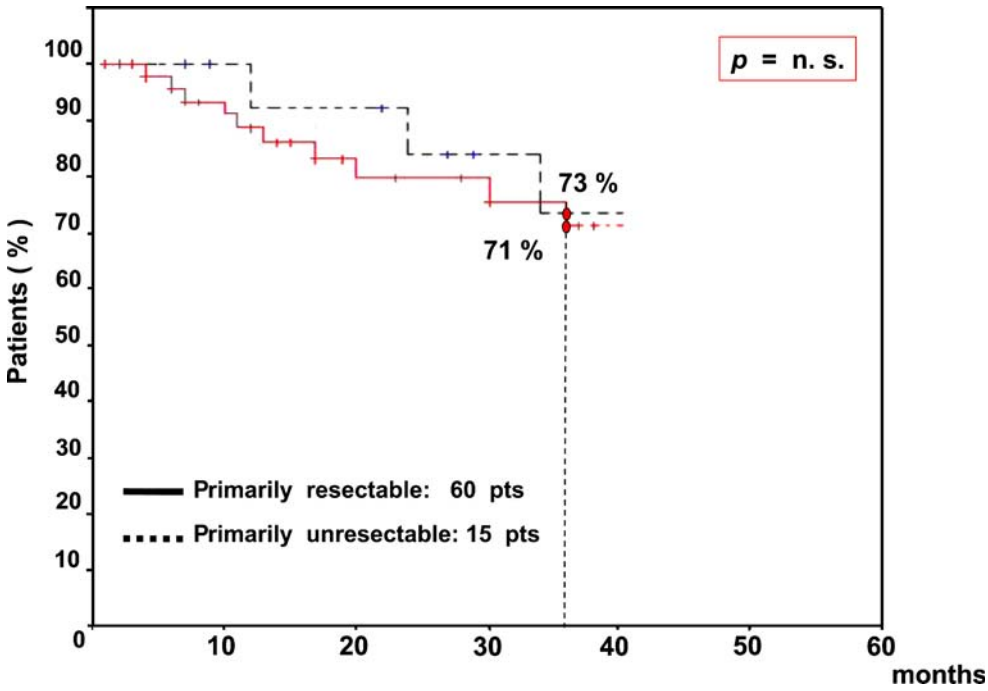

Figure 1 Overall survival after liver resection for primarily resectable CRLM (n=60) vs. primarily unresectable CRLM downsized by chemotherapy (n=15).

Liver Resection and Operative Complications

In Group A 31 patients (31/60=51.6%) underwent a major hepatectomy, whereas in Group B most of the patients (12/15=80.0%) underwent limited resections. No patient in Group B had positive resection margins. Mortality was nil, and morbidity and rate of blood transfusions were similar in both groups (Table 2). Morbidity was 20% in Group A, involving 12 out of 60 patients: seven patients had specific postoperative complications (four had biliary fistula, one transient liver insufficiency and two an infected fluid collection) and five had general complications (three had pulmonary infection, one sepsis, and one bowel obstruction). Morbidity was also 20% in group B, involving three out of 15 patients: one had an infected fluid collection, one a pleural effusion requiring percutaneous drainage, and

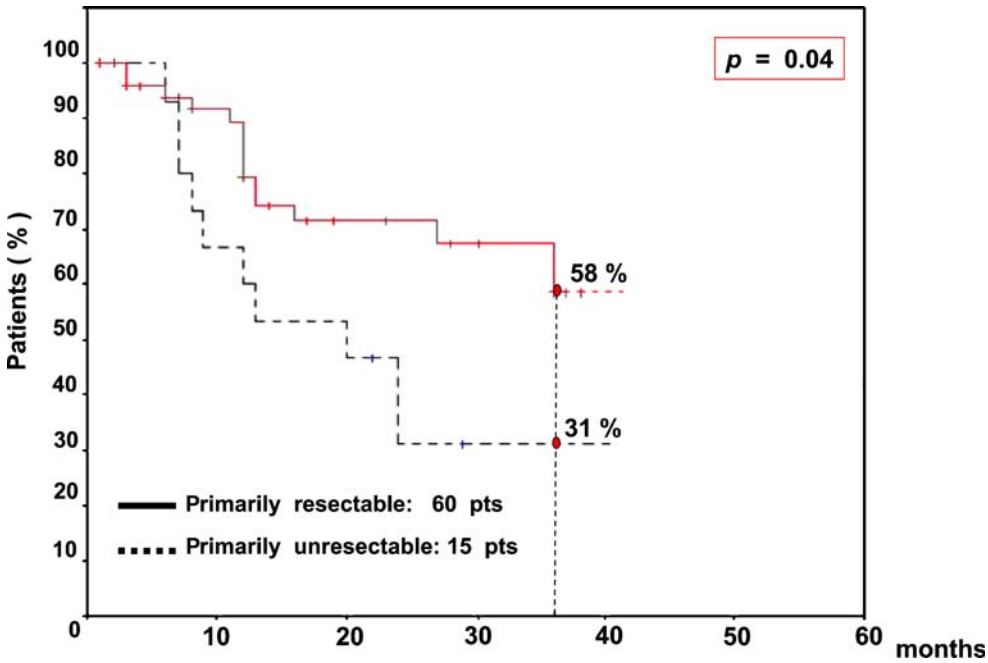

Figure 2 Disease-free survival after liver resection for primarily resectable CRLM (n=60) vs. primarily unresectable CRLM downsized by chemotherapy (n=15).

Table 3 Tumor Recurrence after Surgery

	Group A Primarily Resectable (n=60)	Group B Primarily Unresectable (n=15)	P value
Recurrence	17 (28.3%)	8 (53.3%)	ns
Hepatic	5 (29.4%)	2 (25.0%)	
Extra-hepatic	8 (47.1%)	0	
Hepatic + extrahepatic	4 (23.5%)	6 (75.0%)	

one had bowel obstruction) (Table 2). Data on liver steatosis in the final pathology was available in 12 out of 15 patients: seven had mild, and five moderate to severe steatosis.

Outcome

Median survival was 47 months in Group A (primarily resected patients) and 46 months in Group B (patients resected after downsizing of CRLM). Overall survival was also similar in the two groups, with a 3-year survival rate of 71% in Group A and 73% in Group B (difference not significant) (Fig. 1). However, disease-free survival rate was 58% in Group A and 31% in Group B (p=0.04) (Fig. 2).

At a median follow-up of 34 months (range 4–52), eight patients in Group B (8/15=53.3%) had developed tumor recurrence (hepatic in two cases, hepatic and extrahepatic in six). The difference in the rate observed in Group A (17/60=28.3%) did not reach significance (Table 3). Out of the eight patients with recurrence in Group B, four underwent re-resection (4/8=50%) and are alive at 9 to 67 months from the first resection. In Group A there were no re-resections; one patient was scheduled for the procedure at the time of completion of the study.

Discussion

Although liver resection remains the treatment of choice for patients with resectable CRLM, with a 5-year survival rate of 30–40%,[4–8] the rate of resectability in patients presenting with CRLM only ranges from 10% to 20%.[13,16]

Systemic administration of 5-FU prolongs survival in patients with unresectable CRLM, and an increased overall survival with chemotherapy, compared to no treatment, has been reported.[8] However, the rate of response to a standard protocol of chemotherapy (5-FU) is low (20–30%)[17–19] Hepatic arterial infusion (HAI) of the chemotherapeutic agent may improve its efficacy and increase the rate of response to 50%.[14] However, this is associated with increased toxicity and a higher incidence of complications.[14] Furthermore, the moderate increase in survival observed with HAI did not differ significantly from that observed with systemic chemotherapy.[8]

Over the years, many strategies have been developed to increase the rate of resectability of CRLM; these include portal vein embolization,[32,33] ablation techniques combined with hepatic resection (radiofrequency ablation and cryosurgery),[34,35] two-stage hepatectomy,[36,37] and, of course, new protocols of chemotherapy. With the introduction of new agents such as irinotecan and oxaliplatin, and of new methods of delivery such as systemic chronomodulated chemotherapy,[14,16] an improved efficacy has been observed in terms of overall survival and response rates.[17,20–25] Indeed, with the use of new chemotherapeutic lines combining 5-FU with irinotecan or oxaliplatin, response rates have increased to 40–50%.[15,17,20–25] These good results have motivated the use of chemotherapy for unresectable CRLM also with the intent to allow resection at a later time. Liver resection in patients with initially unresectable CRLM after downsizing of CRLM by chemotherapy has been described some years ago[16,38] and is now adopted more commonly. However, the rates of successful downsizing reported in the literature are variable, ranging from 13% to 30–40%.[14,16,28,38,39] These differences may be explained by the different criteria of unresectability and the different protocols of chemotherapy used in the various hepato-biliary units. With regard to definition of unresectability, we do not have predefined criteria; we simply consider resectable all the patients in whom negative margins of resection and a sufficient volume of functional residual liver (at least 30% of nontumoral liver parenchyma) can be anticipated before the operation. The aim of the operation is to remove all the neoplastic tissue with a free margin of resection of at least 1 cm, whenever possible. For instance, a margin <1 cm may be acceptable for a lesion in the close proximity of a major hepatic vessel. Thus, in our study the size, multinodularity, and ill-location of liver metastases were considered as criteria of unresectability only when denying the possibility of a curative hepatectomy. The absence of positive resection margins in our patients resected after downsizing of CRLM is consistent with the accurate preoperative selection performed.

We included in Group B patients with unresectable CRLM who had no extrahepatic disease, and had not undergone previous hepatic treatments (liver resections or local ablation techniques) or previous chemotherapy for advanced disease. All of them underwent a single protocol

of systemic chemotherapy (FOLFIRI protocol), which allowed subsequently a liver resection in 35.7% (15/42) of the treated cases. In several studies, in particular in those by Bismuth et al.,[16,28] lower rates of downsizing of CRLM (12.5% to 16.0%) were reported; however, these studies collected heterogeneous types of patients, also some having extrahepatic disease, over large periods of time and with the use of different chemotherapeutic agents. Conversely, we wanted to assess the impact of a single line of chemotherapy on patients with colorectal liver-only metastases observed over a recent and brief period of time (June 2000–June 2004), and this is likely to explain the observation of a higher rate of downsizing of CRLM.

We performed liver resection as soon as resectability was technically possible, without waiting for a complete response to chemotherapy, also because the disappearance of liver metastases on CT scan or MR after complete response does not correspond to disappearance of all cancer cells.[28,38] Chemotherapy does not bring about the complete eradication of metastatic disease, residual tumor continues to exist at the site of the metastases and will cause macroscopic recurrence.[40] Another important aspect is that a complete response to chemotherapy may increase the difficulty of intraoperatively localizing and resecting the lesions.

All our patients who were resected after downsizing of metastases (Group B) underwent hepatic resection only, without the use of other specific techniques to improve resectability (portal vein embolization, two-stage hepatectomy, and local ablation technique). The comparison has been made with patients who also underwent liver resection only (primary resection, Group A). Although a larger number of patients would be needed to allow stronger conclusions, it must be emphasized that the treatment and assessment of results in our Group A and B patients took place over the same brief period of time, and without selection bias or confounding by combined modalities of treatment.

The operative risk did not differ in Group B compared to Group A. Mortality was nil and morbidity was 20% in both groups. The absence of operative mortality in Group B is an important issue to highlight the adequacy of an aggressive policy in these patients. In Group B, compared to Group A, there was a similar 3-year survival rate (73% vs. 71%); however, with a significantly lower 3-year disease-free survival (31% vs. 58%) and a trend for more frequent recurrence (53.3% vs. 28.3%), which did not reach significance. This may reflect the presence of more aggressive diseases in patients in Group B and indeed, 80% of them presented already at initial diagnosis with synchronous CRLM. Furthermore, this is likely to bear a negative impact on survival in Group B patients when assessed at a greater distance (>3 years) from the operation. Conversely, it should be emphasized that Group B patients had initially unresectable disease. Therefore, these results, although assessed after only 3 years from liver resection, still deserve consideration.

Our policy after liver recurrence is to perform a second resection, independent of the site recurrence, whenever removal of all the neoplastic tissue is technically possible. Out of the eight patients in Group B who had recurrence, a re-resection was feasible in four patients (50%), who were alive after 9 to 67 months from the first resection. This is consistent with the adequacy of surgical treatment by re-resection, although the small number of cases does not allow general conclusions, and it is also possible that the development of a resectable recurrence reflects the presence of a less aggressive disease with good long-term survival.

Conclusion

Our study shows that systemic chemotherapy with the FOLFIRI protocol, in a selected group of patients, allowed the performance of liver resection in 35.7% of patients with primarily unresectable CRLM. In these patients, the operative risk and survival did not differ from the values observed in primarily resectable patients and, although disease-free survival was lower and recurrence more frequent, re-resection still represented a valid option to continue treatment.

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Survival and Variceal Rehemorrhage After Shunting Support Small-Diameter Prosthetic H-graft Portacaval Shunt

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Abstract This study was undertaken to report variceal rebleeding and survival after small-diameter prosthetic H-graft portacaval shunts (HGPCS) and to compare actual to predicted survival after shunting. Since 1987 we have prospectively followed patients after undergoing HGPCS to treat bleeding varices failing/not amenable to sclerotherapy/banding. One hundred and seventy patients underwent shunting. Cirrhosis was because of alcohol in 56%, hepatitis in 12%, both in 11%, and other causes in 21%. Child class was A for 10%, B for 28%, and C for 62%. Thirty-three patients died by 6 months, 54 by 24 months, 87 by 60 months, and 112 by 10 years, generally because of liver failure. Fifty-one patients are alive at a median of 48.3 months, 76 months±57.8 (mean ± SD). Variceal rehemorrhage was documented in 3 (2%) patients. By child class, 5-year/10-year survival rates were as follows: A 66.7/33.3%, B 48.6/15.6%, and C 29.2/7.0%. Actual survival was superior to predicted survival (Model for End-Stage Liver Disease [MELD]), ($p<0.001$).Variceal rehemorrhage in patients undergoing small-diameter prosthetic H-graft portacaval shunting was very uncommon. Actual survival was superior to predicted survival (MELD). Long-term survival paralleled degree of hepatic function, although long-term survival was possible even with very advanced cirrhosis. Application of HGPCS is encouraged.

Keywords H-graft portacaval shunts · Cirrhosis · Child class · Variceal rehemorrhage

Introduction

In the past, variceal bleeding because of cirrhosis and portal hypertension would have led to operative portasystemic shunting. Today, operative portasystemic shunting is uncommonly undertaken in the United States. Operative portasystemic shunting has fallen into disfavor because of perceived poor outcomes and the development of definitive therapy in liver transplantation. Unfortunately, liver transplantation is not available to all patients with advanced cirrhosis and portal hypertension.

The advent of the transjugular intrahepatic portasystemic shunt (TIPS) and liver transplantation has changed the landscape for portal decompression[1–4]. TIPS has gained widespread acceptance as a first-line therapy for the treatment of variceal bleeding because of portal hypertension, after being initially proposed as a "bridge" to transplantation. Proponents of TIPS believe that outcomes after shunting encourage its application and have led to extrapolation of indications beyond "bridging" to transplantation.

A recent randomized clinical trial documents the superiority of small-diameter prosthetic H-graft portacaval shunt (HGPCS) to TIPS in treating patients with bleeding varices because of portal hypertension and cirrhosis.[5] Also, a recent trial comparing distal splenorenal shunts to TIPS for patients of child class A or B documents improvements in resource allocation after distal splenorenal shunting.[6] Further contemporary experience with operative shunting will better define its role.

To better define outcomes after small-diameter prosthetic HGPCS, we have undertaken this study to report rates of

This study was presented at the American Hepato-Pancreato-Biliary Association, April 2005, Ft. Lauderdale, FL, USA.

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variceal rehemorrhage and long-term survival after shunting. Our hypotheses in undertaking in this study were that survival after shunting would reflect the poor prognosis associated with advanced cirrhosis, but would be, given the poor hepatic function of the patients operated upon, acceptable and would promote application of small-diameter prosthetic HGPCS. Furthermore, we hypothesized that bleeding because of portal hypertension would be well-controlled after shunting.

Methods and Materials

With the approval of the Institutional Review Board, patients with cirrhosis, portal hypertension, and variceal hemorrhage undergoing small-diameter prosthetic HGPCS were followed through a prospectively collected registry. All patients experienced bleeding from esophageal and/or gastric varices or portal gastropathy and all had failed or were not amenable to endoscopic therapy. Shunting was always undertaken as definitive therapy.

Before shunting, severity of cirrhosis was staged by child class. Portal vein patency was documented when opportunity allowed by color-flow Doppler ultrasound imaging. If there were questions regarding portal vein patency after color-flow Doppler ultrasound imaging, mesenteric angiography venous phase study was undertaken. Encephalopathy was assessed as none, mild (controlled through medical management and dietary restriction), or severe (hospital admission(s) required, despite therapy). Ascites was graded as absent, moderate (well-controlled with salt and fluid restriction and diuretics), or severe (profound abdominal distention refractory to salt and fluid restriction with maximum diuretic therapy). Circumstances of shunting were defined as elective (shunting scheduled for convenience in a stable patient), urgent (shunting undertaken within 24 h of encountering the patient), or emergency (shunting undertaken as soon as possible, certainly within 8 h of encountering the patient).

The technique of construction of the small-diameter prosthetic HGPCS was described.[7] In brief, the patients were operated upon through a transverse upper abdominal incision. A limited Kocher maneuver was undertaken. The prosthetic HGPCS were constructed utilizing externally ring-reinforced polytetrafluoroethylene (PTFE) with bevels at each end. Generally, an 8-mm diameter PTFE was used. If an adequate decrease in portal pressure was not noted with an 8-mm graft, then a 10-mm diameter externally reinforced PTFE graft was used. Bevels on the graft were oriented 90° to each other to accommodate for the orientation of the portal vein to the inferior vena cava. A portion of the caudate lobe was generally excised to facilitate placement of the shunt, which was never longer than 3 cm from toe-to-toe and 1.5 cm from heel-to-heel. A large window was cut in the anterior wall of the inferior vena cava to optimize outflow. Measurement of portal vein and inferior vena cava pressures were undertaken before and after shunting. With shunting several changes were sought: a decrease of portal pressure of more than

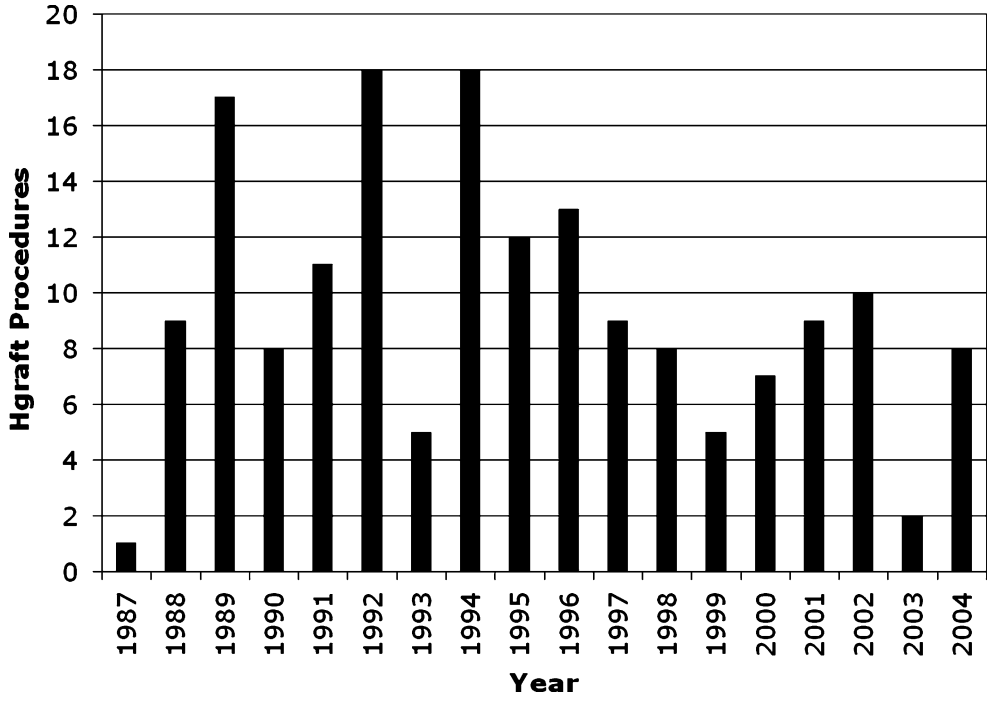

Figure 1 Frequency of shunting stratified by year.

Table 1 Descriptive Data of Patients Undergoing Small-diameter Prosthetic HGPCS

Demographics and other Descriptive Data	
Number of patients	170
Mean age ± SD (years)	55±13.2
Male/Female (%)	68/32
Cause of cirrhosis	
Alcohol	56%
Hepatitis A or B or non-AB	12%
Alcohol + hepatitis	11%
Others	21%
Circumstance of shunting	
Elective	123
Urgent	17
Emergency	30
Child class	
A	10%
B	28%
C	62%
MELD score(median, mean ± SD)	13, 14±5.5
Encephalopathy	22% present
Ascites	47% present

10 mmHg, a decrease in portal vein–inferior vena cava (PV-IVC) pressure gradient of 10 mmHg or more, and a postshunt PV-IVC pressure gradient of less than 10 mmHg. A thrill along the inferior vena cava just cephalad to the graft cava anastamosis helped confirm shunt patency.

Before hospital discharge, shunt patency was documented by transfemoral cannulation of the shunt. Venography was utilized, portal vein (PV) and inferior vena cava (IVC) pressures were measured, and a PV-IVC pressure gradient was determined. Direction and quality of portal flow was noted. Color-flow Doppler ultrasound was not utilized to follow patients after the small-diameter prosthetic HGPCS as orientation of the shunt to the "window" of the liver does not allow for assessment of shunt flow or patency. Color-flow Doppler ultrasound was utilized after shunting only to assess portal vein patency and portal vein flow, particularly for patients with new onset of ascites or sudden deterioration of hepatic function. Therefore, after shunting, all patients were followed to document shunt patency with transfemoral shunt cannulations, which were routinely undertaken at 1, 3, 5, and 10 years for surveillance of shunt patency.

Shunt failure was prospectively defined as an inability to place the shunt, irreversible shunt occlusion, major variceal rehemorrhage after shunting, death because of hepatic dysfunction, or liver transplantation, which was always undertaken to avoid imminent death because of liver failure. Major variceal hemorrhage was defined as gastrointestinal bleeding documented by endoscopy to be emanating from varices or portal gastropathy requiring hospitalization and blood transfusions. Time of transplantation was considered to be time of shunt failure, as transplantation was undertaken to avert death because of progressive hepatic dysfunction. The number of patients reported dead includes the number that were transplanted as transplantation was undertaken to avoid imminent death because of progressive hepatic dysfunction.

Preshunt Model for End-Stage Liver Disease (MELD) and predicted survival after shunting were calculated for

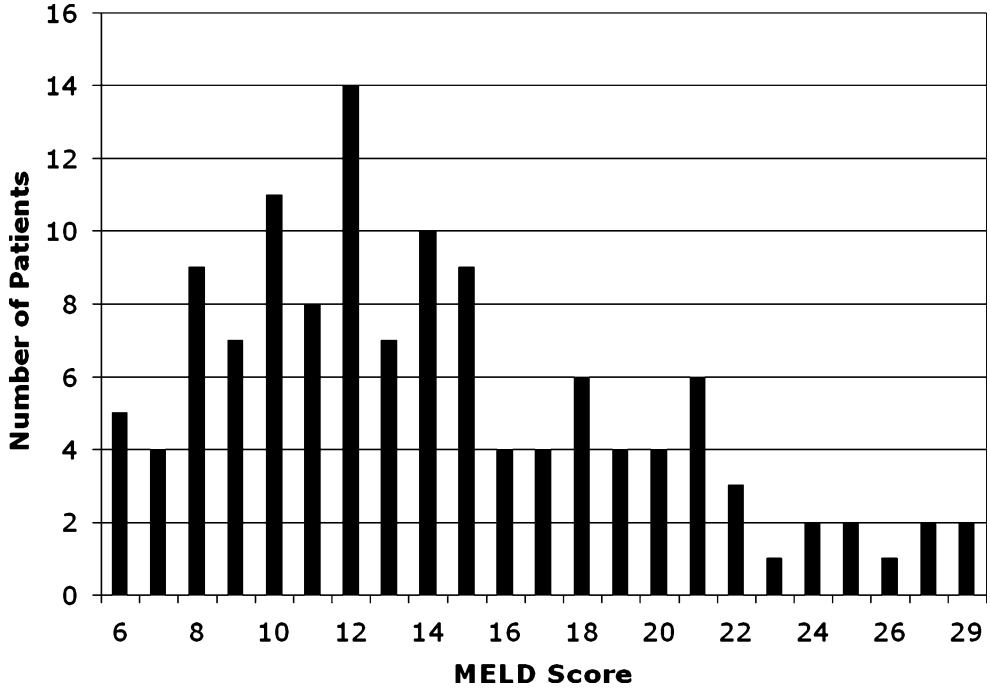

Figure 2 Distribution of MELD Scores.

Table 2 Pressure Changes with 8-mm Prosthetic H-Graft Shunts

	Preshunt	Postshunt	*p* value
Portal pressure (mmHg)	30±6.1	20±5.7	<0.01
PV-IVC gradient[a] (mmHg)	17±5.0	6±2.9	<0.01

Data are presented as mean ± SD. Comparisons are made utilizing paired Student *t*-test.
[a] Portal vein to inferior vena cava pressure gradient

patients retrospectively, given the necessary preshunt laboratory values.[8] MELD is a disease severity scoring system for adult patients, which uses serum creatinine, total bilirubin, and international normalized ratio to provide a numerical value between 6 (minimal hepatic dysfunction) and 40 (maximum hepatic dysfunction). Predicted survival could only be determined for patients with preshunt MELD scores. Comparisons between predicted and actual survival involve only those patients with preshunt MELD scores.

Data, when appropriate, are expressed as median, mean ± SD. Mean and median survival data were determined from survival curve analysis. Data are stored on a spreadsheet registry (Excel, Microsoft Corp., Redmond, WA, USA). Statistical comparisons between actual and predicted survival were undertaken utilizing True Epistat (Epistat Services, Richardson, TX, USA). When chi-square testing was used, methods for retrospective trials were utilized. Statistical significance was assigned with 95% probability.

Results

From 1997 through October 2004, 170 patients, 115 men and 55 women, have undergone small-diameter portasystemic HGPCS (Fig. 1) (Table 1). Their average age was 55 years±13.2. Cirrhosis was because of alcohol in 56%, hepatitis C in 12%, or both in 11% (Table 1). In the remaining 21% of the patients, cirrhosis was noted to be because of "other" causes: hepatitis B for five, autoimmune causes for two, methotrexate toxicity for two, alcohol and hepatitis B for one, biliary cirrhosis for one, sarcoidosis for one, hemochromotosis for one, lupus for one, sclerosing cholangitis for one, and unknown or cryptogenic causes for 21 patients.

Child class was A for 17 (10%), B for 47 (28%), and C for 106 (62%) patients. MELD scores were determined for 125 patients. The median MELD score was 13, the mean score was 14±5.5. Model for End-Stage Liver Disease scores were widely distributed (Fig. 2).

Before shunting, 38 (22%) patients suffered of encephalopathy, whereas 46 (27%) and 35 (20%) patients suffered from controlled or refractory ascites, respectively.

Bleeding emanated from esophageal varices in 75 (44%) patients, gastric varices/gastropathy in 18 (11%), or from both in 77 (45%) patients.

Circumstances of shunting were elective for 123 (72%) patients, urgent for 17 (10%), and emergency for 30 (18%) patients.

Shunting decreased portal vein pressures and PV-IVC pressure gradients in all patients (Table 2). The median decrease in the preshunt portal vein pressure was 10 mmHg; median postshunt portal vein pressure was 20 mmHg. The median decrease in the preshunt PV-IVC pressure gradient was 11 mmHg; median postshunt PV-IVC pressure was 6 mmHg.

Postshunt complications occurred in 48 (28%) patients. Gastrointestinal bleeding occurred in 6 (4%) patients after shunting before hospital discharge. Also, perioperative shunt occlusion occurred in 8 (5%) patients before discharge and was corrected operatively in 7 before discharge. One patient, a morbidly obese man with alcoholic cirrhosis, refused operative correction and was discharged from the hospital with an occluded shunt. Other complications included renal failure,[1] wound infection,[1] partial small bowel obstruction,[1] multiple system organ failure,[2] liver failure,[11] and ileus.[1] Thirty-day perioperative mortality occurred in 23 (13%).

Follow-up after shunting ranges from 1 month to 16 years. Fifty-one patients are alive. Median follow-up of surviving patients is 48.3 months. Median follow-up of deceased patients (i.e., median survival of deceased patients) is 26.1 months.

After discharge, 3 (1.7%) patients experienced gastrointestinal hemorrhage specifically because of portal hypertension and cirrhosis. In all, gastrointestinal hemorrhage occurred in 9 (5%) patients. Gastrointestinal hemorrhage was noted to be from varices or gastropathy in three patients, whereas in six patients bleeding seemed to be from other sources (e.g., ulcer disease and alcohol gastritis).

Perioperative 30-day mortality occurred for 23 (13%) patients, generally because of hepatic dysfunction. By

Table 3 Actual Cumulative Survival and Mortality after Shunting

Time after Shunting (months)	Cumulative Survival (%)	Cumulative Mortality (%)
1	87	13
3	81	19
6	80	20
12	74	26
24	66	34
36	57	43
48	48	52
60	37	63
120	11	89

Table 4 Five- and Ten-year Survival Stratified by Child Class

Child Class	5-Year Survival (%)	10-Year Survival (%)
A	67	33
B	49	16
C	29	7

6 months after shunting, 33 (20%) patients had died (Table 3). By 12 months, this increased to 42 (26%) patients. This increased by 5 and 10 years to 87 (63%) and 112 (89%) patients, respectively. In all, 114 patients have died; 2 died more than 10 years after shunting. Death was because of known causes in 84 (74%) of 114 patients. Death was most often because of progressive hepatic dysfunction (37 patients). Five patients died of cancer. Five died of progressive "body failure" and, ultimately, multiorgan system failure. Three patients died of pneumonia and sepsis.

Stratified by child class, survival at 5 and 10 years decreased with severity of hepatic dysfunction (r^2=0.06, p<0.001); in other words, survival after shunting correlated with degree of hepatic function (Table 4). In addition, by survival curve analysis, patients of child class A or B had significantly better survival than patients of child class C (p=0.0025, p=0.04, respectively). Preshunt MELD scores were determined for 125 patients. Preshunt MELD scores inversely correlated with survival by regression analysis (r^2=0.27, p<0.0001) (Fig. 3).

Predicted survival was determined for up to 2 years after shunting (Table 5). Actual survival was superior to predicted survival over this time period (Mantel–Haenszel chi-square analysis, p<0.001; Table 5) (survival curve analysis, p<0.001, Fig. 4). With time, differences between actual and predicted survival became more pronounced and accentuated the superiority of actual survival (Table 5).

As prospectively defined, shunt failure has occurred 131 times in 124 (73%) patients. The shunt was placed in all patients; in no patients could the shunt not be placed. Upon follow-up, terminal shunt occlusion occurred in three patients. One patient's shunt occluded within days of placement and he refused reoperation and was discharged with an occluded shunt. Two other patients were noted to have occluded shunts on routine follow-up years after shunting. One patient has remained well and one patient experienced variceal rehemorrhage and has successfully undergone hepatic transplantation. Four additional patients were transplanted, although one patient was doing very well and was without symptoms or complaints before transplantation. Nine patients experienced gastrointestinal bleeding, which must be assumed to be because of, at least in part, varices and portal hypertension; one of these patients died. As previously mentioned, 114 patients have died.

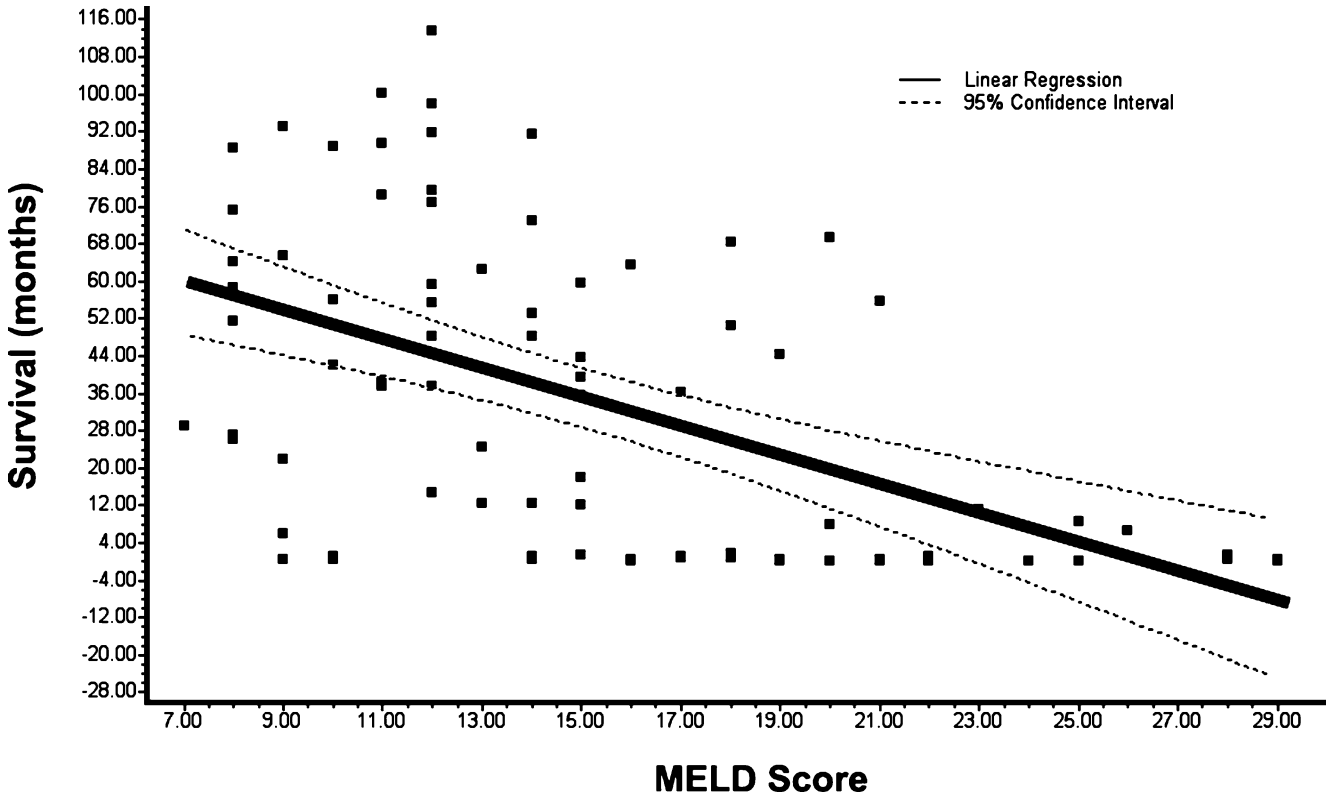

Figure 3 Regression analysis showing a significant relationship between survival and MELD score (asterisk).

Table 5 Actual vs Predicted Survival, Determined Utilizing MELD

Survival	1 day (%)	7 days (%)	3 months (%)	6 months (%)	12 months (%)	24 months (%)
Actual[a]	100	87	81	80	74	66
Predicted	99	96	68	60	54	43

[a] Greater than predicted survival, Mantel–Haenszel Chi-square, $p<0.001$

Discussion

Most surgery residents will not participate in the care of one patient with complicated portal hypertension and few surgeons undertake operative decompression for portal hypertension. In the United States, TIPS has become the favored approach for portal decompression and, both as a consequence and as a driving force, TIPS has limited the role of operative portal decompression. Today, there appears to be little broad-based support for operative portal decompression. Notably, TIPS was embraced by the great majority of health care providers, particularly nonsurgeons, caring for patients with complicated portal hypertension despite any trial documenting outcomes superior to these after operative portal decompression. This report of a relatively large number of patients documents that long-term survival after operative portal decompression attained through small-diameter prosthetic HGPCS correlates with extent of hepatic impairment and that survival after shunting is superior to predicted survival utilizing a conventionally accepted predictor of survival (MELD).

The patients undergoing small-diameter prosthetic HGPCS in this report were generally middle-aged males with advanced cirrhosis because of alcohol, and to a lesser extent, hepatitis. Most shunts were undertaken more than 5 years ago. As a consequence, extended follow-up is possible; median follow-up of surviving patients is more than 4 years. Furthermore, few patients are lost to follow-up.

Median predicted survival, determined utilizing MELD, was very nearly 1 year. A significant number, although a

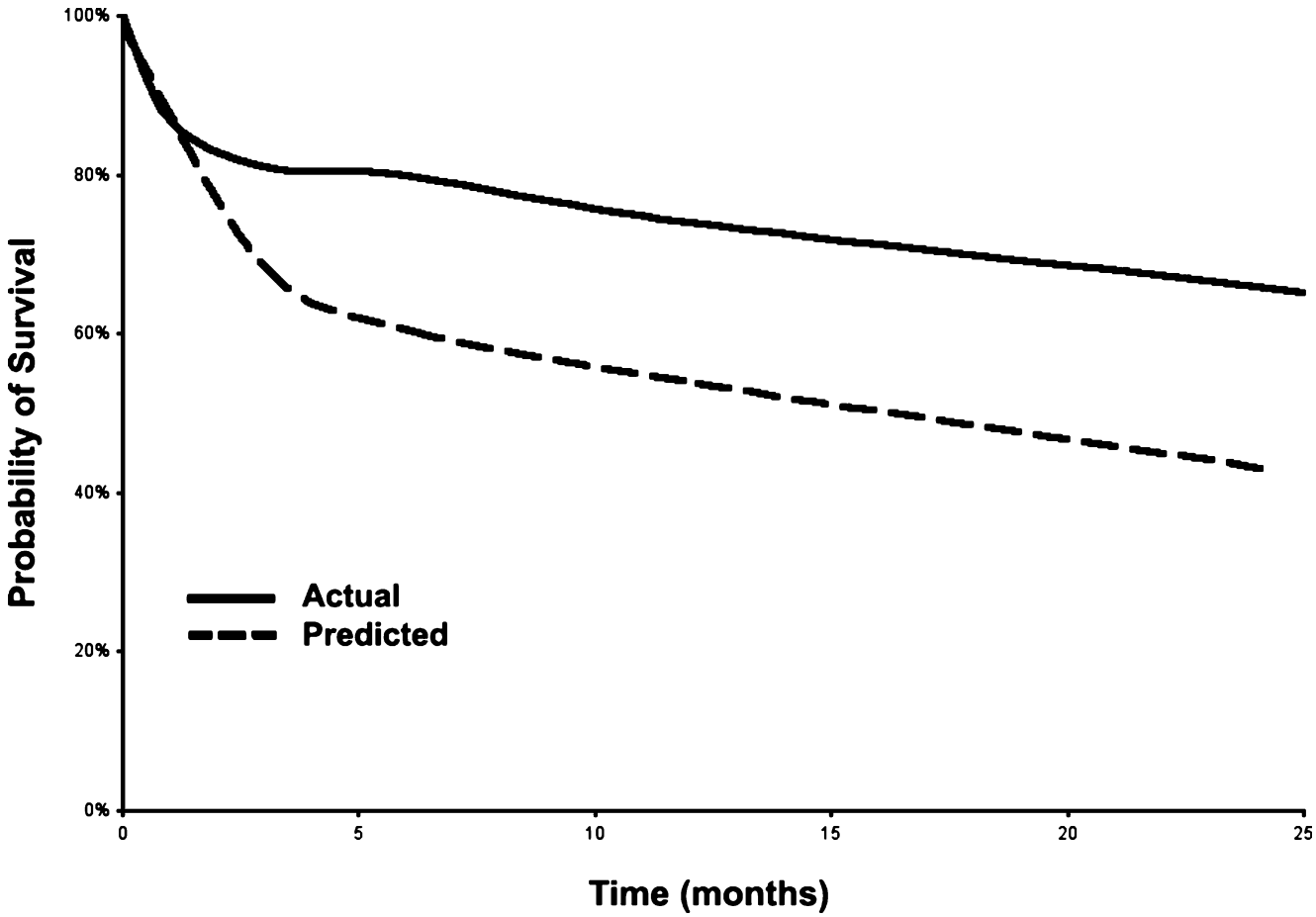

Figure 4 Predicted survival, determined utilizing MELD, and actual survival after shunting.

minority, had encephalopathy to some degree at the time of shunting. Nearly one half suffered of ascites at the time of shunting. This trial of "all comers," in general, consists of patients destined to do poorly.

Shunting, generally involving an 8-mm prosthesis, decreased portal pressures and PV-IVC pressure gradients. After shunting, the PV-IVC pressure gradient was within the normal range.

Ascites is well-controlled with this shunt because of reductions in the PV-IVC pressure gradient. Encephalopathy and hepatic dysfunction were not problems in the majority of patients in the early postshunt period. This was reported previously in more detail.[5,9]

With time, progressive hepatic dysfunction was an issue, being the major cause of late deaths. As expected, survival was better in patients with better liver function. Thus, patients of better child class or with lower MELD scores had better survival. On first glance, survival after small-diameter prosthetic HGPCS was not favorable. Thirty-day perioperative mortality was more than one in ten. Thereafter, the mortality rate decreased. One quarter of the patients was dead by 1 year. One third was dead by 2 years. Half were dead by 4 years. By 10 years, one in ten was alive after shunting. On their own, these numbers do not reflect impressive survival. However, when these survival numbers are considered in the light of underlying hepatic dysfunction, they are more favorably interpreted. Furthermore, when survival after small-diameter prosthetic HGPCS are compared to predicted survival as determined by MELD, survival in this trial is impressive. Model for End-Stage Liver Disease predicted that nearly one half of patients would be dead 1 year after shunting, nearly 100% more than were actually dead.

Actual survival was significantly better than predicted survival for up to 2 years after shunting, which is as far as MELD will predict survival after shunting. At 2 years after shunting, actual survival was more than 50% better than predicted. Graphically, differences between actual and predicted survival are striking (Fig. 4).

It is particularly notable that differences between actual and predicted survival increased with time. Within the first month after shunting, actual survival trended below predicted survival, reflecting the impact of a notable abdominal operation that diverts some blood flow away from the liver. However, by 3 months after shunting the curve of actual survival had crossed above the curve of predicted survival and remained there (Fig. 4).

Small-diameter prosthetic HGPCS controlled variceal bleeding in the vast majority of patients. Less than 1 in 20 patients experienced gastrointestinal bleeding after shunting. The specific causes and sources of the bleeding could always be a point of contention. Alcohol gastritis was implicated in our patients and was reported as such.[9] However, intellectual honesty must allow for the possible role of persistent or recurrent portal hypertension in gastrointestinal bleeding after shunting. Endoscopy and shunt study have failed in these patients, with exceptions noted, to document varices or shunt malfunction. Thus, a substantial proportion of the few patients experiencing gastrointestinal hemorrhage probably have alcohol recidivism as a major, if not primary, cause of their gastrointestinal hemorrhage. Also, for the patient dying with a gastrointestinal hemorrhage, progressive hepatic dysfunction, total body failure, and nutritional depletion played a major role in our inability to stop the progressive "ooze" of blood from broad areas in the distal esophagus, stomach, and duodenum.

Shunt failure was generally because of death in this series. Terminal occlusion occurred in less than a handful of patients. Transplantation was uncommon in this series, reflecting that many patients are neither eligible nor suitable for hepatic transplantation. For the few patients transplanted, the transplant procedure was uneventful and the postoperative course was routine. The shunt and the operation to place it did not seem to interfere with the transplantation operation, recovery from the operation, or long-term well-being.

Small-diameter prosthetic HGPCS control variceal bleeding. Although survival after shunting is superior to predicted survival, long-term survival, or lack thereof, promotes the application of hepatic transplantation. However, because of funding issues, alcoholism, and/or lack of psychosocial support, many patients are not candidates for transplantation or are not eligible for transplantation. Given that ineligibility, small-diameter prosthetic HGPCS seem to be a viable and preferred alternative, particularly given its superiority to TIPS and its relative conservation of resources.[5,10,11]

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Portal Vein Stenting for Portal Hypertension Caused by Local Recurrence After Pancreatoduodenectomy for Periampullary Cancer

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Abstract Portal hypertension after extensive abdominal surgery is an unusual cause of repetitive gastrointestinal bleeding. We report on a 68-year-old male patient with intermittent gastrointestinal bleeding secondary to portal vein stenosis caused by local recurrence of the distal bile duct cancer after pancreatoduodenectomy. Severe portal vein stenosis without sufficient development of portal venous collaterals was detected 25 months after pancreatoduodenectomy. Direct portography using a percutaneous transhepatic approach showed that there was a pressure gradient of 18 mmHg across the portal vein stenosis. Portal vein stenting successfully relieved portal hypertension and bowel congestion. Gastrointestinal bleeding episodes ceased after stenting. The patient died from liver metastasis 14 months after stent insertion and 39 months after pancreatoduodenectomy. Based on this case and literature reports, the possibility of portal vein stenosis should be considered for patients who have undergone pancreatoduodenectomy and then showed unexplained gastrointestinal bleeding. Percutaneous transhepatic stent insertion appears to be the treatment of choice for focal portal vein stenosis.

Keywords Pancreatoduodenectomy · Portal vein stenosis · Expandable stent

Abbreviations
CT Computed tomography
PV Portal vein

Introduction

Gastrointestinal bleeding after pancreatoduodenectomy is a major clinical concern as it was often associated with serious surgical complications such as pseudoaneurysm rupture or anastomotic marginal ulcer[1]. Such bleeding episodes are unusual several months after pancreatoduodenectomy. It is often difficult to correctly and promptly diagnose the cause of intermittent gastrointestinal bleeding episodes, and such diagnosis generally requires the undertaking of a variety of examinations.

Portal hypertension after extensive abdominal surgery is an unusual cause of repetitive gastrointestinal bleeding. Portal hypertension subsequent to pancreatoduodenectomy is most likely to be linked to prehepatic events, such as portal vein (PV) stenosis after concurrent resection and anastomosis of the PV, sequela of radiotherapy or local recurrence around the PV[2–5].

The present report details a case of intermittent gastrointestinal bleeding secondary to severe PV stenosis due to local recurrence of periampullary cancer after pancreatoduodenectomy. We describe the clinical manifestations and treatment using interventional PV stenting, and review the literature pertaining to this condition.

Case Report

A 68-year-old male patient had previously undergone pylorus-preserving pancreatoduodenectomy as treatment

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for distal bile duct cancer. Tumor on the specimen was a 3.5×2.5 ×2 cm moderately differentiated adenocarcinoma with lymph node metastasis around the superior mesenteric artery (14b; one of total eight lymph nodes). All surgical resection margins were tumor-negative. The patient recovered uneventfully from the operation. No adjuvant chemotherapy or radiotherapy was performed after consideration of the patient's age and physical condition.

Follow-up computed tomography (CT) 19 months later revealed a small hypodense lesion around the superior mesenteric artery (Fig. 1a), which was suggestive of local recurrence. No specific treatment was performed on this recurrent lesion because this lesion did not induce any symptom and its treatment did not appear to be tolerable considering his physical condition. However, after 3 months, the patient complained of intermittent episodes of melena. Repeated dynamic CT (Fig. 1b) and selective visceral arteriography did not demonstrate any arterial abnormality suspicious of gastrointestinal bleeding. Gastrofibroscopy revealed no abnormality of the esophagus or stomach. Subsequently, the recurrent mass became slightly enlarged. At this time, the patient displayed intermittent melena, by which hemoglobin level dropped to around 7 g/dL. Because the patient did not have anemia before onset of melena, causes of anemia other than acute blood loss was not suspected. Two units of pack red cells were infused per week. There was no evidence of iron-deficiency anemia. As the reticulocyte count was increased over 3%, erythropoietin was not administrated. Repeated gastrofibroscopy still revealed no definite abnormality other than hemorrhagic gastritis. There was no evidence of esophageal varix. As gastrointestinal bleeding scintigraphy revealed negative finding, capsule endoscopy was not performed.

Meanwhile, the general condition of the patient deteriorated gradually. Repeated CT revealed ascites and swollen bowels implicating peritoneal dissemination (Fig. 2a). At 25 months after pancreatoduodenectomy, we identified a severe stenosis of the PV in the absence of sufficient development of portal venous collaterals (Fig. 1c). A direct portogram was performed using a percutaneous transhepatic approach. There was a definite focal stenosis in the main PV with poor development of collateral veins (Fig. 3). There was a high pressure gradient of 18 mmHg across the PV stenosis. A metallic expandable stent of 1 cm in diameter and 5 cm in length was inserted into the stenotic region (Fig. 4). PV stenting successfully improved portal hypertension secondary to the focal PV stenosis without any procedure-related complications. Any type of anticoagulation was not administered. The patient was observed for 1 week after stent insertion, being anxious about further bleeding, and was then discharged after Doppler ultrasonography revealing full restoration of the portal flow. No bleeding episodes subsequently occurred. The bowel edema resolved completely over 1 month (Fig. 2b). The patient died from liver metastasis and peritoneal dissemination 14 months after PV stent insertion and 39 months

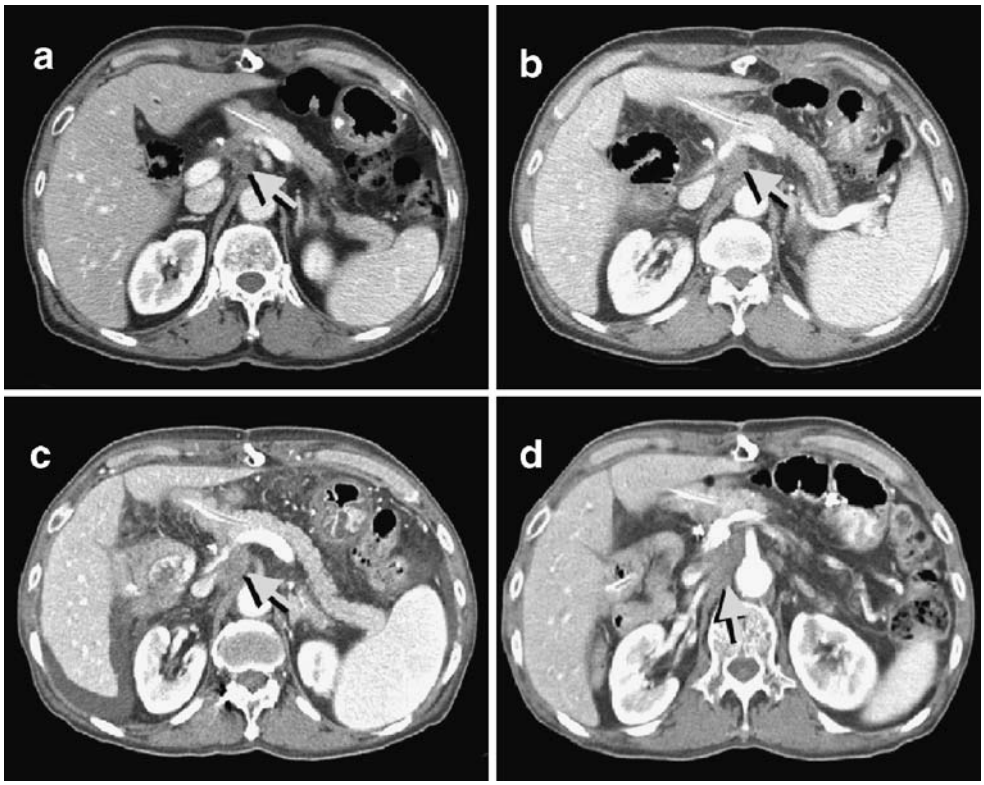

Figure 1 Serial follow-up using computed tomography after pancreatoduodenectomy. (a) At 19 months, a small hypodense lesion was detected around the superior mesenteric artery. (b) This lesion became slightly enlarged at 22 months. (c) At 25 months, the recurrent lesion enlarged significantly and encased the portal vein, resulting in severe portal vein stenosis. (d) At 28 months, 3 months after portal vein stenting, the portal vein remained patent despite extensive tumor encasement. The radio-opaque tube seen at the pancreaticojejunostomy site is an internal stent tube. Recurrent tumor is indicated by arrows.

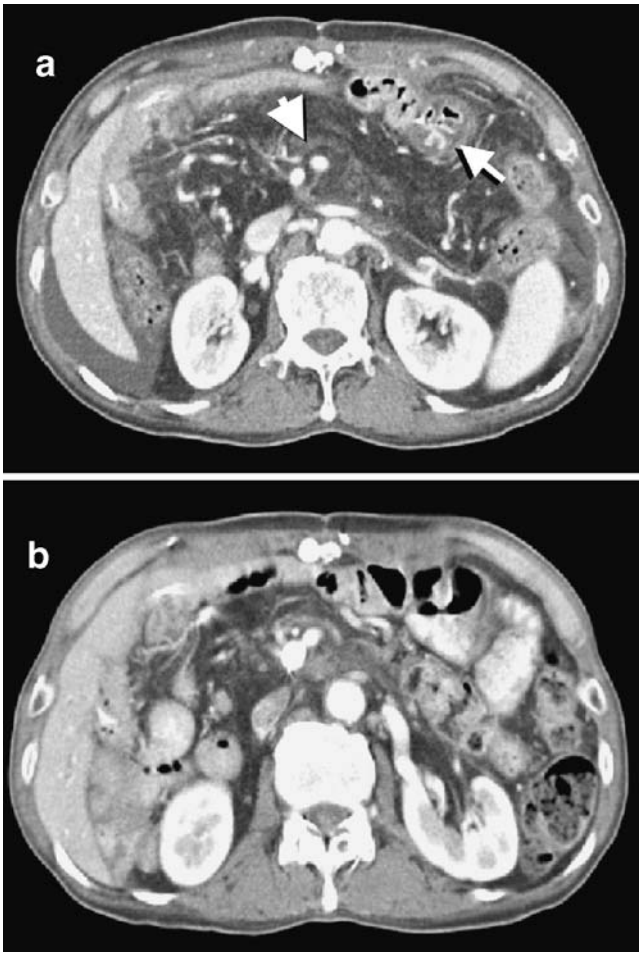

Figure 2 Resolution of the engorged small bowel loops after portal vein stenting. (a) At 25 months, the small bowel and mesentery were seriously thickened (arrows), leading to the misdiagnosis of cancer dissemination. (b) At 28 months, the small bowel and mesentery appeared normal after stenting and resolution of the portal hypertension.

after pancreatoduodenectomy. PV flow was well maintained on the last Doppler ultrasonography taken 2 weeks before his death.

Discussion

Postoperative PV stenosis is a surgical complication usually seen only after concurrent resection and anastomosis of the PV during pancreatoduodenectomy. Such PV stenosis is often transient and subclinical[6], and is therefore not often a focus of attention for the clinicians. Once a patient has passed the early recovery period after PD, it is not usually necessary to monitor the PV flow closely. However, it has been reported that patients undergoing pancreatoduodenectomy and concurrent intraoperative radiation therapy can experience late PV stenosis, which can be successfully treated using PV stenting[2,5].

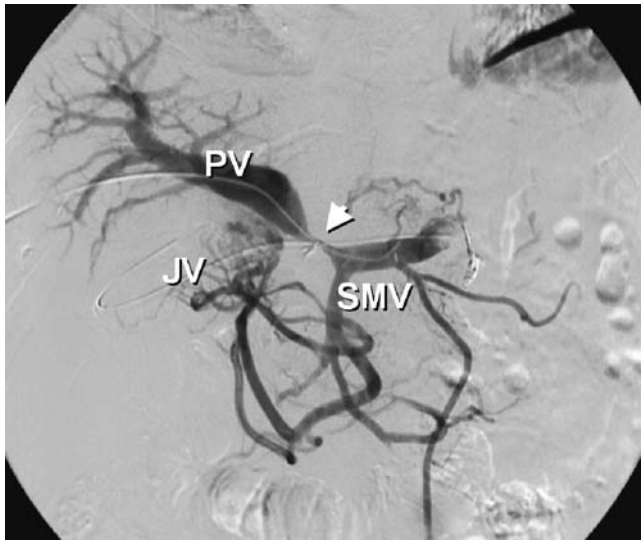

Figure 3 Direct portography revealed severe stenosis (arrowhead) of the portal vein (PV). There is noticeably poor development of portal venous collaterals around the superior mesenteric vein (SMV) branches. Jejunal varices (JV) were formed at the Roux-en-Y jejunal limb close to the hepatic hilum.

PV stenosis also occurs after local recurrence of malignant diseases. Because the areas around the celiac axis, superior mesenteric artery, and portal vein are common sites of periampullary cancer recurrence after pancreatoduodenectomy, local recurrence at these sites can encase the adjacent PV. Such a local recurrence seems to be more common in patients with metastasis to the lymph node 14.

However, as the process of tumor recurrence is usually insidious and slow, it is unlikely that this will cause

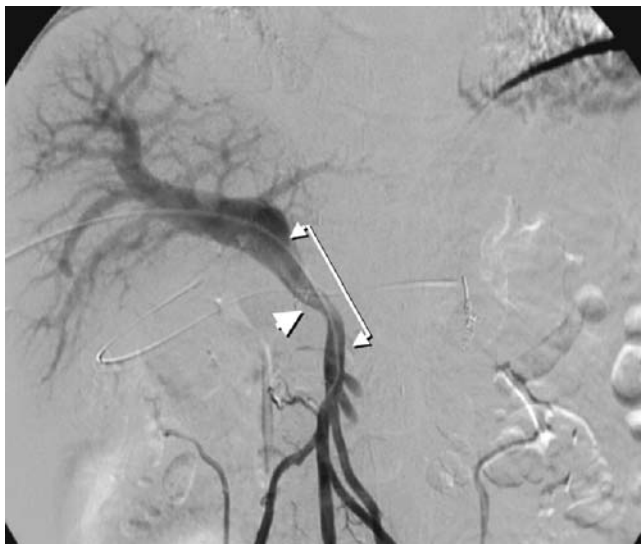

Figure 4 An expandable wall stent (bidirectional arrow) was inserted passing the portal vein stenosis (arrow head). Portal venous pressures proximal and distal to the stenosis were 27 and 9 mmHg, respectively. This pressure gradient of 18 mmHg completely disappeared after portal vein stenting.

significant PV stenosis soon after pancreatoduodenectomy. In addition, by the time the cancer may have recurred, many surgeons believe enough time has elapsed to have allowed development of portal venous collaterals before significant occlusion of the main portal flow pathway. In fact, most recurrent malignant lesions around the superior mesenteric artery have not been associated with significant PV stenosis, which could induce clinical portal hypertension. These typical scenarios indicate why unexplained gastrointestinal bleeding does not immediately suggest local recurrence-associated portal hypertension.

The present case indicates that venous collaterals do not always develop even when there is slow progressive encasement of the PV after pancreatoduodenectomy. In this patient, although the duration of progressive focal stenosis of the portal vein was estimated to be at least 3 months, we found little evidence of development of large-sized collaterals (Fig. 3). Direct portography indicated jejunal varices (Fig. 4). Had the patient not undergone pancreatoduodenectomy, there would have been a high probability to develop certain venous collateral pathways such as the coronary vein or minute veins at the omentum or hepatoduodenal ligament like in patients with liver cirrhosis. However, these potential pathways were not available due to precedent pancreatoduodenectomy, which is likely to explain the poor development of collaterals. It suggests that 3 months after pancreatoduodenectomy might be too short to develop new venous collaterals as opposed to dilatation of preexisting venous channels in patients who did not undergo pancreatoduodenectomy.

Portal flow stagnation would cause serious venous engorgement of the small bowel mesentery or jejunal varices[4,5]. As bleeding from such jejunal varices is usually intermittent and insidious in nature, such a diagnosis takes much effort and time. Endoscopic examination usually fails to identify a bleeding focus. Engorged jejunal veins are not always indicative of a bleeding site. Gastrointestinal bleeding scintigraphy often misses bleeding points except when bleeding is actively occurring. Three-dimensional reconstruction of the PV using CT data appears to be more beneficial for detection of PV stenosis than conventional cross-sectional CT images[6,7].

The only method to securely control bleeding from jejunal varices may be restoration of the normal portal flow pathway. After pancreatoduodenectomy, reexploration around the PV might not be feasible because of heavy adhesion and possible tumor invasion. Thus, a direct surgical approach does not seem to be indicated in most cases. Rather, it is generally accepted that PV stenosis is treated by transhepatic placement of an expandable wall stent as it is more effective and less invasive than other treatments (Table 1).

Since the 1990s, percutaneous transhepatic PV stenting has been used in nonsurgical patients with malignant PV obstruction to relieve the symptoms of portal hypertension[8]. Another common indication for PV stenting is PV complications after living donor procedures and split liver transplantations[9–12]. Our experience of PV stenting during living donor liver transplantation has shown that a surgical approach using a small jejunal vein branch can be a safe route if the percutaneous transhepatic approach appears risky due to a poor coagulation profile. We do not believe any anticoagulation treatment is necessary to prevent thrombosis within the expandable PV wall stent because the PV is a large-caliber high-flow vessel. Neointima will cover the exposed metal wires within a few weeks[13]. If the stenotic portion is not fully expanded and hypercoagulability concurrently exists, it may be reasonable to use anticoagulation treatment after stent insertion.

Before diagnosis of PV stenosis in the present patient, we had reasoned the bowel edema and ascites may have been caused by cancer dissemination. However, within a few weeks after PV stenting, bowel status rapidly returned to normal (Fig. 2b). It might be necessary to evaluate the PV thoroughly when the bowel on CT images appears too large or too aggravated considering the level of tumor progression.

In conclusion, when a patient who has undergone pancreatoduodenectomy shows unexplained gastrointestinal

Table 1 Outcomes of Percutaneous Transhepatic Portal Vein Stenting for Gastrointestinal Bleeding After Pancreatoduodenectomy

Authors	Publication year	Case no.	Cause of stenosis	Bleeding timing*	Complication	Anticoagulation	Rebleeding	Follow-up
Hiraoka et al., [6]	2001	1	IORT	1 yr	None	No	No	6 yr
Shimizu et al., [2]	2005	1	IORT	9 mo	None	No	No	54 mo
Yamazaki et al., [3]	2005	2	Tumor recurrence	NA	None	Yes†	No	14 mo and more
Ota et al., [4]		1	Unknown	8 yr	None	Yes	No	32 mo
Present case		1	Tumor recurrence	25 mo	None	No	No	14 mo

*Onset of gastrointestinal bleeding after pancreatoduodentectomy
†Only during stent-inserting procedure
IORT=intraoperative radiotherapy; NA=not available

bleeding, the possibility of PV stenosis should be considered. Percutaneous transhepatic stent insertion appears the treatment of choice as it is effective and minimally invasive.

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Predictive Factors of Malignant or Invasive Intraductal Papillary-Mucinous Neoplasms of the Pancreas

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Abstract The aim of this study was to identify useful preoperative diagnostic findings indicative of malignant or invasive intraductal papillary-mucinous neoplasms (IPMN) of the pancreas to determine an optimal operative procedure for IPMN. Sixty-two IPMNs, which consisted of 29 adenomas, 10 borderline tumors, 11 adenocarcinomas in situ, and invasive adenocarcinomas were reviewed from 1990 to 2003. Preoperative predictive factors of malignant or invasive IPMN were analyzed among 10 factors by univariate and multivariate analysis. Diameter of the main pancreatic duct (≧6 mm) and cytological examination of the pancreatic juice (the presence of malignant cells) were identified as independent predictive factors of malignant IPMN, and only cytological examination of the pancreatic juice (the presence of malignant cells) was identified as an independent predictor of invasive IPMN by multivariate analysis ($P<0.05$). There was no recurrent disease in patients with adenoma and adenocarcinoma in situ, whereas recurrences occurred in 6 of 12 patients with invasive IPMN. Patient survival in noninvasive IPMN was significantly ($P=0.018$) better than that in invasive IPMN (The overall 5-year survival rates were 87.2% and 49.2%, respectively). These results might be useful for selecting an optimal surgical procedure for IPMN.

Keywords Intraductal papillary-mucinous neoplasm (IPMN) · Pancreatic duct · Cytological examination · Pancreatic juice · Malignant IPMN · Invasive IPMN

Introduction

Since Ohhashi et al.[1] reported four cases of mucous-secreting pancreatic cancer for the first time in 1982, reports concerning intraductal papillary-mucinous neoplasms (IPMN) of the pancreas have strikingly increased in the English literature. This tumor is apparently distinct from mucinous cystic tumor of the pancreas by clinico-pathological features.[2] This tumor mainly develops at the pancreatic head in elderly men, and imaging examinations of this tumor demonstrate dilatation of the main and/or branch pancreatic ducts, which is caused by copious mucin secretion. Pathologicallly, IPMN is characterized by a tendency to spread intraductally and the dilated duct being lined with mucin-producing columnar epithelial cells, which frequently reveal papillary growth.[3,4] Prognosis of this tumor is more favorable than that of common ductal adenocarcinoma of the pancreas.[5–10]

Because IPMN is frankly malignant or premalignant,[11] surgical resection should be the first choice for treatment of IPMN. However, an optimal operative method for IPMN remains undetermined because IPMN includes a wide range of pathological conditions, such as adenoma, borderline tumor, adenocarcinoma in situ, and invasive adenocarcinoma.[3,4] According to the previous literature, extensive surgical resection including pancreatoduodenectomy is required for patients with invasive adenocarcinoma of IPMN because metastasis to the regional lymph nodes or invasion to the surrounding organs frequently occurs in

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Table 1 Operative Procedures for Intraductal Papillary-Mucinous Neoplasms of the Pancreas

Operative procedure	Adenoma (n=29)	Borderline tumor (n=10)	Adenocarcinoma in situ (n=11)	Invasive adenocarcinoma (n=12)
Pylorus-preserving PD	6	5	9	8
Conventional PD	1		1	1
Total pancreatectomy		1		2
Distal pancreatectomy				
With splenectomy	4	1		1
Without splenectomy	2			
PHRSD	7	2		
Segmental pancreatectomy	6			
DPPHR	1	1		
Enucleation	1			
Resection of the pancreatic process	1		1	

PD = pancretoduodenectomy, PHRSD = pancreatic head resection with segmental duodenectomy, DPPHR = duodenum-preserving pancreatic head resection

these patients.[5,8,12–14] Conversely, organ-preserving pancreatic resection is advocated for patients with adenoma or adenocarcinoma in situ of IPMN.[12,13,15–17] However, preoperative differential diagnosis between benign and malignant IPMN, or between noninvasive and invasive IPMN, remains difficult despite the development of new imaging modalities.[5,14,17–23] In the present study, the reliable predictive factors for malignant or invasive IPMN were sought by univariate or multivariate analysis to determine the optimal operative procedure for IPMN.

Patients and Methods

Sixty-two patients with IPMN of the pancreas who were treated at the Department of Surgery, Hiroshima University Hospital between June 1990 and September 2003 were reviewed retrospectively. All patients underwent tumor resection and had a confirmed pathological diagnosis. Preoperatively, all patients underwent transabdominal ultrasonography (US) and computed tomography (CT). In addition, endoscopic ultrasonography (EUS; 59 patients), endoscopic retrograde cholangiopancreatography (ERCP; 60 patients), and magnetic resonance cholangiopancreatography (MRCP; 42 patients) were performed.

Variables analyzed were gender, age at operation, location of the tumor, serum carcinoembryonic antigen levels, serum carbohydrate antigen 19-9 levels, size of the cystic mass, diameter of the main pancreatic duct, the presence of patulous papilla, the presence of mural nodule, and cytological examination of the pancreatic juice at ERCP. Size of the cystic mass and the presence of mural nodule were mainly measured by EUS. In three patients who did not undergo EUS, they were measured by transabdominal ultrasonography. Diameter of the main pancreatic duct was measured by images of ERCP. It was evaluated by MRCP in two patients who could not undergo ERCP because of Billroth II reconstruction after distal gastrectomy. The presence of patulous papilla was judged by ERCP, and two patients who could not undergo ERCP were judged by pathological examination of the resected specimens. The pancreatic juice for cytological examination was obtained by ERCP, but it could not be obtained for two patients because of the reason mentioned above.

Operative Procedures

Pylorus-preserving pancreatoduodenectomy was performed in 28 patients, conventional pancreatoduodenectomy in three, pancreatic head resection with segmental duodenectomy[16] in nine, duodenum-preserving pancreatic head resection in two, total pancreatectomy in three, resection of the pancreatic process in two, segmental pancreatectomy in six, distal pancreatectomy with splenectomy in six, distal pancreatectomy without splenectomy in two, and enucleation of the cystic tumor in one. There was no mortality in any of these patients (Table 1).

Cytological Examinations

The cytology sample of the pancreatic juice was immediately smeared on at least three slides, fixed in 95% ethanol, and stained with the Papanicolaou technique. All specimens were diagnosed as the guidelines reported by Robins et al.[24] Major criteria were as follows: (1) overlapping nuclei/crowded group, (2) nuclear contour irregularity, and (3) chromatin clearing and/or clumping. Minor criteria were as follows: (1) single epithelial cells, (2) necrosis, (3) mitosis, and (4) nuclear enlargement. To diagnose carcinoma, either

Table 2 Univariate Predictors of Malignant Intraductal Papillary-Mucinous Neoplasms of the Pancreas

Factor	Benign (n=39)	Malignant (n=23)	P value
Gender			
Male	31	15	0.215
Female	8	8	
Age, yr			
<65	14	8	0.929
≧65	25	15	
Location			
Head	26	22	0.008
Body–tail	13	1	
Serum CEA levels, ng/ml			
<2.7	18	10	0.862
≧2.7	18	11	
Serum CA 19-9 levels, U/ml			
<18	21	14	0.603
≧18	16	8	
Cyst size, mm			
<28	26	8	0.015
≧28	13	15	
Diameter of MPD, mm			
<6	31	7	<0.001
≧6	8	16	
Patulous papilla			
Yes	13	17	0.002
No	26	6	
Mural nodule			
Yes	24	19	0.082
No	15	4	
Cytology of the pancreatic juice			
Benign	37	9	<0.001
Malignant	1	13	

CEA = carcinoembryonic antigen, CA 19-9 = carbohydrate antigen 19-9, MPD = main pancreatic duct

two or more major criteria and one minor criterion or one major criterion and three minor criteria were required.

Pathological Investigations

After resection of the tumor, hematoxylin and eosin staining was performed. All resected specimens were examined pathologically and the tumors were classified into adenoma, borderline tumor, adenocarcinoma in situ, and invasive adenocarcinoma according to the World Health Organization[3] and the Armed Forces of Pathology [4] criteria. Based on this classification, pathological examination of the resected specimens revealed adenoma in 29 patients, borderline tumor in 10 patients, adenocarcinoma in situ in 11 patients, and invasive adenocarcinoma in 12 patients. For purposes of analysis, benign IPMN included both adenoma and borderline tumor, and malignant IPMN included both adenocarcinoma in situ and invasive adenocarcinoma, and noninvasive IPMN included adenoma, borderline tumor, and adenocarcinoma in situ. Duodenal invasion, choledochal invasion, and lymph node metastasis were also examined pathologically.

Survival

The outcomes after operation were collected by telephone or personal interview. If a patient died, we recorded the survival time after operation and the cause of death. For surviving patients, the postoperative survival time and status of recurrence were recorded. Postoperative survival was compared between benign and malignant IPMN, and between noninvasive and invasive IPMN. The median follow-up time after operation was 46 months (range 3 to 165 months) for the 62 patients. Fifty-five percent of the patients were followed for more than 3 years.

Statistics

Statistical comparison was carried out between benign and malignant IPMN and between noninvasive and invasive IPMN. The χ^2 test was used to compare two proportions for univariate analysis. Factors found to be significant on univariate analysis were subjected to multivariate analysis that was performed using a multiple logistic regression model. Postoperative survival was calculated using the Kaplan–Meier method and differences in the survival curves were compared by log-rank test. $P<0.05$ was considered statistically significant. Statistical analysis was carried out using the Macintosh version of StatView (version 5.0; SAS Institute, Cary, NC, USA).

Results

Predictive Factors of Malignant IPMN

Among the 10 factors, five factors, including location of the tumor, size of the cystic mass, diameter of the main pancreatic duct, the presence of patulous papilla, and

Table 3 Multivariate Predictors of Malignant Intraductal Papillary-Mucinous Neoplasms of the Pancreas

Factor	Relative risk	95% CI	P value
Diameter of MPD, mm			
<6	1.0	1.5–50.3	0.016
≧6	8.7		
Cytology of the pancreatic juice			
Benign	1.0	3.1–371.9	0.004
Malignant	33.9		

MPD = Main pancreatic duct

Table 4 Univariate Predictors of Invasive Intraductal Papillary-Mucinous Neoplasms of the Pancreas

Factor	Noninvasive (n=50)	Invasive (n=12)	P value
Gender			
Male	37	9	0.943
Female	13	3	
Age, yr			
<65	28	6	0.708
≧65	22	6	
Location			
Head	37	11	0.189
Body–tail	13	1	
Serum CEA levels, ng/ml			
<2.9	26	6	0.786
≧2.9	21	4	
Serum CA 19-9 levels, U/ml			
<24	34	5	0.087
≧24	13	6	
Cyst size, mm			
<26	31	2	0.005
≧26	19	10	
Diameter of MPD, mm			
<8	41	3	< 0.001
≧8	9	9	
Patulous papilla			
Yes	19	10	0.005
No	31	2	
Mural nodule			
Yes	31	12	0.010
No	19	0	
Cytology of the pancreatic juice			
Benign	42	3	< 0.001
Malignant	6	9	

CEA = carcinoembryonic antigen, CA 19-9 = carbohydrate antigen 19-9, MPD = main pancreatic duct

cytological examination of the pancreatic juice, were significantly associated with malignancy by univariate analysis (Table 2). Multivariate analysis was performed incorporating these five variables, and diameter of the main pancreatic duct (≧6 mm) and cytological examination of the pancreatic juice (the presence of malignant cells) were identified as independent predictive factors of malignant IPMN (Table 3).

Predictive Factors of Invasive IPMN

Predictive factors of invasive IPMN were sought by univariate and multivariate analysis. Size of the cystic mass, diameter of the main pancreatic duct, the presence of patulous papilla, the presence of mural nodule, and cytological examination of the pancreatic juice were significantly associated with invasive IPMN by univariate analysis (Table 4). These five factors were entered into multivariate analysis. Only cytological examination of the pancreatic juice (the presence of malignant cells) was identified as an independent predictor of invasive IPMN (Table 5).

Table 5 Multivariate Predictor of Invasive Intraductal Papillary-Mucinous Neoplasms of the Pancreas

Factor	Relative risk	95% CI	P value
Cytology of the pancreatic juice			
Benign	1.0	2.6–137.1	0.004
Malignant	18.7		

Pathological Evaluation

There were 28 main duct IPMNs and 34 branch duct IPMNs. Main duct IPMNs consisted of five adenomas, six borderline tumors, seven adenocarcinomas in situ, and 10 invasive adenocarcinomas, whereas branch duct IPMNs consisted of 24 adenomas, four borderline tumors, four adenocarcinomas in situ, and two invasive adenocarcinomas. The rate of malignant IPMN in main duct type (61%) was significantly (P<0.001) higher than that in branch duct type (18%). A variety of surgical procedures including organ-preserving pancreatic resection were performed for patients with adenoma or borderline tumor. In contrast, extended pancreatic resection with lymph node dissection was mainly performed for patients with adenocarcinoma in situ or invasive adenocarcinoma (Table 1). Duodenal invasion, choledochal invasion, and lymph node metastasis were not found in patients with adenoma, borderline tumor, and adenocarcinoma in situ. However, among the 12

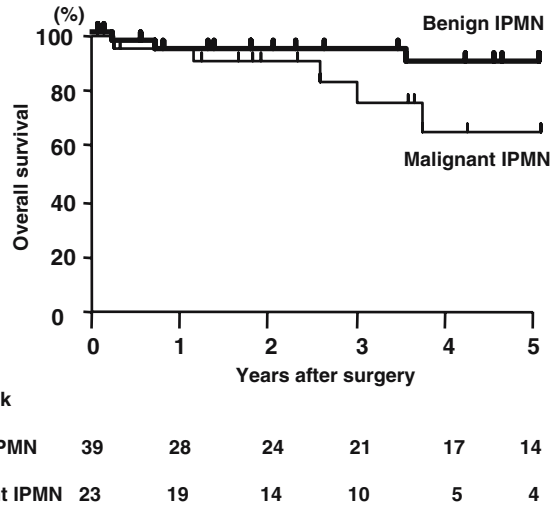
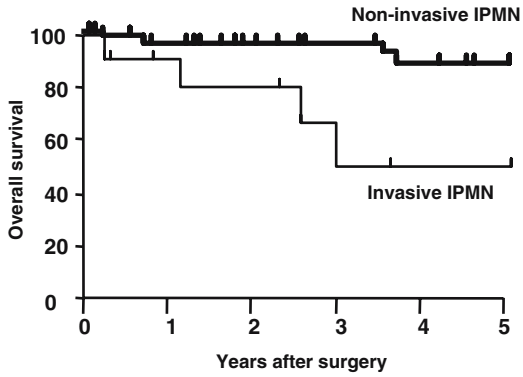


Figure 1 Survival in patients with benign IPMN and patients with malignant IPMN (P=0.241 by log-rank test).



No. at risk						
Non-invasive IPMN	50	39	31	27	20	16
Invasive IPMN	12	8	7	4	2	2

Figure 2 Survival in patients with noninvasive IPMN and patients with invasive IPMN (P=0.018 by log-rank test).

patients with invasive adenocarcinoma, choledochal invasion occurred in three (25%) patients, duodenal invasion in five (42%), and metastasis to the regional lymph nodes in four (33%). *There were three patients with invasive carcinoma who did not develop choledochal invasion, duodenal invasion, and metastasis to the regional lymph nodes.*

Survival

Four patients with adenoma and one patient with adenocarcinoma in situ died of other diseases, but there was no recurrent disease in patients with adenoma, borderline tumor, and adenocarcinoma in situ. Four patients with invasive adenocarcinoma, which underwent pyrolus-preserving pancreatoduodenectomy (two patients), conventional pancreatoduodenectomy (one patient), and total pancreatectomy (one patient), died of recurrent disease of IPMN. Two developed liver metastasis, and two had peritoneal dissemination. Another two patients with invasive adenocarcinoma, which underwent pyrolus-preserving pancreatoduodenectomy (one patient) and total pancreatectomy (one patient), were alive with liver metastasis. However, the other six patients with invasive adenocarcinoma, which underwent pylorus-preserving pancreatoduodenectomy (five patients) and distal pancreatectomy with splenectomy (one patient), have been alive without recurrence for 7 to 118 months although four of six patients had lymph node metastasis or choledochal invasion. The overall 5-year survival rates were 89.2% in patients with benign IPMN, and 62.5% in patients with malignant IPMN. The difference in the survival rates between the two groups was not significant (P=0.241) (Fig. 1). In contrast, the overall 5-year survival rates in noninvasive and invasive IPMN were 87.2% and 49.2%, respectively, and patient survival in noninvasive IPMN was significantly better than that in invasive IPMN (P=0.018) (Fig. 2).

Discussion

There have been many reports concerning the survival of patients with IPMN. According to these reports, noninvasive IPMN including adenoma, borderline tumor, and adenocarcinoma in situ recurs infrequently after complete resection, and survival is much more favorable regardless of the degree of epithelial dysplasia in the tumor. The 5-year survival rate of noninvasive IPMN has been reported to be 85–100%.[5–10] In the present study, there was no death related to recurrence of the tumor in noninvasive IPMN, and the 5-year survival rate of noninvasive IPMN was 87.2%. Conversely, patient survival is very poor when the tumor has reached the stage of invasive IPMN. Invasion to the duodenum or choledochus, perineural invasion, and lymph node involvement frequently occur in patients with invasive IPMN. The 5-year survival rate of invasive IPMN was reported to be 24–65%.[5–10] Similar to these reports, six of the 12 patients with invasive IPMN recurred in our series, and the 5-year survival rate of invasive IPMN was 49.2%. However, six patients with invasive IPMN, which underwent extended pancreatic resection, have been alive without recurrence during the follow up periods of 7 to 118 months, although four of six patients had lymph node metastasis or choledochal invasion. Based on these results, extended pancreatic resection with lymph node dissection might be recommended for invasive IPMN because invasive IPMN frequently invades the surrounding organs, and involves the regional lymph nodes. In contrast, organ-preserving pancreatic resection should be advocated for noninvasive IPMN because only complete resection of the tumor results in favorable prognosis. For these reasons, preoperative differential diagnosis between noninvasive and invasive IPMN is more important than that between benign and malignant IPMN for selecting an optimal operative procedure for IPMN.

Many investigators have attempted to make preoperative differential diagnosis between benign and malignant IPMN using various imaging modalities, and have reported that predictive factors of malignant IPMN are jaundice,[22] abnormal liver function test,[22] elevated serum CA19-9 levels,[22] tumor size (≧30 mm[2,5] or ≧40 mm[19]), dilatation of the main pancreatic duct (≧7 mm[23] or ≧10 mm[19]), presence of mural nodule,[2,5,19] and patulous papilla,[25] using univariate analysis. However, there have been few reports concerning multivariate analysis on differential diagnosis between benign and malignant IPMN. Kitagawa et al.[22] reported that a predictor of malignancy was any abnormal liver function test, and another author reported that independent predictive factors were the presence of mural nodule and diameter of the main pancreatic duct (≧7 mm).[23] In our series, on univariate analysis, location at the pancreatic head, cyst size (≧28 mm), diameter of the

main pancreatic duct (≧6 mm), patulous papilla, the presence of mural nodule, and cytological examination of the pancreatic juice (the presence of malignant cells) were significantly associated with malignant IPMN, and using multivariate analysis, diameter of the main pancreatic duct (≧6 mm) and cytological examination of the pancreatic juice (the presence of malignant cells) were the independent predictors. These results are almost identical to the previous reports.

There has been only one report concerning predictive factors of invasive IPMN in the previous literature. Sugiyama et al.[23] analyzed 62 patients with IPMN, and reported that seven factors, including the presence of symptoms, jaundice, main duct or combined type, tumor location, the presence of mural nodule, diameter of the main pancreatic duct (≧7 mm), and patulous papilla, were significant in the prediction of invasive IPMN by univariate analysis, and three variables (mural nodule, main duct or combined type, and jaundice) remained significant on multivariate analysis. In this study, five factors were associated with invasive IPMN by univariate analysis, and only cytological examination of the pancreatic juice (the presence of malignant cells) was a significant predictor of invasiveness.

There have been several reports concerning preoperative cytological examination of the pancreatic juice. Uehara et al.[26] reported that cytological examination of aspirated pancreatic juice during ERCP was a better method than EUS for differentiating between benign and malignant IPMN. Inoue et al.[27] reported that the combination of cytological examination and telomerase activity in the pancreatic juice was useful for distinguishing benign from malignant IPMN preoperatively. In contrast, several authors reported that the result of cytological analysis of the pancreatic juice from the pancreatic duct was disappointing.[19,21,22] The problem with cytological examination is that the sensitivity of this examination is low, although specificity is high, as reported by several investigators.[21,22] For this reason, few pancreatic duct cells can be obtained by ERCP when IPMN is earlier-stage disease such as adenocarcinoma in situ. However, adequate pancreatic duct cells can be obtained from invasive IPMN, so the sensitivity increases in invasive IPMN. As a result, cytological analysis of the pancreatic juice is a significant predictor of invasive IPMN in our study.

Differential diagnosis by molecular examination, including K-ras point mutation,[28] p53 overexpression,[29] and telomerase activity,[27,30] has recently been reported for distinguishing benign from malignant IPMN, using the pancreatic juice obtained by ERCP preoperatively. These molecular examinations are useful for distinguishing benign from malignant IPMN. Concerning the differential molecular diagnosis between noninvasive and invasive IPMN, Luttges et al.[31] reported that the result that noninvasive IPMN lacks MUC1 expression but expresses MUC1 when they become invasive might be used as a marker indicating the step of progression from noninvasive to invasive IPMN. Although molecular diagnosis might be useful for the differential diagnosis of IPMN, further studies are required to determine definite differential diagnosis.

Various authors have tried to assess the malignant or invasive potential of IPMN by imaging methods including US, CT, ERCP, MRCP, EUS, and intraductal ultrasonography.[20] However, as demonstrated in this study, what is important for assessing the malignant or invasive potential of IPMN is evaluating the size of the cystic mass, the diameter of the main pancreatic duct, the presence of patulous papilla, the presence of mural nodule, and cytological findings of the pancreatic juice. EUS is useful for evaluating the size of the cystic mass, the diameter of the main pancreatic duct, and the presence of mural nodule, whereas ERCP is useful for evaluating the presence of patulous papilla and cytological findings of the pancreatic juice. EUS and ERCP are essential for assessing the malignant or invasive potential of IPMN.

Conclusions

Predictors of malignant IPMN were diameter of the main pancreatic duct (≧6 mm) and cytological examination of the pancreatic juice (the presence of malignant cells), and only cytological examination of the pancreatic juice (the presence of malignant cells) was identified as an independent predictor of invasive IPMN by multivariate analysis. These results might be useful for selecting an optimal operative procedure for IPMN of the pancreas.

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Staple Line Reinforcement Reduces Postoperative Pancreatic Stump Leak After Distal Pancreatectomy

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Abstract Pancreatic stump leak is the major source of morbidity after stapled distal pancreatectomy. We hypothesized that reinforcement of the stapler system with a buttress mat can improve leak rates when compared to standard stapling alone. We performed 13 consecutive distal pancreatectomies using our reinforced stapler system, forming our experimental group. A historical control group was composed of 18 patients undergoing stapled pancreatic closure without reinforcement. The main outcome measure was pancreatic leak in the postoperative period. Pancreatic leaks included fistulas and fluid collections (sterile or infected). Hospital length of stay was recorded as a secondary measure. Postoperative pancreatic leak rate was zero in the experimental group, but 39% in the control group ($P=0.025$). Development of a pancreatic leak resulted in prolonged hospital stays: 13.6 vs 8.3 days ($P<0.03$). We conclude that staple line reinforcement is a simple and effective method of reducing pancreatic stump leakage after distal pancreatectomy. The economic impact of lower leak rates is reflected in significantly shorter hospital stays. The results of our study should be validated in a randomized controlled trial.

Keywords Pancreatectomy · Stapler · Fistula

Introduction

An ideal method to close the pancreatic stump after distal pancreatectomy remains elusive. A variety of techniques have been postulated through the years, and these can be grouped into two main categories: hand-sewn vs stapled. Perhaps the most popular hand-sewn technique is stump closure with full-thickness mattress sutures and individual ligation of the pancreatic duct[1]. Alternatively, simple division of the pancreas with a linear stapler has been shown to be safe and gives equivalent results[2]. More recent studies have focused on the roles of octreotide[3], fibrin glue[4,5], or pancreatic duct stenting[6] as adjuncts to surgical technique, but have not demonstrated a significant benefit.

Leakage from the pancreatic stump is the main source of morbidity after distal pancreatectomy. As such, it is the primary measure by which different pancreatic closure techniques can be compared. A recent meta-analysis of leak rates after distal pancreatectomy involving 10 studies and 1,080 patients underscores the magnitude of the problem[7]. Stump leakage ranges from 0 to 61%, with an average of 21%. The meta-analysis could not identify an individual stump closure technique with optimal results, and no significant difference between hand-sewn and stapled techniques could be demonstrated.

The goal of this study was to test a new staple closure method. Stapled closure techniques are rapidly gaining popularity, particularly with the introduction and adaptation of laparoscopic distal pancreatectomy[8]. Our study evaluated whether reinforcement of the pancreatic staple line can improve stump leak rates over standard (nonreinforced) stapled closure.

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Methods

Patients included in the study underwent elective stapled distal pancreatectomy and splenectomy at our institution between September 2003 and May 2006. No trauma cases were included. Pancreatic transection was done with a linear stapler in all cases. All operations were performed by one of four surgeons (including authors REJ and WPM).

The main therapeutic intervention involved reinforcement of the pancreatic closure staple line using a biodegradable buttress mat. The addition of the reinforcement "sleeves" to the stapler cartridges takes seconds and does not change the firing mechanism of the stapler gun (Fig. 1). This material is commercially available from W.L. Gore (Newark, DE, USA) and is marketed under the name Gore Bioabsorbable Seamguard® Reinforcement. Seamguard® is approved for reinforcement of staple lines in pulmonary, bariatric, and colon surgery. The use of this product in pancreatic surgery is an off-label application.

All consecutive patients treated between July 2005 and May 2006 had staple line reinforcement and constituted the experimental group. These patients were entered prospectively into our database. A control group was collected retrospectively and included all stapled (nonreinforced) distal pancreatectomies performed between September 2003 and June 2005.

The main outcome measure was pancreatic stump leak in the perioperative period (30 days). Pancreatic stump leak included fistulas and fluid collections (sterile or infected). Fistula was defined as surgical drain output greater than 30 cm^3/day of amylase-rich fluid beyond postoperative day 5. All patients had at least one surgical drain placed at the time of surgery, and drain fluid amylase was routinely checked on postoperative day 6.

Fluid collections were diagnosed by postoperative abdominal CT scan. CT scans were not obtained in every patient on a routine basis. Scans were obtained when clinically indicated as in cases of persistent fevers, elevated WBC, unexplained hemodynamic instability, persistent nausea and vomiting, bleeding, and abdominal pain.

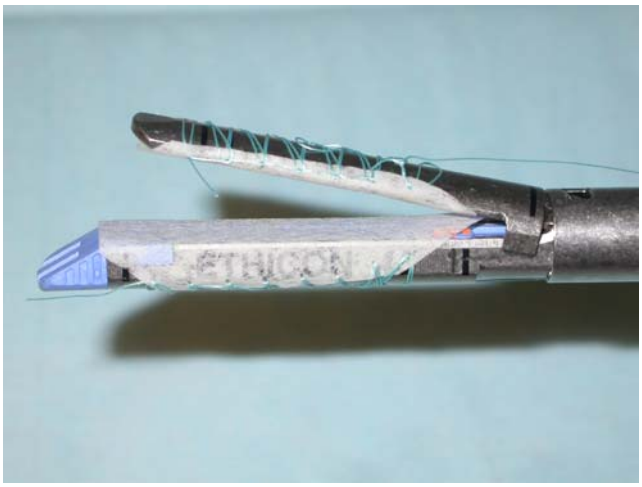

Figure 1 Bioabsorbable reinforcement "sleeves" mounted on a 45-mm linear stapler.

Given that pancreatic texture is a major determinant of postoperative pancreatic leak, this variable was also incorporated in our analysis. Pancreatic texture was assessed and recorded prospectively only in the experimental group. Gland texture was classified as "soft" or "hard" based on intraoperative palpation by a single observer (REJ). We did not have accurate pancreatic texture information for the control group (collected retrospectively). We did not try to speculate about texture information in the control group based on clinical history, operative report, or pathologic findings.

Secondary outcome measures assessed included all other postoperative complications, reoperations, other nonsurgical therapeutic interventions, hospital length of stay, hospital readmissions, and mortality. Follow up included the longer of either the perioperative period (30 days) or the initial discharge from the hospital.

All statistical comparisons were done using either the Student's *t* test or Fischer's exact test depending on the data to be analyzed. For all analyses, a P value of ≤ 0.05 was considered statistically significant. Software used for statistical analysis was MedCalc® version 8.2.0.1. This study was approved by the Institutional Review Board at our hospital.

Results

Our study population included 31 patients. Their clinicopathologic features are summarized in Table 1. The control and experimental groups were identical in age but differed in gender distribution. Males comprised 61% of the control group and 23% of the experimental group ($P=0.067$).

Table 1 also details the spectrum of diagnoses in the study population. Pancreatic adenocarcinomas, neuroendocrine neoplasms, and cystic neoplasms comprised 75% of patients in each group. Pancreatectomies in the setting of nonpancreatic pathology were more prevalent in the control group. Diagnoses in these patients included splenic cyst, renal cell carcinoma, sarcoma, gastric lymphoma, and adrenocortical carcinoma.

All distal pancreatectomies in the study also included splenectomy. Twenty-eight of the operations were open procedures. Three operations were started laparoscopically: two were completed in minimally invasive fashion, and the third was converted to open surgery.

Perioperative morbidity data are summarized in Table 2. For all patients, operative and perioperative mortality was zero. The vast majority of perioperative morbidity was related to pancreatic leaks, which was our main outcome

Table 1 Clinicopathologic Features

	All patients	Control group	Experimental group	*P* value
N	31	18	13	NS
Age	63	63	63	NS
Gender (male:female)	14:17	11:7	3:10	NS (0.067)
Diagnosis				
Adenocarcinoma	8 (26)	5 (28)	3 (23)	NS
Neuroendocrine neoplasm	8 (26)	5 (28)	3 (23)	NS
Cystic neoplasms	7 (23)	3 (17)	4 (30)	NS
Chronic pancreatitis	2 (6)	1 (5)	1 (8)	NS
Solid and papillary tumor	1 (3)	0 (0)	1 (8)	NS
Nonpancreatic pathology	5 (16)	4 (22)	1 (8)	NS
Pancreatic texture				
Soft:hard	N/A	N/A	7:6	NA

Cystic neoplasms included serous cystadenomas, mucinous cystic neoplasms, and intraductal papillary mucinous tumors. Numbers in parenthesis represent percentages. NA = not applicable, NS = not significant, N/A = information not available

measure. Pancreatic leak occurred in 39% of patients in the control group, but in none of the 13 consecutive patients in the experimental group. This difference was statistically significant with a *P* value of 0.025. While no leaks were observed in the experimental group, more than half (54%) of these pancreatic transections were performed in soft or high-risk glands.

Pathologic diagnoses for patients who developed a leak included adenocarcinoma (2), cystic neoplasm (2), neuroendocrine neoplasm (1), chronic pancreatitis (1), and nonpancreatic pathology (1). The management of pancreatic leaks is also included in Table 2. Six of the seven (86%) leaks were managed in conservative fashion, and only one patient required reexploration. One patient had a sterile fluid collection noted on postoperative CT scan, which was not drained during our study follow up period. The collection became symptomatic 2 years later, prompting drainage at that time.

Other postoperative complications included postoperative bleeding (1), pleural effusion (3), pulmonary embolus (1), deep venous thrombosis (1), and *Clostridium difficile* colitis (1). Three of these seven (43%) complications occurred in association with a pancreatic leak. Finally, length-of-stay information is summarized in Table 3. The presence of a pancreatic leak extended hospital stay by 5 days, and this was shown to be statistically significant.

Table 2 Perioperative Morbidity

	All patients	Control group	Experimental group
N	31	18	13
Overall morbidity	11 (35)	9 (50)*	2 (15)*
Pancreatic leak	7 (23)	7 (39)**	0**
Treatment of leak			
Surgical drain retained	2	2	
IR drain	3	3	
Reoperation	1	1	
None	1	1	

Numbers in parenthesis represent percentages.
IR = interventional radiology.
*P=0.066, control vs experimental group.
**P=0.025, control vs experimental group.

Discussion

This study demonstrates that pancreatic stump closure with a reinforced staple line results in significantly lower leak rates than standard nonreinforced staple closure. The surgical technique described herein is new, and no similar study has been published in the medical literature.

Our results confirm that pancreatic stump leak is a major source of morbidity after distal pancreatectomy, and this fact is often underestimated. For comparison, published pancreatic fistula rates after pancreaticoduodenectomies (in large patient series) range from 4 to 12.5%[9–11]—rates which are two to three times lower than in distal resections. Yet, the bulk of surgical literature on pancreatic fistula pertains to pancreaticoduodenectomies. It is time that we recognize the incidence and morbidity of pancreatic leakage after distal pancreatectomy.

Our findings also demonstrate that pancreatic leaks can often be successfully managed without repeat surgical

Table 3 Effect of Postoperative Pancreatic Leak on Length of Hospitalization

	N	Length of stay in days (range)
All patients	31	9.5
Pancreatic leak	7	13.6 (5–28)*
No pancreatic leak	24	8.33 (5–21)*

*P<0.03, leak vs no leak.

intervention[12,13]. Only one of our patients with a leak required reoperation, and in this case, percutaneous drainage by interventional radiology was not deemed to be safe. However, the clinical impact of a postoperative pancreatic leak is best reflected in the lengths of hospital stays. As we have shown, a leak results in prolongation of length of stay by an average of 5 days. Prevention of pancreatic stump leaks is therefore critical in reducing the current morbidity and cost of this operation.

The primary advantages of our stump closure technique lay in its simplicity and applicability. The addition of the biodegradable reinforcement to the stapler system takes minimal time and is not technically demanding. The reinforced stump closure appears to work well regardless of pancreatic texture. Perhaps more importantly, the method can be easily applied to laparoscopic cases without any change in operative strategy. Our technique undoubtedly holds promise in improving current results for minimally invasive distal pancreatectomy.

A specific explanation of why the reinforced staple line seals better than a standard staple line is not evident from our study. The pancreatic capsule, parenchyma, and duct can be very thin, soft, and fragile, particularly in the setting of a normal gland without prior pancreatitis. This is in contradistinction to the bowel, where the wall of the intestine (and specifically the submucosa) provides a strong surface to hold suture or staple material. We believe that the standard individual staples by themselves can "cut" through the pancreatic tissue without effectively achieving any compression or seal. The reinforcement acts as a scaffold for the individual staples, preventing them from cutting through the tissues and allowing even tension distribution along the closure line. Ultimately, this results in a strong compression closure of the stump between two slabs of reinforcement material held together by staples. Animal studies confirm that reinforcement improves staple line sealing in lung and intestinal tissue[14,15].

Several weaknesses can be identified in this study. First, the study population is small, and consequently, the power of the study is low. Secondly, the experimental and control groups are not equal, as has been shown for gender as well as distribution of diagnosis. Last, but most importantly, this is not a randomized-controlled trial. As such, the results of our study must be validated in randomized controlled fashion before reaching any further conclusions or generalizations.

Despite these shortcomings, our results are compelling, particularly with respect to the 13 consecutive reinforced pancreatectomies without a leak. We do not have the referral basis or the patient volume to complete a randomized controlled trial in adequate and timely fashion at our institution. We hope that this study can provide a stimulus for a large pancreatic surgery center to test our idea and confirm or disprove our results.

Conclusion

Staple line reinforcement is a simple and effective method of reducing pancreatic stump leakage after distal pancreatectomy. The economic impact of lower leak rates is reflected in significantly shorter hospital stays.

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Impact of Lymph Node Involvement on Long-term Survival after R0 Pancreaticoduodenectomy for Ductal Adenocarcinoma of the Pancreas

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Abstract Pancreaticoduodenectomy remains the only potentially curative treatment for adenocarcinoma of the pancreas. The aim of this study was to analyze prognostic factors impacting survival after R0 pancreaticoduodenectomy for adenocarcinoma in the head of the pancreas. Between 1995 and 2002, a potentially curative (R0) pancreaticoduodenectomy with pancreatogastrostomy for ductal adenocarcinoma in the head of the pancreas was performed in 81 patients (42 women and 39 men) with a mean age of 64 years (range 35–84). Patients were identified from a prospective database and records were reviewed retrospectively. Postoperative mortality was 1%, and 40% of patients had complications. Median survival was 18 months, and the 5-year survival was 24%. Fifteen patients were alive at 5 years. Factors associated with poor survival in multivariate analysis were (1) two or more positive lymph nodes, (2) tumor diameter greater than 30 mm, and (3) age greater than 70 years. In patients with no or with one positive lymph node, the 5-year survival was 44%. On the other hand, in patients with two or more positive lymph nodes, both the 3- and 5-year survival was 5%. The main risk factor associated with poor survival after an R0 pancreaticoduodenectomy for adenocarcinoma in the head of pancreas was lymph node status: The presence of two or more positive lymph nodes was associated with decreased survival.

Keywords Adenocarcinoma · Pancreaticoduodenectomy · Lymph node

Introduction

Ductal adenocarcinoma of the head of the pancreas remains a tumor with a poor prognosis despite intensive study.[1] Pancreaticoduodenectomy is still the only potential cure for tumors localized to the head of the pancreas. The aim of surgery is to achieve a curative resection (R0) because incomplete resection (R1 and R2) is associated with a poor prognosis.[2–4] Conversely, if a pancreaticoduodenectomy can achieve an R0 resection, a 5-year survival of 10 to 36% was reported.[5–8] An R0 resection is generally achieved in 50[9] to 93%[10] of patients undergoing pancreaticoduodenectomy.

In an attempt to increase the number of R0 resections, systematic frozen section examination of the pancreatic and choledochal resection margins was recommended.[11] In case of venous involvement, resection of the portal vein associated with pancreaticoduodenectomy was proposed and is increasingly performed.[12–14] Tumor infiltration of the superior mesenteric or hepatic arteries is generally considered a contraindication to resection and pancreaticoduodenectomy with arterial resection is only performed in very selected cases.[15] Extended lymph node dissection in the retroperitoneum was not shown to improve survival rates.[10,16–18]

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Several studies have analyzed the determinants of survival in patients after resection of pancreatic cancer.[9,19–21] However, these studies included various types of pancreatic resections (pancreaticoduodenectomy, total, subtotal, or distal pancreatectomy) performed for ductal adenocarcinoma located throughout the gland. Furthermore, they included 26[20] to 50%[9] of patients with incomplete resections (R1 and R2), which are not curative. Consequently, little is known about the prognostic factors for survival after R0 pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas. Thus, the aim of this study was to analyze prognostic factors for survival after R0 pancreaticoduodenectomy for adenocarcinoma in the head of the pancreas.

Patients and Methods

This study was performed at a single institution. Between January 1995 and December 2002, a potentially curative (R0) pancreaticoduodenectomy with pancreatogastrostomy for ductal adenocarcinoma in the head of the pancreas was performed in 81 patients. In this period, 18 other patients had incomplete (R1 or R2) resection for ductal adenocarcinoma of the head of the pancreas and were excluded from the present study.

Outcome data were recorded from follow-up consultations with patients. Contact was maintained by mail and telephone calls to referring physicians, general practitioners, and directly to the patients or their families. Patients were followed after their operations by referring physicians, including oncologists, gastroenterologists, surgeons, and general practitioners. The follow-up schedule included an abdominal ultrasound or CT scan and CA 19.9 measurements every 6 months. No patient was lost to follow-up. Follow-up of living patients was at least 3 years. End points were survival, mortality, and morbidity.

In this series, pancreaticoduodenectomy with pancreatogastrostomy was performed in 81 patients (42 women and 39 men) with a mean age of 64 years old (range 35–84). Thirty-four patients were older than 70 years.[22] Medical comorbidities registered in the 81 patients were diabetes mellitus (n=20), ischemic heart disease (n=15), chronic pulmonary disease (n=2), and liver cirrhosis (n=1).

Patients presented initially with jaundice (n=64), weight loss greater than 10 kg (n=49), and abdominal pain (n=42). Twenty-one patients had preoperative endoscopic retrograde pancreaticocholangiography and biliary stents were placed in 10 patients.

All patients underwent a pancreaticoduodenectomy with lymphadenectomy of the anterior and posterior pancreaticoduodenal nodes, the hepatoduodenal ligament, the celiac axis, and the retropancreatic margin along the right lateral aspect of the superior mesenteric vessels. Lymph nodes were sampled in the interaortocaval region.[23] Pyloric preservation was performed in six patients.[6] Reconstruction was realized with a pancreatogastrostomy,[24] a hepaticojejunostomy and a transmesocolic gastrojejunostomy, or in case of pyloric preservation, a pylorojejunostomy.

Frozen section of the distal pancreatic and choledochal resection margins was performed intraoperatively in all patients. In two patients, there was evidence of tumor cells on pancreatic frozen section. A reresection of the pancreas was performed until the pancreatic margin was free of tumor cells. Choledochal resection margins were free of tumor cells in all 81 patients on frozen section and final histopathological examination. The specimens were sent for routine histopathological examination with hematoxylin and eosin staining. They were analyzed for location and size of the tumor, number and involvement of lymph nodes, grade of differentiation, portal vein invasion, and resection margin. Special attention was applied in analyzing the retroperitoneal resection margin. Tumor differentiation was defined based on the World Health Organization Union criteria.[25] Tumor stage was determined according to the 2002 TNM classification system.[26]

Table 1 Forty-one Complications After Pancreaticoduodenectomy for Ductal Adenocarcinoma of the Head of the Pancreas in 32 Patients

Complications	
Surgical	
Bleeding of pancreatic cut surface	3[a]
Biliary stenosis	1[a]
Pancreatic fistula	1
Delayed gastric emptying	1[a]
Intestinal obstruction	1
Abdominal fluid collection	4
Wound infection	2
Gastric ulcer	1
Cardiopulmonary	
Deep venous thrombosis	1
Pulmonary embolism	1
Infections	
Pneumonia	4
Septicemia	3
Urinary tract infection	11
Miscellaneous	
Acute renal insufficency	1
Stroke or confusion	2
Profuse bleeding by thrombopenia	1
Diabetes (worsened or newly diagnosed)	3

[a] Three patients with bleeding of the pancreatic section, one patient with biliary stenosis, and one patient with delayed gastric emptying were reoperated.

Table 2 Univariate Analysis for Overall Survival after Pancreaticoduodenectomy for Adenocarcinoma of the Head of Pancreas in 81 Patients with R0 Resection

	No. of Patients	3-Year Survival (%)	Median (months)	*p* Value
Gender				
Male	39	33	22	0.398
Female	42	27	15	
Age				
<70	47	35	22	0.114
≥70	34	24	15	
Period of resection				
1995 to 1998	27	37	20	0.498
1999 to 2002	54	26	18	
Jaundice				
No	17	18	20	0.746
Yes	64	33	16	
Biliary stent				
No	71	29	16	0.549
Yes	10	40	22	
Weight loss >10 kg				
No	32	32	20	0.396
Yes	49	29	18	
Lymph nodes resected				
Number <20	36	31	20	0.920
Number ≥20	45	29	16	
Invaded lymph nodes				
Number 0 or 1	41	55	43	<0.0001
Number ≥2	40	5	12	
Largest tumor size				
≤30 mm	42	43	28	0.025
>30 mm	39	16	14	
Portal vein invasion				
No	63	35	22	0.048
Yes	18	12	12	
Transfusion				
No	31	36	23	0.122
Yes	50	26	16	
Adjuvant therapy				
No	14	21	25	0.528
Yes	67	32	20	
Tumor differentiation				
Well	17	29	12	0.541
Moderately	48	31	22	
Poorly	16	27	14	
TNM T-stage				
T 1 or 2	8	50	32	0.341
T3	73	28	16	
Pylorus preservation				
Yes	6	33	23	0.976
No	75	30	16	
Postoperative morbidity				
No	49	37	20	0.033
Yes	32	19	14	

Adjuvant radiochemotherapy (5-fluorouracil [5-FU]+cisplatin) was given in 65 patients and adjuvant chemotherapy (5-FU+cisplatin) in 2 patients. Survival rates were calculated by the Kaplan–Meier method and were compared using the log-rank test for univariate analysis. The level of significance was defined as a p value of less than 0.05. A multivariate analysis of survival was performed using a stepwise Cox model, which included all outcome variables with $p<0.2$ in the univariate analysis. All analyses were performed with the Statview® Software.

Table 3 Multivariate Analysis with a Cox Model for Survival after Pancreaticoduodenectomy for Adenocarcinoma of the Head of Pancreas in 81 Patients with R0 Resection

	p Value	Hazard Ratio	CI
Number of invaded lymph nodes			
≥2 vs 0 or 1	0.0001	4.2	2.4–7.5
Tumor size			
>30 vs ≤30 mm	0.018	1.9	1.1–3.1
Age			
≥70 vs <70 years	0.017	1.9	1.1–3.0

CI=95% confidence interval

Results

Pathological Analysis

Tumors were classified according to the 2002 TNM classification system.[26] There were 2 patients with pT1, 6 patients with pT2, and 73 patients with pT3 tumors. Median tumor size was 32 mm (range 13–90). Tumor grade was well differentiated in 17 patients, moderately differentiated in 48 patients, and poorly differentiated in 16 patients. Lymph node dissection and analysis were performed in all 81 patients and revealed positive lymph nodes in 55 patients (68%). The median number of resected lymph nodes for all patients was 21 (range 8–60, mean 23). There was no difference (p=0.997) in the number of resected lymph nodes for the six patients with a pylorus preserving pancreaticoduodenectomy (range 10–55, mean 23) vs standard pancreaticoduodenectomy. In patients with positive lymph nodes, a median number of two nodes were positive (range 1–18). Twenty-four patients underwent portal vein resection for suspected tumor invasion and, in 18 patients, invasion of the portal vein was confirmed by histological examination. In all cases, the venous invasion was completely resected resulting in a R0 resection.

Mortality and Morbidity

The perioperative mortality after pancreaticoduodenectomy with pancreatogastrostomy was 1% (n=1). This occurred in a 76-year-old female on postoperative day 14. On postoperative day 1 she suffered a stroke and then developed renal insufficiency and pneumonia. On postoperative day 7 she was reoperated on upper gastrointestinal bleeding. Hemostasis of a small vessel on the pancreatic remnant was performed. She died on postoperative day 14 due to a sepsis and multiorgan failure.

The postoperative course was otherwise uneventful in 49 patients. Forty-one postoperative complications occurred in 32 patients (40%) and are listed in Table 1.

Survival Analysis

At last follow-up (December 2005) 65 patients had died and 16 patients were still alive. Of those patients that died the median survival was 14 months (range 0.5–108). Of the 16 surviving patients the median follow-up was 65 months (range 38–97). Ten are still disease-free. Therefore, the

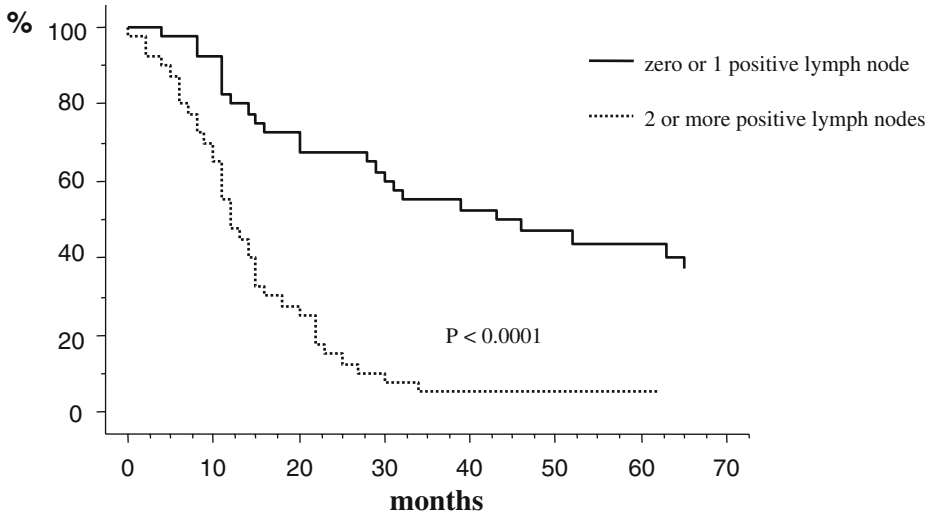

Figure 1 The influence of lymph node involvement for survival in 81 patients after pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas. For patients with zero or only one involved lymph node, a median survival of 43 months and a 5-year survival rate of 44% were observed. On the other hand, patients with two or more involved lymph nodes had a median survival of 12 months and a 3- and 5-year survival rates of 5%.

Number of patients at risk

	0 year	1 year	2 years	3 years	4 years	5 years
N 0 or 1	41	33	27	22	16	14
N ≥ 2	40	22	6	2	2	1

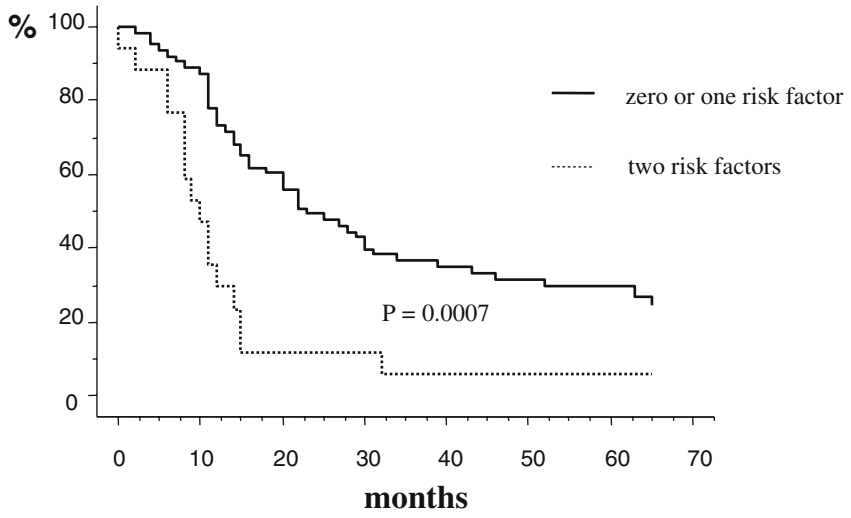

Figure 2 Survival for 81 patients after pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas according to the presence of preoperatively known risk factors: age greater than 70 years and tumor size greater than 30 mm. Even in patients with both risk factors, 5-year survival was possible.

Number of patients at risk

	0 year	1 year	2 years	3 years	4 years	5 years
0 or 1 factor	64	49	31	23	17	14
2 factors	17	6	2	1	1	1

overall survival for the 81 patients was 64% at 1 year, 41% at 2 years, 30% at 3 years, and 24% at 5 years. Median overall survival was 18 months.

Risk factors for poor overall survival found in the univariate analysis were the number of two or more positive lymph nodes, a tumor diameter greater than 30 mm, the presence of portal vein invasion, and postoperative morbidity (Table 2). However, the multivariate analysis showed that the number of two or more positive lymph nodes, a tumor diameter greater than 30 mm, and an age greater than 70 years were independent risk factors for poor overall survival (Table 3).

The survival of patients with only one positive lymph node did not differ significantly when compared with patients with negative lymph nodes (p=0.12). On the other hand, a statistically significant difference (p<0.0001) was noted between patients with two or more positive lymph nodes vs patients with negative nodes or with only one positive lymph node (Table 2). Therefore, as patients with negative lymph nodes and patients with only one positive lymph node showed similar clinical behavior, these patients (zero and only one positive lymph node) were combined for uni- and multivariate analyses and compared with patients with two or more positive lymph nodes. The influence of lymph node involvement on survival is shown in Fig. 1. For patients with zero or one positive lymph node (n=41) a median survival of 43 months and 5-year survival of 44% was observed. On the other hand, patients with two or more positive lymph nodes had a median survival of 12 months and 3- and 5-year survival rates of 5%, respectively (Table 3).

The influence of the two other risk factors on survival, age greater than 70 years and tumor size greater than 30 mm, is shown in Fig. 2. Patients with zero or only one risk factor had a significantly better survival than patients with both risk factors (p=0.0002). However, long-term survival was possible even in patients with both risk factors.

Portal vein invasion was found to be a risk factor for poor survival in uni- but not in multivariate analysis. Out of the 18 patients with portal vein invasion, 6 patients had negative (n=4) or only one positive lymph node (n=2). These six patients had a median survival of 20 months (range 11–77 months). There was no difference in survival between these six patients with portal vein invasion and the 35 patients with zero or one positive lymph node without portal vein invasion (p=0.786). The 12 patients with portal vein invasion and two or more positive lymph nodes showed similar survival to the 28 patients without portal vein invasion and two or more positive lymph nodes (p= 0.38). Portal vein invasion was not more commonly associated with lymph node involvement (p=0.14).

Discussion

In this study, the presence of two or more involved lymph nodes was the strongest risk factor for poor survival after potentially curative (R0) pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas (Table 3).

It also provides further evidence that resection of adenocarcinoma of the head of the pancreas can be performed with a very low mortality and an acceptable

morbidity. Indeed, we registered a perioperative mortality of 1% and a morbidity of 40% in this series of 81 patients. Recent studies have shown a similar mortality rate of 0 to 5%[7,8,10,16,18,22] and a morbidity rate of 29 to 46%.[6,8,10,17,22] Overall median survival after R0 pancreaticoduodenectomy was 18 months with a 5-year survival rate of 24% in the present series, which is similar to median survival times of 14 to 21 months[5,8,10,19] and to a 5-year survival rate of 19 to 36% previously reported.[7,10,20] The results of this study oppose the results of Kuhlmann et al. who reported a 5-year survival rate of 8% for 160 patients after pancreaticoduodenectomy.[9] However, in their study, 80 patients (50%) had a palliative resection because of a positive margin. Moreover, the median follow-up of 16 living patients in our study was 65 months, which was longer than the median follow-up of 22 living patients in the study of Kuhlmann et al. with 32 months.[9]

In this study, the mean number of resected lymph nodes, 23, was in the range of the number of resected lymph nodes (mean 20 to 28) after extensive retroperitoneal lymphadenectomy performed in randomized controlled studies.[10,16,17] Lymph node involvement in 68% of patients in this study correlates with rates of 60 to 80% reported for ductal adenocarcinoma of the pancreas.[10,17]

The multivariate analysis identified lymph node involvement of two or more nodes, tumor diameter over 30 mm, and age greater than 70 years as risk factors for poor survival. However, in this study, the most important prognostic factor was involvement of two or more lymph nodes (Table 3). The finding that lymph node involvement is an important prognostic factor is supported by several studies. However, differences remain concerning the number of positive lymph nodes associated with poor survival. For some authors, the presence ($n \geq 1$) of positive lymph nodes is associated with poor survival.[5,6,10,16,20,29] On the other hand, Lim et al. showed that the presence of four or more positive lymph nodes resulted in decreased survival.[19] However, the lymph node dissection was not standardized in their study and the number of resected lymph nodes was not given. Furthermore, no data about the resection margins were reported, leaving open the question of how many patients actually had a curative R0 resection. Finally, a review of the pathology specimen was not possible in their study because of the anonymous data. Consequently, it is not clear if all patients in their study had ductal adenocarcinoma of the pancreas.

The present study is the first to show that the number of two or more positive lymph nodes is associated with poor survival after curative resection of ductal adenocarcinoma of the head of the pancreas. Therefore, based on the results of this study, the introduction of a subclassification for lymph node involvement can be proposed for the next revision of the TNM classification for pancreatic adenocarcinoma: N1a for patients with one positive lymph node and N1b for patients with two or more positive lymph nodes.

A tumor size greater than 30 mm and an age greater than 70 years were independent risk factors for poor survival in this study. However, long-term survival was possible even in patients with both risk factors. The prognostic significance of tumor size was already reported.[5,8,9,19,21,28,29] Age was an independent risk factor for poor survival in some studies[28,30] but had no influence in other series.[5,8,19,20]

Portal vein invasion was not found to be an independent prognostic factor in the multivariate analysis in this study. One third of the patients, presenting with portal vein invasion at the histopathological examination after portal vein resection, had zero or only one involved lymph node. Long-term survival is possible for these patients and their survival rate was not different from the survival rate of patients without portal vein invasion and zero or one involved lymph node. Therefore, portal vein resection should be realized, if it can be done safely, as there is a reasonable chance (33% in this study) to belong to a group with rather favorable long-term survival.[27]

Postoperative morbidity was a risk factor for poor survival in uni- but not in multivariate analysis in this study. To our knowledge, up to now, only one other study[29] has shown this association after resection of pancreatic carcinoma. On the other hand, this association was reported by several studies after resection of colorectal liver metastases and colorectal surgery.[31,32] Therefore, there is a need for further investigations about the influence of postoperative morbidity on long-term survival in pancreatic surgery.

In conclusion, after a potentially curative resection of pancreatic head ductal adenocarcinoma, lymph node involvement of two or more nodes was the strongest risk factor for poor survival in this study. On the other hand, patients with no or only one involved lymph node had a rather favorable long-term survival in this study.

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Treatment of Acute Pancreatic Pseudocysts After Severe Acute Pancreatitis

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Abstract Treatment of acute pancreatic pseudocysts (APP) after an episode of severe acute pancreatitis (SAP) remains controversial. Both population heterogeneity and limited numbers of patients in most series prevent a proper analysis of therapeutic results. The study design is a case series of a large, tertiary referral hospital in the surgical treatment of patients with APP after SAP. An institutional treatment algorithm was used to triage patients with complicated APP and organ failure based on Sequential Organ Failure Assessment scores to temporizing percutaneous or endoscopic drainage to control sepsis and improve their clinical condition before definitive surgical management. Over a 10-year period of study (December 1995 to 2005), 73 patients with APP after an episode of SAP were treated, 43 patients (59%) developed complications (infection 74.4%, perforation 21%, and bleeding 4.6%) and qualified for our treatment algorithm. Percutaneous/endoscopic drainage was successful in controlling sepsis in 11 of 13 patients (85%) with severe organ failure and allowed all patients to undergo definitive surgical management. The morbidity (7 vs 44.1%, $P=0.005$) and mortality rates (0 vs 19%, $P=0.04$) were significantly higher in complicated vs uncomplicated APP. Acute pancreatic pseudocysts after SAP are unpredictable and have a high incidence of complications. Once complications develop, there is a significantly higher morbidity and mortality rate. In complicated APP with severe organ failure, percutaneous/endoscopic drainage is useful in controlling sepsis and allowing definitive surgical management.

Keywords Acute pancreatic pseudocysts · Complicated acute pancreatic · Pseudocysts · Severe acute pancreatitis · Organ failure · Pancreatic necrosis

Introduction

Significant advances were made in the last 10 years in our understanding and treatment of patients with severe acute pancreatitis (SAP) and pancreatic necrosis.[1–3] Despite this progress, the timing and treatment of patients who develop acute pancreatic pseudocysts (APP) after an episode of SAP remains controversial.[4–6] Many of the reasons for this controversy reside in imprecise definitions, mixed case series of treatment outcomes in both acute and chronic pancreatic pseudocysts, and the fact that the disease process of SAP with pancreatic necrosis represents a wide spectrum of tissue destruction, fluid sequestration, and systemic toxicity, which is often difficult to accurately categorize.[1,7]

Acute pancreatic pseudocysts are defined as a collection of amylase-rich pancreatic fluid, enclosed in a well-circumscribed wall, that has been present for more than 4 weeks after the episode of SAP.[8] Confusion often arises in discriminating pancreatic and peripancreatic necrosis with associated fluid sequestration from pancreatic necrosis with an APP. All patients with APP have some component of pancreatic necrosis,[9] whereas not all patients with pancreatic and/or peripancreatic necrosis develop APP.[7] Pancreatic pseudocysts that develop in this setting, particularly when greater than 6 cm in diameter and present for more than 4 weeks, have a high incidence of complications including infection, perforation, and bleeding if not recognized and treated expeditiously.[7,10] Current clinical guidelines rec-

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ommend that all patients with pancreatic necrosis be managed medically until documentation of infection in the pancreatic necrosis can be confirmed.[3] Based on our clinical experience, we are in agreement with the Argentine Pancreas Club that APP should be distinguished from pancreatic necrosis with associated peripancreatic fluid collections and their presence should dictate surgical treatment.[11]

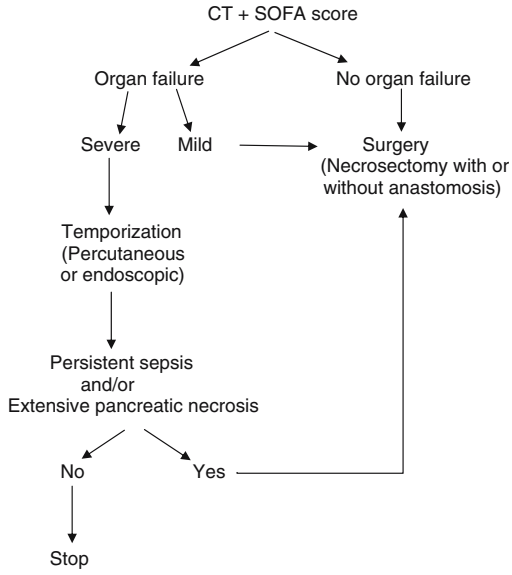
Once identified, the timing and surgical treatment of patients with APP after an episode of SAP remains a topic of considerable debate.[7] Some authors advocate treatment of all pancreatic pseudocysts, which remain present for more than 6 weeks after the onset of SAP, citing a dramatic increase in complication rates for longer periods of observation,[12] whereas others have shown no severe complications in carefully selective patients who were managed nonoperatively.[13,14] There remains a paucity of evidence in the literature to guide surgical decision making in patients who develop APP after an episode of SAP. The aim of this study is to evaluate the clinical results of a treatment algorithm targeted at the surgical management of patients who develop APP after an episode of SAP.

Materials and Methods

All patients hospitalized on the hepatopancreaticobiliary unit of the Argerich Hospital with the diagnosis of APP after a documented episode of SAP from December 1995 to 2005 were available for study. SAP was defined as the clinical diagnosis of pancreatitis (abdominal pain, nausea, vomiting, and hyperamylasemia) with a Ranson score >3 or acute physiology and chronic health evaluation (APACHE) II score >8.[8] A dynamic, contrast-enhanced computed tomography (CT) was done on all patients at admission and it was used to determine pseudocyst size, extent of pancreatic necrosis (categorized as <30%, 30–50%, or >50%), and presence of retroperitoneal gas indicative of infection. Diagnosis of APP was based both on clinical grounds and CT findings showing a dominant collection of fluid in the lesser sac surrounded by a well-circumscribed wall, associated with pancreatic parenchymal necrosis but no peripancreatic necrosis, and identified at least 4 weeks from the inciting episode of SAP.

Complicated APP were defined as APP that progressed to infection, rupture, and/or bleeding. Infection in a pseudocyst was confirmed by direct analysis or cultures taken at the time of surgical intervention or during percutaneous drainage. Rupture of the pseudocyst into the abdominal cavity was diagnosed by the onset of acute pain, and CT and abdominal ultrasound examinations showing new onset-free fluid in the abdomen in a patient with a previously documented pseudocyst. Rupture into the gastrointestinal tract was defined as the drainage of a pseudocyst into a hollow viscus demonstrated either by endoscopy, radiographic investigation, or during surgery. Bleeding was defined as the presence of fresh blood or clots found in the pseudocyst cavity during operation, or as the development of high density debris seen by CT or ultrasound examination.

Patients with APP greater than 6 cm in diameter and present for more than 6 weeks after their episode of SAP had elective surgical treatment consisting of laparotomy, cyst cavity debridement, and internal anastomosis of their cyst wall into the gastrointestinal tract. Patients with complicated APP were treated based on our institutional algorithm (Fig. 1). Infected pancreatic pseudocysts in patients with no organ failure or mild organ dysfunction (Sequential Organ Failure Assessment [SOFA][15] <3) and who were acceptable surgical risks were treated by laparotomy and cyst cavity debridement; and if a thick-walled pseudocyst was found, an internal anastomosis to the stomach or small intestine was performed. Patients with thin-walled pseudocysts underwent debridement and external drainage or gauze packing depending on the extent of necrosis found in association with the pseudocyst. In patients with limited pancreatic necrosis and complete debridement, external drainage and abdominal closure was the preferred therapeutic option. In patients with extensive necrosis who had incomplete debridement of their cavity, gauze packing was done. When gauze packing was used, patients were returned to the operating room every 48 h for repeated debridement and washout until the cavity was clean. Final operation included external drainage and abdominal closure if feasible.



CT: Computed Tomography, **SOFA**: Sequential Organ Failure Assessment

Figure 1 General algorithm and treatment of complicated APP.

Table 1 Demographic and Clinical Characteristics of 43 Patients with Acute Complicated Pseudocysts

Age (mean, range)	52.4 years (21–78)
Sex (M/F)	24/19
Initial APACHE II score (mean)	7.2
SOFA score (mean)	4.3
Biliary pancreatitis	39 (90%)
Alcohol pancreatitis	2 (5%)
Idiopathic pancreatitis	2 (5%)
Time from onset to admission (mean)	53.2 days

In patients with severe organ dysfunction (SOFA ≥3) and/or high surgical risk (American Society of Anesthesiologist [ASA] ≥IV), percutaneous or endoscopic drainage was performed as a temporizing measure. This approach was designed to control sepsis and improve a patient's clinical condition sufficiently to allow definitive surgery to be undertaken at a later time. Patients who presented with signs and symptoms of an acute abdomen and evidence on CT or ultrasound of pseudocyst rupture into the abdominal cavity were treated by percutaneous drainage of their ascites in an attempt to control the pancreatic fistula externally. Pseudocysts that ruptured into the stomach were managed medically with supportive care. Pseudocysts that ruptured into the colon had laparotomy, diverting ileostomy, and Hartmann's procedure with external drainage of their pseudocyst.

Variables including age, sex, APACHE II score, time from onset of SAP to admission, location and type of pancreatic pseudocyst, and SOFA scores were recorded. A SOFA score of less than 3 was considered mild organ dysfunction whereas a SOFA score of 3 or greater was considered severe organ dysfunction.[14] All patients were categorized according to the ASA risk stratification. All procedures, including obtaining written informed consent from the patient or a responsible relative, were conducted in accordance with the recommendations of the Ethics Committee of the Cosme Argerich Hospital.

Statistical analysis of the groups was performed using the Student's *t* test for continuous data, and the two-tailed chi-square or Fisher's exact tests for ordinal data. Probability values <0.05 were considered significant.

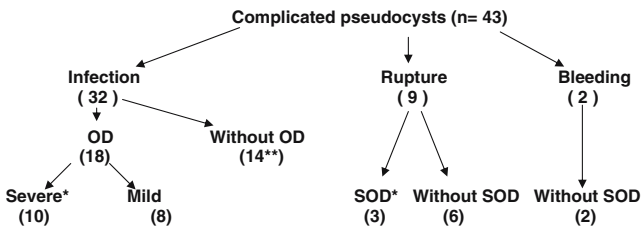
Results

Seventy-three patients with APP after an episode of SAP treated in our hospital qualified for study. Thirty patients (41%) had uncomplicated APP and 43 patients (59%) had complicated APP based on the findings of infection (n=32), perforation (n=9), or bleeding (n=2). Thirty-nine patients (90.6%) with complicated APP had been treated in conservatively form at other hospitals; these patients were transferred to our unit once the complication was established.

All patients with uncomplicated APP greater than 6 cm in size were operated on electively regardless of symptoms after 6 weeks of medical management. Their mean age was 53.75 years and the mean time from their onset of SAP to admission to our facility was 60.6 days. The mean sizes of the pseudocysts were 10.07 cm (range 7–15 cm) and their mean APACHE II score was 5.5. Pancreatic necrosis was judged to be <30% in 10 patients (33.3%) and >30% in 20 patients (66.6%). All patients had laparotomy, cyst cavity debridement, and internal anastomosis of their cyst wall into the gastrointestinal tract (cystojejunostomy Roux-en-Y in 11 patients and cystogastrostomy in 19 patients). There postoperative morbidity was 7% (one patient developed pneumonia and the others wound infection) and there was no postoperative mortality.

Demographic and clinical characteristics of the 43 patients with complicated APP are shown in Table 1. The mean size of pseudocysts as measured by CT scanning was 10.28 cm (range 6–18 cm). Pancreatic necrosis was judged to be <30% in 8 patients (18.6%), 30–50% in 21 patients (48.8%), and >50% in 14 patients (32.6%). Complications consisted of infection in 27 patients (62.7%), infection plus rupture in 5 patients (11.6%), rupture in 9 patients (21%), and bleeding in 2 patients (4.6%) (Fig. 2). Sepsis was suspected in 18 patients (42%) with complicated APP clinically at the time of their admission. Unsuspected sepsis was diagnosed operatively in an additional 14 patients: 10 had purulent, foul smelling fluid and 4 had positive pseudocyst fluid cultures.

Infected Pseudocysts Initial organ failure based on SOFA scores was found in 18 of 32 patients (56.2%) with infected pseudocysts. Organ dysfunction was classified as severe (SOFA ≥3) in 10 patients (56%) and mild (SOFA <3) in 8 (44%) (Fig. 2). All patients with severe organ dysfunction underwent initial percutaneous (n=9) or endoscopic drain-



OD: Organ Disfunction, SOD: Severe Organ Disfunction,
*** treated iniatially with percutaneous or endoscopic drainage**
**** 5 of 14 patients had infection plus rupture**

Figure 2 Complications and treatments in the 43 patients with complicated acute pseudocysts.

Table 2 Treatment and Results in 18 Patients with Infected Pseudocysts and Organ Failure

	Drainage (%)	No Drainage (%)	*P* Value
Number of patients	10	8	
APACHE II score (mean)	10.1	6.37	<0.05
Necrosis			
<30%	0	1 (12)	
30–50%	5 (50)	3 (38)	NS
>50%	5 (50)	4 (50)	
SOFA score (mean)	7.3	3.6	<0.05
Cystoenteric anastomosis (*n*)	3	0	NS
Morbidity (*n*)	7 (70)	7 (88)	NS
Mortality (*n*)	3 (30)	2 (25)	NS

age ($n=1$) and intravenous antibiotics. Definitive surgical intervention was delayed in this group for, on average, 8.9 days after initial drainage, and this temporization was effective at sepsis control and allowed clinical improvement in eight (80%). All 10 patients managed in this fashion eventually underwent definitive operation: 3 patients (30%) had debridement followed by cystoenteric anastomosis, 3 patients (30%) had debridement and external drainage, and 4 patients (40%) had debridement and abdominal packing. Of the 22 patients with either no organ failure or mild organ dysfunction, 12 (54.4%) had cystoenteric anastomosis, 7 (31.8%) had debridement and external drainage, and 3 (13.6%) had debridement and abdominal packing.

Table 2 compares patients with infected pseudocysts and organ failure treated with or without temporizing drainage. Although patients managed by initial drainage had higher APACHE II and SOFA scores than those who did not undergo drainage, there were no differences in overall mortality rates between the groups. In patients with infected pancreatic pseudocysts without organ dysfunction ($n=14$), cyst cavity debridement and cystoenteric anastomosis ($n=12$) or external drainage ($n=2$) was done with no operative mortality and a 19% perioperative morbidity.

Ruptured Pseudocysts Of 14 patients (isolated rupture in 9 and infection plus rupture in 5 patients) with pseudocyst rupture, 8 (57%) ruptured freely into the abdominal cavity, 4 (29%) ruptured into the stomach, and 2 (14%) ruptured into the colon. Pseudocyst rupture into the abdomen produced acute pain and a systemic inflammatory response in 7 patients. Rupture into a hollow viscus was associated with milder clinical symptoms. Improvement in abdominal pain and pseudocyst resolution was noted in three patients, two of whom had evidence on CT scan pseudocyst resolution and new onset retroperitoneal gas, whereas one patient had pseudocyst resolution and the development of turbid, amylase-rich fluid from the nasogastric tube. Abdominal pseudocyst rupture was confirmed by surgery in five patients and by CT in three. Rupture into the stomach was corroborated by endoscopy, surgery, nasogastric tube fluid analysis, and gastroduodenal radiographs (one case each). Rupture into the colon was confirmed by radiographs or surgery (one case each). The surgical treatment and clinical course of 14 patients with ruptured APP are shown in Table 3. In three patients with rupture into the abdomen and severe organic failure, initial percutaneous drainage was performed (Fig. 2). All eight patients who ruptured freely into the abdominal cavity ultimately had definitive operation and three were able to have cystoenteric anastomosis. Two patients with rupture into the stomach had necrosis debridement and cystogastric anastomosis, and in two patients no further treatment was necessary. Rupture into the colon required diverting ileostomy, debridement, and abdominal packing in one patient, and diverting ileostomy and external drainage in another. Mortality rate in these complex patients was 50%.

In all, initial percutaneous or endoscopic drainage was used as a temporizing measure in 13 patients (30.2%) with complicated APP. The pseudocysts complications in these patients were infection ($n=10$) and rupture into the abdomen ($n=3$). There were no complications related to the initial drainage procedure. Sepsis control and clinical improvement was achieved in 11 of 13 patients (85%). Mortality rates were 31% (4/13) for patients treated initially with percutaneous or endoscopic drainage and 13.3% (4/30) for those who had no percutaneous or endoscopic drainage, a difference which did not reach statistical significance ($P=0.36$).

Eight patients (19%) with complicated pseudocysts died because of sepsis and multiple organ failure. Four patients had infected pancreatic pseudocysts, two patients had rupture into the abdomen, one patient had both infection and rupture into the abdomen, and one patient had rupture into the colon. Table 4 compares patients with complicated and uncomplicated APP. Patients with complicated pseudocysts showed higher APACHE II scores at admission,

Table 3 Treatment and Results in 14 Patients with Ruptured Pseudocysts

	Abdomen ($n=8$)	Stomach ($n=4$)	Colon ($n=2$)
Infection	2	1	2
Drainage	3	0	0
Necrosis excision	7	2	2
Cystoenteric anastomosis	3	2	0
Morbidity (%)	5 (63)	0	2 (100)
Mortality (%)	3 (38)	0	1 (50)

Table 4 Comparison of Treated Uncomplicated and Complicated Pseudocysts

	Uncomplicated (n=30)	Complicated (n=43)	P Value
Age (mean in years)	53.75	52.4	NS
Time from onset to admission (mean in days)	60.6	53.2	NS
APACHE II score (mean)	5.5	7.2	<0.05
SOFA score (mean)	0.58	4.3	<0.05
Mean size (cm)	10.07	10.28	NS
Length of Hospital Stay (mean in days)	14.7	37.7	<0.05
Necrosis			
<30%	10	8	NS
>30%	20	35	
Morbidity (n)	2	19	<0.05
Mortality (n)	0	8	<0.05

more severe organ dysfunction, longer hospital stays, and a higher morbidity and mortality rate. Age of patients, pseudocyst size, extent of pancreatic necrosis, and time from the initial episode of pancreatitis to admission were not significantly different.

Discussion

Surgical treatment of APP that develop after an episode of SAP remains controversial and incompletely defined.[7] This study demonstrates that when the treatment of APP secondary to SAP is delayed until complications develop, morbidity and mortality rates rise significantly (0 vs 19%, P<0.001). In this series, we could identify no clinical variable or imaging findings that would reliably differentiate patients with pseudocysts who developed complications from those who did not.

Our results differ dramatically from those of previous case series where asymptomatic pancreatic pseudocysts were treated conservatively with reported success rates using nonoperative management of 48 and 60%.[13,14] Surgery in these series was performed only for persistent abdominal pain, pseudocyst enlargement, or complications. In the group managed without operation, 60% had complete resolution of their cysts in the series from Johns Hopkins[14] whereas in the Mayo Clinic series,[13] 83% of pseudocysts less than 5 cm in diameter while only 50% of pseudocysts greater than 5 cm in diameter resolved. In both of these series, over three fourth of patients had pseudocysts secondary to chronic pancreatitis. This is in striking contrast to our experience where only 2 of 73 (2.7%) had pseudocysts secondary to alcoholic causes and 90% of patients had APP secondary to biliary pancreatitis, an etiology that has been shown to carry a significantly higher complication rate and mortality rate than alcoholic pancreatitis.[16] Reasons for this discrepancy lie in the fact that the pathogenesis and clinical course of pseudocysts in patients with chronic pancreatitis differs significantly from those after an episode of SAP.[7,10,16,17] Chronic pseudocysts or retention cysts result from calcification or stenosis of the pancreatic duct secondary to parenchymal fibrosis and pancreaticolithiasis, leading to duct dilatation, hypertension, and duct blowout.[18] As a consequence of this process, these pseudocysts remain clinically stable and characteristically have a duct–cyst communication. In contrast, pseudocysts secondary to an episode of SAP result from an acute inflammatory process with necrosis and the collection of pancreatic secretions and the products of the inflammatory response with or without major duct disruption.[7] These APP, particularly those with neck or body pancreatic necrosis with viable upstream pancreatic tissue, are more prone to develop complications.[19] This observation is supported by the 59% incidence of complications identified in APP in our series.

It is important to bear in mind that this series is highly selected and does not represent the majority of patients with APP. Most patients admitted to our hospital have large pseudocysts and associated severe pancreatic necrosis requiring a highly specialized surgical unit. Treatment of these high risk patients is associated with an increased mortality rate.[10,20] Our series compares favorably with that of Behrman et al.[10] who reported a morbidity rate of 65% and mortality rate of 25%, treating a similar group of patients. The clinical paradox remains in differentiating an APP from benign peripancreatic fluid collections, which are often coincident to pancreatic necrosis, contain little or no amylase-rich fluid, and require no definitive treatment.

The severity of the episode of SAP and the extent of associated pancreatic necrosis was also found to influence the rate of spontaneous pseudocyst resolution and need for surgical intervention.[21] In our series, necrosis by contrast-enhanced CT was calculated to be <30% in 18 (24.6%) and >30% in 55 (75.4%), findings indicative of a high rate of main pancreatic duct disruption in this series and the need for eventual operative intervention. It should be emphasized that all patients in this series had been managed medically for at least 4 weeks after their episode of SAP before intervention. This period of time allows the demarcation of necrotic tissue, maturation of the pseudocyst wall, and abatement of the initial systemic inflammatory response syndrome associated with SAP.[1–3] After 4 weeks of medical management, however, in patients with APP, their high rate of complications (59% in this series) and elevated morbidity (44.1%) and mortality rates (19%) once complications develop (vs morbidity rates of 7% and mortality rate of 0% for uncomplicated APP) argues for

pseudocyst directed surgical management as previously recommended.[11]

Accurate diagnosis of an infected pancreatic pseudocyst before either percutaneous or operative intervention remains imprecise. Whereas the definition of an infected pseudocysts states that it is characterized by organisms in a fluid collection secondary to acute pancreatitis, present for more than 4 weeks, surrounded by a nonepithelialized wall, and associated frequently to pancreatic necrosis seems clear, its clinical distinction from a noninfected pancreatic pseudocyst or peripancreatic fluid collection is difficult. Infection should be suspected in all patients with a known pancreatic pseudocyst and clinical signs or symptoms of sepsis. Diagnosis is confirmed by a CT scan showing gas and/or the finding of organisms in the fluid or necrosis collected by pseudocyst puncture or surgery. Definitive operation is based on the persistence of sepsis and/or the findings of residual necrosis based on dynamic CT evaluation. In patients with infected pancreatic pseudocysts, which were present for more than 6 weeks after the initial episode of pancreatitis, have CT images showing a well-developed cavity with a thick wall, and have absent or mild organ failure, definitive surgical treatment consists of fluid drainage, necrosis debridement, and cystoenteric anastomosis. We have previously established the importance of necrosis debridement in both infected and noninfected pancreatic pseudocysts.[22] Debridement of necrotic debris from a pseudocyst cavity should be carried out at the time of definitive drainage to avoid retroperitoneal sepsis and it attendant high morbidity and mortality rates.[23,24]

Once complications develop in APP, systemic sepsis and organ failure often preclude definitive surgical management. In this series, we followed an institutional algorithm in which patients with objective criteria for severe organ dysfunction as assessed by a SOFA score >3 and/or a high surgical risk, defined as an ASA ≥IV, were treated by initial percutaneous or endoscopic drainage and systemic antibiotics as a temporizing measure. This intervention was done to control sepsis and improve a patient's clinical condition sufficiently to allow subsequent definitive surgery at a later time. This strategy was utilized in 13 patients (18%) in this series with complicated APP and organ dysfunction and was successful in controlling sepsis and allowing for clinical improvement in 86% of patients in whom it was applied. Our results with percutaneous drainage were similar to those previously reported by Criado et al.[25] In their series of 42 patients with pancreatic pseudocysts, percutaneous drainage was effective for sepsis control and clinical improvement in all 23 patients with infected pseudocysts. In our subgroup of patients with infected pseudocysts, despite the fact that those treated with initial percutaneous drainage had greater organ failure as assessed by SOFA score than those who did not undergo initial drainage, mortality rates for both groups were not significantly different (P=0.633). The clinical benefits derived from both of these experiences suggest that the indication for initial drainage could be extended to patients with infected pseudocysts and mild organ dysfunction.

The underlying pathophysiologic mechanism for pseudocyst rupture is unclear. Many factors may be involved, including increasing intracystic pressure, infection, pancreatic enzyme activation with wall digestion, wall necrosis, or abdominal trauma.[7] Because most APP in the setting of SAP are associated with necrosis, pancreatic duct with subsequent accumulation of pancreatic fluid may lead to progressive growth and rupture. Viable pancreatic tissue proximal to the area of duct disruption was found in 14 of 16 patients (88%) in this series who had ruptured pseudocysts. This disconnected pancreatic duct syndrome was implicated in persistent pancreatic fistulas after pancreatic debridement and external drainage in SAP.[26] Increased pressure may also affect the blood supply, leading to necrosis and rupture. Morbidity and mortality rates for ruptured pseudocysts in our series were 50 and 29%, respectively, figures which are similar to those previously reported.[6,27]

Conclusion

In summary, APP associated with pancreatic necrosis after an episode of SAP requires careful evaluation and treatment. In patients with complicated APP and organ failure, percutaneous or endoscopic drainage should be performed as a temporizing measure to alleviate sepsis and improve the patient's condition. Definitive therapies depend on the clinical course and residual pancreatic necrosis assessed by dynamic CT. Complications in APP in this setting are unpredictable and when conservative measures fail, surgical treatment as salvage carries a high morbidity and mortality rate. Based on these observations, we recommend that APP of more than 6 cm in diameter, resulting from acute biliary pancreatitis, and associated with pancreatic necrosis should be treated electively before complications develop, usually 6 weeks after onset, regardless of symptoms.

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The Dagradi-Serio-Iacono Operation Central Pancreatectomy

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Abstract Central pancreatectomy (CP) is a segmental pancreatic resection indicated to remove benign or low-grade malignant tumors of the isthmus and proximal part of the body of the pancreas. The main advantage of this operation compared with major resections is that it permits to spare normal pancreatic parenchyma; moreover, spleen and upper digestive and biliary tracts are saved. The description of the complete operation was reported for the first time by Dagradi and Serio in 1984 and subsequently spread worldwide by Iacono and Serio. In our opinion, it should be called the *Dagradi–Serio–Iacono operation*, by the names of the surgeons who first performed it (Dagradi and Serio), and by the names of the surgeons responsible for reporting it worldwide with precise indications (Iacono and Serio). Operation requires a midline or a bilateral subcostal incision; the lesser sac is entered through dissection of the transverse colon from the omentum or by transecting the gastrocolic ligament. The pancreatic segment harboring the lesion is then mobilized and its posterior surface carefully dissected from the splenic vein and artery. Subsequently, the pancreatic portion harboring the tumor is isolated at its superior margin from the splenic artery after the pancreas is transacted. The extent of the resection of the central segment is limited on the right by the gastroduodenal artery and on the left by the need to leave at least 5 cm of normal pancreatic remnant. The resected pancreatic specimen is sent to the pathologist for confirmation of diagnosis and to check if the resection margins are adequate. Hemostasis of the two raw surfaces is achieved with interrupted 5 or 4/0 nonabsorbable stitches. When it is not stapled, the Wirsung's duct of the cephalic stump is sutured selectively with a figure-of-eight nonabsorbable stitch. An end-to-end invaginated pancreaticojejunostomy is carried out with a single layer of interrupted stitches. The operation is concluded with the construction of an end-to-side jejuno-jejunostomy about 50 cm distal to the pancreatic anastomosis. Other techniques for reconstruction of the distal stump using jejunum or stomach have been described. One or two soft drains are brought out on the right side. The fluid collected from this drain is checked for amylase level on postoperative days 3, 5, and 7; if the level is low or absent, the drain is removed. Central pancreatectomy is a safe technique for benign or low malignant tumors of the pancreatic neck that allows curing the tumor with evident functional results without increasing the risk for the patient. We can say that CP has a clear role like pancreaticoduodenectomy and distal pancreatectomy and we think that a pancreatic surgeon has to include this procedure in his/her technical skills. In order to obtain excellent results, correct indications and experience in pancreatic surgery are recommended.

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Introduction

Central pancreatectomy (CP) is a segmental pancreatic resection indicated to remove benign or low-grade malignant tumors of the isthmus and proximal part of the body of

the pancreas. Therefore, functional pancreatic parenchyma, spleen, and upper digestive and biliary tracts are preserved.

History

Dagradi and Serio in 1982 performed the first CP to resect an insulinoma of the pancreatic isthmus (Fig. 1), and described the technique in 1984 in *Enciclopedia Medica Italiana*[1] (Fig. 2). Subsequently, other authors have reported this technique.[2–4] In 1990, at the Congress of the American Pancreatic Association[5] held in Chicago, we presented our preliminary experience on this technique, referring to it as "intermediate pancreatectomy;" subsequently, in 1990, 1992, and 1993 at the 3rd World Congress of the World Association of Hepato-Pancreato-Biliary Surgery in London,[6] at the World Congress of the International Hepato Biliary Pancreatic Association in San Diego,[7] and at the European Congress of World Association of Hepato-Pancreato-Biliary Association in Paris,[8] respectively, we presented a video detailing the surgical technique. Three years later, at The Pancreas Club, held in San Diego in 1995, we reported the surgical and clinical results of 11 treated cases[9] and for the first time we named this operation "central pancreatectomy."

In 1997 at the Society for Surgery of the Alimentary Tract meeting in Washington DC, after several cases and after having carried out functional controls, we put forward a question: Is there a place for CP in pancreatic surgery?[10] However, amazingly, American authors have redescribed this operation; in fact Warshaw et al., in 1998, published a paper entitled "Middle segment pancreatectomy: a novel technique for conserving pancreatic tissue."[11]

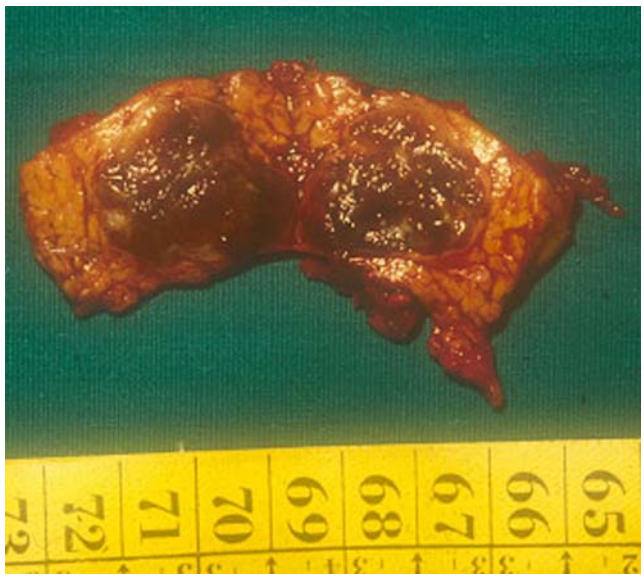

Figure 1 Surgical specimen of the first CP for insulinoma performed by Dagradi e Serio in the 1982.

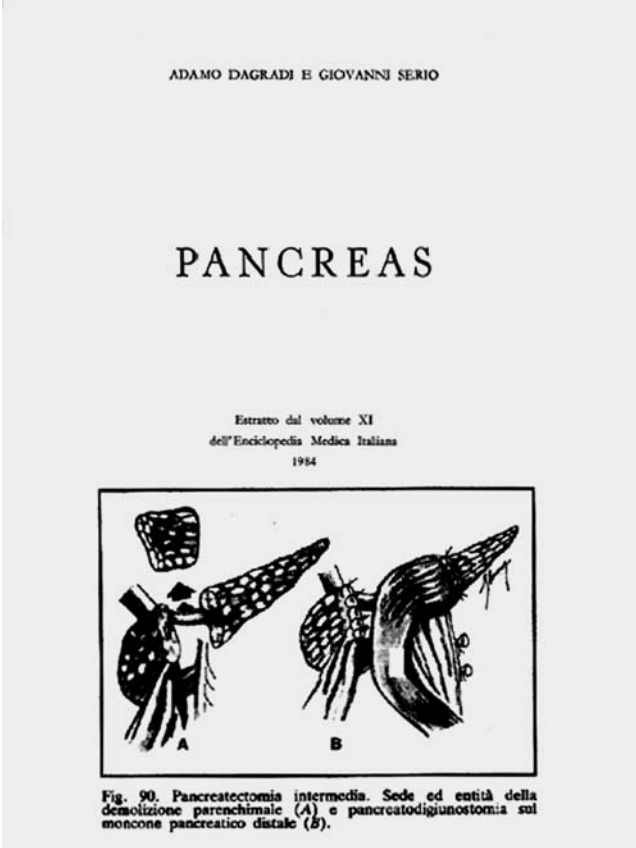

Figure 2 Schematic drawing of the CP, original from "Enciclopedia Medica Italiana" published in 1984 (with permission of UTET Scienze Mediche, Torino).

Neither Guillemin and Bessot,[12] in 1957, nor Letton and Wilson, in 1959,[13] described this technique as thought by some; in fact, these two operations dealt only with the reconstructive aspect. The French authors[12] carried out only a transection of the isthmus followed by a double digestive anastomosis of the two pancreatic stumps to an omega-shaped jejunal loop in patients with chronic pancreatitis, whereas Letton and Wilson[13] performed only the reconstructive part after burying the cephalic stump and carrying out a pancreaticojejunostomy to the distal stump after a traumatic transection of the neck.

Technically, the first step of CP is the resection of the central segment, isthmus, and proximal body, followed by the reconstructive part consisting in suturing the cephalic stump and performing digestive anastomosis of the distal stump.[1] The description of the complete operation was reported for the first time by Dagradi and Serio[1] in 1984 and subsequently spread worldwide by Iacono and Serio.[5–10,14,15] The precedence of the first description of a segmental pancreatic resection must be given to Beger[16] in 1980 (Beger procedure); however, the site of the resection was different.

We therefore believe that this technique should be called the *Dagradi-Serio-Iacono operation*, by the names of the surgeons who first performed and described it (Dagradi and

Serio),[1] and by the names of the surgeons responsible for reporting it worldwide with precise indications (Iacono and Serio)[5–10,14] and who, for the first time, fully described it in a treatise of surgical techniques.[15]

Rationale for CP

The rationale for CP is to remove the neoplasm, preserving functional parenchyma and avoiding a major resection such as pancreaticoduodenectomy or left splenopancreatectomy. Therefore, there is no risk of diabetes and exocrine insufficiency and the upper digestive and biliary anatomy is maintained with consequent digestive, immunologic, and coagulative advantages.

Indications

Basic conditions are:

- Tumor size between 2 and 5 cm, where a simple enucleation entails a high risk of injury to the main pancreatic duct
- Small tumors that are deeply located in the gland and are therefore not eligible for enucleation (functioning endocrine tumors such as insulinoma—Fig. 1)
- Benign or low-grade malignant tumors [endocrine tumors, serous and mucinous cystadenomas (Fig. 3), noninvasive intraductal mucinous producing tumors (IMPT), solid pseudopapillary tumors] in which a conservative resection can be carried out with free margins
- Nonneoplastic cystic lesions (lymphoepithelial, dermoid, and hydatid cysts) not suitable for enucleation
- Solitary metastases to the pancreatic neck (especially renal metastasis) and pancreatic endocrine tumors with metastases undergoing multimodality treatment
- Focal chronic pancreatitis with isolated and short stenosis of Wirsung's duct

Contraindications

Contraindications are represented by:

- Large lesions for which it is not possible to preserve at least 5 cm of distal pancreatic stump.
- Distal body–tail atrophy.
- Malignant tumors (especially ductal carcinoma).
- Neoplastic involvement from other organs (stomach, transverse colon).
- Diffuse chronic pancreatitis or focal pancreatitis not involving the central part of the gland.
- Central pancreatectomy is contraindicated when the body–tail of the pancreas receives its arterial blood supply exclusively from the transverse pancreatic artery (left branch of the dorsal pancreatic artery) (Fig. 4); this anatomical variant of vascularization, which can be

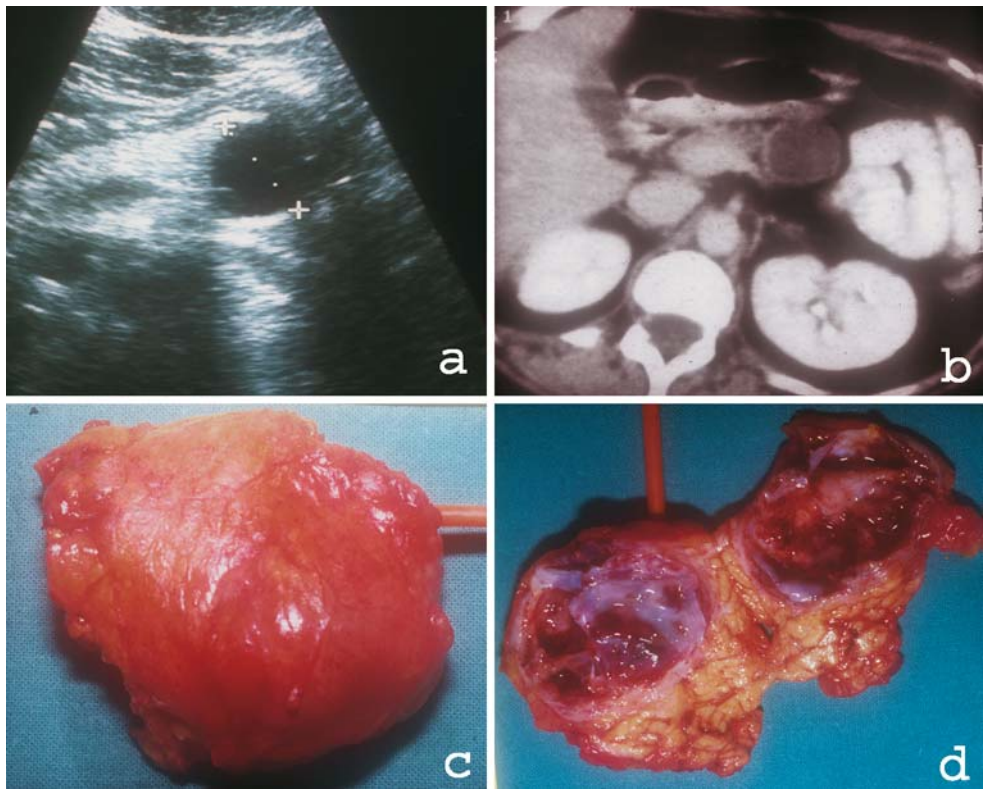

Figure 3 Central pancreatectomy for mucinous cystadenoma. **a** US. **b** CT. **c**, **d** Surgical specimen.

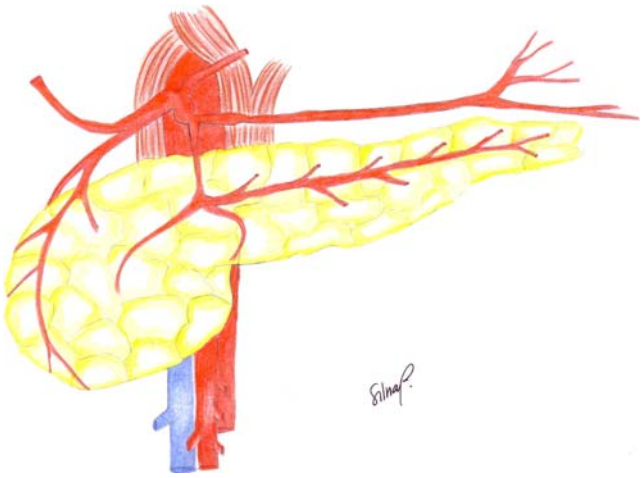

Figure 4 Pancreatic body–tail vascularization supported exclusively by transverse pancreatic artery, left branch of the dorsal pancreatic artery (type III according to Mellière and Moullé), contraindicates CP.

clearly seen on angiography, angio-CT or angio-magnetic resonance (MR), is defined by Mellière and Moullé[17] as type III and was present in about 25% of their cases.

Diagnostic Work-up

Preoperative functional studies are directed to assess the nutritional status of the patient with complete laboratory tests. Serum carcinoembryonic antigen, Ca 19-9, neuron specific enolase, and α-chromogranin are determined. In case of suspected endocrine neoplasm, specific hormone levels are assessed.

Imaging studies [ultrasound (US), CT, MR scanning, and endoscopic retrograde cholangiopancreatography] provide important information about characteristics of the lesion. In particular, dynamic CT scanning and MR pancreatography give useful details regarding the neoplasm blood supply and its relationship with vessels and the pancreatic duct. Fine needle aspiration cytology for differential diagnosis can be performed with percutaneous approach or with endoscopic ultrasound guidance.

Exocrine and endocrine function studies are valued preoperatively to diagnose possible insufficiency and to compare with postoperative results. Endocrine function is evaluated by serum glucose level, glycosylated hemoglobin, insulin, C-peptide levels, and oral glucose tolerance test. Exocrine function is assessed by pancreo-Lauryl test, assay of fecal fat excretion, and/or determination of fecal elastase-1.

Preoperative Preparation

Antibiotic and antithrombotic prophylaxis is given. Prophylaxis with somatostatin analogs to prevent pancreatic fistula have not been shown to clearly benefit the patient and are not routinely utilized.

Surgical Technique

The surgical technique includes resection of the central segment (Fig. 5), isthmus and proximal body, and a reconstructive part consisting of closing the cephalic stump and performing a digestive anastomosis to the distal stump (Figs. 2 and 6);

Incision and Exposure

The patient is placed supine with the feet slightly lower than the head. The type of incision chosen has to provide an excellent exposure and it can be either a midline incision from over the xiphoid to below the umbilicus or a bilateral subcostal incision with a midline extension to the xiphoid in obese patients.

Exploratory Step

After entering the lesser sac by separating the transverse colon from the omentum, or by transection of the gastro-colic ligament, the pancreas is exposed and intraoperative diagnostic work up can be completed with ultrasonography; fine-needle aspiration cytology; pancreatography; or, in case of IMPT, pancreatoscopy (after resection).

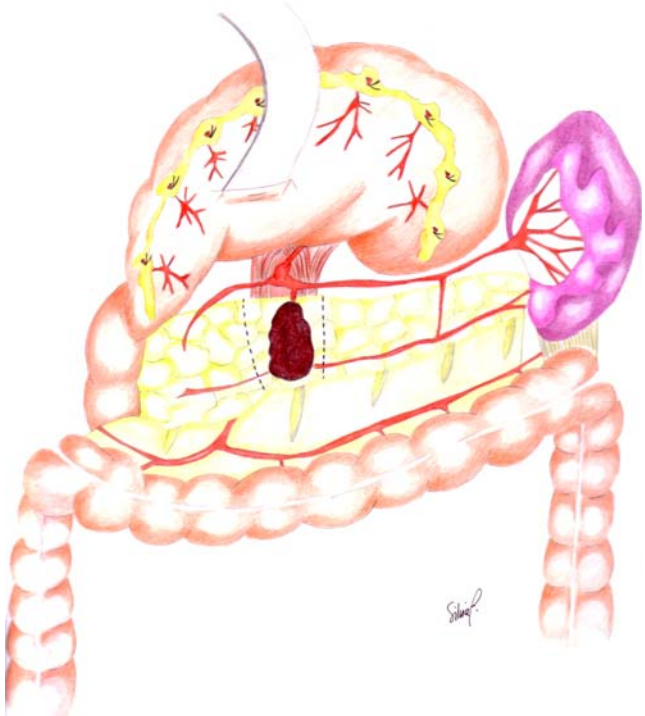

Figure 5 The limits of CP (gastroduodenal artery on the cephalic side and a minimum length of 5 cm of distal stump) are marked with *dotted lines*.

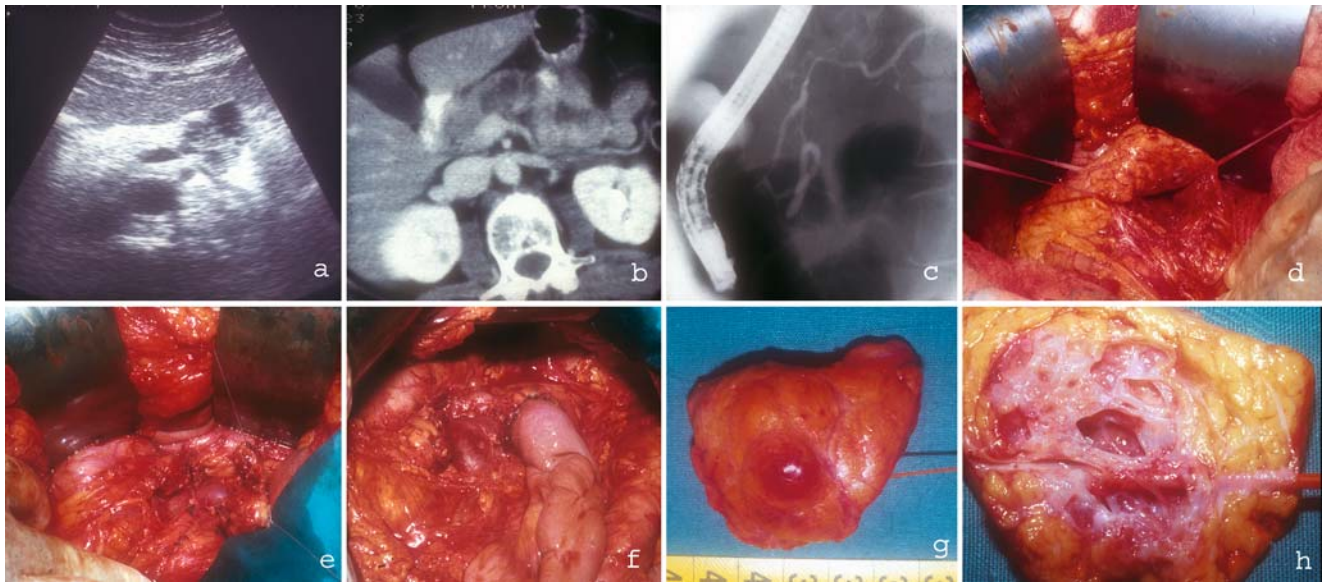

Figure 6 Central panceatectomy for symptomatic serous cystadenoma. **a** US, **b** CT, **c** endoscopic retrograde cholangiopancreatography, **d** pancreatic segment harboring the tumor is dissected from the splenic vessels, **e** proximal and distal stumps after the resection of the isthmus, **f** the proximal stump and the end-to-end invaginated pancreaticojejunostomy, **g** the specimen of CP, and **h** the section demonstrating the involvement of the Wirsung duct.

Resection Step

Incisions are made in the posterior peritoneum along the superior and inferior margins (Fig. 7) of the central segment of the pancreas. After passing a vessel loop around the isthmus, the spleno-mesenteric axis is dissected free from the posterior surface of the gland dividing some pancreatic veins (Figs. 6 and 8). To ease this phase of the operation, transection of the pancreas on the cephalic side can be performed to mobilize the pancreatic stump toward the left,

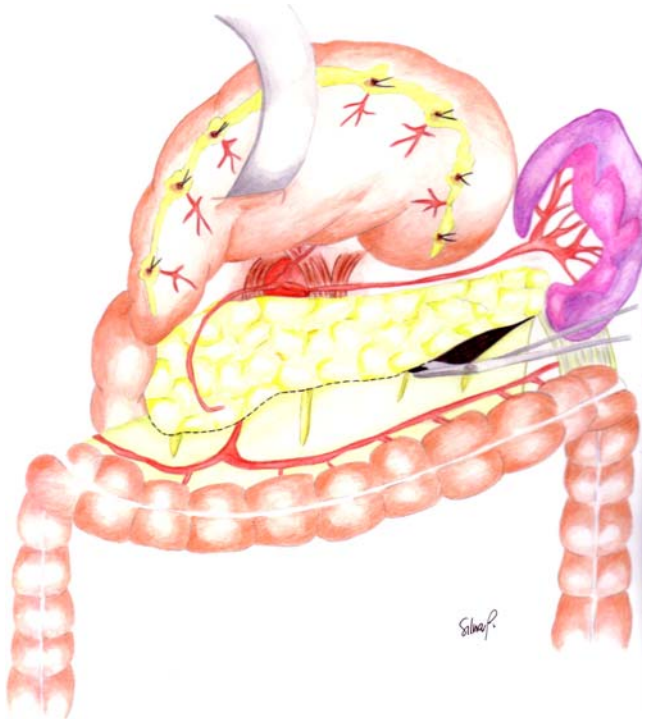

Figure 7 After entering the lesser sac, the posterior peritoneum along superior and inferior margins of the pancreas is incised.

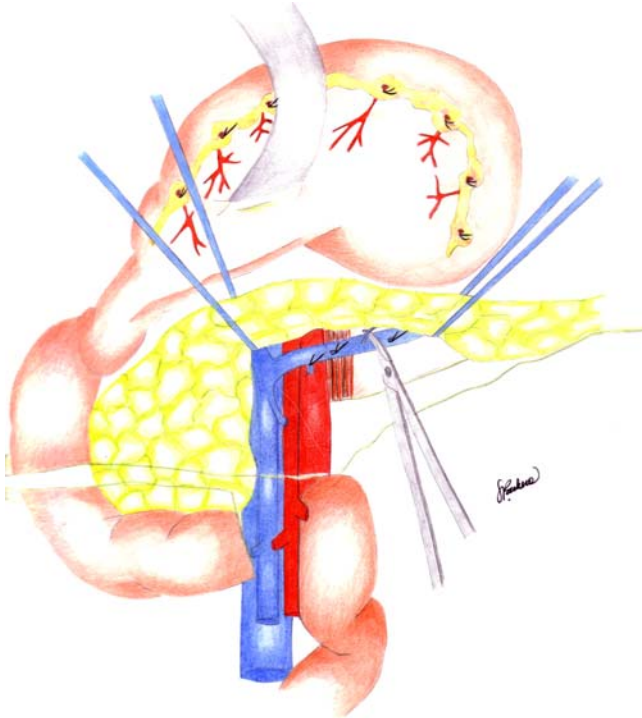

Figure 8 Pancreatic segment harboring the lesion is suspended with two surgical loops to allow easier dissection of pancreatic veins from the splenic vein and better mobilization of the pancreatic body.

exposing all the slim pancreatic veins that can be severed more easily.

Another vessel loop is passed around the splenic artery, and its collaterals are divided, including the dorsal pancreatic artery, but a large size of this artery must raise the suspicion of vascularization to the left pancreas maintained only by the transverse pancreatic artery, that is, the left branch of the dorsal artery (Fig. 4), and this represents a contraindication to CP to avoid necrosis of the left pancreas.

The next step is transection of the gland: on the cephalic side, the limit is the gastroduodenal artery and on the caudal side, it is a minimum length of 5 cm distal of the remaining pancreas (Fig. 9). Two hemostatic stitches are positioned on the margins of both sides: the transection is performed with a knife. The cephalic stump may be stapled. The two raw surfaces (Fig. 9) are inspected to insure good vascularization, particularly on the distal stump that has to be anastomosed; otherwise, the resection must be extended for 2–3 cm more.

The specimen is then sent to the pathologist for frozen section to confirm the diagnosis and clear margin of resections. If the pathologist diagnoses malignant disease, the operation has to switch to pancreaticoduodenectomy or left splenopancreatectomy with extended lymphadenectomy according to the extension of the lesion towards the head or the body–tail. In the presence of IMPT, pancreatoscopy is performed, just after resection, through the main pancreatic duct in both stumps to rule out other ductal lesions.

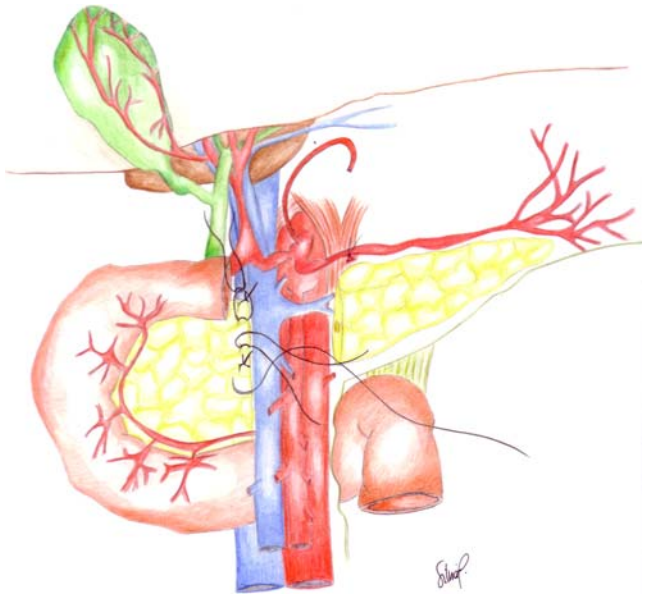

Figure 10 Wirsung duct is ligated electively and mattress stitches are passed through the entire gland to suture cephalic stump.

Reconstructive Step

After completion of hemostasis with 4/0 or 5/0 selective monofilament stitches, the cephalic stump is closed with mattress stitches after separate closure of the main pancreatic duct with a figure-of-eight stitch (Figs. 6, 10, and 11). Some authors carry out an anastomosis also of the cephalic stump using the same jejunal loop.

The distal pancreatic stump is separated for 2 cm from the splenic vessels to easily carry out the anastomosis to a jejunal loop or stomach.

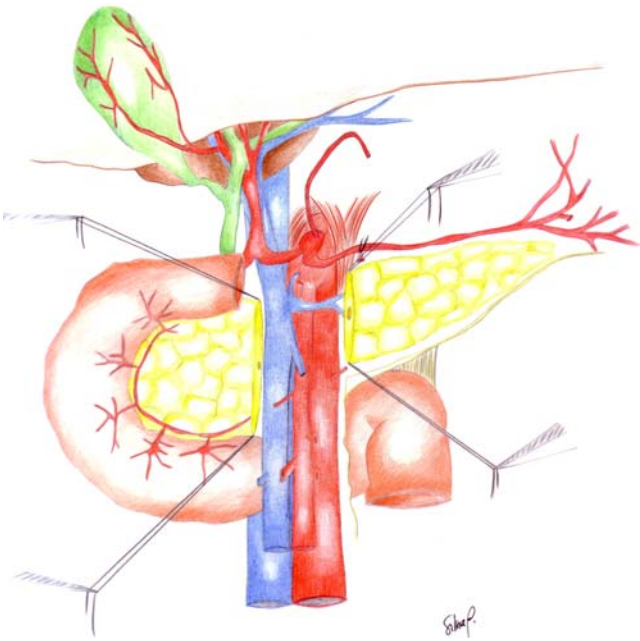

Figure 9 Proximal and distal pancreatic stumps after resection of the isthmus.

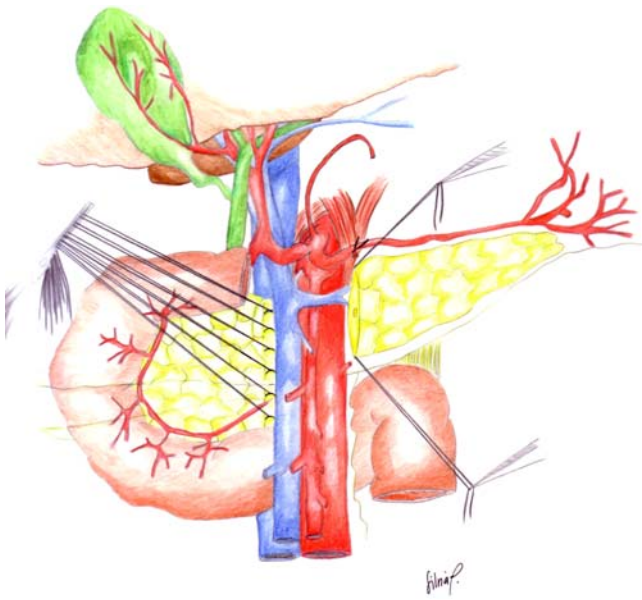

Figure 11 Pancreatic stump has been sutured and body–tail stump is mobilized to be anastomosed.

1. Pancreaticojejunostomy can be carried out in different ways:
   (a) End-to-end (Figs. 2, 6, and 12). Simple invagination or telescopic invagination. The first method is carried out with a single layer of interrupted stitches between the pancreatic parenchyma capsule and the intestine, even if the easier method is less utilized. In the simple invagination technique, the pancreatic stump is invaginated into the jejunal loop for 15–20 mm and sutured all around with interrupted stitches. For the telescopic method, two layers of sutures are carried out: the first outer suture line consists of interrupted stitches between the pancreatic capsule and the seromuscular coat of the bowel in the posterior surface, at 2 cm from the pancreatic resection surface and the free margin of the jejunal loop. The second inner layer is completed between the pancreatic capsule at the margin of resection and the free margin of the bowel; this suture of interrupted stitches starts from the posterior to the anterior aspect to complete the inner layer of the anastomosis all around the stump. An outer suture line is completed on the anterior surface again at 2 cm from the free margin as in the posterior side.
   (b) End-to-side (Fig. 13). It is performed a few centimeters proximal to the end of the jejunal loop, in either a single or a double layer.

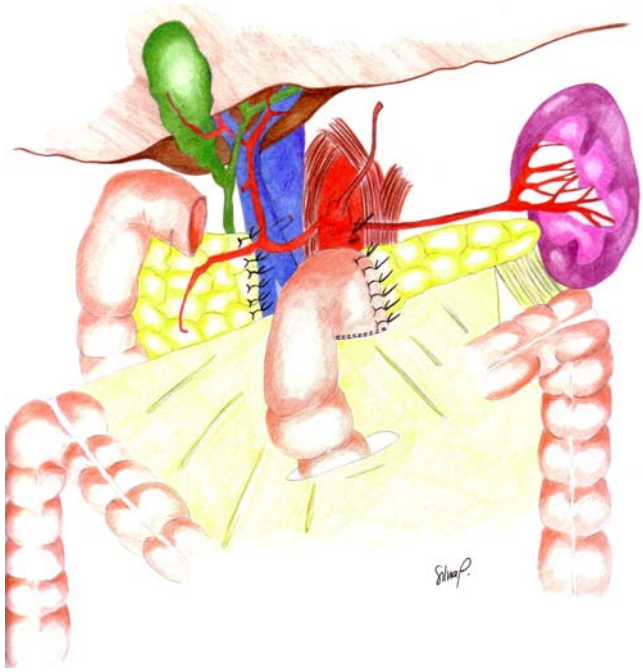

Figure 13 End-to-side pancreaticojejunostomy for the distal stump.

   (c) Duct-to-mucosa (Fig. 14). The anastomosis is carried out with 5/0 interrupted absorbable stitches between a lateral 5-mm opening on the bowel and the Wirsung duct, with or without stenting it.
   (d) Side-to-side (Fig. 15). The ventral surface of distal pancreas is opened longitudinally from the margin

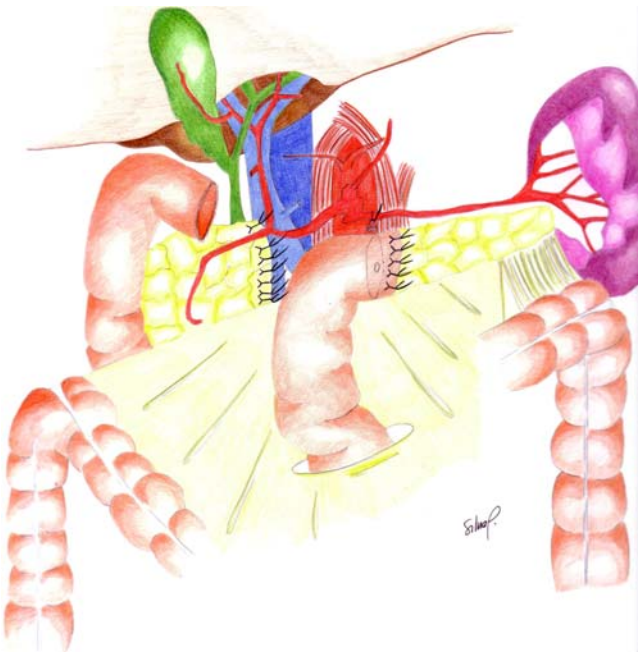

Figure 12 Pancreaticojejunostomy on Roux-en-Y jejunal loop is constructed in single or double layer and brought up through an opening in the mesocolon.

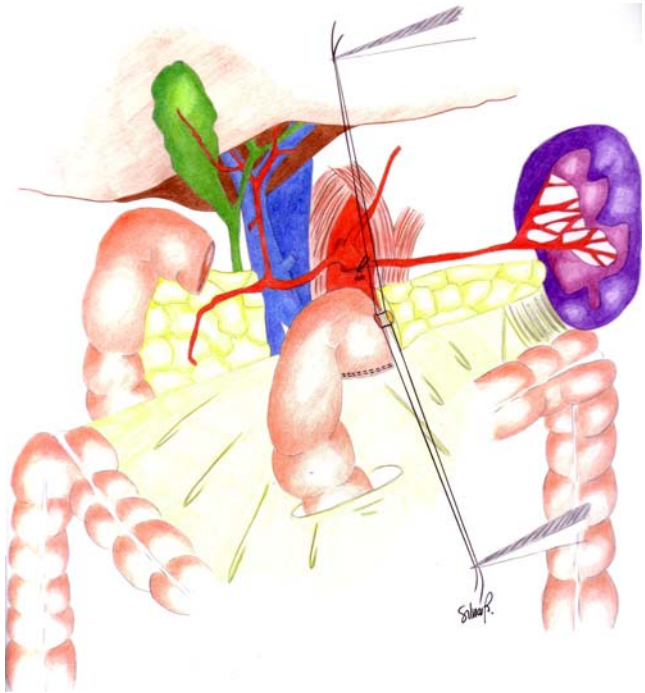

Figure 14 Duct-to-mucosa pancreaticojejunostomy for the distal stump.

of resection to the tail and a side-to-side anastomosis is performed as a Puestow or Partington–Rochelle technique. It is indicated when the Wirsung duct is dilated, for example, in chronic pancreatitis with a dilated Wirsung duct.

(e) Double pancreaticojejunostomy either end-to-side and side-to-side (Fig. 16) or both side-to-side.

2. Pancreaticogastrostomy (Fig. 17). For this anastomosis, different variants have been proposed; however, the implantation of the open end of the pancreas directly into the gastric pouch through a 2–3-cm opening in its posterior surface is the most frequent technique. This technique is the most frequently used by French[18–20] and, recently, American authors[21–24]; it has a very low rate of pancreatic fistula and the anastomosis can be directly visualized by endoscopy; the disadvantages are mainly related to the alteration of digestive enzymes, particularly lipase, caused by gastric juice, resulting in an impairment in exocrine function. In our opinion, the alteration of exocrine pancreatic function represents a failure of this conservative operation.
3. Closure of pancreatic stump. In exceptional cases (pancreatic stump atrophic, pancreatic duct not evident, etc.), the pancreatic stump is closed; usually, drains are placed near the pancreatic closure.
4. Closure of the main pancreatic duct of the distal stump and injecting synthetic glue[25] is preferred by some authors; however, this technique results in pancreatic atrophy and diabetes.

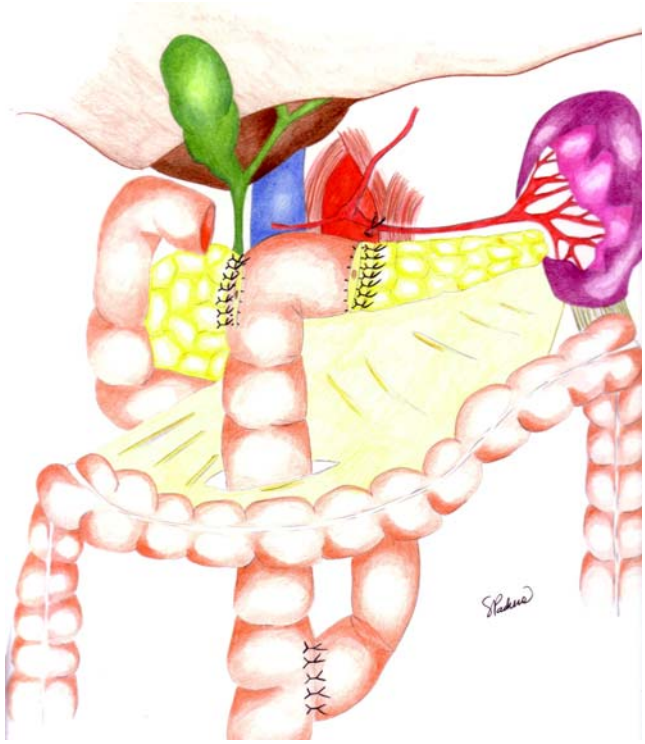

Figure 16 Reconstruction with a double jejunal loop anastomosed in both the stumps.

To complete reconstruction, an end-to-side jejunojejunostomy is then constructed 40–50 cm distal to the pancreatic anastomosis. One or two soft closed drains are placed near

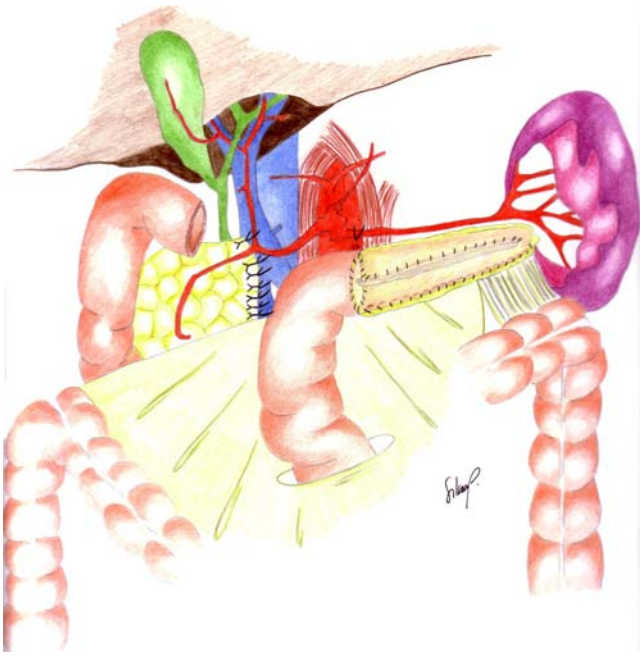

Figure 15 Side-to-side pancreaticojejunostomy according to Partington–Rochelle after the opening of Wirsung's duct on distal stump in patients with chronic pancreatitis and dilated duct.

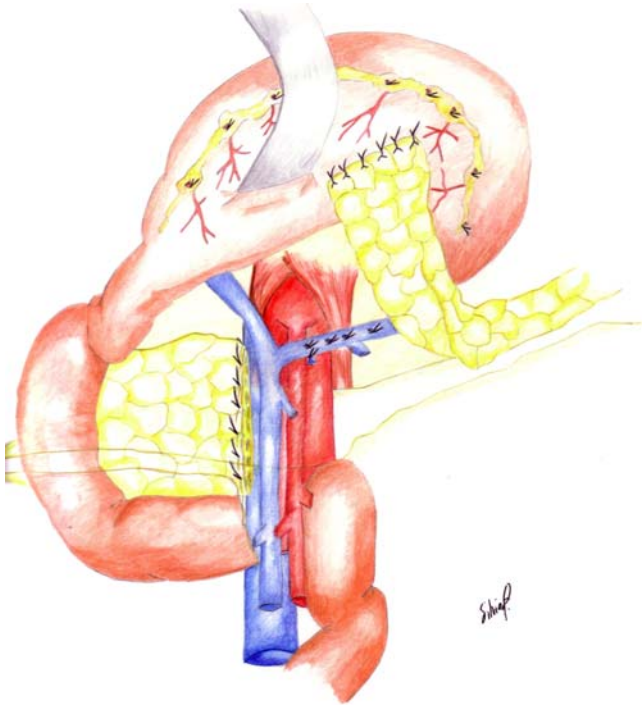

Figure 17 Reconstruction of distal stump with pancreaticogastrostomy.

the anastomosis and sutured cephalic stump and are brought out on the right abdominal side or on the right and left sides.

Early Postoperative Course

The nasogastric tube is removed after 24 h and the patient is placed on clear diet on postoperative day 2 and solid diet on day 3. The fluid collected from the drains is checked for amylase level on postoperative days 3, 5, and 7; if the level is low or absent, the drains are removed on postoperative days 6 through 8.

Postoperative Complications and Management

Central pancreatectomy morbidity rates have a great variability in the literature, ranging from 0 to 75%.[2–4,9–11,14,18–36] Mortality is low and only one case is reported of a severe complication leading to death (Table 1). In this case, the patient underwent reoperation for leakage of the pancreaticojejunostomy; during surgery, a splenoportal confluence thrombosis was also observed.[20] The patient underwent distal pancreatectomy with portal trombectomy, but he died after the operation from multiple organ failure. The most frequent complication reported in the literature is a pancreatic fistula, with a frequency that varies from 0 to 63%;[2–4,9,10,14,18–37] this wide difference is due to the small series of reported cases; however, its incidence seems to be slightly higher than that reported after pancreaticoduodenectomy. It appears to be in the same range after distal pancreatectomy as reported in the most recent literature.[38–40] Pancreatic fistula in CP usually heals spontaneously with maintenance of the drains, parenteral nutrition, and the use of somatostatin-analog drugs because the leak from the proximal stump or from the pancreaticojejumostomy is not exposed to enzymatic activation of bile like in a pancreatic fistula after pancreaticoduodenectomy.

Table 1 Postoperative Morbidity and Mortality Rates of CP

Author	Year	No. of cases	Morbidity rate (%)	No. of cases of local complication	No. of cases of systemic complication	Reoperation (no. of cases)	Mortality rate (%)
Fagniez[2]	1988	2	0	0	0	0	0
Asanuma[4]	1993	2	0	0	0	0	0
Rotman[3]	1993	14	29	4	1	3[a]	0
Ikeda[26]	1995	24	12.5	3	0	0	0
Fernandez-Cruz[30]	1997	3	0	0	0	0	0
Iacono[10]	1998	13	30	3	1	0	0
Partensky[19]	1998	10 (10)	40	4	0	1	0
Warshaw[11]	1998	12	25	3	0	0	0
Takeyoshi[27]	1999	3	0	0	0	0	0
Sperti[28]	2000	10	40	3	1	0	0
Yamaguchi[34]	2000	10	40	4	NA	NA	0
Celis[32]	2001	6	0	0	0	0	0
Shibata[35]	2002	10	50	4	1	0	0
Su[33]	2002	4	75	3	0	0	0
De Clavier[18]	2002	11 (9)	63	6	1	2	0
Sauvanet[20]	2002	53(25)[b]	41	22	2	3	2
Balzano[25]	2003	32[c]	62	16	4	1	0
Christein[29]	2003	3	0	0	0	0	0
Goldstein[21]	2004	12 (12)	25	0	3	0	0
Efron[22]	2004	14 (14)	50	5	2	2[d]	0
Siech[31]	2004	6	NA	NA	NA	NA	NA
Muller[36]	2005	25	24	3	NA	1	0
Iacono[14]	2005	20	35	5	2	0	0
Brown[24]	2006	10 (4)	60	5	NA	0	0
Christein[37]	2006	8	65	5	NA	2	0
Roggin[23]	2006	10 (1)	60	3	3	1	0

In brackets are reported the number of patients with pancreaticogastrostomy
NA = not available
[a] One patient had been reoperated for infiltrated margin
[b] Multicentric report
[c] In 20 cases, distal stump was treated by Wirsung duct occlusion
[d] For GI bleeding in one immediately postoperatively and one 10 days after CP

Table 2 Late Outcome of CP

Author	Year	No. of cases	No. of cases of exocrine insufficiency	No. of cases of endocrine insufficiency	Recurrence rate (%)
Fagniez[2]	1988	2	0	0	0
Asanuma[4]	1993	2	1[a]	0	0
Rotman[3]	1993	14	0	1	0
Ikeda[26]	1995	24	0	2[b]	0
Fernandez-Cruz[30]	1997	3	0	0	0
Iacono[10]	1998	13	0	0	0
Partensky[19]	1998	10	0	0	0
Warshaw[11]	1998	12	0	0	0
Takeyoshi[27]	1999	3	0	0	0
Sperti[28]	2000	10	0	0	0
Yamaguchi[34]	2000	10	0	0	0
Celis[32]	2001	6	0	0	0
Shibata[35]	2002	10	1	0	0
Su[33]	2002	4	0	0	0
De Clavier[18]	2002	11	1	1	0
Sauvanet[20]	2002	53[c]	2[d]	3[d]	8[e]
Balzano[25]	2003	32	3[f]	2 mild diarrhea	0
Christein[29]	2003	3	0	0	0
Goldstein[21]	2004	12	2	0	0
Efron[22]	2004	14	0	0	0
Siech[31]	2004	6	NA	NA	NA
Muller[36]	2005	25	NA	NA	NA
Iacono[14]	2005	20	0	0	0
Brown[24]	2006	10	0	0	0
Christein[37]	2006	8	0	1[g]	0
Roggin[23]	2006	10	1	0	0

NA = not available
[a] The patient returned to normal value 36 months after operation
[b] Two patients with chronic pancreatitis
[c] Multicentric report
[d] One patient had a wide CP (15 cm) and another patient developed exocrine insufficiency 104 months after CP for fibrotic stenosis of Wirsung duct after severe pancreatitis
[e] Four patients: one had gastric cancer invading the pancreas, one had pancreatic metastasis from renal cancer, and two had IMPT
[f] In all three cases, the distal stump was treated by Wirsung duct occlusion with synthetic glue
[g] One patient transiently required oral pancreatic enzyme supplementation

Other surgical complications reported in literature are intra-abdominal abscess and fluid collection, splenic vein thrombosis with infarction of the spleen, pancreatitis, and delayed gastric emptying. Intra-abdominal collections and abscess can usually be managed with percutaneous drainage under CT or US guidance, the surgical approach is reserved as the second line of treatment. Complications of the spleen are frequently treated with splenectomy, but in selected cases, a splenic abscess can be drained percutaneously.

Digestive and intra-abdominal bleeding is reported as early or late complications secondary to vascular erosion or pseudoaneurysm of a peripancreatic artery. Severe and early

Table 3 Central Pancreatectomy for Chronic Focal (Segmental) Pancreatitis and Pseudocysts of the Pancreatic Neck or Proximal Portion of Body of the Pancreas

Author	Year	No. of cases of focal pancreatitis	No. of cases of pseudocyst
Rotman[3]	1993	–	1
Ikeda[26]	1995	7	–
Fernandez-Cruz[30]	1997	1	2
de Clavier[18]	2002	1	–
Sauvanet[20]	2002	4	3
Efron[22]	2004	1	1
Muller[36]	2005	12	–
Brown[24]	2006	1	–

Table 4 Laparoscopic CP

Author	Year	No. of cases	Pathology	Pancreodigestive anastomosis
Baca and Bokan[42]	2003	1	Cystadenoma	End-to-side PJJ
Ayav et al.[43]	2005	1	Insulinoma	NA
Orsenigo et al.[44]	2006	1	Neuroendocrine tumor	Duct-to-mucosa PJ
Rotellar et al.[45]	2006	1	NA	Duct-to-mucosa PJ

PJJ = pancreaticojejunostomy, NA = not available

bleeding complications[20,21,23,37] require immediate surgery; conservative approach with angiographic embolization is the treatment of choice for late bleeding. Other frequent medical complications are pleuro-pulmonary and urinary tract infections requiring specific antibiotic therapy.

Long-term Outcome After CP

Central pancreatectomy preserves exocrine and endocrine function; in the literature, only six cases of exocrine insufficiency have been reported, one by Rotman[3] and two by Ikeda[27] that underwent CP for chronic pancreatitis and three by Sauvanet[20] (Table 2). Balzano[25] reported two cases of mild diarrhea (2–3 bowel movements/day), and in the Mayo Clinic experience,[37] one patient transiently required oral pancreatic enzyme supplementation.

Diabetes or impaired glucose tolerance has been observed in six cases in the literature, two reported by Goldstein[21] and two by Sauvanet,[20] one by de Clavière,[18] and one by Asanuma.[4] In this last case, the postoperative alterations were transient and returned to normal within 36 months after the operation (Table 2). Balzano[25] adds three other cases of postoperative diabetes, but the distal stump had been closed by means of Neoprene injection. In the Memorial Sloan–Kettering Cancer Center experience,[23] a case of persistent postoperative hyperglicemia treated with dietary modifications and administration of an oral hypoglycemic agent was reported.

In theory, the aim of CP is to preserve all normal pancreatic tissue, especially the body–tail segment where islet cells seem to be more numerous. In our previous report,[10] we evaluated preoperative and postoperative exocrine and endocrine function and no functional impairment was demonstrated.

The real incidence of diabetes after left pancreatectomy is still a matter of debate. The literature data are contradictory and there have been no studies comparing pancreatic function tests (exocrine and endocrine) before and after left pancreatectomy. However, in a study in pancreatic transplant donors who underwent left pancreatectomy, Kendall, at the Minneapolis Transplantation Center,[41] showed a 25% incidence of glucose intolerance after 1 year. However, comparative studies between CP and distal pancreatectomy have shown a grater incidence of diabetes in distal pancreatectomy.[33–35]

The local recurrence rate is related to indication, and it is nil when the indication is correct. Four cases of local relapse are reported in the literature:[20] two cases of IMPT, a case of gastric cancer involving the pancreas, and another case of pancreatic metastasis from renal cancer. Regarding IMPT, intraoperative frozen section was not performed in one of the two cases reported by Sauvanet,[20] and in the other patient, either intraoperative or final pathology showed moderate dysplasia in the proximal portion where the recurrence developed (Table 2). The presence of epithelial hyperplasia in the intraoperative frozen section did not influence recurrence of the disease as observed in the John Hopkins experience.[22] Other techniques, as intraoperative pancreatoscopy reported by Japanese authors, can improve results and reduce the risk of local recurrence. In chronic pancreatitis, CP can rarely be utilized, the unique indication is in patients with a focal stricture in the isthmus[3,18,20,22,24,26,30,36] (Table 3).

New approach: Laparoscopic CP

Recently, this technique, like other pancreatic resective procedures, has been performed laparoscopically. Four cases of laparoscopic CP are reported in the literature (Table 4).[42–45]

Conclusions

Central pancreatectomy is a surgical technique that offers the best results in benign and low-grade malignant tumors. It guarantees the highest preservation of functional parenchyma and avoids the potential infective and thrombotic complications of splenectomy.

We can say that CP has a clear role like pancreaticoduodenectomy and distal pancreatectomy and we think that a pancreatic surgeon has to include this procedure in his or her technical skills. To obtain excellent results, correct indications and experience in pancreatic surgery are recommended.

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Surgery for Obesity: A Review of the Current State of the Art and Future Directions

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Abstract The number of patients undergoing surgery for the treatment of obesity, and the proportion of the health care budget dedicated to this health problem, is growing exponentially. There are several competing surgical approaches for the management of morbid obesity. We review the literature relating to four of these: gastric bypass, biliopancreatic diversion, gastric banding, and gastric pacing. Our review finds that while enhancing the malabsorptive activity of these procedures may induce an incremental increase in excess body weight loss, the proportion of patients who fail to lose more than 50% of their excess body weight is similar no matter how radical is the surgery performed. There is little guidance from the literature as to appropriate patient selection for the varying procedures, and anonymously reported registries have yet to show that patients who undergo bariatric surgery have enhanced longevity. To date, the bariatric surgical community has not conducted adequately powered randomized prospective trials to elucidate key elements of the surgical procedure such as optimal bypass length, to determine whether mixed operations are superior to those that offer intake restriction only, and to define what constitutes success after bariatric surgery. As a public health measure, bariatric surgery in the United States is being pursued in an irrational manner, being concentrated in areas where there are fewer morbidly obese patients, and used disproportionately among the population of white obese females.

Keywords Obesity · Surgical treatment · Biliopancreatic diversion · Roux-en-Y gastric bypass · Adjustable gastric banding · Gastric pacing

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Introduction

The startling and ominous rise in obesity worldwide has been well documented in both the lay press and medical journals. Concomitant with this explosion in the prevalence of morbid obesity has been the exponential rise in the number of patients seeking surgical remediation of their obesity. The visibility of celebrities who have undergone the surgery, expansion of insurance coverage for bariatric interventions, and, most important, the dissemination of practitioners trained in bariatric surgery, especially laparoscopic Roux-en-Y gastric bypass, have served to fuel this continuing expansion. Nevertheless, as will be seen from our review, there are a host of unanswered questions about the optimal application of the surgical approach to obesity, ranging from "What is the preferred procedure for specific patients?" to "How should the surgical community define success following bariatric operations?" As a result of its application to a limited number of patients until the last decade or so, there is a dearth of adequately powered studies to guide the bariatric surgeon in making many of the

crucial decisions regarding procedural details and patient selection. The consequence is that bariatric surgery has been, for the most part, an empirical enterprise to this point, but as more resources are diverted to the problem of obesity and its surgical management, all parties involved require a more rigorous application of surgical science. With that in mind, this review will examine the presently ascendant technologies of gastric bypass and gastric banding, potential alternatives such as gastric pacing and the more radical but less often used biliopancreatic diversion, and highlight some of the long-term problems resulting from these procedures of which all surgeons, both bariatric and nonbariatric, need to be made aware.

Roux-en-Y Gastric Bypass

Mason and Ito introduced the concept of gastric bypass for weight loss in 1967. With time, the operation has evolved through many modifications into the Roux-en-Y gastric bypass (RYGB), which has become the most frequently performed bariatric surgery in North America. In 1991, the National Institutes of Health (NIH) Consensus Development Conference Panel for gastrointestinal surgery for the treatment of severe obesity identified RYGB as one of the two recommended surgical procedures for the treatment of those with severe obesity.[1] The RYGB procedure has since been considered the "gold standard" to which all other bariatric surgeries are compared.

Technique

The first alteration to normal enteral flow occurs in the stomach. The proximal stomach is partitioned to create a gastric pouch of 30 ml or less in volume. The pouch should be constructed from the gastric cardia to the exclusion of the acid-producing fundus, with preservation of the lesser curve vasculature and of vagal innervation to the distal stomach and gallbladder. A divided gastric pouch is favored to decrease the chance of gastrogastric fistula formation that is seen more commonly with nondivided gastroplasties. Having been excluded from enteral flow, the gastric remnant is left in situ; Csendes and colleagues[2] have proposed resection of the distal gastric remnant as a way of reducing marginal ulceration and gastrogastric fistulas, but this approach has not been widely accepted in North America.

The next division of the alimentary tract occurs in the proximal jejunum to create a Roux limb. There remains a disagreement as to how distal from the ligament of Treitz the jejunum should be divided. Higa and colleagues[3] recommend transection of the jejunum approximately 15 cm distal to the ligament of Treitz based on a theoretical decrease in malabsorptive complications. Investigators Sarr (50–75 cm), Shauer (50 cm), DeMaria (30 cm), and Buchwald (40–50 cm) propose more distal division of the jejunum, resulting in a longer biliopancreatic limb and consequently a longer bypass of the proximal alimentary tract.[4,5] The investigators are unanimous in stating that the transection point be placed so as to facilitate mobilization of the Roux limb for the creation of a tension-free gastrojejunostomy. Suggested lengths of the efferent Roux limb vary between 50 and 150 cm, with many authors and centers favoring longer lengths for patients with a body mass index (BMI) greater than 50 kg/m^2. Justification for the use of longer bypass lengths is controversial, and this is discussed further in the section on the more radical malabsorptive procedures.

A gastrojejunostomy is then created between the gastric pouch and the distal limb of jejunum. Varieties of anastomotic techniques have been used, including suturing, linear stapling, and circular stapling to create an anastomosis 10–25 mm in diameter. Banding of the anastomosis with Silastic bands, polypropylene mesh, suture, or the laparoscopic adjustable gastric band has been touted by Fobi and Lee,[6] Capella and Capella,[7] Gleysteen,[8] and others as a mechanism to prevent anastomotic dilatation and the theoretical potential for regaining weight. To date, there are no randomized controlled data to support anastomotic banding. When informally surveyed, a minority of American Society for Bariatric Surgery (ASBS) members were found to practice this modification. Finally, bowel continuity is restored by the creation of a jejunojejunostomy between the Roux and biliopancreatic limb.

Three potential internal hernia spaces result from the RYGB operation (Fig. 1). If a retrocolic path is chosen for the Roux limb, two potential hernia spaces are created. The first is at the transverse mesocolon where the Roux limb passes through the mesenteric window. The second is the oft-mentioned Petersen's defect that arises between the mesentery of the Roux limb and the base of the mesentery of the transverse colon. Closure of these defects is important to prevent the formation of internal hernias, particularly when a laparoscopic RYGB is performed. Passage of the Roux limb in an antecolic fashion has been touted as way of obviating the need for closing the Petersen's space. With this modification, the space persists, but it is more wide open. Based on retrospective analyses, Champion and Williams[9] and Felsher et al.[10] described a decrease in the incidence of internal hernias requiring reoperation for small bowel obstruction after switching to the antecolic technique. The third internal hernia defect occurs between the mesenteries of the Roux and biliopancreatic limbs at the jejunojejunostomy. This defect is present regardless of the path taken by the Roux limb and should always be fastidiously closed.

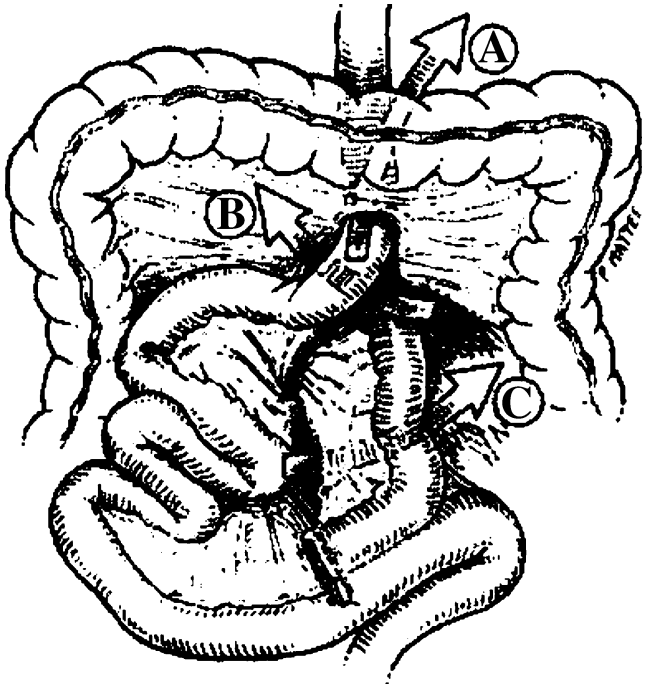

Figure 1 Potential mesenteric opening that could lead to internal hernia after Roux-en-Y gastric bypass. (A) Transverse mesocolon defect. (B) Petersen hernia (space between mesentery of Roux limb and transverse mesocolon). (C) Jejunojejunostomy mesenteric defect. (Reprinted from Schweitzer MA, DeMaria EJ, Broderick TH, Sugerman HJ. J Laparoendosc Adv Surg Tech A 2000;10:173–175, with permission from Obesity Surgery, FD-Communications, Inc. Toronto, Ontario).

In 1994, Wittgrove and Clark[11] reported the first RYGB performed laparoscopically. Subsequently, the laparoscopic technique has evolved to become one the most commonly performed minimally invasive surgeries, and by 2003, the laparoscopic Roux-en-Y gastric bypass (LRYGB) was the most commonly performed bariatric operations worldwide.[12] Some groups have even promoted LRYGB as an outpatient procedure.

An infrequently used alternative to RYGB or LRYGB, although infrequently used, is the operation known as minigastric bypass. This technique of gastric bypass harkens back to the formative days of the operation, as it approximates the original technique of Mason and Ito. Rutledge[13] first reported its use laparoscopically. The technique of minigastric bypass consists of creating a divided vertical gastric tube, approximately 1.5 cm in diameter, along the lesser curvature that runs from the incisura angularis to the angle of His. A loop gastrojejunostomy is then formed about 200 cm from the ligament of Treitz (Fig. 2). The minigastric bypass currently has few proponents and is not commonly performed in the United States due to concerns about alkaline reflux gastritis/esophagitis.

Results

Weight loss after RYGB, whether open or laparoscopic, generally occurs within the first 2 postoperative years. The expected weight loss, as a percentage of initial excess body weight (IEBW), ranges from 50% to 80%. In a review of 11 randomized clinical trails and well-documented case series of RYGB, Buchwald and Williams[14] reported a 68.6% mean and a 70.1% case-weighted mean IEBW loss. A meta-analysis of English-language bariatric surgery articles published between 1990 and 2003 found RYGB led to a mean IEBW loss of 61.56%. The range of IEBW lost was 33–77% for the 4204 pooled patients. Notably, when only randomized controlled trials were considered, the results were less impressive, with means for IEBW loss of 45%–54%.[15]

Comparative effectiveness Compared with vertical banded gastroplasty (VBG), the purely restrictive operation with the longest follow-up on which to base comparison, RYGB results in superior weight loss, although the absolute difference is surprisingly modest. In a recent meta-analysis of bariatric surgical procedures, Maggard and colleagues[15] found that controlled trials of RYGB versus VBG favored RYGB in respect to total weight lost at 12- and 36-month follow-up. RYGB patients lost a mean of 7.97 and 9.29 kg

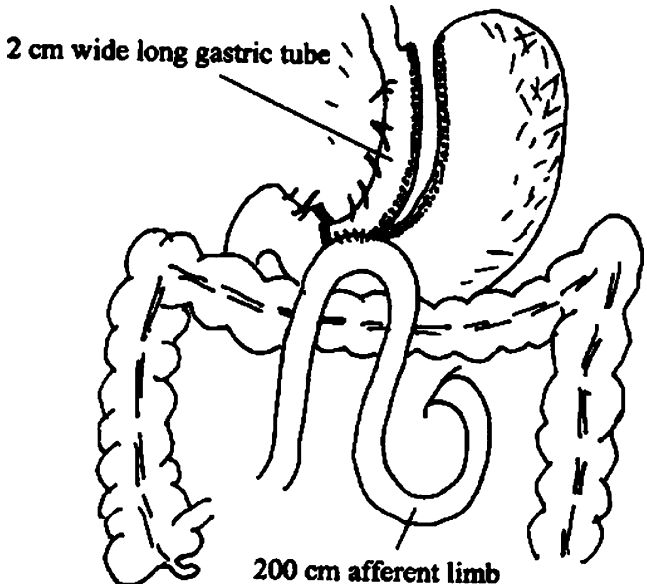

Figure 2 View of completed laparoscopic mini-gastric bypass. The narrow gastric tube, roughly the diameter of esophagus (approximately 1.5 cm wide), is created parallel to the lesser curvature and up to the angle of His. Intraoperative endoscopy is used as a stent during the division of the stomach and assists in the anastomosis. The antecolic gastroenterostomy is created at the small bowel 200 cm distal to the Trietz ligament. (Reprinted from Lee WJ, et al. Ann Surg 2005;242:225, with permission from Lippincott Williams and Wilkins).

more than VBG patients at 12- and 36-month follow-up, respectively. When all studies of 10 or more patients were considered, those receiving RYGB lost a mean of 43.46 and 41.46 kg at 12 and 36 months postoperatively, compared with 32.16 and 32.03 kg for VBG patients, respectively, at the same time intervals. No large-scale controlled trials of RYGB versus biliopancreatic diversion (BDP) or with the duodenal switch variant exist. Pooled data from trials and case series from the same meta-analysis favor biliopancreatic diversion over RYGB. Patients receiving a BPD lost on average 10 kgs more than the RYGB patient at both the 12- and 36-month follow-up point.

Three randomized controlled trials comparing laparoscopic RYGB and open RYGB exist.[16–18] No significant difference in weight loss was seen in any of the trials between the two approaches to RYGB. The only prospective randomized trial of LRYGB versus laparoscopic minigastric bypass showed that IEBW lost was equivalent between the two surgeries (59.2% and 64.4%, respectively) at a 2-year minimum follow-up.[19]

Complications

Anastomotic leak and hemorrhage The most feared complication after RYGB is an anastomotic leak or gastric pouch staple line dehiscence. Leak rates after open RYGB and LRYGB range from 1% to 5%. In their meta-analysis, Maggard and colleagues[15] reported a 2.2% leak rate for RYGB from 30 case series and randomized trials. Leak rates for both open and laparoscopic forms of the operation tend to be higher in randomized trials than in case series, reflecting perhaps a selection bias characteristic of single-institution uncontrolled investigation. Data from the three controlled trials of open RYGB versus LRYGB showed equivalent rates for gastrojejunal anastomotic leak.[16–18] In a multivariate analysis of a single-institution series of more than 3000 gastric bypass operations, Fernandez and colleagues[20] described a 3.2% overall incidence of gastrojejunal anastomotic leak. In subgroup analysis, revision to an RYGB was found to produce the highest leak rate at 6.9%. For 2271 open RYGBs, a 2.3% leak rate was reported compared with a 4.2% rate for 571 LRYGBs. The authors concluded from their analysis that increasing age, male gender, sleep apnea, diabetes mellitus, and the type of procedure performed (revision to RYGB > LRYGB > RYGB) were independent risk factors for anastomotic leak.

Although used by many surgeons, routine postoperative upper gastrointestinal contrast studies or computed tomography (CT) scans to detect anastomotic failure have not been shown to consistently reduce either morbidity or mortality from leaks in randomized trials.

The risk of gastrointestinal hemorrhage after gastric bypass surgery ranges from 0.6% to 4%.[21] There is a suggestion that LRYGB carries a higher risk of bleeding than RYGB. Gastrointestinal hemorrhage usually occurs at or from staple lines used to form divisions in bowel or mesentery or to create anastomoses. Hemorrhage can be either intraluminal or intraabdominal in nature. The use of staple cartridges with a *more narrow* closed-staple height, 2.5 mm versus 3.5 mm or 3.5 mm versus 4.8 mm, has been touted as a way of preventing staple-line-associated hemorrhage. This practice, however, goes against the recommendation, based on animal models, to use staple cartridges with a *larger* closed height as a preventive measure against staple-line failure or leak. In a study of the mechanics of applying staplers to the gastrointestinal tract, Baker and colleagues[22] showed that the use of undersized cartridges (i.e., those with smaller closed-staple heights) increase the risk of creating a malformed staple-line. They also found that undersized staple cartridges tend to overly compress tissue, leading to tissue tearing and perforation. A solution to this conundrum may be incorporating staple-line reinforcement materials that allow for the use of a cartridge with a larger closed-staple height, while at the same time decreasing the bleeding through the staple line. The application of expanded polytetrafluorethylene (ePTFE), bovine pericardium, or a bioabsorbable copolymer for the reinforcement of staple lines has been shown in a few studies to increase the burst pressure of the staple line while decreasing staple-line-associated hemorrhage. It is hoped that as experience with the various products available for staple-line reinforcement grows, more definitive data about their utility in gastrointestinal surgery will become available.

Bowel obstruction Small bowel obstruction (SBO) occurs in about 3% of laparoscopically performed RYGBs and in 2% of open cases.[23] Perioperative SBO is almost never seen after open RYGB but represents about 15% of the obstructions seen after laparoscopic RYGB. Most of these latter blockages occur at the jejunojejunostomy and are due either to narrowing at the anastomosis (as a consequence of the double-staple technique used to close the common enterotomy) or to angulation of the two limbs. The use of suture closure of the common enterotomy and the use of an antikinking suture may reduce the incidence of this complication.

Late SBO in the laparoscopic patient is usually a consequence of internal hernia. Even with meticulous closure of the mesentery at the jejunojejunostomy and of the defect in the transverse mesocolon created when the efferent limb is passed in a retrocolic fashion, hernia defects can develop. With weight loss, suture used to close these hernia spaces can lose their purchase and result in the

reformation of internal hernias. Further, the potential space below the mesentery of the efferent limb (Petersen's hernia) is always present no matter how the efferent limb is brought to the gastric pouch. The reduction in adhesions seen with laparoscopic surgery is especially disadvantageous in this regard, as this space remains chronically open. Most obstructions that follow open RYGB are adhesive in nature.

Marginal ulceration The incidence of ulceration at the gastrojejunostomy is difficult to estimate, although it is a frequent topic of discussion on the Members' Forum of the ASBS. From the data of Scopinaro et al.[24] on biliopancreatic diversion (BPD), an operation thought more likely to be ulcerogenic than the transected RYGB, stomal ulceration rates were found to be 5.6–8.3%. Marginal ulceration initially was in excess of 15% until they modified the procedure by reducing gastric pouch size.[24] These rates were subsequently lowered to 3.2% by the addition of H_2-blocker prophylaxis postoperatively. The consequences of marginal ulceration range from mild epigastric pain to chronic anemia to frank hemorrhage requiring urgent endoscopic or operative intervention. Chronic perianastomotic ulcerations after RYGB may also be a cause of recurrent stricture formation, leading to multiple endoscopic dilatations or ultimately operative revision.

Three etiologies have been proposed to explain ulceration at the gastrojejunostomy, none of them particularly persuasive. The first and most obvious is acid exposure of the small bowel at the gastrojejunostomy. However, given the miniscule pouch size of the RYGB and the routine use of acid suppression by many bariatric surgeons, it is unclear how much acid is actually present at the anastomosis. Others have imputed the ulceration to ischemia, but with the peak incidence occurring during the second postoperative year, one is hard pressed to explain why the ischemia would develop after such an extended period. Finally, there is the possibility that bile reflux may be the cause, but with a Roux limb of adequate length this should not be a common occurrence.

Work-up of the marginal ulceration patient includes upper endoscopy to assess the status of the pouch and anastomosis and to take a biopsy sample to check for the presence of *H. pylori*. If the latter is found to be present, appropriate eradication measures should be pursued. Upper gastrointestinal series and/or CT scans should be performed to evaluate for a fistula between the pouch and the excluded stomach. Serum gastrin should be obtained to assess for unsuspected gastrinoma or G-cell hyperplasia. On occasion, pH probe of the pouch may be helpful to quantify acid or alkaline exposure.

The need for surgical correction of the ulceration is determined by symptom severity or level of chronic blood loss. If a gastrogastric fistula is present, takedown of the fistula with interposition of small bowel to protect the gastric pouch staple line should be curative. If there is no fistula present, downsizing of the pouch with revision of the gastrojejunostomy by a hand-sewn technique is generally suggested based on anecdotal experience. Some bariatric surgeons believe that truncal vagotomy, either transabdominal or transthoracic, should be added, but this carries other consequences such as postvagotomy diarrhea, increased risk of gallstone formation, and atony of the pylorus that can result in potentially dangerous dilatation of the excluded stomach. Others have even suggested combining removal of the distal stomach with vagotomy to eliminate any stimulatory gastrin production and the possibility of acute gastric dilatation. At present, there is no consensus as to the most appropriate surgical intervention should *H. pylori* eradication and/or proton pump inhibitors fail to heal marginal ulceration.

Deep venous thrombosis/pulmonary embolism Morbid obesity is a known risk factor for deep venous thrombosis (DVT) and pulmonary embolism (PE). The incidence of DVT is thought to be approximately 2% for bariatric surgery patients.[25] In a 2000 survey of members of the ASBS, the self-reported incidence of DVT was 2.63% and the incidence of PE was 0.95%.[26] A more recent analysis using the 2002 Nationwide Inpatient Sample found DVT/PE to occur at a rate of 3.4 per 1000 discharges.[27] Using pooled data from two prospective randomized trials comparing RYGB to LRYGB, DVT/PE rates were comparable at 1.0% and 0.9%, respectively.[15]

A variety of prophylactic measures have been advocated, including unfractionated heparin, low-molecular-weight heparin, sequential compression stockings, and inferior vena caval (IVC) filter placement. It appears that the combination of low-molecular-weight heparin and compression stockings is the most frequently used prophylaxis in bariatric surgery patients. There is no randomized trial data available to answer the question of what is the most efficacious VTE prevention strategy for bariatric surgery. The availability of the removable IVC filter had rekindled interest in its use in high-risk obesity patients. Obesity hypoventilation syndrome (Pickwickian syndrome), cor pulmonale, history of prior PE and/or DVT, pulmonary hypertension, evidence of venous stasis, and known hypercoagulable state have all been suggested as indications for preoperative vena caval filter placement.[25,28]

Hernia Wound complications are the bane of open surgical procedures. Bariatric surgery patients are at higher risk than nonobese surgical patients for wound complications, especially incisional hernias. When patients receiving RYGB and patients receiving total colectomy for ulcerative colitis were compared, severe obesity and its associated

morbidities were found to be more potent factors for the development of an incisional hernia than chronic steroid use.[29] The rate of incisional hernia formation after RYGB has been estimated to be between 18% to 20%.[25] Surprisingly, however, data from three controlled trials of RYGB versus LRYGB have shown lower rates of hernia formation after open surgery, 8.2% for RYGB, than would have been predicted.[16–19] Most controlled trials of LRYGB have shown a 0% incisional hernia rate.

Strzelczyk and colleagues[30] have proposed the addition of polypropylene mesh to standard closure techniques for RYGB as a prophylaxis against postoperative hernia formation based on 0% hernia rate after its use in a nonrandomized study. This technique has not demonstrated wide appeal because of concerns with mesh infection when placed during a clean contaminated case. Treatment of hernias already present at the time of RYGB or LRYGB has been made simpler with the advent of biocompatible hernia meshes (Alloderm, Surgisis). Eid and colleagues[31] from the University of Pittsburgh showed, in a retrospective study, a 0% recurrence rate for concomitant hernia repair with Surgisis mesh versus a 22% recurrence rate for concomitant primary repair at an average of 2-year follow-up. The biocompatible meshes present a lower risk of infection compared to polypropylene and PTFE; however, their high cost likely precludes their use as a routine buttress to conventional methods of abdominal wall closure.

Metabolic and Hormonal Changes

Over the past few years, a coherent but incomplete picture of the pathways concerning the drive to eat, satiety, and energy homeostasis has been developing. The roles and interactions of gastric leptin, ghrelin, cholecystikinin, amylin, glucagon-like peptide 1, apolipoprotein A-IV, peptide tyrosine-tyrosine, and others are slowly being understood. The elucidation of the mechanism by which bariatric surgery influences the function and expression of gastrointestinal hormones is also in its infancy. As shown in Table 1, gastric bypass surgery has been shown to change the levels of gastrointestinal hormones including ghrelin, enteroglucagon, and glucagon-like peptide 1.[49] The studies on levels of ghrelin, an orexigenic hormone produced by the stomach, after gastric bypass surgery offer a mixed bag of results. Four studies have shown a decline in ghrelin levels, two studies have shown an increase in ghrelin levels, and one study showed no changes in ghrelin levels after RYGB.[32–37,50]

For many years, it has been observed that type 2 diabetes mellitus often improves or resolves with relatively small amounts of postoperative weight loss.[51] Evidence for an endocrine mechanism for the resolution to type 2 diabetes mellitus induced by gastric bypass surgery has been sought. Rubino and colleagues[52] showed an association with changes in various hormone levels including gastric inhibitory polypeptide, glucagon-like peptide 1, leptin, and insulin-like growth factor and the resolution of type 2 diabetes mellitus. In their study, glucose metabolism was shown to normalize before any significant changes in BMI were induced by LRYGB. Further studies will hopefully better elucidate the role of bariatric surgery in altering the hormonal pathways controlling satiety, appetite, and glucose metabolism, perhaps lending foundation for making rational modifications in the procedural technique in regard to pouch size, stoma diameter, and limb lengths.

Table 1 Effects of Bariatric Surgery on Gastrointestinal Intestinal Hormones

Surgery	Hormone	Change	Reference
Gastric bypass (Roux-en-Y)	Ghrelin	↓	32
	Ghrelin	↑	33
	Ghrelin	↓	34
	Ghrelin	No change	35
	Ghrelin	↓	36
	Ghrelin	↓	37
	Ghrelin	↑	38
	Enteroglucagon	↑	39
	Enteroglucagon	↑	40
	GLP-1	↑ (NS)	41
	CCK	No change	39
Gastric banding	Ghrelin	↓	34
	Ghrelin	↓	35
Vertical-banded gastroplasty	PYY	↑	42
Biliopancreatic diversion/duodenal switch	Enteroglucagon	↑	43
	Enteroglucagon	↑	44
	Enteroglucagon	↑	45
	Ghrelin	↓ (Initial only)	46
Jejunoileal bypass	CCK	↑ (Cell no.)	47
	CCK	↑	48
	PYY	↑	48
	Enteroglucagon	↑	45
	GLP-1	↑	48

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Malabsorptive Bariatric Operations

The use of more radical bariatric procedures for inducing greater weight loss has generally been more popular outside of the United States. U.S. surgeons' use of malabsorptive procedures such as BPD remains cautious, perhaps due to their negative experiences with jejunoileal bypass (JIB). First suggested as a bariatric procedure by Varco and then

by Kremen et al. in 1954, JIB came into more frequent use in 1963 after Payne et al. published a series of 11 patients (Fig. 3). Despite several modifications, the JIB carried with it an irreducible risk of liver and renal failure, disabling arthralgias, and unrelenting urolithiasis.[53] The operation was already in its twilight in 1977 when an article written by Griffin et al.[54] reported the results of a randomized prospective trial, showing that the JIB did not induce greater weight loss at 1 year than a nontransected gastric bypass. Given that the latter operation carried a significantly reduced risk of long-term complications, with equivalent perioperative complication rates, the gastric bypass quickly replaced the JIB. Although it persisted for a period as the preliminary operation for superobesity popularized at Duke University by Grant,[55] it eventually passed into surgical history.

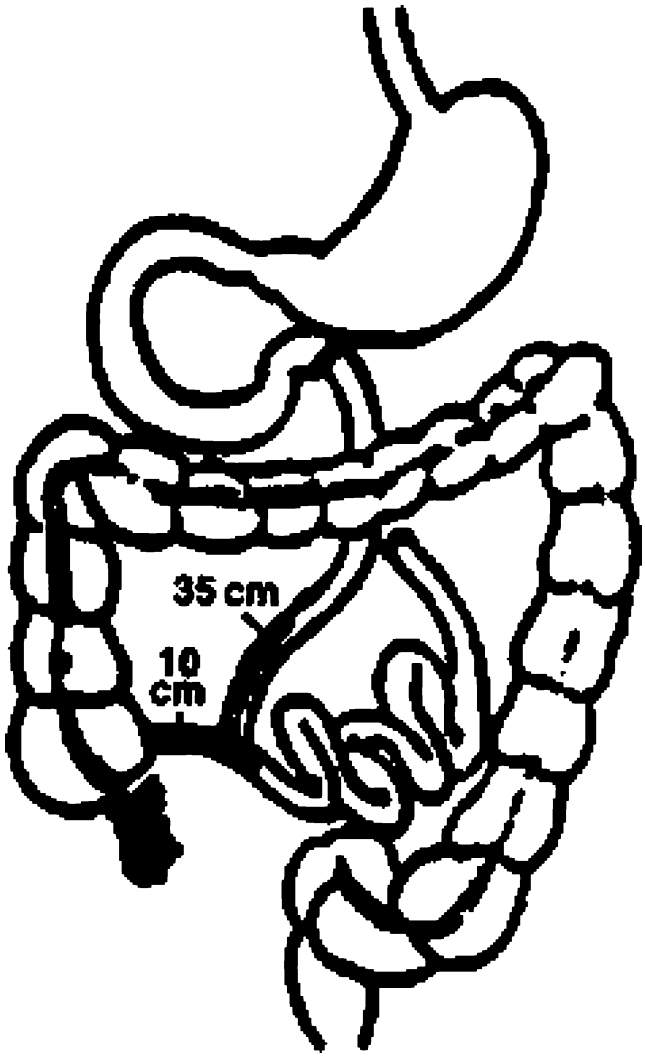

Figure 3 Jejunoilieal bypass. The original operation described by Payne involved an end-to-side jejunoileostomy, anastomosing the proximal 35 cm of the jejunum to the distal ileum, 10 cm proximal to the ileocecal valve. (Reprinted from DeMaria EF, Jamal MK. Gastroenterol Clin North Am 2005;34:127–142, with permission from Elsevier).

With the increasing proportion of patients presenting for weight loss surgery in the superobese category, more attention has been focused on radical malabsorptive procedures for weight loss. Presently, there are three approaches used to augment weight loss beyond that routinely achievable by the standard "short limb" RYGB. They are the BPD, the duodenal switch variation of the same, and the very long limb RYGB.

Much of the morbidity of the JIB was attributed to the fact that a long segment of bowel was left with no flow of either enteric contents or biliopancreatic secretions through it. It was thought that this engendered a blind loop syndrome to which the hepatic and renal dysfunction was attributable. In 1979, Scopinaro et al.[24] suggested an alternative operation known as BPD. Modified several times since the original publication, the operation consists first of what Scopinaro and colleagues refer to as an ad hoc distal gastrectomy (Fig. 4). The volume of the gastric remnant is calibrated to "preoperative excess weight and other individual characteristics (e.g., sex, age, eating habits, socioeconomic status, and expected degree of compliance)." Befitting its ad hoc label, these determinant characteristics of the ad hoc distal gastrectomy are never explicitly stated in the BPD literature. What we know is that the higher-BMI patients, especially men and binge eaters, undergo creation of a 200-ml pouch (division point on the greater curvature 15 cm from the angle of His), which is coupled to an alimentary limb 200 cm in length. A 400-ml pouch (division point at the lowest short gastric artery) is anastomosed to a 300-cm alimentary limb in all other patients. A 50-cm common channel is created in both groups.

A variation on the BPD of Scopinaro et al. that has gained some popularity in North America is the duodenal switch procedure. Its main advocates have included Marceau and coinvestigators[56] in Canada, and the Hess[57] and Rabkin[58] groups in the United States. These investigators modified the BPD by first replacing the distal gastrectomy with a sleeve resection of the stomach (Fig. 5). This resulted in the creation of a lesser curve gastric tube and pyloric preservation, and relocated the afferent limb anastomosis to a divided second portion of the duodenum, rather than using a gastrojejunostomy. It was thought that these changes would reduce diarrhea due to the retention of the pylorus and that the rate of marginal ulceration would be decreased by the maintenance of a "duodenal switch." Common channel length was also increased from the fixed 50 cm as originally used by Scopinaro et al.[24] Marceau and colleagues went to a fixed common channel length of 100 cm, whereas Hess's group championed the use of a variable distance based on 8–12% of the total small bowel length, up to a maximum length of 100 cm.[59] Hess et al. also found that the optimal alimentary limb length was

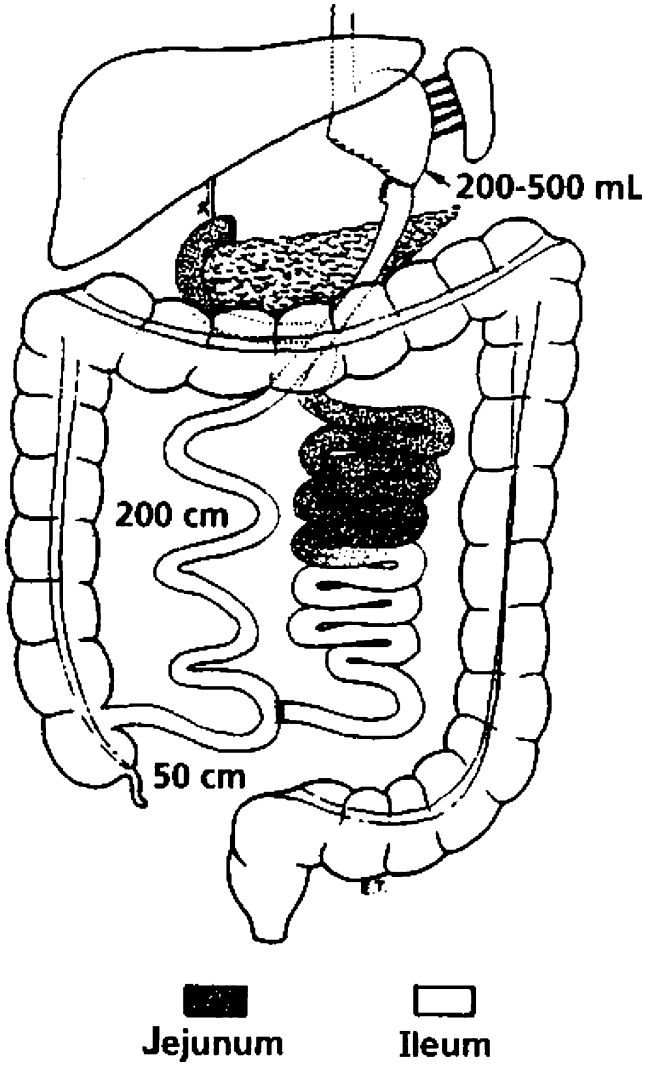

Figure 4 Biliopancreatic diversion (Reprinted from Scopinaro N. Surgery 1996;119:261–268, with permission from Elsevier).

between 38% and 42% of total small bowel length. Making the common channel longer, it was hoped, would reduce diarrhea and protein malnutrition without sacrificing weight loss.

Assessment of the perioperative and long-term complication rates of the two BPD procedures, vis-à-vis the RYGB, is complicated by the highly selective and limited nature of the BPD experience. Furthermore, because both of these procedures are generally offered to the superobese patient, early morbidity and mortality would be expected to be higher based simply on the higher-BMI population. BPD is a more complex procedure than RYGB, creating a duodenal stump (per Scopinaro) or requiring peripancreatic resection to mobilize the second portion of the duodenum for anastomosis (duodenal switch). The use of more distal and thin-walled bowel for the alimentary limb, when brought under more tension to the smaller gastric remnant as recommended by Scopinaro, is likely to increase both leak and stricture rates. Advocates of these procedures report somewhat varying 30-day mortality. Hess et al.[57] reported the mortality in 1200 BPD patients as 0.5%, analogous to RYGB. In a series of 700 patients, Marceau et al.[56] reported a 1.75% mortality rate, with the incidence slightly higher in the duodenal switch variation. Scopinaro et al.[24] included 1350 patients in a study, dividing the series into three chronological groups: the first 856 patients, the subsequent 250, and then the most recent 250. They reported a "stable reduction of operative mortality to less than 0.5%," without revealing the starting point for that reduction. Taking into account the riskier population on which these procedures are performed, there appears to be no significant difference in operative mortality versus RYGB, assuming that the surgeon has an ample BPD experience.

Given the short length of the BPD common channel, malabsorptive symptoms, such as diarrhea, bowel frequency, dumping, and flatulence, are invariably more prominent than those seen after standard RYGB. The main concerns about the BPD include the incidence of protein-calorie malnutrition and bone demineralization. In their recent review, Scopinaro et al.[24] assessed the results of 2241 patients over 21 years and reported no increase in bone complaints when compared with standard RYGB. In addition, they reported a 3% rate of protein malnutrition, seemingly not much higher than that seen with gastric bypass. Similarly, using the duodenal switch variant, Hess et al.[57] observed a 3% rate of excessive weight loss, accompanied in some cases by hypoproteinemia. Although encouraging, these results should be evaluated carefully as both operations varied over time with regard to limb lengths and, in the case of Scopinaro and colleagues, pouch size. The most recent (and best) results being reported are generally applicable to only a minority of patients gathered from within each series (about 10% of patients in both cases).

The third suggested alternative to achieving augmented weight loss is to perform a standard RYGB and combine it with a shortened common channel. Initially used as a revision operation by Torres and Oca in 1987, Brolin et al.[60] published a small prospective trial of 45 patients who were randomized to common channel lengths of either 75 or 150 cm. The longer limb group had greater mean weight loss at 2 years (64% versus 50%) and had more patients achieve greater than 50% excess weight loss (19 of 23 versus 11 of 22). The Mayo Clinic published another small series of an even longer bypass, coupling a transected RYGB to a common channel of 100 cm, as in the biliopancreatic diversion.[61] In that study, 19 of these very, very long limb RYGB patients were compared with 11 Scopinaro-type BPD. All weight loss measures favored the

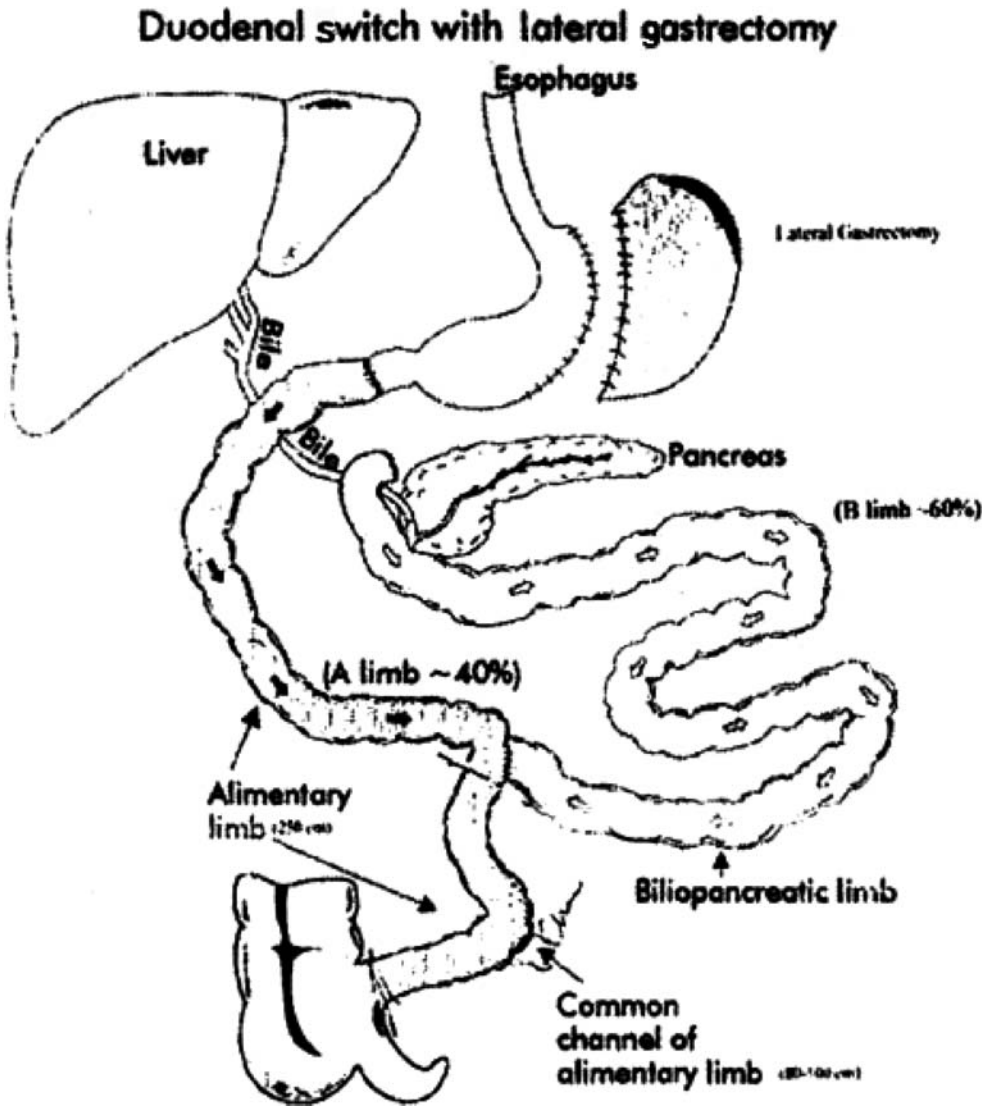

Figure 5 Lateral gastrectomy with duodenal switch and biliopancreatic diversion. In lateral gastrectomy with duodenal switch and biliopancreatic diversion, the small intestine, which receives food (alimentary limb), is shortened to approximately 250 cm, and the segment, which receives bile and pancreatic secretions (common channel), is only 100 cm. (Reprinted from Deveney CW, et al. Am J Surg 2004;187:655–659, with permission from Excerpta Medica, Inc.).

BPD patients: excess body weight loss at 2 years was 68% compared with 53%, and at 4 years, 71% compared with 57%. The percentage of patients with greater than 50% EBWL was 100% versus 62%, respectively. However, the lack of sufficient numbers of patients precluded finding a significant advantage favoring BPD. It is interesting to note that in the Mayo series, the very, very long limb RYGB resulted in a similar incidence of nutritional complications compared with BPD and did not appear to enhance weight loss at 4 years compared with a standard 100- to 150-cm RYGB.

The evaluation of malabsorptive operations is difficult, as studies are generated by a single surgeon or by a surgical group performing one procedure, instead of by a multicenter trial approach. Reliable follow-up data on surgeries are hampered by procedural modifications over a 20-year time frame, as is the case for the Scopinaro et al. data. With this in mind, it appears that at 5-year follow-up, the mean EBWL is nearly 75%, with 15% of patients failing to lose greater than 50% EBW.[62] The duodenal switch procedure, as used in studies by Rabkin, Hess and Hess, and Marceau, achieves similar long-term weight loss results. Recently, two retrospective series, both using the same duodenal switch BPD with a fixed 100-cm common channel, found a mean EBWL of only 60% at 3 years.[63,64] When they compared weight loss at 2 years, they found no significant difference between their duodenal switch BPD patients and those of a concurrent group of patients in whom a 150-cm RYGB was performed. Thus, whereas there is a suggestion that BPD operations may augment long-term weight loss in the range of 10–15% over standard RYGB, this conclusion cannot be considered definitive as it is not based on studies in which one can have a high level of confidence, (i.e., randomized prospective multi-institutional trials.)

To many surgeons, the use of long-limb gastric bypass is more appealing than the BPD owing to its greater operative

simplicity. Unfortunately, there are even less data that support this approach as having substantial merit. The primary American proponent for the very, very long limb gastric bypass has been Brolin's group. In 2002, he and co-investigators published a retrospective series of superobese patients who had undergone very, very long limb gastric bypass (75-cm common channel), 150-cm RYGB, or short-limb gastric bypass.[65] At 5-year follow-up, peak EBWL was 64% for the very long group, 61% for the 150-cm group, and 56% for the short-limb bypass. Whereas claiming this confirmed the benefit of using a short common channel, it could be argued that a 3% advantage over the long-limb bypass is too negligible to justify the added nutritional complications of the short common channel. Furthermore, the results of Brolin et al. have not been confirmed by additional studies looking at limb lengthening as a strategy for increasing postsurgical weight loss. Two prospective trials of long-limb bypass have been negative in this regard. One study by Inabnet et al.[66] showed an early but not sustained weight loss advantage in patients with a BMI greater than 50, as did two retrospective series by Freeman et al.[67] and Feng et. al.[68] At the 2004 ASBS meeting, two presentations evaluated longer Roux limbs in the superobese and found no evidence that maintained weight loss was greater at the longer limb lengths.[69,70] One study examined a retrospective database of 200 patients in whom 200-cm Roux limbs had been created but common channel lengths distal to the jejunojejunostomy had been measured intraoperatively. At 1 year, with common channels ranging from 200 to greater than 600 cm, no correlation could be found between percent EBWL and common channel length.

It would appear that if any malabsorptive operation is to be preferred, the BPD or the duodenal switch variation should be used rather than the very long limb bypass. However, the weight loss advantage of these operations is surprisingly modest and comes at the cost of greater long-term complications. Until a randomized prospective trial to compare the efficacy of these operations versus the standard RYGB is completed, a definitive conclusion is lacking.

Notwithstanding, the BPD or the duodenal switch variation should be recommended only for the superobese patient in whom the proportional weight loss advantage of these procedures may confer a quality of life or medical benefit.

Gastric Banding

History

The idea of placing a restrictive band around the upper portion of the stomach was first suggested in 1976 by Wilkenson.[71] In 1986, Kuzmak et al.[72] implanted an adjustable silicone band connected to a subcutaneous port. At first, the band was implanted via laparotomy, but in 1993 Belachew et al.[73,74] implanted a modified laparoscopic band device called the LAP-BAND (Allergan, Inc, Irvine, CA).

The allure of gastric banding is obvious. In contrast to RYGB, the LAP-BAND is easily placed via minimally invasive techniques. With no need for the creation of anastomoses and an extremely brief operating time, gastric banding results in a much reduced perioperative complication and mortality rate. The gastrointestinal tract is relatively preserved compared to other bariatric procedures, so that long-term nutritional deficiencies would be expected to be less frequently encountered.

Clinical trials of the laparoscopic band were initially conducted in Europe.[75] After a larger series of placements of the LAP-BAND system in Belgium were reported by Belachew et al.[76] in September 1993, use quickly expanded to involve many other European countries, as well as Australia, South America, Mexico, New Zealand, Israel, and Saudi Arabia.

The Food and Drug Administration (FDA) initiated a monitored clinical trial in the United States in April 1995.[77] This initial trial A included eight centers with 292 patients. In this trial, 259 of the 292 patients had the band placed laparoscopically, and the remaining 33 patients had the band placed by open laparotomy, with 13 of these being conversions from laparoscopy. Weight loss results were mediocre (20–30% EBWL) and inconsistent with the non-U.S. literature.[77,78] In comparison, Rubenstein[79] reported a series of 350 patients (277 female, 73 male) with mean preoperative BMI of 43 kg/m^2. At 12 months, the mean EBWL was 60%, and this level was maintained up to 3 years.

Trial B, a second FDA-monitored clinical trial, has resulted in one publication. Rubenstein reported his experience with a series of 63 patients.[79] His results were more consistent with the non-U.S. literature, showing 53.6% EBWL at 36 months. Consequently, the FDA approved the LAP-BAND system in June 2001. Unfortunately, expansion of the American LAP-BAND experience has been halting, predominantly due to the slow acceptance of the procedure as reimbursable by private and government insurers.

Evolution of Technique

The initial placement technique of the LAP-BAND was a perigastric one. A window was created adjacent to the lesser curvature 3 to 4 cm distal to gastroesophageal junction, and the band was then passed around the cardiac portion of the stomach adjacent to the angle of His. This approach has since been implicated as a causative factor in

the high rates of band prolapse/slippage reported in the early American experience.[80] The perigastric approach resulted in variable positioning of the LAB-BAND and required partially tightening the band by injecting 2 ml of sterile saline. The resulting constellation of factors, including a sizable gastric pouch above the band, entry into the lesser sac, variable dissection length, and a tight band at the onset, led to an unacceptable high rate of gastric herniation. The approach currently favored is referred to as the *pars flaccida* technique, described later. This procedure emphasizes minimal dissection and placement of the band such that it does not traverse the lesser sac by incorporating both the stomach and the lesser omentum within the band.[81]

Variations in port placement and positioning should be considered and tailored to the individual surgeon's experience. Whether the operator is positioned to the side or between the patient's legs (via split leg table or Allen stirrups), a Nathanson liver retractor is quite usefully positioned in the subxiphoid location. This is placed through a 5-mm port.

The pars flaccida or lesser omentum is viewed, and a window is created through this avascular plane with avoidance of the hepatic branch of the vagus nerve, especially in those patients without previous cholecystectomy. The right crus of the diaphragm is exposed just inferior and medial to the caudate lobe of the liver. After incising the peritoneum just medial to the right crus, the dissection is carried out from this point to the angle of His with the assistance of an articulating instrument such as the Greenstein dissector in this retroesophageal plane. This instrument is equipped with an aperture that will accept the silicone tube of the band. After the band is positioned appropriately, the buckle is closed and several gastrogastric (at least four) sutures are placed anteriorly in a manner that embeds the band but not the buckle portion. This creates a gastric pouch from the anterior portion of the stomach proximal to the band of approximately 15 ml in size. The port is then fixed with permanent suture to the anterior abdominal fascia.

Complications

Prolapse As previously discussed, among the complications associated with placement of the laparoscopic adjustable band, band prolapse or slippage was described frequently in several of the initial reports. This complication occurs as the stomach herniates cephalad through the band. It may occur anteriorly or posteriorly. It is associated with varying degrees of obstruction at the point of prolapse. Fielding and Allen[81] report a 1.8% prolapse rate using the pars flaccida technique. Before the popularization of this technique, reported prolapse rates were upward of 15%. Correction of the prolapse could usually be effected laparoscopically.

Gastric Pouch and Esophageal Dilation In one series, gastric pouch dilation was the most common complication with LAP-BAND placement.[82] It occurred in 6.8% of the 500 patients and was associated with symptoms of gastroesophageal reflux disease (GERD), retrosternal chest pain, and progressive dysphagia. Spivak et al.[82] report this was easily remedied nonoperatively with removal of fluid from the band via the access port.

Esophageal dilatation was reported in association with gastric pouch dilation and, on occasion, as an isolated finding. In most cases, the dilatation reversed with deflation of the band cuff. Initial concerns raised by Kothari et al.[78] regarding what they considered as achalasia-like dysmotility and its sequelae have not been confirmed in the larger international series.[77,83,84]

Band erosions This particular complication is encountered rarely, in approximately 0.2–5% of LAP-BAND placements (Table 2). Fielding and Allen reported erosions to occur in 34 of their first 500 patients and none in the next 600. They contend the reason for this reduction was change in technique.[81] The gastric-to-gastric sutures were previously placed over the buckle portion of the band, which is firmer and thus potentially more prone to erosion.[81]

Rarely, band erosion can occur acutely and, in this setting, leads to free intraperitoneal perforation, necessitating emergency exploration. Much more commonly, the band erodes into the gastric lumen incrementally, slowly exposing it to the gastric juices. Several dramatic cases have been reported where the band has been found to ultimately reside entirely in an intragastric position. In the chronic presentation, the patients may be completely asymptomatic except for signs of an infection of the port site. In fact, band erosion should be considered in the case of *any* port site infection. Other signs suggesting band erosion include nonfunctioning band or sudden loss of restriction of oral intake.[82]

Port site difficulties The majority of LAP-BAND complications relate to the port and tubing complex. These include infections, tubing breaks, leaks, kinking, and disconnection. Most of these are easily remedied, with either antibiotics or exploration of the port site under local anesthesia. When initially placing the port, particular attention should be paid to adequately stabilize the port to avoid excessive movement with patient ambulation.

Outcomes

Bariatric procedures are generally considered successful if they induce greater than 50% EBWL. More modest weight loss was achieved in clinical trial A, being 38% EBWL at

Table 2 Summary of Clinical Trials Showing Number and Type of Postoperative Complications, Including Associated Mortality, Resulting from Bariatric Surgical Procedures

Author	*n*	Postoperative Complications (%)		
		Erosions	Prolapse	Mortality
Holloway et al.[38]	502	1 (2)*	5 (28)	.2 (1)
O'Brien and Dixon[80]	1120	3 (34)	25 (First 500) 47 (Second 600)	0
Fielding and Allen[81]	335	0	3.6	—
Weiner et al.[85]	184	1.1	2.2	0
Vertruyen[86]	543	4.6	1	—
Belachew et al.[76]	763	.9	8	—
Favretti et al.[87]	830	.5	10	—
Cardiere et al.[88]	652	.3	3.8	—
Spivak et al.[82]	500	.2	2.8 (14)	0
Ren et al.[89]	445	.2 (1)	3.1 (14)	—
Ren et al.[90]	500	<1 (1)	2 (2)	0

*Number in parentheses represents number of complications in each group.

36 months.[77] After this comparatively mediocre start, more profound weight loss is being seen as more data are accumulated in the United States. Several U.S. studies have been completed (Table 3), referencing results comparable to both the international LAP-BAND literature and the gastric bypass studies.[79,80,82,89,92]

Conclusion

The initially disappointing results of trial A may be attributable to several factors. The perigastric approach, in addition to leading to high rates of prolapse, also allowed for gastric pouch expansion, which may have led to a higher caloric intake in the early patients. There was no agreement at the time concerning the optimal postoperative regimen in regard to how quickly to fill the band implantable cuff or how frequently the patient should be seen as an outpatient. One of the factors that has been invoked to explain the more substantial weight loss seen in the Australian series was the monthly follow-ups with frequent band adjustments being made based on patient weight loss and perceived satiety. Further, as will be discussed in association with gastric pacing, appropriate selection algorithms will likely allow for the choosing of patients most suitable for the LAP-BAND.

Gastric Pacing

An emerging technology, not yet available outside of clinical trials in the United States for the treatment of moderate morbid obesity, is gastric pacing. A gastric stimulator, similar to the pulse generator for a cardiac pacemaker, is implanted subcutaneously. The leads for the generator are then placed laparoscopically into the wall of stomach, generally about 8 cm proximal to the pylorus along the lesser curvature. Intraoperative endoscopy is then performed to ensure that there has been no luminal penetration. If luminal penetration occurs, the pacer will not work appropriately and there is the risk of leakage of gastric contents along the wire tract. As would be expected from the straightforward nature of this procedure, no major operative complications have been reported to occur in any of the three multicenter gastric pacing studies.

The mechanism of action by which gastric stimulation induces weight loss remains speculative. The gastric production of ghrelin, which acts in the hypothalamus as an orexigenic hormone along with Peptide YY and leptin to regulate appetite, is suppressed by gastric pacing. Reduction of ghrelin release normally accompanies the entrance of food into the stomach; thus, it is thought that pacing effects on hormone secretion mimic satiety in this manner. Other researchers emphasize the influence of the pacing on gastric motility as the prime effect. Chen[93] writes, "Gastric electrical stimulation induces gastric distension, reduces gastric accommodation, and inhibits stomach peristalsis in the fed state. The stimulation-induced gastric distension is expected to activate the stretch receptors, thus, increasing satiety before meals. The reduced gastric accommodation [will] increase satiety during, and at the end of, the meal. The suppression of peristalsis [will] delay gastric emptying and may, therefore, increase satiety between meals."

Three trials using gastric pacing have been reported in the literature: the LOSS study from Europe, and O-01 and DIGEST from the United States.[94–96] The LOSS study (69 patients) was conducted in a nonrandomized prospective manner, as was the DIGEST (30 patients) study. In the O-01 study, 103 patients had a gastric pacer

Table 3 Summary of Clinical Trials in Literature Showing Mean Excess Weight Loss from LAP-BAND and Gastric Bypass Studies

Author	*n*	Mean Excess Weight loss (%)					Country
		1 yr*	2 yr	3 yr	4 yr	5 yr	
Watkins et al.[91]	138	48.2	—	—	—	—	USA
Spivak et al.[82]	500	39	45	47	—	—	USA
Ren et al.[89]	99	44	—	—	—	—	USA
Ren et al.[90]	115	41.6	—	—	—	—	USA
Rubenstein[79]	63	39	46.5	53.6	54	54	USA
O'Brien & Dixon[80]	709	47	52	53	52	–	Australia
Dargent[92]	500	56	65	64	—	—	France
Holloway[38]	502	50	61	65	—	—	USA

*Follow-up time.

implanted, but the pacers were activated in only half of the patients in a double-blind manner. The two nonrandomized trials reported similar results, with a mean excess weight loss of approximately 20% at greater than 1 year postoperatively in one trial and a greater than 20% EBWL observed in a third of patients in a separate trial. By comparison, the weight loss in the O-01 study was less impressive. At 1-year follow-up, mean EBWL was only 2.5%, with no significant difference between the gastric pacer group and placebo group. However, the O-01 investigators were able to formulate a screening algorithm, incorporating preoperative patient characteristics such as gender, age, and BMI and patient perceptions of their physical and emotional status, to determine which factors were highly predictive of postoperative weight loss in both American trials. Accordingly, another U.S. study of gastric pacing has been embarked on, the SHAPE (Screened Health Assessment and Pacer Evaluation) trial. This placebo-controlled, multicenter, prospective randomized trial will limit enrollment to those patients whose preoperative scores on the screening algorithm are predictive of greater success with the gastric stimulator.

Evidence from the gastric stimulator trials do not yet warrant its general use in the morbidly obese. In unselected groups, weight loss appears to be too modest to justify the expense of implantation. However, proper patient selection, in combination with adjunctive measures such as behavioral therapy, diet modification, and exercise, may make the gastric pacer a major player in the treatment of moderate obesity in the near future. The low level of complications, both implantation related and long term, is a compelling reason to continue to study the efficacy of this modality in inducing excess body weight loss.

Definitions of Success in Bariatric Surgery

The number of bariatric procedures performed has burgeoned in the last decade. Generally absent from this newfound enthusiasm for surgical intervention as an option in the treatment of obesity has been a coherent discussion of what the goals of bariatric surgery should be for the obese patient, particularly in the superobese (preoperative BMI >50). With many bariatric programs having been in existence for only 10 years or less, the results reported in the bariatric literature have concentrated on short-term weight loss results and perioperative complication/mortality rates.

Most series measure success by the quantity of EBWL or the percentage reduction in BMI. As can be seen from our previous discussions of the three major surgical strategies, the mean long-term EBWL resulting from the various malabsorptive and mixed procedures hovers in the range of 50–65%. This range, on first glance impressive when compared with medical therapy and dieting, subsumes a widely varying rate of success due to institutional practices, patient selection criteria, and medical reporting biases. Approximately two-thirds of patients will maintain between 50% and 70% of EBWL, but in the case of the superobese, what does this level of weight loss translate into? If one considers 65% EBWL a good result from bariatric surgery (probably only consistently achievable with BPD), simple math illustrates the challenge presented by the superobese. For example, consider a 40-year-old woman who stands 5 ft 4 in. tall and weighs 400 lbs. Her excess body weight is approximately 270 lbs and her BMI is 68.8 kg/m^2. Were she to lose 65% of her EBW after a RYGB, this would represent a 175-lb weight loss. Yet, she would still be almost 100 lbs over her ideal weight, and her BMI would remain a morbidly obese 38.7 kg/m^2. In a series in which long-limb bypass was offered to superobese patients, Brolin et al.[65] reported that 17% of patients stabilized at a BMI of less than 30 kg/m^2 (approximately 20% overweight) and only 6% reached a BMI of less than 25 kg/m^2 (normal weight) at the *nadir* (my emphasis) of weight loss. Brolin and coauthors concluded, "These BMI data provoke the question of what are realistic and worthwhile weight loss goals for superobese patients after gastric bypass operations."

If weight loss is a poor measure of success, what are the alternatives? The most compelling outcome would appear to be resolution of life-threatening obesity-associated comorbidities and the resultant favorable impact on life expectancy.[97] In fact, two recent studies suggest that surgically induced weight loss does have a salubrious effect on life expectancy in the morbidly obese.[98,99] This is a noteworthy finding, as previous studies of medical dieting have shown either no enhancement of life expectancy or have shown a deleterious effect, the latter the result of the negative physiologic consequences of the "yo-yo" pattern of weight loss/weight gain seen in prolonged dieting. Surgical weight loss causes a profound reduction in hypertension, hyperlipidemia, and occurrence of sleep apnea and perhaps, most importantly, results in rapid normalization of serum glucose in the type 2 diabetic. The effect of surgical weight loss on cancer mortality remains uncertain as the reversal of obesity in middle age, a time when many individuals seek surgical intervention, may do little to abrogate the now-acknowledged increased risk for epithelial malignancies of the colon, prostate, breast, uterus, and pancreas. It thus seems more appropriate to evaluate and recommend bariatric surgery for the obese for its beneficial effects on comorbidities, rather than the absolute weight loss achieved. If we accept this last proposition, a new consideration comes into play, namely, how much weight loss is really needed to reverse the medical consequences of morbid obesity?

In *Obesity Surgery* (2001), Deitel[100] writes that in the superobese, maximal effects achieved by weight loss with regard to hypertension, diabetes, and cardiac disease are achieved early in the course of weight loss with as little as 10 kg of weight loss and, in some cases, with a 20% loss of excess weight. With this in mind, a question arises as to whether the patient gains anything from the more malabsorptive procedures that are addressed in this review. Even if the biliopancreatic diversion and its variants result, on average, in an additional 10–15% EBWL, the benefit is coming at the cost of higher rates of early and late complications compared with standard RYGB and restriction only operations. In the superobese patient, the loss of 20 to 40 more pounds, as represented by that additional 10% EBWL, seems unlikely to engender additional improvement in either quality-of-life measures or resolution of medical comorbidities. In addition, despite the higher level of EBWL, the BPD has a rate of failure in achieving 50% EBWL (about 13%) that differs little from either RYGB or LAP-BAND. Therefore, will the BPD patient recognize any true long-term benefit by maximizing weight loss, and should they place themselves at a higher risk to achieve it?

The same argument can be extended to a comparison of restrictive procedures, such as the LAP-BAND, with the RYGB in the obese patient whose BMI is in the 40 kg/m^2 range. For the American patient who hovers near the 100 lbs over ideal body weight level, if the LAP-BAND leads to a 45-pound maintained weight loss versus 55 lbs for a laparoscopic RYGB, how does one justify the increased operative risk and more profound nutritional consequences of the RYGB? Edward Mason, considered the American "father of bariatric surgery," made this very point in a recent publication by Zhang et al.[99] of results derived from the prospectively collected information in the International Bariatric Surgery Registry. Looking at almost 19,000 bariatric procedures, performed from 1986 through 1999, with a mean follow-up of over 8 years, there was no difference in the death rates among patients who had undergone restrictive operations versus those who had mixed or malabsorptive procedures performed. Interestingly, a lack of benefit from operations that engendered more weight loss was seen despite the fact that BMI remained an independent predictor of survival during the follow-up period.

For those patients whose BMI is less than 35 but who have serious comorbidities, such as sleep apnea and diabetes, the low medical risk of LAP-BAND implantation appears to make it the optimal choice if bariatric surgery is to be offered. Finally, if the objective for bariatric surgery is the resolution of medical comorbidities and this can be achieved by modest weight loss as suggested previously by Deitel, continued investigation into even lower risk methods of surgical weight loss, such as gastric pacing, is justified.

Late Complications of Bariatric Surgery

Failure to Lose Weight or Regain of Weight

Approximately 15% of bariatric surgery patients will not lose more than 50% of excess body weight. This is true even for patients undergoing BPD or extended-length RYGB (Table 4). Whereas 2-year postoperative results have reported mean EBWL of RYGB as high as 66%, it must be emphasized that figure represents most patients' weight nadir, and at 5-year follow-up, the mean has dropped to 53%. Similar numbers are seen in the LAP-BAND follow-up, mostly from non-American trials. The BPD results are somewhat better: 77% and 78% at 2 and 5 years, respectively, in the single-institution series of BPD advocates, and 55–67% and 64% in small series in which BPD was compared with other bariatric procedures. Nevertheless, this sizeable minority of weight loss "failures" leads to the surgeon seeing patients who are dissatisfied with their weight loss many years after their bariatric operations.

There is much more anecdotal literature than scientific evidence about the management of these patients. Two major reasons for failure to lose weight are the lack of patient compliance with the postoperative diet and intestinal adaptation.[101,102] The former is clearly not amenable to surgical correction, whereas the latter is arguably so.

The initial assessment in the patient with failure to achieve weight loss consists of a nutritional consultation for evaluation of the patient's dietary pattern and choices (including interviewing family and friends to confirm the veracity of the patient self-report), obtaining the operative note of the original bariatric procedure, and performance of an upper gastrointestinal series to assess pouch configuration and emptying. A psychological evaluation is strongly recommended to rule out postoperative eating disorders and ongoing depression. It is also critical to reassess the patient's quality of life and to quantify any residual obesity-associated comorbidities. In fact, the majority of

Table 4 A comparison of Clinical Trials Showing Estimated Weight Loss (% EWL) Over Time and the Associated Failure Rate for a Variety of Bariatric Surgical Procedures

Procedure	1 yr	2 yr	>5yr	Failure*	References
RYGB	70	66	53	13	51
BPD/DS	64	77	78	13	24,56,57
LAP-BAND	62	62	53	15	76,80,84,88,92

*Failure rate is equivalent to <50% EWL.

these patients will have experienced excellent results from their surgery, with resolution of many or all of their medical illnesses. What the patient is truly dissatisfied with is that he or she has not lost as much weight as he or she wanted to (having had a numerical weight loss target) and thus is not "skinny" enough.

Surgically, the only reproducible anatomic cause of failure to lose weight is disruption of the partitioning staple-line in a nontransected pouch RYGB. This situation is less commonly seen today, given the preference for a transected pouch in present-day RYGB. If this gastrogastric fistula is demonstrated to be sizeable, it is reasonable to consider it a cause for weight loss failure, as food is simply entering the stomach proper as before without restriction or "bypass." Other surgeons report pouch dilatation, anastomotic dilatation, and inadequate length of intestinal bypass as potentially correctable causes of weight loss failure. However, there exists no body of evidence of adequate statistical power to suggest that any of these factors are the root cause of inadequate weight loss. As a result, the literature is marked by a multitude of potential solutions: downsizing of the gastric pouch, banding of the gastrojejunostomy (some suggest using a LAP-BAND for this purpose), or conversion to a more malabsorptive operation such as very long limb gastric bypass or BPD.[24,103] It is impossible to draw any conclusions regarding the efficacy of these approaches due to the small number of patients studied. As revision operations carry a far greater morbidity and mortality, especially in the case of partial reconstitution of the stomach with BPD, it is heartily recommended that the bariatric surgeon ascertain whether behavioral or medical conditions exist that negate the ability to lose more weight.

Protein Malnutrition

Protein malabsorption is an expected consequence of bariatric surgery, especially when bypassing the duodenum, where the majority of protein absorption is accomplished. Other factors that limit protein uptake in the bariatric patient are the shortened common channel, delayed protein cleavage by pepsinogen (predominantly from the excluded stomach) until after food bolus passage beyond the jejunojejunostomy, and reduced production of pancreatic enzymes from loss of CCK production. As a result, protein malnutrition commonly results from any number of bariatric procedures.[104] Even with the mildly malabsorptive, short-limb gastric bypass, protein malnutrition occurs in 5% of patients, and this figure may underestimate its incidence. Scopinaro et al.[24] report that the incidence of this complication after BPD varies depending on changes in gastric remnant size and alimentary limb length. Early in their use of BPD, the incidence was 30%, with a 10% recurrence rate; later series show a range of 4–10% in occurrence with 1–7% recurrence rates. There is some evidence that even higher levels of protein malnutrition are seen after distal RYGB, which combines the very short common channel of a BPD with an extremely small gastric pouch.

It should be noted that protein malnutrition does not simply represent the inability of the bariatric patient to absorb dietary protein but also represents an unexplained and inappropriate response of the patient to starvation.[105] When faced with starvation, the body's response should be protein sparing, using fat catabolism and ketosis to generate energy while attempting to spare lean body mass. Hypoalbuminemia is considered a late outcome of starvation, yet it is often found early in bariatric patients who have not lost substantial body weight. Although the average time to diagnosis of protein malnutrition is 18 months after surgery, some patients will experience it within 3 months. It is also important to realize that only a slight majority of patients diagnosed with protein malnutrition are below a BMI of 30 kg/m^2 at the time of diagnosis, with very few below a BMI of 22 kg/m^2. In fact, a substantial number of patients with protein malnutrition will present at BMI levels of greater than 40 kg/m^2.[106]

After bariatric surgery, protein malnutrition should be suspected in the patient who reports recurrent vomiting or ambulatory weakness, by the presence of diffuse edema ranging up to anasacra, and if there are manifestations of hypercoagulability. Diagnosis is confirmed by the finding of depressed serum values of albumin or TIBC (total iron binding capacity). Mortality from protein malnutrition has been reported to be as high as 1%, due to either complications of hypercoagulability such as pulmonary embolus or immunosuppression leading to infections with common pathogens or by unusual ones such as tuberculosis.

When bariatric patients present with protein malnutrition, the first order of business is to replenish nitrogen and find/or remedy the cause later. It is expected that about half of all patients will tolerate a high-nitrogen diet orally, whereas the remaining patients may require anywhere from a small amount of oral supplementation to complete enteral feeding.[106] Enteral feeding in the bariatric patient with protein malnutrition is better accomplished by placing a gastrostomy in the excluded gastric remnant, rather than by using a nasal feeding tube into the gastric pouch. Feeding into the excluded remnant takes advantage of the higher level of pepsinogen for cleaving proteins and exposes the amino acids to duodenal absorption, thus eliminating the need for more expensive predigested elemental formulas. The gastrostomy either can be placed into the excluded pouch laparoscopically or, in some cases, done percutaneously under CT guidance.[105] Very few patients require the institution of total parental nutrition. Monitoring of serum

phosphate, calcium, and magnesium should be instituted to avoid refeeding deficiencies. In patients with recurrent vomiting and protein malnutrition, vitamin supplementation should be undertaken, especially the water-soluble B vitamins.

Once nitrogen repletion is initiated, the etiology of the malnutrition should be investigated. In patients with vomiting, at least half will have anastomotic strictures that can be dilated endoscopically. In those patients without a history of vomiting or in those with vomiting without an anatomic etiology as determined by upper gastrointestinal series and endoscopy, the possibility of a postsurgical eating avoidance disorder (PSEAD) should be considered.[107] This syndrome has been suggested as a DSM-IV diagnosis, with features that overlap anorexia nervosa, bulimia, and binge-eating disorder. The patients manifest an intense fear of going back to the preoperative weight and have body image distortions similar to those with anorexia and bulimia. This can lead to food avoidance similar in magnitude to those with anorexia. Psychiatric evaluation is recommended for these patients.

Fortunately, protein malnutrition is usually not recurrent. If it becomes a chronic problem, even without any indication of PSEAD, reversal of the bariatric procedure or shortening the length of the bypass segment may be indicated.

Acute Postgastric Reduction Surgery Neuropathy

In 2002, the American Academy of Neurology adopted the term acute postgastric reduction surgery or APGARS to describe the seemingly idiopathic neuropathies that develop after weight loss surgery. The classic triad of APGARS is progressive vomiting, with lower extremity weakness and hyporeflexia generally limited to the region of weakness only. Associated symptoms may include pain, numbness, urinary and fecal incontinence, and visual disturbance. Physical examination will reveal a symmetric proximal lower extremity weakness (quadriceps affected to the greatest degree) and gaze-induced nystagmus. Electromyography is generally consistent with polyneuropathy. Cerebrospinal fluid chemistries and cytologies are unremarkable, and nerve biopsies, if obtained, show myelinated fiber degeneration without inflammation.[108]

When this syndrome first appeared, the disorder was often classified as either Guillain–Barre syndrome, neuropathic beriberi, Wernicke–Korsakoff syndrome, or B_{12} deficiency.[109] However, the symptoms and findings associated with APGARS do not wholly fit any of these four diagnoses. In Guillain–Barre, the presenting complaint is usually ascending paralysis, not just weakness, with pain in the same region in 90% of the cases. Further, the cerebrospinal fluid (CSF) and electromyographic findings of Guillain–Barre are characteristic and do not match those seen in APGARS. Wernicke's, thiamin deficiency usually associated with chronic alcohol abuse, is known for a completely different symptom triad: ophthalmoplegia, ataxia, and mental disturbance such as apathy, disorientation, and memory derangement. The neuropathic form of beriberi (dry variant), another thiamin deficiency, manifests with progressive weakness of the distal lower extremity, muscle atrophy in the area of the weakness (atrophy not common in APGARS), and sensory alterations, characteristically a burning sensation in the soles of the feet. Because of the physiology of gastric bypass, B_{12} deficiency would seemingly best explain the etiology of APGARS, but again the symptomatology of APGARS is not consistent with this. In B_{12} polyneuropathy, the weakness is *generalized* as a "pins and needle" sensation in the affected area, originating in the distal portion of an extremity, and as the disease progresses, spasticity and gait ataxia ensue.

After completing a full history and physical examination of the patient with APGARS, serum values of B_{12}, folate, and thiamin should be determined. In addition, heavy metals and serum porphyrins should be measured due to overlap of heavy metal toxicity and porphyria with some of the APGARS symptomatology. Neurology consultation will generally lead to spinal tap for CSF chemistries and cytology, electromyography/nerve conduction velocity (NCV), and peripheral nerve biopsy. If the patient is vomiting, esophagogastroduodenoscopy (EGD) and upper gastrointestinal studies should be obtained to rule out gastrojejunostomy strictures and small bowel obstruction.

If work-up does not make the diagnosis of one of the aforementioned recognized causes of polyneuropathy, the patient is considered, by exclusion, to have APGARS. Treatment consists of rehydration if vomiting is present, empiric high-dose B vitamin administration, and enteral alimentation. If the symptoms of APGARS do not show improvement in a relatively short period, the treatment regimen shifts to that used in Guillain–Barre, with use of intravenous IgG and/or plasmapheresis. Recovery rates from APGARS are lower in females and in patients who present with a thiamin deficiency.[108]

Conclusions

The field of bariatric surgery can essentially be divided into two periods. The first era began with the intestinal bypass in the 1960s, encompassed a short period of ascendancy for restrictive operations such as the vertical-banded gastroplasty, and culminated with the modifications to Mason's original gastric bypass leading to the preference, among American surgeons, for the RYGB. During this period, the actual numbers of surgeries performed was, relative to

2005, small, and advocacy of surgery as an appropriate treatment for obesity rested on a very limited number of pioneering surgeons. The bariatric literature of the time consisted almost exclusively of uncontrolled, nonprospective, single-institution trials that were at times self-promoting or, even worse, self-congratulatory.

With the increasing public and official apprehension of the obesity epidemic, the introduction of laparoscopic techniques, and performance of obesity surgery on various portly celebrities, the second era of bariatric surgery began. The number of cases performed is rising exponentially; by 2004, more than 120,000 operations are performed annually. Health care expenditures for bariatric surgery are exploding, doubling every 2 years, and leading to, not surprisingly, a backlash from the commercial and government payers. The number of published series regarding bariatric surgery has reached daunting numbers. Sadly, the quality and structure of that research have changed little from the early years of bariatric surgery, save for the patient numbers being larger. As one recent attempt to produce an evidence-based meta-analysis of the surgical treatment of obesity blandly stated, "The primary limitation of this review....is the quality of the original studies."[15]

Similar to others who have reviewed the topic systematically, we found that observational series show surgical treatment is more effective at inducing weight loss and reversing the major obesity-associated comorbidities than nonsurgical treatment in the morbidly obese. It is also clear that bariatric surgery can be performed with a reproducibly low rate of operative mortality and perioperative morbidity, especially when both the surgeon and the facility are doing a high volume of obesity-related surgery. Although not dealt with specifically in our review, we concur with Maggard et al.[15] that the value of surgery for patients with BMIs of 35–40 remains unproved, except perhaps in those with type 2 diabetes. There is also a paucity of data regarding the utility of obesity surgery in the older patient and in the adolescent population.

Myriad questions remain unanswered in regard to bariatric surgery. Many of these revolve around the fact that we still do not understand the molecular/genetic basis of obesity. Given that fact, it is hardly surprising that the surgical literature is so fractured, with various authors championing their modification of RYGB or offering alternatives to it such as LAP-BAND or BPD. As our review has demonstrated, there is little evidence favoring, for example, modifications such as banding of the gastrojejunostomy or lengthening the bypass limb in the RYGB patient. Whereas the BPD, with or without duodenal switch, may result in an additional 10–15% of maintained weight loss compared with the RYGB, does this result have any substantive impact on the patient's quality of life or longevity? What should be the role of the less risky procedures such as gastric pacing or LAP-BAND? Why do 15% of bariatric surgery patients still fail to lose more than 50% of their excess body weight? Does that matter, and, if it does, is there anything to be done to enhance their weight loss post-RYGB?

As Brolin stated in his contribution to the 2004 ASBS Consensus Conference, "the risks associated with bariatric operations must be contrasted with their short-term and long-term efficacy."[110] The evolution of bariatric surgery has lowered the short-term risks to a "respectable" level in that operative mortality with RYGB in the 1970s ranged as high as 5%, despite the fact that the patients were generally not as obese as those encountered today. Furthermore, modifications of the operation, use of adjunctive medications such as Actigall and acid-reducing agents, and increasing physician awareness of postoperative nutritional deficiencies have helped to make the long-term anatomic and nutritional complications less numerous and severe. Nevertheless, the bariatric surgery community has yet to show, in a scientifically valid manner, that the mixed malabsorptive procedures are efficacious, when compared to both best nonoperative treatment and to the less risky restrictive approaches. Yes, patients lose weight, but do they live longer, return to work (studies would appear to indicate that the vast majority of the preoperatively disabled do not), or enjoy an enhanced quality of life?

With greater than 120,000 bariatric procedures being performed annually in the United States alone, and likely twice that number worldwide, there is no longer any excuse for the paucity of level I evidence in the bariatric literature. This number of available subjects rivals that seen with breast cancer, a disease in which myriad randomized clinical trials are reported annually. To quote liberally from Dixon, writing again in the 2004 ASBS Consensus Conference,"... it is time to recognize the limitations of the current clinical evidence... . To date, there have been no published randomized clinical trials of the current candidate surgical interventions in comparison with nonsurgical therapy....at best, we have a low level (3 and 4) of evidence—not a strong basis on which to hang clinical recommendations of most appropriate or recommended therapy."[111] Whereas Dixon states that it is most imperative to first finish a randomized clinical trial of surgery (although he begs the question of which procedure) versus alternative therapy, given the trajectory of bariatric surgery, it is unlikely that a sizeable trial with a no-surgery arm could be mounted outside of the minimally obese in the BMI 30–40 group. A trial that has a greater chance of success, and might in fact answer a more fundamental question regarding how much weight loss is needed to show surgical efficacy, would compare, most likely, LAP-BAND with standard RYGB. Whereas U.S. surgeons have demonstrated an overwhelming preference for RYGB,

restrictive procedures such as LAP-BAND enjoy great popularity elsewhere. Thus, an international cooperative trial could be mounted with a high likelihood of adequate accrual and statistical power.

The bariatric surgery community has expended much energy in trying to overcome structural impediments to providing greater access to obesity surgery, in particular the issues of malpractice coverage and ensuring that bariatric surgery is a covered benefit under public and private insurance. What it also needs to address is the increasingly irrational utilization of the resources presently available.[112] Poulose et al.[27] reviewed 70,000 patients who underwent bariatric surgery in the United States in 2002. There were surprising regional disparities in the use of bariatric surgery. Although the proportion of morbidly obese is highest in the Midwest and South, these two regions had the lowest rate of procedures per 100,000 morbidly obese persons. In some age and gender groups, the rate of bariatric surgery was more than four times higher in the Northeast than in the South. Their study also validated a fact that every bariatric surgeon is aware of—that the vast majority of bariatric surgery is performed on women. In their study group, 85% of the patients were female; estimates are that only 60% of the morbidly obese population is female. Other studies have also noted the paucity of non-white patients undergoing bariatric operations.

In summary, with no medical or genetic manipulation on the horizon to address the obesity epidemic that is sweeping the developed world, surgery stands as the only presently effective means of inducing, and maintaining, substantial weight loss. Because of the empirical character of the seminal research and the increasing application of bariatric surgery to a more diverse group of patients, many fundamental questions need to be answered before lighting upon the best approach. Until that time, the choice of bariatric operation will remain dependent on physician and patient preference, degree of obesity, and estimates of the quantity of weight loss needed to achieve reversal of comorbidities.

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Intrahepatic Cholangiocarcinoma Mimicking Hepatic Inflammatory Pseudotumor

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Abstract A 50-year-old male with hepatitis B was referred for a small intrahepatic nodule. Magnetic resonance images raised strong suspicion of a benign lesion, such as an inflammatory pseudotumor, while the other radiological studies were equivocal. Furthermore, the high-intensity image on diffusion magnified-weighted imaging with a low B value strongly suggested a benign tumor. In spite of the absence of typical clinical or radiological findings, needle biopsy revealed an intrahepatic cholangiocarcinoma (ICC). The diagnosis of peripheral ICC rich in fibrous tissue seems to require needle biopsy for pathological examination with immunohistochemical staining because it frequently mimics other diseases, including benign tumors.

Keywords Intrahepatic cholangiocarcinoma · Inflammatory pseudotumor (IPT) · Bile duct adenoma (BDA) · Diffusion magnified-weighted imaging

Introduction

Despite remarkable progress in diagnostic ability for hepatic tumors by technological advances in radiological studies in recent years, the diagnosis of intrahepatic cholangiocarcinoma (ICC), particularly in the case of peripheral ICC without distal intrahepatic bile duct dilatation, remains difficult because of its diversity of histological components. We report a case of peripheral ICC that simulated a hepatic inflammatory pseudotumor (IPT) on imaging.

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Case

An asymptomatic 50-year-old man was admitted to our hospital after the detection of a small lesion in the periphery of the liver on computed tomography (CT) during follow-up for hepatitis B. The tumor, measuring 2×2×2 cm, was found in the peripheral part of segment III. Laboratory data indicated chronic liver dysfunction, but neither inflammatory signs nor elevations of serum tumor markers were presented.

The abdominal nonenhanced CT showed a well-defined, low-density mass (Fig. 1a). In the CT with contrast medium, this nodule was lightly enhanced in the arterial phase, which was increasingly enhanced in the portal phase, while the contrast was retained in the venous phase (Figs. 1b, d and 2c). Consequently, this tumor was suspected to be a well-differentiated hepatocellular carcinoma (HCC) on the initial CT.

Ultrasonography revealed a tumor that was not encapsulated and had no obvious border with the surrounding hepatic parenchyma. The inside was hypoechoic and the shape of this nodule was irregular. However, the internal echo of this tumor assumed a high vascularity, and a vein toward to the center of this tumor was definitely visible. Furthermore, the parenchymal echo of the left lobe was diffusely coarse with deposits of fat (Fig. 2). As a consequence, the tumor was suspected to be an arterio-portal (A-P) shunt with fatty liver.

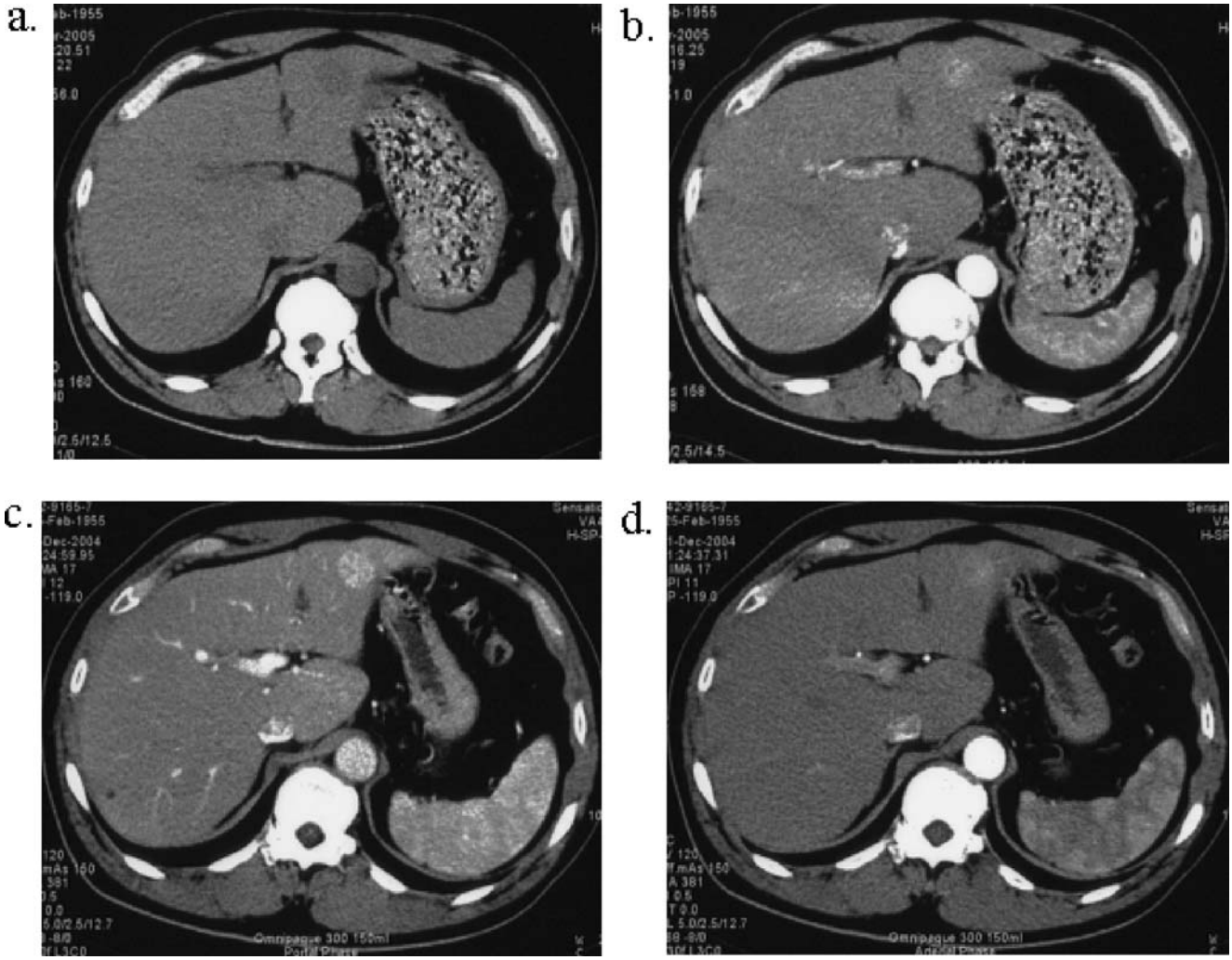

Figure 1 CT. **a** Nonenhanced CT demonstrated a well-defined, low-density mass in segment III without bile duct dilatation. **b** Enhanced CT of the arterial phase shows a slightly enhanced mass. **c** The mass exhibited progressive enhancement in the portal phase. **d** Some contrast medium was retained in the nodule during the venous phase.

MRI showed a tumor with low intensity on T1-weighted images and with very light high intensity on T2-weighted images (Fig. 3a). The intensity was too low for HCC on diffusion magnified-weighted imaging with a high B value (1,000 s/mm^2) (Fig. 3b). The findings of enhancement on delayed MR images were against the diagnosis of an A-P shunt. In addition, this tumor exhibited high intensity on diffusion magnified-weighted imaging with a low B value (50 s/mm^2) (Fig. 3c). Because of these findings, especially the low B value, this nodule was strongly suspected to be an IPT on MRI.

Although serum tumor markers were normal and radiological studies were not diagnostic for hepatic maligmancy, we performed a percutaneous needle biopsy for this nodule to make a definitive diagnosis. The pathology revealed ICC as the definitive diagnosis (Fig. 4). Based on this diagnosis, the patient underwent surgery.

Operative findings The tumor was firm and slightly protracted from the surface of the liver. The intraoperative pathological examination of lymph nodes in the hepatoduodenal ligament was negative, and the lateral segment of the liver was hypertrophic. Therefore, lateral segmentectomy without hepatic hilar lymph node resection was performed.

Pathological findings Macroscopically, the cut surface of the resected specimen demonstrated a yellowish-white tumor measuring 22×26×19 mm. The margin of this tumor was discrete despite the absence of a fibrous capsule (Fig. 5). The intrahepatic bile duct was not dilated, nor was there cholestasis. Histologically, the structure of the liver was completely altered. The parenchyma already formed small pseudonodules. This finding was consistent with liver cirrhosis, in which a light straw small nodule was found. This nodule had partly replaced the pseudo bile duct network, and the network had transformed into ICC. A

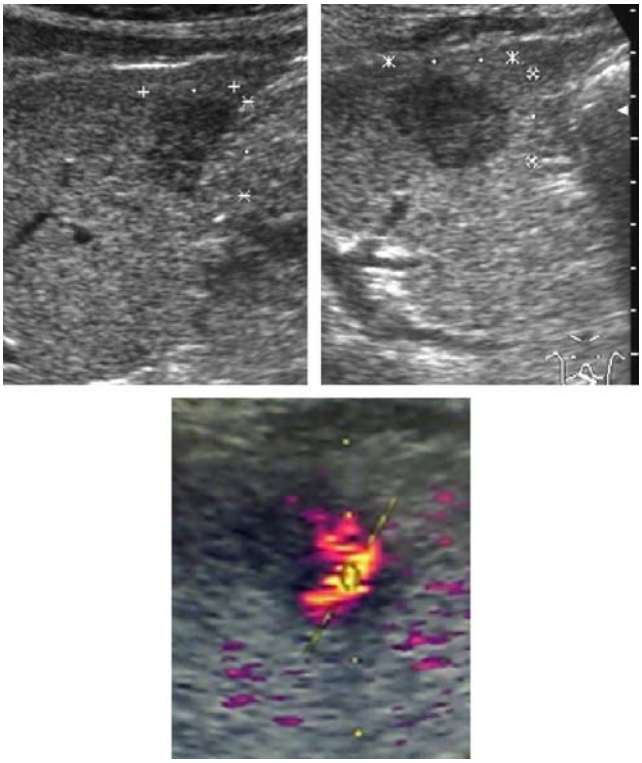

Figure 2 Ultrasonography of the liver demonstrates a hypoechoic mass with no capsule in the lateral segment. The shape of the mass is not round but extends perpendicularly with dents. A fairly large vessel passes through the mass.

lump of spindle-shaped cells rested in several parts of the nodule and had the appearance of hepatoid stigma. The tumor had no capsule and was well differentiated, ly0, v0, p0, and n0. No inflammatory granulation tissue was found in this nodule (Fig. 6).

Discussion

Cholangiocarcinoma is classified into three types by location and incidence, of which ICC accounts for only 5–10%.[1] However, the incidence of ICC is rising in contrast to the decline of extrahepatic cholangiocarcinoma.[2–5] Hepatitis B and C viruses have been associated with cholangiocarcinoma, although not as much as HCC. The fact that hepatocytes and cholangiocytes share the same progenitor supports the influence of the virus on cholangiocarcinoma. ICC displays various radiological features according to the location, size, and intratumoral component. For ICC, peripheral biliary duct dilatation, thickening of the bile ducts, and the presence of lymphadenopathy are typical signs. With the subcapsular type among all peripheral ICCs, such as in our patient, specific findings are lacking, and particularly, for those with abundant fibrous tissue, findings may mimic subcapsular benign tumors such as IPT. Kato et al. described the possibility that MRI with superparamagnetic iron oxide is effective in differentiating ICC from IPT,[6] but this technique has not yet been established. Therefore, the diagnosis is difficult without histology because of the wide range of alternative diagnoses.

There is another important disease that must be included in the differential diagnosis with ICC, i.e., intrahepatic

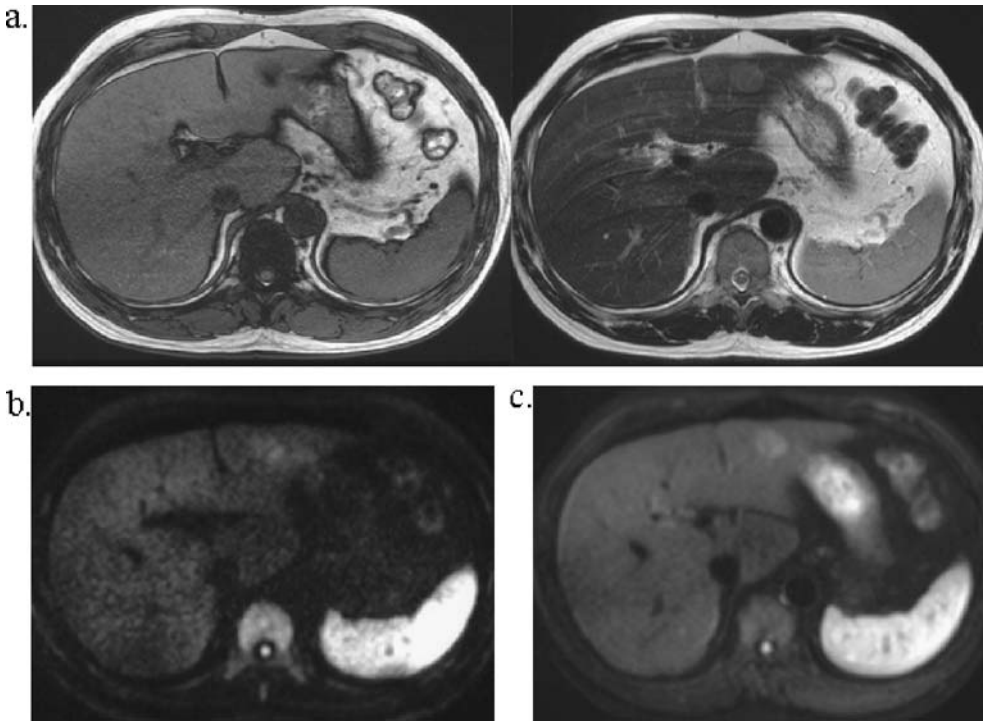

Figure 3 **a** The unenhanced T1-weighted MR image demonstrated a hypointense nodule (*left*), which exhibited moderate hyperintensity on the T2-weighted MR image (*right*). **b** The diffusion magnified-weighted image with a high B value shows a low intensity nodule. **c** This nodule exhibited high intensity on a diffusion magnified-weighted image with a low B value.

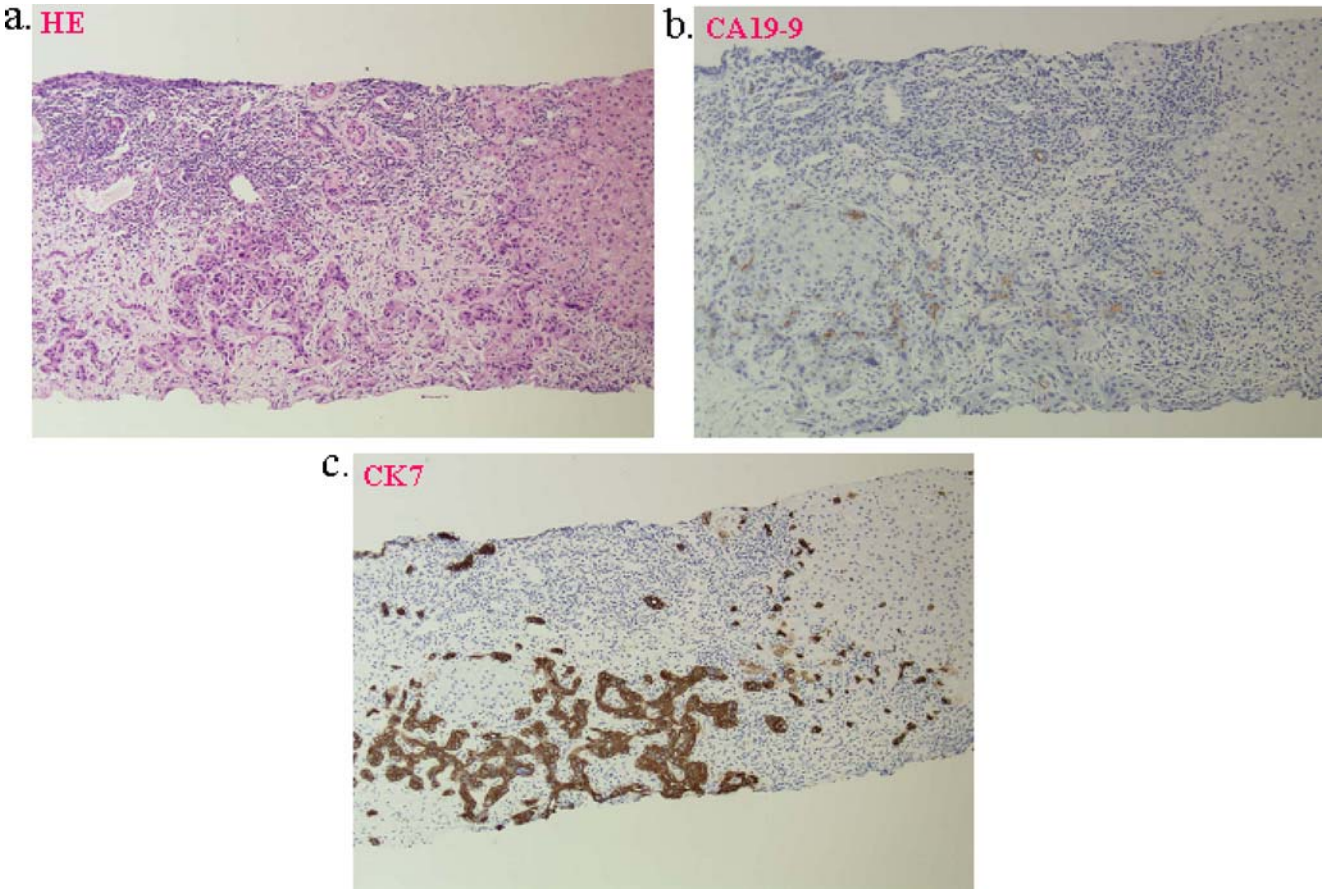

Figure 4 Microscopic specimen obtained by needle biopsy of the nodule. **a** Widely necrotic hepatocytes are replaced by fibrotic tissues. In these tissues, irregularly dispersed bile ductules can be seen. Hematoxylin–eosin, ×100. **b** Immunostaining for CA19-9 demonstrates positive nuclear staining of cells; ×100. **c** Immunostaining for cytokeratin 7 shows strongly stained cells; ×100.

peripheral bile duct adenoma (BDA). BDA is a rare hepatic tumor and an asymptomatic nodule discovered incidentally in nearly all cases. BDA is similar to peripheral IPT and cholangiocarcinoma. It is a grayish-white, firm nodule, usually subcapsular, ranging in size from 1 to 20 mm, and is well circumscribed but nonencapsulated. It is regarded as a reactive process to a focal injury rather than a true neoplasm or a developmental anomaly, but the origin and pathogenesis remain obscure. Histologically, BDA is composed of benign, noncystic ductules and variable degrees of inflammation and fibrosis. In particular, the early lesion contains numerous ductules and a significant inflammatory infiltrate composed by lymphocytes and neutrophils.[7] Therefore, it can be confused with granulomas or IPT. Among all intrahepatic nodules, peripheral ICC is the most difficult lesion to distinguish from BDA because of the lack of dysplastic features and may appear "benign".[8]

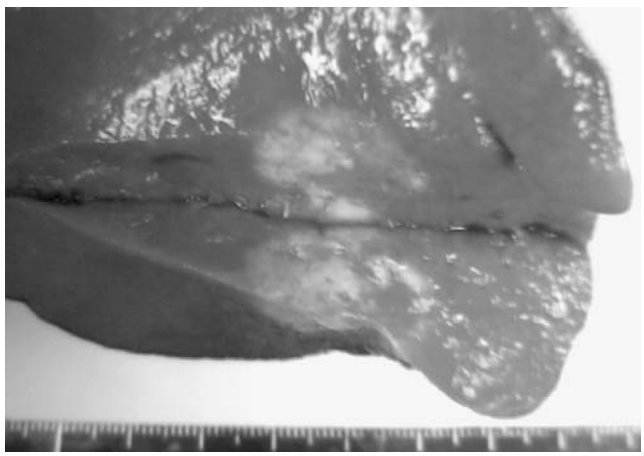

Figure 5 The cut section of the resected specimen. The nodule is a yellowish-white tumor measuring 22×26×19 mm. The margin of this nodule is clear, despite the absence of a fibrous capsule.

IPT have the appearance of a solid tumor, but they are histologically benign lesions with an excellent prognosis that occur in various organs, including the lungs, digestive tract, ovaries, kidneys, spleen, brain, lymph nodes, breast, and retroperitneum. The incidence of IPT is rare, and this hepatic lesion is quite infrequent. Nevertheless, it is necessary to know its behavior well because the differential diagnosis from other hepatic masses, particularly with malignancy, is always an important issue.

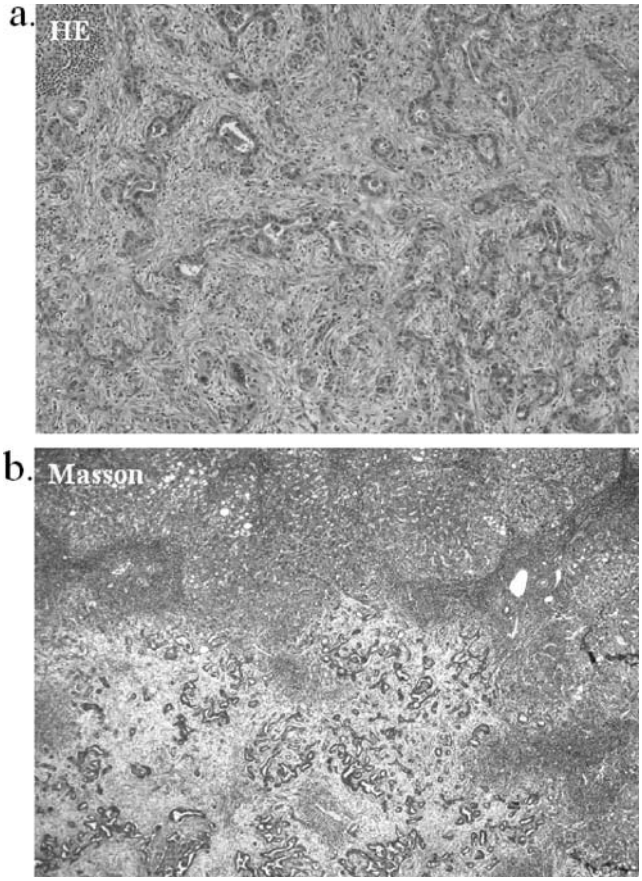

Figure 6 Histological appearance of the resected specimen. **a** Bile ductules have irregularly shaped and various-sized nuclei, of which some invade the adjacent liver parenchyma. Hematoxylin–eosin, × 100. **b** Normal hepatic architecture has been destroyed and replaced by multiple pseudonodules. Masson, ×100.

Radiologically, IPT of the liver is reported as a well-circumscribed, low-density mass on CT[9] or a distinct low echoic mass with strong internal echoes on ultrasonography.[10] In this case, the diffusion magnified-weighted imaging with a low B value was one of the most decisive examination findings suggestive of IPT. When a lesion exhibits high intensity by diffusion MRI with a low B value, it is usually a benign lesion, such as IPT reflecting intratumoral high perfusion of water. However, this method is now in the developmental state and has not yet been established. At the present time, it is noteworthy that IPT has no characteristic findings on imaging, due to the variety of internal components of the nodule. Thus, differentiation from other hepatic diseases, including malignant tumors, is difficult without histology.

Guangming et al. described immunohistochemical staining for p53 is useful in distinguishing ICC from benign nodules.[11] However, percutaneous needle biopsy for a suspicious nodule carries the risk of needle-track neoplastic seeding.[12] Furthermore, IPT in general has a close histological resemblance to certain malignant tumors, such as fibrous histiocytoma and epithelioid hemangioendothelioma.[13]

Conclusion

Peripheral ICC is the lesion that still remains difficult to differentiate from other intrahepatic diseases, including benign tumors. The strategy for treatment is quite different by the diagnosis; thus, the great importance of the diagnosis for ICC warrants more investigation including radiological techniques.

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