Outcome Following Surgical Therapy for Gastrointestinal Stromal Tumors

Maneesh Gupta, M.D., Brett C. Sheppard, M.D., Christopher L. Corless, M.D., Ph.D., Karen R. MacDonell, M.D., Charles D. Blanke, M.D., Kevin G. Billingsley, M.D.

We have pursued an approach of complete resection for patients with gastrointestinal stromal tumors (GISTs), including multivisceral resection, for patients with disease involving adjacent organs. We have also extended the limits of resection to include patients with metastatic disease who were treated with imatinib mesylate. The aim of this study is to report the outcomes and prognostic factors associated with this clinical approach. Study subjects were identified using the pathology database at our institution; for inclusion in the study group, patients must have undergone surgical resection for a KIT-positive gastrointestinal stromal tumor between January 1992 and March 2004. We calculated survival by using the Kaplan-Meier method. Univariate and multivariate analysis was performed using log-rank analysis and the Cox proportional hazards model. Thirty-four patients met the study criteria. Fifty-nine percent of patients had GISTs of gastric origin, 20.6% had duodenal GISTs, and the remainder was comprised of a variety of other sites. Twenty-two (64.7%) patients underwent single-organ resection, and 12 patients (35.3%) underwent multivisceral resection. Estimated actuarial survival at 5 years was 65.2%. Seven patients (five patients with metastases, one patient with locally advanced disease, and one patient with organ-confined disease) received imatinib mesylate. Independent predictors of poor survival included incomplete resection, metastatic disease at presentation, and high mitotic index. Mitotic index and the presence of metastases remain the primary predictors of postoperative survival. Complete surgical resection, even if multivisceral resection is required, is associated with improved survival. (J GASTROINTEST SURG 2006;10:1099–1105)

KEY WORDS: Gastrointestinal stromal tumors, KIT, gastrointestinal tract, imatinib mesylate

Gastrointestinal stromal tumors (GISTs) are a distinct pathologic entity. Most GISTs arise as a result of oncogenic activation of the KIT tyrosine kinase or its homologue platelet-derived growth factor receptor alpha.[1,2] Developmentally, GISTs share common lineage with interstitial cells of Cajal.[3,4] In past decades, there was confusion and controversy over the differentiation of GISTs from histologically similar smooth muscle tumors and schwannomas. This has largely been resolved with accurate pathological diagnosis using immunohistochemical staining for KIT (CD117), CD34, desmin, vimentin, S-100, and various other markers.

The clinical approach to treatment of patients with advanced or metastatic GISTs has undergone a major change with the introduction of the targeted molecular therapy imatinib mesylate (Gleevec). However, surgical treatment remains the primary therapy for patients with localized disease. In recent years, we have pursued an approach of operating on all patients with GISTs if the disease appears to be completely resectable.

For patients with large GISTs, we have performed multivisceral resection involving the en bloc resection of any adjacent involved organs. Since the advent of imatinib in 2002, we have extended this approach

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From the Departments of Surgery (M.G., B.C.S., K.G.B.), Pathology (C.L.C., K.R.M.), and Medicine (C.D.B.), Oregon Health & Science University, Portland, Oregon; and the Health & Science University Cancer Institute (B.C.S., C.L.C., C.D.B., K.G.B.), Portland, Oregon.
Reprint requests: Kevin G. Billingsley, M.D., Department of Surgery, Division of Surgical Oncology, Oregon Health & Science University, Surgical Oncology, L223A, 3181 SW Sam Jackson Park Road, Portland, OR 97239. e-mail: billingk@ohsu.edu

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to patients with metastatic disease that has responded to imatinib therapy. The aim of this report is to describe the outcome of this approach of aggressive surgical resection, as well as to identify prognostic factors for this group of surgically treated patients.

MATERIAL AND METHODS

Patients

Thirty-four patients were identified from the pathology database of Oregon Health & Science University. All these patients underwent surgical resection of KIT-positive GISTs (defined by standard immunohistochemistry) between 1992 and 2004. Thirty-one patients presented primarily to this institute, and three patients underwent surgery elsewhere for primary disease and presented at our institution with recurrence. Data on demographics, surgical treatment, tumor pathology, and survival data were collected from patient charts. Follow-up data was obtained from clinical records or direct contact with patients or family members. Patient demographics included age and gender. Tumor size was determined by measurement of pathologic specimens. Location of resected tumor was divided into stomach, duodenum, small bowel (jejunum, ileum), pelvis, retroperitoneum, omentum, and metastatic sites. The study protocol and design were approved by the Oregon Health & Science University Institutional Review Board and Cancer Institute (IRB study 8324; July 9, 2004).

Pathology tumor characteristics included size, mitotic index, CD117 and CD34 reactivity, presence or absence of ulceration, mucosal or serosal invasion, and immunohistochemical staining with S-l00, vimentin, and desmin. Limited information was available for KIT gene mutation status. Completeness of resection was determined based on microscopic margins of tumor specimens, with a tumor extending to less than 0.1 mm designated as a positive margin.

Clinical Definitions

The extent of disease at presentation was defined as organ confined, locally advanced, or metastatic. Organ-confined disease was defined as tumor(s) limited to a single viscus without invasion of adjacent organs. Any disease invading adjacent organs was considered locally advanced. Presence of noncontiguous spread of tumor was defined as metastatic disease. This included liver metastases or involvement of the mesentery or peritoneum. We defined extent of resection by using two criteria: presence or absence of gross disease following surgery, and microscopic margins. R0 and R1 resections were defined as the resection of all clinically evident disease with negative or positive microscopic margins. R2 resection involved the presence of gross residual disease. Type of resection was classified as single organ or multivisceral resection (resection of two or more organs). Single organ resection included limited wedge resection (wedge gastrectomy) and radical resection.

Surgical Approach

The surgical approach in this group of patients was tailored to the extent of disease. All patients underwent a complete abdominal exploration to assess the peritoneal cavity for metastatic disease. For patients with small tumors that could be completely resected without compromising organ function, we performed limited, organ-sparing resections. These operations included wedge gastric resections and segmental bowel resections. Radical resections encompassing the involved organ were performed when necessitated by the extent of disease or inability to preserve a functional organ following complete resection. Patients that presented with locally advanced disease involving adjacent organs were treated with multivisceral resection, with an aim to completely resect the disease en bloc with circumferentially clear margins. Routine lymphadenectomy was not performed.

Statistical Analysis

We used the Kaplan-Meier method to estimate survival following surgery. Univariate and multivariate analyses of prognostic factors were performed using log-rank analysis and the Cox proportional hazard model, respectively. For multivariate analysis, factors found to be significant ($P < 0.05$) in the univariate model were entered in a forward selection model. SPSS version 13.0 (SPSS Inc., Chicago, IL) was used for the analyses.

RESULTS

Demographics and Clinical Presentation

Thirty-four patients meeting study criteria were identified from the Oregon Health & Science University pathology database (Table 1). Thirty-one presented primarily to this institute with the remainder operated elsewhere for primary disease and treated at our institution for recurrence. Mean age of presentation in this series was 57.7 ± 2.6 years (mean ± SEM). The median age was 59.5 years. The two genders were equally represented. The most common site of occurrence of GISTs was the stomach (n = 20). Other sites included the

Table 1. Clinical and demographic data

Demographics		Extent of disease at presentation: Organ confined[†]	Locally advanced	Metastatic	All patients* (N = 34)
Age (yr)	0–59 (%)	11 (64.7)	2 (11.8)	4 (23.5)	17 (50)
	⩾60	9 (52.9)	2 (11.8)	6 (35.3)	17 (50)
Gender	Male (%)	10 (62.5)	2 (12.5)	4 (25.0)	16 (47.1)
	Female	10 (55.6)	2 (11.1)	6 (33.3)	18 (52.9)
Site	Gastric (%)	14 (70.0)	1 (5.0)	5 (25.0)	20 (58.8)
	Duodenal	5 (71.4)	1 (14.3)	1 (14.3)	7 (20.6)
	Other[‡]	1 (14.3)	2 (28.6)	4 (57.1)	7 (20.6)
Symptoms	Pain (%)	5 (33.3)	3 (20.0)	7 (46.7)	15 (44.1)
	GI bleed[§]	6 (75.0)	1 (12.5)	1 (12.5)	8 (23.5)
	Weight loss	1 (25.0)	1 (25.0)	2 (50.0)	4 (11.8)
	Anemia	6 (60.0)	1 (10.0)	3 (30.0)	10 (29.4)
	Incidental finding	8 (100.0)	0 (0.0)	0 (0.0)	8 (23.5)

*No. of patients (percent of patients of N = 34).
[†]No. of patients (percent of patients based on total number in the demographic group).
[‡]Other sites include remaining small bowel, retroperitoneal and pelvic masses, mesentery, omentum, unknown primary site.
[§]GI bleed includes acute bleed melena, or heme-positive stools.

duodenum (n = 7; 20.6%), remaining small bowel (n = 3; 8.8%), omentum (n = 1; 2.9%), retroperitoneum (n = 1; 2.9%), pelvic (n = 1; 2.9%), and unknown primary (n = 1; 2.9%). One patient presented with two separate primary GISTs (esophageal and gastric). This was confirmed with different c-kit mutation patterns from the two tumors.

Common presenting symptoms included pain and gastrointestinal hemorrhage. Fifty-nine percent of patients (n = 20) presented with organ-confined disease and 29.4% (n = 10) of patients presented with metastatic disease. Four patients (11.8%) had locally advanced disease.

Therapy

All patients underwent surgical therapy (Table 2). Complete resection of GISTs was accomplished in 65% of patients (n = 22), whereas six patients (17.6%) had gross residual disease. Five patients

Table 2. Surgery

Surgical treatment		Extent of disease at presentation: Organ confined (n = 20)	Locally advanced (n = 4)	Metastatic (n = 10)	All patients (N = 34)
Surgery					
Single organ*	Limited (%)	7 (87.5)[‡]	0 (0.0)	1 (12.5)	8 (23.5)[§]
	Radical	11 (78.6)	2 (14.3)	1 (7.14)	14 (41.2)
Multivisceral		2 (16.7)	2 (16.7)	8 (66.7)	12 (35.3)
Extent of resection[†]	R0 (%)	18 (81.8)	1 (4.6)	3 (13.6)	22 (64.7)
	R1	1 (20.0)	3 (60.0)	1 (20.0)	5 (14.7)
	R2	0 (0.0)	0 (0.0)	6 (100.0)	6 (17.6)
	NA	1 (100.0)	0 (0.0)	0 (0.0)	1 (2.9)
Surgical Margins	Negative (%)	18 (69.2)	2 (7.7)	6 (23.1)	26 (76.5)
	Positive	1 (20.0)	2 (40.0)	2 (40.0)	5 (14.7)
	NA	1 (33.3)	0 (0.0)	2 (66.7)	3 (8.8)

NA = Not assessted no data.
*Limited Single organ resection limited to wedge resection or removal of tumor only; Radical resection includes partial or complete organ resection.
[†]R0 = gross disease removed with negative margins; R1 = gross disease removed with positive margins; R2 = gross disease not completely removed.
[‡]No. of patients (percent based on extent of surgical criterion).
[§]No. of patients meeting surgical criteria (percent of all patients, N = 34).

(14.7%) had microscopically involved margins that were identified in pathology specimens. One patient had incomplete pathologic data, and the margin status could not be ascertained. Complete resection was achieved in 90% of patients with organ-confined disease.

Eight patients received imatinib therapy. Two out of the eight were treated with both neoadjuvant imatinib (21.9 and 2.3 months) and adjuvant imatinib (9.6 and 12.4 months). Both patients who received neoadjuvant imatinib had metastatic disease at presentation. They went to operation to resect residual disease that was metabolically active on positron emission tomographic scan. The other patients were treated with adjuvant imatinib, with treatment duration ranging between 3.7 months to 56 months. The dose of imatinib used was between 400 to 600 mg/day. Three patients received standard chemotherapy.

Pathology

Mean tumor size at presentation was 9.2 ± 1.8 cm (mean ± SEM), with a median of 4.7 cm (Table 3). Fifteen percent of GISTs had epithelioid features in addition to spindle cell morphology. All tumors were KIT positive. CD34 was positive in 21 of 23 patients (91.3%). KIT gene mutation status was available for 12 patients. Six patients had exon 11 mutation, and one patient had an exon 9 mutation. The remaining five patients had neither exon 9 or 11 mutation. S-100 staining was available in 18 patients, with 17 being negative. Lymph nodes were negative for metastases in the 15 patients with submitted nodal specimens, even in cases with extensive metastases.

Recurrence

Nine patients in this series had recurrence, with six of these presenting with recurrence or progression within 5 years of initial disease. Three of these patients presented primarily with recurrence after the original surgery was done elsewhere. All of the recurrences were intra-abdominal (liver, omentum, pelvic, mesentery, or local) with no extra-abdominal spread. Surgical resection was attempted in eight of these cases, ranging from complete resection to palliative, subtotal resection only.

Survival and Prognostic Factors

Median survival following surgery has not been reached. The estimated actuarial survival at 5 years was 65.2 %. Mean follow-up time was 32.8 ± 5.8 months, with median follow-up of 23.5 months (Fig. 1). One-year actuarial survival was 80%.

On univariate analysis, the three factors predictive of poor survival were high mitotic count, incomplete resection, and age ($P < 0.001$). The extent of disease at presentation, type of surgery performed (single organ vs. multivisceral), tumor size, and serosal invasion were also predictors of survival ($P < 0.05$) (Fig. 2). Independent factors influencing outcome were assessed using Cox multivariate regression analysis (Table 4).

Table 3. Gastrointestinal stromal tumor pathology

Pathologic characteristic		GIST location: Gastric (n = 20)	Duodenal (n = 7)	Other (n = 7)	Total (N = 34)
Tumor size, cm	0–4 (%)	8 (53.3)*	6 (40.0)	1 (6.7)	15 (44.1)†
	>4	11 (64.7)	1 (5.9)	5 (29.4)	17 (50.0)
	ND	1 (50.0)	0 (0.0)	1 (50.0)	2 (5.9)
Mitotic count, per 50 HPF	0–5 (%)	12 (63.2)	6 (31.6)	1 (5.3)	19 (52.9)
	>5	8 (53.3)	1 (6.7)	6 (40.0)	15 (23.5)
Histology	Spindle (%)	17 (58.6)	6 (20.7)	6 (20.7)	29 (85.3)
	Epithelioid‡	3 (60.0)	1 (20.0)	1 (20.0)	5 (14.7)
Serosal invasion	Absent (%)	13 (76.5)	3 (17.7)	1 (5.9)	17 (50.0)
	Present	2 (28.6)	3 (42.9)	2 (28.6)	7 (20.6)
	ND	5 (50.0)	1 (10.0)	4 (40.0)	10 (29.4)
Mucosal ulceration	Absent (%)	9 (81.8)	1 (9.1)	1 (9.1)	11 (32.4)
	Present	8 (57.1)	5 (35.7)	1 (7.1)	14 (41.2)
	ND	3 (33.3)	1 (11.1)	5 (55.6)	9 (26.5)

ND = No data or not applicable.
*Tumors with GIST location (percent of total number of patients pathological with characteristic).
†No. of patients with pathological characteristic (percent of total patients, N = 34).
‡Epithelioid features only or in addition to spindle cell morphology.

Multivariate analysis demonstrates that the most significant predictors of poor survival were high mitotic count, metastatic disease at presentation, and incomplete resection. Serosal invasion and tumor size greater than 5 cm were significant clinical factors but were less predictive of outcome than mitotic count, metastatic disease, and extent of resection (Table 4).

DISCUSSION

Prediction of the biologic behavior of resected GISTs has been a challenge and is a matter of considerable debate and research. In this study, we selected cases that were confirmed as GISTs based on positive KIT immunohistochemical staining. The primary aim of this study was to define the outcome and prognostic factors for patients with GISTs, treated with a surgical approach that emphasizes complete resection with liberal use of multivisceral resection for tumors that involve adjacent organs. The estimated 5-year actuarial survival in this series is 65.2% (Fig. 1). This is consistent with the results from other published series.[5,6] Like other investigators, we observed that recurrent disease occurs primarily in the abdomen with very few extra-abdominal metastases.[7–9] In the majority of cases in this series, disease recurrence or progression occurred within 5 years of initial presentation. This is similar to previous reports.[5,10]

In our analysis of prognostic factors, we examined disease extent at presentation. Out of 34 patients in this study, 20 patients had organ-confined disease, with the remainder presenting with advanced disease (locally advanced or metastatic). We found that disease extent at presentation was a significant prognostic factor for survival, both in univariate and multivariate analysis. The poor survival in this group was primarily related to the poor survival of the subset of patients with metastatic disease. Imatinib mesylate was used preoperatively in two patients with metastatic disease. However, this series does not include enough patients with imatinib to allow us to analyze the survival of these patients when treated with imatinib followed by surgery. Additional prognostic factors in this study included tumor size and mitotic count. In our series, we found that a mitotic count of greater than 5/50 HPF is a highly significant ($P < 0.001$) and independent prognostic indicator of poor survival. These observations parallel the results of other large series.[11] A Scandinavian series with a large retrospective cohort of 1460 patients also points out the importance of both tumor size and mitotic index as major predictors of survival.[12] A recent consensus report on the prognostication of primary GISTs emphasizes size and mitotic index as the two key elements in risk stratification.[13]

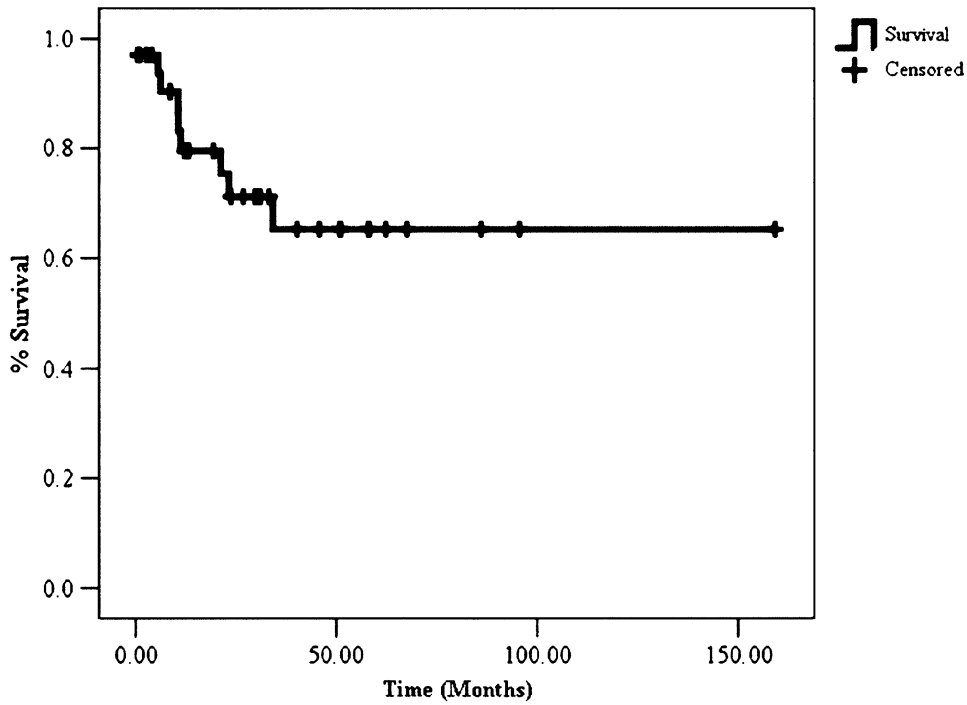

Fig. 1. Kaplan-Meier survival curve for all patients.

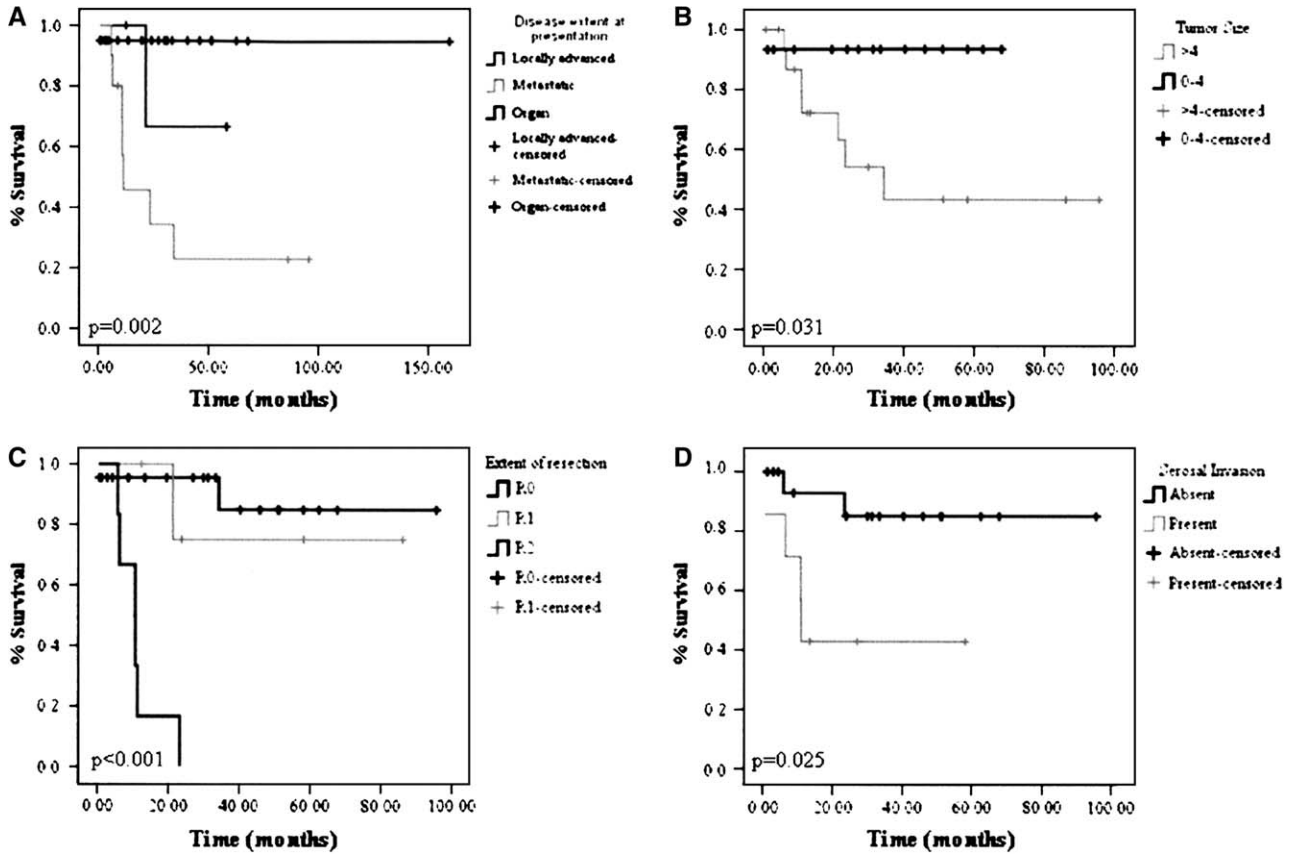

Fig. 2. Survival curves using univariate prognostic factors (P = significance calculated using the Kaplan-Meier method). (**A**) Extent of disease at presentation. Organ-confined disease limited to organ wall with no invasion of adjacent organs, locally advanced disease invading adjacent organs, and noncontiguous spread of tumor were defined as metastatic disease, including liver metastases or extensive involvement of the mesentery or drop metastasis ($P = 0.002$). (**B**) Tumor size (0–4 cm or >4 cm; $P = 0.031$). (**C**) Extent of resection. R0 and R1 resections are defined as all gross disease removed at surgery, with negative or positive microscopic margins, and R2 resection with gross disease or metastatic disease left intact ($P < 0.001$). (**D**) Serosal invasion ($P = 0.025$).

Although low mitotic count generally indicates a more favorable prognosis, it is important to note that low count does not indicate benign clinical behavior with certainty.[9,13,14] Serial follow-up is necessary in all GIST cases to detect any recurrence in a timely manner.

The importance of microscopic surgical margins in the surgical treatment of GISTs remains controversial. Singer et al.[15] reported that resection margin status is a significant factor on univariate analysis but is not an independent predictor of survival. Intuitively, a complete resection of tumor should improve both disease-free survival and overall survival. It has been suggested by DeMatteo et al.[6] that resection margins are not as significant because even when margins are negative, tumor cells may be shed directly into peritoneal cavity, especially in cases of exophytic growth. In the present study, we considered complete resection (R0) as removal of all gross disease with negative microscopic margins. We found that extent of resection was a significant predictor of survival, although the most significant survival difference was between patients with gross residual disease (R2 resection) and all others. Survival was similar for patients with clear margins and microscopically involved margins (R1, Fig. 2). The association between complete surgical resection and long-term survival has been supported by other studies.[16] Bauer et al.[17] have also shown that resection of advanced metastatic disease is possible with previous induction with imatinib.

We also took into account mucosal ulceration and serosal invasion by the GIST. We found serosal invasion to be an independent negative prognostic factor. We speculate that tumors which have progressed to involve the serosa are more likely than lesions that

Table 4. Prognostic significance

Prognostic factor	Univariate analysis (*P* value)	Multivariate analysis (*P* value)
Mitotic count (<5 per 50 HPF)	<0.001	0.001
Extent of resection*	<0.001	<0.001
Age	<0.001	0.121
Type of surgery†	0.002	0.053
Disease extent (presentation)‡	0.002	0.001
Serosal invasion	0.025	0.025
Tumor size	0.031	0.026
Tumor site	0.111	—
Tumor histology	0.699	—
Mucosal ulceration	0.766	—
Gender	0.858	—

*Extent of resection. R0 = cross disease removed with negative margins; R1 = gross disease removed with positive margins; R2 = gross disease not completely removed.

†Type of surgery. Limited single organ resection limited to wedge resection or removal of tumor only, radical resection includes partial or complete organ resection, and multivisceral resection (resection of two or more organs).

‡Disease extent (presentation). Organ confined limited to organ wall with no invasion of adjacent organs, locally advanced is disease invading adjacent organs, and metastatic is presence of noncontiguous spread of tumor, including liver metastases or extensive involvement of the mesentery or peritoneum.

are more limited to shed cells into the peritoneum, which will give rise to peritoneal implants and distant metastasis.

CONCLUSION

Although biologic factors such as the mitotic count and the presence of metastasis are the major predictors of outcome following the resection of GISTs, our findings confirm the importance of complete surgical resection. Long-term survival is possible even for a subset of patients that requires extensive, multivisceral resection. Our findings underscore the importance of the mitotic index as a prognostic factor. Despite the overall favorable prognosis of patients with completely resected GISTs, patients with a high mitotic index remain at high risk for relapse. These patients may provide an ideal subset of individuals to be treated with adjuvant therapy with imatinib mesylate. Future efforts should focus on the enrollment of patients in adjuvant trials of imatinib mesylate and other targeted therapies.

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Postoperative Morbidity and Long-term Survival After Pancreaticoduodenectomy With Superior Mesenterico–Portal Vein Resection

Hartwig Riediger, M.D., Frank Makowiec, M.D., Eva Fischer, Ulrich Adam, M.D., Ulrich T. Hopt, M.D.

The role of superior mesenteric–portal vein resection (SM-PVR) for vein invasion or tumor adherence during pancreatoduodenectomy (PD) is still under debate. We investigated morbidity, mortality, and long-term survival in patients who underwent PD with or without SM-PVR. Between July 1994 and December 2004, 222 PD (78% pylorus preserving, 19% Whipple, and 3% total pancreatectomy) were performed for malignant disease. Fifty-three patients (24%) had PD with SM-PVR. Sixty-eight percent of the venous resections were performed as wedge excisions and 32% as segmental resections. Long-term survival was analyzed in 165 patients with pancreatic (n = 110), ampullary (n = 33), or distal bile (n = 22) duct cancer using univariate (log-rank) and multivariate (Cox regression) methods. In patients undergoing PD with SM-PVR and conclusive histologic examination of the resected vein specimen (n = 42), 60% had true tumor involvement of the venous wall, whereas 40% had no proven tumor infiltration. In the complete study group, negative resection margins were obtained in 69% of patients with SM-PVR and in 79% of patients without SM-PVR ($P = 0.09$). Median duration of surgery was 500 minutes (SM-PVR) versus 440 minutes (no SM-PVR; $P < 0.001$). Volume of intraoperatively transfused blood was 600 ml (median) in both groups. Postoperative surgical complications/mortality occurred in 23%/3.8% (SM-PVR) versus 35%/4.1% (no SM-PVR); $P = 0.09/0.9$. Analysis of long-term survival in all 165 patients included 41 with SM-PVR. Five-year survival rates were 15% in cancer of the pancreatic head, 22% in ampullary cancer, and 24% in distal bile duct cancer ($P = 0.02$). Long-term survival was not influenced by the need for SM-PVR in any of the different tumor entities. In multivariate analysis, a positive resection margin ($P < 0.01$, relative risk [RR]: 1.8, 95% confidence interval [CI]: 1.2–2.7), a histologically undifferentiated tumor ($P = 0.01$, RR: 1.7, 95% CI: 1.1–2.5), and the tumor entity ($P < 0.01$) were significant predictors of survival. Univariate survival analysis of the 110 patients with cancer of the pancreatic head revealed that a histologically undifferentiated tumor ($P = 0.05$) and positive resection margins ($P = 0.02$) were associated with a poorer survival. In multivariate analysis, the resection margin ($P = 0.02$, RR: 5.1, 95% CI: 1.1–2.8) and a histologically undifferentiated tumor ($P = 0.05$, RR: 3.8, 95% CI: 1.0–2.5) significantly influenced survival. After PD, perioperative morbidity and long-term survival in patients with SM-PVR were similar to those of patients without vein resection. In case of tumor adherence or infiltration, combined resection of the pancreatic head and the vein should always be considered in the absence of other contraindications for resection. (J GASTROINTEST SURG 2006;10:1106–1115)

KEY WORDS: Portal vein resection, pancreatoduodenectomy, periampullary cancer, pancreatic cancer, survival

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From the Department of Surgery, University of Freiburg, Freiburg, Germany.
Reprint requests: Dr. Frank Makowiec, Department of Surgery, University of Freiburg, Hugstetter Str. 55, D-79106 Freiburg, Germany. e-mail: Frank.Makowiec@uniklinik-freiburg.de

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Pancreatic cancer is still associated with a very poor prognosis. Five-year survival rate after pancreatoduodenectomy (PD) is in the range of 10–20% in most series.[1–3] Negative resection margins is one important prognostic factor.[2,4] Further improvements of long-term survival might be achievable by postoperative chemotherapy or chemoradiation.[5,6]

The extent of resection of pancreatic or periampullary cancer is under discussion since many years. Extended lymphadenectomy did not show a survival benefit compared to standard lymphadenectomy.[1,7] "Regional pancreatectomy" with complex vascular resections had an increased perioperative mortality and arterial infiltration led to survival rates comparable to those of irresectable patients.[8,9] Furthermore, morbidity and mortality were higher in some of these reports, with lower quality of life after extended lymphadenectomy leading to the conclusion that extended resection provides no benefit for the patients. However, a differentiated point of view has been established regarding surgical management of isolated tumor involvement of the portal or superior mesenteric vein. During the past two decades, an increasing number of PD with superior mesenteric–portal vein resections (SM-PVR) have been reported from many centers, while arterial resections remain the exception.[10]

Resection of the superior mesenteric–portal vein (SM-PVR) during PD has been reported without a relevant increase of morbidity and mortality.[3,11–15] In addition, survival after PD with SM-PVR was comparable to survival after PD without vein resection in the majority of these studies.[3,14,16,17]

We report our experience with PD and SM-PVR. Of 222 patients undergoing PD for malignant disease, 53 had concomitant vein resection. Survival data were available and analyzed in 165 patients with pancreatic, ampullary, or distal bile duct cancer.

METHODS

Patients

At the university hospitals of Rostock (1994–2001) and Freiburg (2001–2004), 222 PDs were performed for malignant disease by one team of surgeons. Perioperative patient data were documented in a prospective database and accomplished by long-term follow-up data from the regional tumor registries and telephone interviews with home physicians and/or patients.

At time of surgery, median patient age was 64 years (range: 16–83) and 55% were male. Indications for PD were cancer of the pancreatic head (56%), ampullary cancer (19%), distal bile duct cancer (15%), and other entities (10%). SM-PVR was performed in 53 patients with cancer of the pancreatic head (n = 40), distal bile duct cancer (n = 8), ampullary cancer (n = 2), and other tumors (n = 3).

Long-term survival was analyzed in 165 patients with complete pathologic reports (cancer of the pancreatic head [n = 110], ampullary cancer [n = 33], and distal bile duct cancer [n = 22]). Forty-one of those patients had SM-PVR. Although survival times were available, 12 further patients were not considered for survival analysis because of incomplete pathologic reports from the early years of our study or tumor entities other than pancreatic or periampullary cancer.

Preoperative Work-up

Specific preoperative work-up consisted in computed tomography (CT; 94%), magnetic resonance imaging (MRI; 40%), angiography (59%), and endoscopic ultrasound (55%). Since 1998, MRI was used increasingly in addition or alternatively to CT, angiography, and endoscopic ultrasound. Routine preoperative angiography was abandoned in 2001 with increasing accuracy of MR angiography or better vessel imaging by CT.

Operative Technique

In 79%, pylorus-preserving pancreaticoduodenectomy, in 19%, classic Whipple resection (including distal gastrectomy), and in 3%, total pancreatectomy were performed. All pancreatic resections were carried out or supervised by one of four staff surgeons.

Lymphadenectomy was carried out along the hepatoduodenal ligament, common hepatic artery, vena cava, superior mesenteric vein, and along the right side of the superior mesenteric artery. Until 2003, a pancreatojejunostomy was the routine reconstruction procedure and was performed by anastomosing the pancreatic parenchyma to the jejunal mucosa in an end-to-side single-layer full-thickness anastomosis. Since 2004, pancreatogastrostomy is also performed in our department and was done in 17 patients of this study (8%). For pancreatogastrostomy the pancreatic stump is pulled into the stomach and fixed by purse-string suture. The anastomosis is then carried out by interrupted polydioxanone sutures. Octreotide as routine application in all patients was abandoned in 2003. Since then, it was restricted to patients with a potentially high risk for pancreatic fistulas as judged by the responsible surgeon.

Portal vein resection was performed when suspected vein infiltration was the only presumed barrier to negative resection margins. Total occlusion of the superior mesenteric–portal vein was always a contraindication for resection. In the case of limited tumor contact to the right side of the vein tangential clamping was performed before resection of the vessel wall. Reconstruction was then achieved by a running suture (n = 34). A venous patch was used in two patients. In case of more extended tumor infiltration, segmental resection with an end-end anastomosis was performed (n = 17). Vascular prostheses were not used in our study population.

Partial thromboplastin time–guided anticoagulation (partial thromboplastin time: 40–50 seconds) was applied for 5 days after segmental vein resection. All other patients received low-dose heparin therapy (SC) as for standard thrombosis prophylaxis.

Definition of Postoperative Complications

Pancreatic fistulas were defined as the presence of at least one of the following conditions: leakage demonstrated at reoperation, need for a CT-guided drainage of symptomatic fluid collections with high amylase content or secretion of amylase-rich (>3 times serum level) fluid via the silicon drains placed at the end of surgery, beyond day 6 postoperatively.[18] Delayed gastric emptying was defined as the inability to eat a regular diet after the tenth postoperative day. Intra-abdominal complications, wound infection, and postoperative bleeding (abdominal or gastrointestinal) were summarized as surgical complications. Mortality rate was defined as death during the hospital stay and/or during the first 30 postoperative days.

Statistics

The results of our study were gained by retrospective analysis of our prospective database. Patients were grouped by PD with SM-PVR and PD without SM-PVR. Differences between the groups were analyzed using the χ^2 test and the Mann-Whitney test where appropriate.

Patients who died during the postoperative period (n = 9) were excluded from survival analysis. Univariate analysis of survival was performed using the Kaplan-Meier method with a log-rank test to evaluate prognostic factors.

Multivariate (independent factor) analysis of survival was then undertaken by entering all clinical and histopathologic parameters as shown (see Table 3 later) into a Cox proportional hazard model (cutoff for inclusion: $P < 0.05$). Independent risk factors were here analyzed with a forward selection strategy using a likelihood ratio statistic.

All statistical analyses were calculated with SPSS for Windows, release 13 (SPSS Inc., Chicago, Illinois).

RESULTS

Duration of Surgery and Transfusion Requirements

PD with SM-PVR was associated with significantly longer operative times (median 500 minutes (range: 300–785 minutes) versus 440 minutes (range: 255–860 minutes) in patients without SM-PVR ($P < 0.01$). The median volume of intraoperatively transfused packed red cells was 600 ml in both groups (Table 1).

Table 1. Demographic, tumor-related, and operative data for 222 patients undergoing Pancreatoduodenectomy

	PD without SM-PVR (n = 169)	PD with SM-PVR (n = 53)	*P*
Age (median yr, range)	64 (16–79)	64 (37–83)	0.27
Male (n, %)	91 (54%)	31 (58%)	0.33
Preoperative biliary drainage (n, %)	91 (54%)	31 (58%)	0.6
Primary tumor			
Pancreatic head cancer (n, %)	85 (50%)	40 (75%)	0.01
Distal bile duct cancer (n, %)	25 (15%)	8 (15%)	
Ampullary cancer (n, %)	40 (24%)	2 (4%)	
Other (n, %)	19 (11%)	3 (6%)	
Procedure			0.09
Whipple (n, %)	31 (18%)	10 (19%)	
PPPD (n, %)	136 (81%)	39 (74%)	
Pancreatectomyi (n, %)	2 (1%)	4 (8%)	

PPPD = pylorus-preserving pancreatoduodenectomy; PD = pancreatoduodenectomy; SM = superior mesenterico; PVR = portal vein resection.

Morbidity and Mortality

Perioperative morbidity and mortality of groups are shown in Table 2. PD with SM-PVR was not associated with a higher complication rate. Mortality was 4% in both groups. Postoperative length of stay was also comparable between the groups.

SM-PVR itself did not cause specific complications postoperatively. We did not observe any case of mesenteric vein thrombosis, portal hypertension, or bleeding in relation to portal vein resection.

Characterization of Tumors

Tumors of the pancreatic head required more frequently SM-PVR during PD than ampullary or distal bile duct cancer (Table 1; $P < 0.01$). In the SM-PVR group, tumors were larger than in the group without SM-PVR (median: 30 mm versus 22 mm; $P = 0.06$).

Resection Margins

A detailed and conclusive pathologic analysis of the resection margins was available in 199 patients (in 51 of the 53 patients undergoing PD with SM-PVR).

Free resection margins were achieved in 152 of 199 cases (76.4%). Thirty-nine patients (19.6%) had a R1 resection, and eight patients (4%), a R2 resection. Among the 51 patients with PD and SM-PVR, complete R0 resection was obtained in 35 patients (69%), and 16 patients (31%) had an R1 situation. It is of note that none of the patients undergoing SM-PVR had evidence of macroscopic tumor residuals (R2) at the end of surgery.

Histologic Examination of the Resected Vein

In 42 of 53 patients with SM-PVR, a conclusive pathologic analysis regarding the presence or absence of infiltration of the venous wall was available. Twenty-five of those 42 patients (60%) had proven tumor infiltration of the venous wall, whereas 17 patients (40%) had only peritumoral inflammatory adherence to the venous wall. SM-PVR resulted in free margins at the venous resection site in 23 of 24 patients with tumor infiltration.

Long-term Survival

Analysis of long-term survival in all 165 evaluated patients (including 41 with SM-PVR) showed that SM-PVR did not have a prognostic influence in any of the three tumor entities (cancer of the pancreatic head, ampullary cancer, distal bile duct cancer). In the complete study group, 5-year survival rates after PD with SM-PVR (17.9%) and after PD without SM-PVR (17.0%) were almost identical ($P = 0.93$). Five-year survival rates were 15% for cancer of the pancreatic head, 22% for ampullary cancer, and 24% for distal bile duct cancer ($P = 0.02$). In univariate analysis, the resection margin and tumor grading (G1/G2 versus G3/G4) had a significant prognostic influence on survival ($P < 0.01$). In multivariate survival analysis of all 165 patients, again, a positive resection margin ($P < 0.01$, relative risk [RR]: 1.8, 95% confidence interval [CI]: 1.2–2.7), low tumor

Table 2. Perioperative course after pancretoduodenectomy in 222 patients

	PD with SM-PVR (n = 53)	PD without SM-PVR (n = 169)	*P*
Intraoperative			
Median duration of surgery (min, range)	500 (350–755)	440 (255–860)	<0.01
Median blood transfusion (ml, range)	600 (0–4200)	600 (0–5700)	0.7
Postoperative			
Total morbidity (n, %)	22 (42%)	81 (50%)	0.39
Surgical complications (n, %)	12 (23%)	59 (35%)	0.09
Wound infection (n, %)	2 (4%)	21 (12%)	0.07
Pancreatic fistula (n, %)	4 (8%)	30 (18%)	0.07
Intra-abdominal abscess (n, %)	4 (8%)	20 (12%)	0.37
Intra-abdominal bleeding (n, %)	4 (8%)	8 (5%)	0.43
Delayed gastric emptying (n, %)	0	7 (4%)	0.13
Repeat laparotomy (n, %)	4 (8%)	15 (9%)	0.76
Interventional therapy of complications (n, %)	5 (9%)	27 (17%)	0.2
Median postoperative LOS (days, range)	16 (10–123)	18 (10–385)	0.19
Mortality (n, %)	2 (4%)	7 (4%)	0.9

LOS = length of postoperative hospital stay; PD = pancreatoduodenectomy; SM = superior mesenterico; PVR = portal vein resection.

grading ($P = 0.01$, RR: 1.7, 95% CI: 1.1–2.5), and the tumor entity (pancreatic versus ampullary versus distal bile duct cancer; $P < 0.01$) were independent negative prognostic factors.

In further subgroup analyses of survival in the 110 patients with cancer of the pancreatic head (PD with SM-PVR: n = 36), 5-year survival was 10.9% after PD with SM-PVR and 16.6% after PD without SM-PVR ($P = 0.7$, Fig. 1). Univariate survival analysis revealed that a histologically undifferentiated tumor ($P = 0.05$) and positive resection margins ($P = 0.02$) were associated with a poorer survival (Table 3). In multivariate analysis, a positive resection margin ($P = 0.02$, RR: 1.7, 95% CI: 1.1–2.8) and a histologic undifferentiated tumor ($P = 0.05$, RR: 1.6, 95% CI: 1.0–2.5) were independent predictors of poorer survival.

In a further subgroup analysis of patients with cancer of the pancreatic head and histologic examined portal vein, 5-year survival was 11% for those with malignant vein infiltration (n = 14) versus 51% for patients without malignant infiltration (n = 12; $P = 0.14$; Fig. 2). Although this is not significant because of the low numbers of patients in this evaluation, it is of note that 4 of the 12 patients without vein infiltration were alive at the end of follow-up (2–7 years after surgery).

DISCUSSION

More than two decades ago, pancreatic surgery was associated with a high perioperative morbidity and mortality. Today, a perioperative mortality rate of less than 5% is realized in specialized pancreatic units.[19–21] Despite these advances in surgical technique and perioperative care, pancreatic cancer is still associated with a dismal prognosis.[1,22] Radical tumor removal (R0 resection) is one of the most important prognostic factor in long-term survival after pancreatic head resection.[2,4,10,23]

Vascular infiltration is frequently a limiting factor for complete tumor removal. In 1973, Fortner[8] published the concept of "regional pancreatectomy," which included venous (type I) and arterial (type II) resection. Initially, extended resections had

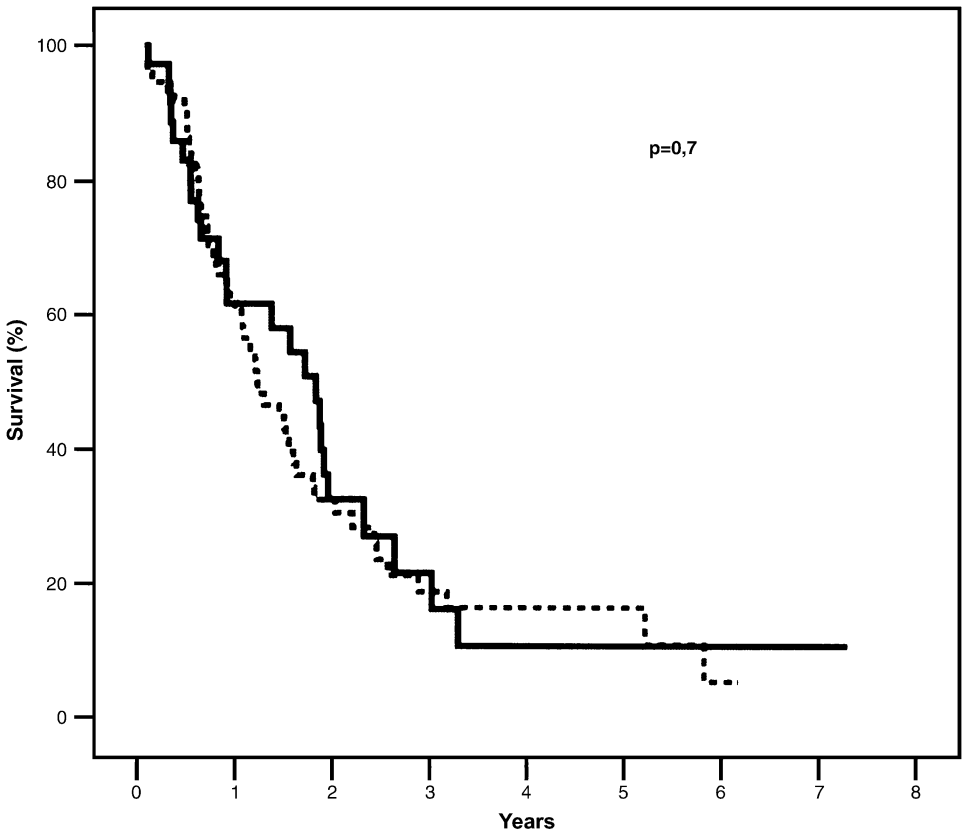

Fig. 1. Long-term survival in patients with pancreatic head cancer (n = 110). SM-PVR = superior mesenteric–portal vein resection. Solid line indicates SM-PVR (n = 36), and dashed line indicates no SM-PVR (n = 74).

Table 3. Univariate analysis of long-term survival after Pancreatoduodenectomy for cancer of the pancreatic head in patients with complete datasets (n = 110)

Factor	No.	2-Year survival	5-Year survival	*P*
Age (yr)				
<65	58	32%	17%	0.55
⩾65	52	34%	10%	
Gender				
Female	58	29%	10%	0.07
Male	52	37%	21%	
Preoperative biliary drainage				
Yes	64	30%	12%	0.81
No	46	36%	18%	
Blood transfusions				
Yes	79	29%	13%	0.13
No	31	43%	—*	
Lymph nodes				
Positive	78	29%	10%	0.18
Negative	32	41%	27%	
Resection margins				
Positive	30	13%	9%	0.02†
Negative	80	40%	17%	
Grade				
1 + 2	72	36%	20%	0.05†
3 + 4	38	26%	7%	
Tumor size (mm)				
⩽30	55	38%	11%	0.7
>30	55	28%	18%	
SM-PVR				
Yes	36	33%	11%	0.7
No	74	33%	17%	

SM = superior mesenterico; PVR = portal vein resection.
*No patient at risk after 5 years in this subgroup.
†Significant.

a morbidity rate of up to 76% and a high mortality. After that procedure was established, morbidity rates decreased and mortality fell to 8% at his institution.[24] Nevertheless, regional pancreatectomy remained a high-risk procedure and was rejected by others.[25] Combined arterial and venous resection had a higher mortality rate (43%) than isolated venous resection (9%).[9]

Tumor invasion of the celiac or mesenteric arteries, therefore, is today regarded as a contraindication to PD by almost all surgeons. Mesenteric arteries, in contrast to the portal vein, are surrounded by lymphatic tissue as well as nerve plexus. Tumor spread within this tissue is almost certain in case of arterial infiltration. As a consequence, oncologic radicality is limited due to margin positivity.[12,26] It is not surprising that plexus infiltration reduces survival rates to those of unresected patients.[23] Furthermore, extended lymphadenectomy and resection of the retroperitoneal nerve plexus may cause severe diarrhea and reduce quality of life.[23,27] Thus, resection of the mesenteric arteries is still limited to highly selected cases. During the past 20 years in Japan, the rate of arterial resection remained below 5% while portal vein resections increased from 18% to 30%.[10]

In contrast to the superior mesenteric artery, the portal venous system is not surrounded by perivascular neural plexus and lymphatic tissue. Portal vein involvement is therefore in many cases the only barrier to radical tumor removal.

In our patients, wedge excision of the vein was sufficient to achieve free margins at the venous site in most patients undergoing PD with SM-PVR. However, if segmental resection of the portal vein is necessary, mobilization of the mesenteric base can be helpful in order to perform a tension-free end-to-end anastomosis. A distance of up to 8 cm can be gained by this procedure.[28] In terms of long-term survival, wedge excision and segmental resection seem to be oncologically equivalent.[3] Alternatively, the use of venous grafts (e.g., internal jugular vein) or prostheses has also been reported.[12,28] As pancreatic surgery always bears a risk of infectious complications, the application of allografts should not be recommended in general.

In our study, PD with SM-PVR had longer operation times without a relevant increase of blood loss. SM-PVR did not have any influence on morbidity and mortality rates or the length of hospital stay, as has already been published by other groups.[14,17,23,29] Recently, mortality rates as low as 0% were reported after SM-PVR.[3,11]

Before or during surgery, the differentiation between malignant or inflammatory adherence of the superior mesenteric or portal vein is frequently not possible. Current cross-sectional or even angiographic imaging may not detect or exclude microscopic invasion of the venous wall in the absence of relevant stenosis of the vessel. Intravascular ultrasound has shown a rather high accuracy in the demonstration of tumor involvement of the vein wall, but reports on this technique are rare and its use is certainly limited to a few specialized centers.[30,31] In our practice, however, a potential detection of tumor invasion into the venous wall without other contraindications for resection (i.e., vein occlusion or circumferential involvement greater than 180 degrees) would not change the indication for PD and concomitant SM-PVR.

In the case of inflammatory adherence of the tumor to the superior mesenteric or portal vein, the safety margin might be only minimal or even absent

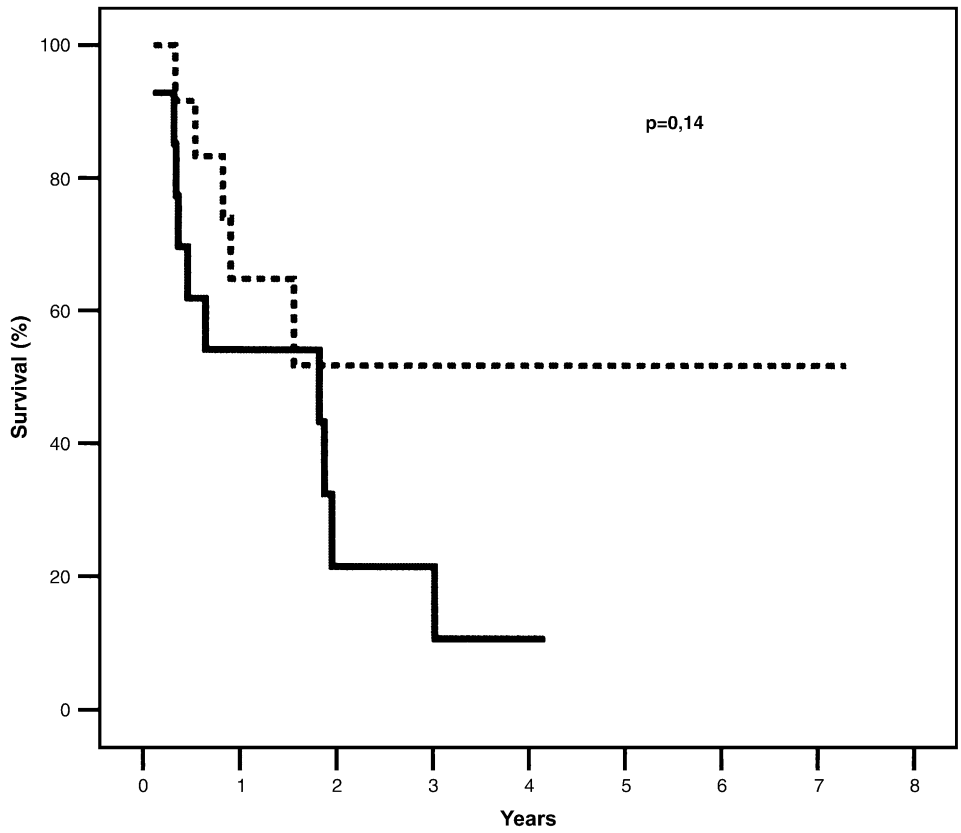

Fig. 2. Kaplan-Meier analysis of survival in patient with cancer of the pancreatic head after pancreatoduodenectomy with superior mesenteric–portal vein resection and histologically examined infiltration of the superior mesenteric–portal vein (n = 26). Comparison of patients with (n = 14) and without (n = 12) tumor infiltration into the venous wall. Solid line indicates infiltration (n = 14), and dashed line indicates no infiltration (n = 12).

after tumor dissection from the vessel wall. Because of its low specific morbidity, especially in cases of simple wedge excisions, SM-PVR may be indicated during PD even in the case of tumor adherence when the surgeon cannot exclude true tumor infiltration intraoperatively to exclude positive resection margins at the venous site.

Additional analyses of survival rates in relation to the depth of tumor infiltration into the vessel have been performed.[9,26,32] Almost all patients with intimal tumor infiltration die within 12 months after surgery. Likewise, a tumor thrombosis or complete tumor occlusion of the portal vein is associated with very short survival rates and thus is no indication for resection.[33]

Our initial (but statistically limited) survival results depending on the status of infiltration (Fig. 2) may also indicate a possible negative prognostic effect of tumor infiltration into the vein. Four of 12 patients with a margin-free resection of pancreatic cancer and no infiltration of the venous wall are alive after 2 to 7 years, whereas patients with tumor infiltration had a very poor prognosis, with only 1 of 14 patients alive more than 12 months after surgery.

In our multivariate survival analyses, tumor grading and the resection margin status had a significant independent influence on long-term survival. It is of interest that in some recent reports from experienced centers, negative resection margins did not have a significant prognostic influence.[14,34,35] This might be due to a more frequent application of multimodal therapies in these studies or just underline the fact that many patients have micrometastases that are not removed during surgery.

Nevertheless, we conclude from our data that complete tumor removal is the most important factor in pancreatic resections that can be influenced by the surgeon. Survival data from large series demonstrate a significant influence of negative resection margins.[2,4] In summary, SM-PVR can be performed safely during PD in order to obtain negative resection margins. According to our results and the

Table 4. Recent series of pancreatoduodenectomy with superior mesenterico–portal vein resection in patients with adenocarcinoma of the pancreatic head

Author, year	Type of resection (n)	Pancreatic head resections		No. of histological vein infiltration/ No. of examined specimens (%)	Positive margins		Median survival (mo)	
		Without vein resection	With vein resection (%)		Without vein resection	With vein resection	Without vein resection	With vein resection
Present study, 2005	PD (n = 125)	85	40 (32%)	16/29 (55%)	19 (24%)	13 (33%)	15	22
Tseng, 2004	PD (n = 291)	181	110 (38%)	38/62 (61%)	21 (12%)	24 (22%)	26	23
van Geenen, 2001*	PD (n = 215)	181	34 (16%)	10/34 (29%)	NR	20 (59%)	NR	14
Shibata, 2001	PD (n = 74)	46	28 (38%)	9/12 (75%)	8 (17%)	8 (29%)	10	10
Leach, 1998	PD (n = 75)	44	31 (41%)	13/18 (72%)	7 (16%)	4 (13%)	20	NR
Harrison, 1996	All pancreatic resections (n = 332)	274	58 (17%)	NR	65 (24%)	15 (27%)	17	NR
Nakao, 1994	All pancreatic resections (n = 101)	12	89 (88%)	49/89 (55%)	NR	NR	NR	13
Takahashi, 1994†	PD (n = 137)	58	79 (58%)	43/70 (53%)	NR	39 (49%)	18	19

NR = not reported; PD = pancreatoduodorectomy.
*Van Geenen included carcinomas of the periampullary region.
†Takahashi included 4 pancreatectomies and 13 patients with additional arterial resection.

results of several published reports, long-term survival is not influenced by a concomitant SM-PVR in the entire study group,[3,9,13,14,17,26] but a subgroup of patients with certain malignant vein infiltration may have a poorer prognosis.[9]

CONCLUSION

SM-PVR during PD might be essential for free resection margins and complete local tumor control. Morbidity, mortality, and long-term survival after PD with vein resection are comparable to patients not undergoing vein resection. Therefore, combined resection of the pancreatic head and the vein may be considered in case of tumor infiltration or adherence and in the absence of other contraindications for resection.

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Post–Gastric Bypass Hyperinsulinism With Nesidioblastosis: Subtotal or Total Pancreatectomy May Be Needed to Prevent Recurrent Hypoglycemia

Thomas E. Clancy, M.D., Francis D. Moore, Jr., M.D., Michael J. Zinner, M.D.

Symptomatic hyperinsulinemic hypoglycemia and pancreatic nesidioblastosis have recently been described in a small series of patients after gastric bypass surgery for morbid obesity. In the limited published reports of patients with this condition, hyperinsulinism and nesidioblastosis have been managed with distal or subtotal pancreatectomy, with the extent of resection guided by calcium angiography. However, nesidioblastosis may involve the pancreas diffusely, and limited pancreatic resections may predispose patients to further hypoglycemic episodes. We have treated two patients with refractory hyperinsulinism and symptomatic hypoglycemia after successful gastric bypass surgery. One patient underwent an approximately 80% pancreatectomy with good results but subsequently experienced recurrent drop attacks and fainting from hyperinsulinism; a completion pancreatectomy via a pancreaticoduodenectomy was then required. A second patient had profound hyperinsulinemic hypoglycemia and was treated successfully with a subtotal (95%) pancreatectomy. Our experience, the third published report of post–gastric bypass nesidioblastosis, suggests that the risk of recurrent symptomatic hyperinsulinism after limited pancreatectomy is significant and relative euglycemia may be achieved with subtotal or total pancreatectomy.
(J GASTROINTEST SURG 2006;10:1116–1119)

KEY WORDS: Hyperinsulinism, nesidioblastosis, obesity, pancreatectomy

Pathologic hyperplasia of pancreatic beta cells, or nesidioblastosis, with associated hyperinsulinemic hypoglycemia, is extremely rare in the adult population. Described by Service et al.[1] as noninsulinoma pancreatogenous hypoglycemia, nesidioblastosis is far less common than insulinoma as a cause of hyperinsulinemic hypoglycemia.[2] The condition of postprandial neuroglycopenic hyperinsulinemic hypoglycemia and pancreatic nesidioblastosis has recently been described in small series of patients after gastric bypass surgery for morbid obesity[3,4]; the incidence of nesidioblastosis in these patients far exceeds the incidence of nesidioblastosis in the general population. A precise causal link between Roux-en-Y gastric bypass and nesidioblastosis has not been established, although some have suggested a post–gastric bypass expansion of pancreatic beta cells, perhaps mediated by the intestinal hormone glucagon-like peptide 1 (GLP-1).[4]

The optimal surgical approach for post–gastric bypass nesidioblastosis has not been defined. Harness et al.[5] recommended a minimum resection of 75–80% of the pancreas in adult nesidioblastosis to prevent recurrence, and studies from the pediatric literature suggest that lesser resections may result in a failure rate up to 50%.[6] The certainty of postoperative insulin-dependent diabetes with near-total pancreatectomy has led to the use of gradient-guided pancreatic resection based on preoperative arterial calcium stimulation,[7] where the degree of resection is tailored to the predicted site of disease. We report two patients with diffuse nesidioblastosis after gastric bypass; these patients achieved adequate glucose control with total pancreatectomy or near-total pancreatectomy.

CASE REPORTS

Case 1

The patient was a 36-year-old black woman with a longstanding history of morbid obesity as well as recurrent lightheadedness. A vertical-banded gastroplasty was created in 1994 with subsequent weight

From the Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts.
Reprint requests: Dr. Thomas E. Clancy, Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. e-mail: tclancy@partners.org

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loss but without any resolution of lightheadedness. Due to erosion of Prolene mesh into the gastric pouch, she was therefore converted to a Roux-en-Y gastric bypass in 1996. Her total weight loss over 2 years following her gastroplasty was approximately 115 pounds, from 265 pounds in August 1995 to 150 pounds in May 1997. The patient subsequently experienced refractory episodes of lightheadedness with documented simultaneous hypoglycemia. Her symptoms were attributed to a dumping syndrome and were not responsive to conservative measures; she therefore underwent a reversal of the Roux-en-Y bypass in 1997. Unfortunately, reversal of the bypass did not result in improvement of her symptoms, and symptoms of lightheadedness and syncope continued with simultaneous severe hypoglycemia to as low as 28 mg/dl. A work-up by her primary care physician and endocrinologist noted that hypoglycemic episodes occurred primarily after meals, although she occasionally experienced symptomatic hypoglycemia when fasting.

On referral to our care in 2002, work-up revealed hypoglycemia with blood sugar of 30 mg/dl, in the setting of mildly elevated insulin to 39 UIU/ml (reference range, 0–16), high-normal C-peptide of 2.6 ng/ml (reference 0.8–3.1), and high-normal proinsulin of 6.3 pmol/L (reference <8.8). Preoperative intraoperative ultrasound was negative for pancreatic mass, octreotide scan was negative, and calcium angiography failed to document an insulin gradient. A subtotal (approximately 80%) pancreatectomy was performed, with the resection extending just to the right of the splenic vein/superior mesenteric vein confluence. Pathology demonstrated diffuse islet cell proliferation consistent with nesidioblastosis. The patient remained normoglycemic in the initial postoperative months, although she experienced progressive episodes of symptomatic hypoglycemia over the next 2 years. With a diagnosis of recurrent nesidioblastosis, she was taken back to the operating room in 2004 for a completion pancreatectomy (pylorus-preserving pancreaticoduodenectomy). Pathology from the second resection again demonstrated diffuse nesidioblastosis in the pancreatic head. She has subsequently achieved glucose control with the assistance of a continuous-infusion insulin pump.

Case 2

The patient was a 50-year-old woman who had undergone Roux-en-Y gastric bypass 3 years prior to presentation. The patient noted specific episodes of weakness and dizziness that were relieved by oral intake, dating years prior to her obesity surgery. Her weight loss was noted to be over 200 pounds after gastric bypass. She experienced numerous episodes of disorientation, slurred speech, and dizziness 3 months prior to presentation; these episodes were thought to be similar to those that had predated her bypass. On several occasions, blood glucose was noted to be below 45 mg/dl when symptomatic. Simultaneous laboratory values included markedly elevated insulin of 252 UIU/ml, elevated proinsulin to 14, elevated C-peptide to 7.3, and serum glucose of 42 mg/dl. She was admitted to the hospital and maintained on glucose infusion. Despite continuous infusion of 10% dextrose solution, blood glucose was repeatedly measured below 40 mg/dl. Urine sulfonylureas were negative.

Cross-sectional imaging did not identify a pancreatic mass. On exploration, intraoperative ultrasound was also negative for pancreatic mass. Given her Roux-en-Y bypass, piecemeal resection of the pancreas was required. The distal pancreas to the left of the Roux limb was removed first, and that to the right of the Roux limb subsequently removed. A near-total pancreatectomy ("95%" pancreatectomy) was performed, including the uncinate process, with resection occurring up to the common bile duct and leaving an approximately 1-cm rim of pancreatic tissue along the duodenal sweep. Intraoperatively, blood glucose measurements were serially performed; after resection of the distal pancreas, the dextrose infusion was slowed as glucose levels climbed. With resection of the neck, distal head, and uncinate, the dextrose infusion was changed to a 5% solution. Postoperatively, the patient has required 10 U of sustained-release insulin daily, and glucose levels have been well controlled. Pathology demonstrated diffuse nesidioblastosis throughout the pancreas.

CONCLUSIONS

Nesidioblastosis, defined in 1938 as "a diffuse or disseminated proliferation of islet cells," is the leading cause of hyperinsulinemia in newborns and infants but is extremely rare in adults.[5] Service et al.[1] described a syndrome of "noninsulinoma pancreatogenous hyperinsulinemic hypoglycemia" with islet cell hypertrophy characteristic of nesidioblastosis but without characteristic genetic mutations common to the infantile variety of nesidioblastosis. Still, insulinoma is far more common as a cause of hyperinsulinemic hypoglycemia in the adult population.

The association of hyperinsulinemic hypoglycemia in rare patients after Roux-en-Y gastric bypass has brought new attention to this rare disorder. Service et al.[3] were the first to describe six patients with hyperinsulinemic hypoglycemia and nesidioblastosis after gastric bypass, and three similar patients have

been recently reported.[4] A causal link has not been established between gastric bypass and hyperinsulinism, although the few reported cases indicate that nesidioblastosis is far more common in the setting of gastric bypass than in the general population. With a rapid increase in the number of operations for obesity (now over 100,000 operations for obesity annually in the United States),[8] any such association is a potential cause for concern.

Several mechanisms have been proposed to account for the finding of nesidioblastosis after weight reduction surgery. Some authors have suggested that rapid delivery of food to the distal ileum after bypass surgery may result in elevated systemic levels of (GLP-1 or another intestinal hormone, leading to hyperplasia of pancreatic islet cells. Others have recently found hyperinsulinemic hypoglycemia after gastric banding and have suggested that weight loss reduces insulin resistance in the setting of islet hypertrophy and hyperfunction often seen in obesity.[9] Still others have suggested that hyperinsulinism might be temporarily masked in some obese patients. The anabolic nature of insulin, coupled with the relief of hypoglycemic symptoms from eating, might theoretically lead to obesity in a population of patients with primary hyperinsulinism who are subsequently rendered hypoglycemic without the protective mechanism of a high-carbohydrate diet. This would suggest that the true incidence of primary hyperinsulinism is higher than previously reported and only revealed in the era of obesity surgery.

The most appropriate surgical management of nesidioblastosis in the post–gastric bypass patient is undefined. The correct surgical management of nesidioblastosis in the pediatric population has been the subject of debate in the literature.[6] Distal pancreatectomy alone, limited to the left of the mesenteric vessels, may result in a failure rate up to 50%.[10] Even with resections up to 95%, in which the pancreas and uncinate process are resected back to the level of the common bile duct, recurrence of hyperinsulinism may occur. Extensive resections were therefore recommended to avoid persistent hypoglycemia; in one study, recurrent hypoglycemia was only prevented by "near-total" pancreatectomy, with resection of pancreatic tissue along the duodenum and skeletonization of the common bile duct.[6]

In an attempt to limit the extent of pancreatic resection and thus avoid subsequent diabetes and exocrine insufficiency, selective arterial calcium stimulation has been used to guide pancreatectomy. Using a technique described to localize small insulinomas,[11] calcium injection into the splenic, superior mesenteric, or gastroduodenal arteries may result in increased insulin concentrations in the hepatic veins and thus localize an area of concern. This technique was used in the Mayo Clinic report of 10 surgically treated patients with noninsulinoma pancreatogenous hypoglycemia,[7] as well as their report of six post–gastric bypass patients with nesidioblastosis.[3] Of note, 3 of 10 patients reported by Thompson et al.[7] experienced at least temporary return of neuroglycopenia. In the report of post–gastric bypass nesidioblastosis by Service et al.,[3] one patient underwent a distal pancreatic resection only and subsequently suffered recurrence of hypoglycemia, presumably due to the failure to remove all involved pancreatic tissue.

In perhaps the largest single report of adult nesidioblastosis, Anlauf et al.[12] from Germany note that while focal nesidioblastosis has been well described in children, only diffuse nesidioblastosis has been observed in adults. In their series of 15 patients, 12 underwent distal pancreatectomy only. Three of these patients experienced recurrent hypoglycemia, also likely due to retained pancreas with diffuse islet cell hypertrophy.

The literature contains a very small but growing number of reports of post–gastric bypass nesidioblastosis; to our knowledge this is the third such published report. Our first case was notable in that 80%, pancreatectomy was initially successful in achieving normoglycemia. Several years later, however, repeated attacks of hypoglycemia led to the need for completion pancreatectomy. The lack of initial success with calcium angiography may be due to the diffuse nature of islet hyperplasia in this case. The refractory nature of hypoglycemia in the second case and our prior experience with this condition were the basis for performing a 95% pancreatectomy in our second case. This patient has subsequently enjoyed relatively stable glucose control with the addition of 10 U of long-acting daily lantus insulin. The small number of patients reported with post–gastric bypass nesidioblastosis are likely not sufficient to recommend routine preoperative screening for hyperinsulinism in patients prior to bariatric surgery. At the current time, these patients represent a very small fraction of the total number of patients undergoing gastric bypass surgery annually.

Given the relatively young age of most patients undergoing obesity surgery, definitive management of postbypass nesidioblastosis is highly desirable. The occurrence of recurrent hypoglycemia after partial pancreatectomy for adult nesidioblastosis[3,4,12] is a cause for concern and suggests that more extensive pancreatic resection may be indicated in some patients. It is quite possible that patients with post–gastric bypass nesidioblastosis constitute a diverse group with variable presentation and varying degrees of symptomatic hypoglycemia. The patients in our series may represent one extreme, with many

patients experiencing significantly less or even clinically unrecognized hypoglycemia. As such, one management strategy may not be appropriate for all patients, and longer-term follow-up of a greater number of patients will be required to arrive at definitive recommendations. Still, our experience challenges the notion that limited pancreatic resection guided by calcium angiography can provide long-term glucose control in all patients with adult nesidioblastosis and suggests that near-total or total pancreatectomy may be required for definitive management of this condition.

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Anti-inflammatory Effects of PPAR-γ Agonists Directly Correlate With PPAR-γ Expression During Acute Pancreatitis

Michael D. Rollins, M.D., Sharon Sudarshan, M.D., Matthew A. Firpo, Ph.D., Brooke H. Etherington, M.D., Brandon J. Hart, M.D., Heidi H. Jackson, M.D., Jeffrey D. Jackson, M.D., Lyska L. Emerson, M.D., David T. Yang, M.D., Sean J. Mulvihill, M.D., Robert E. Glasgow, M.D.

Peroxisome proliferator-activated receptors (PPARs) are ligand-inducible transcription factors that regulate cellular energy and lipid metabolism. PPAR-γ agonists also have potent anti-inflammatory properties through down-regulation of early inflammatory response genes. The role of PPAR-γ in acute pancreatitis has not been adequately examined. In this study, we determined the effect of PPAR-γ agonists on the severity of pancreatitis and sought to correlate PPAR-γ expression in pancreatic acinar cells and the severity of acute pancreatitis in vivo. Acute pancreatitis was induced in mice by hyperstimulation with the cholecystokinin analog, cerulein. PPAR-γ agonists were administered by intraperitoneal injection 15–30 minutes before induction of pancreatitis (pretreatment) or at various times after induction of pancreatitis (treatment). Pancreata and serum were harvested over the course of 24 hours. Serum amylase activity and glucose levels were measured. Pancreata were used for histological evaluation as well as protein and mRNA analysis. Pretreatment of mice with the PPAR-γ agonists 15-deoxy-Δ12, 14-prostaglandin J_2, or troglitazone significantly reduced the severity of pancreatitis in a dose-dependent manner. This reduction was indicated by reduced serum amylase activity and histological damage (leukocyte infiltration, vacuolization, and necrosis). Although cerulein decreased PPAR-γ expression in the pancreas, pretreatment with agonists maintained PPAR-γ expression early in acute pancreatitis. The expression of PPAR-γ inversely correlated with pancreatitis severity and expression of the proinflammatory cytokines, interleukin-6, and tumor necrosis factor-α. Treatment with troglitazone after the induction of pancreatitis reduced serum amylase activity. The results suggest that PPAR-γ plays a direct role in the inflammatory cascade during the early events of acute pancreatitis. Our data are the first to demonstrate that PPAR-γ agonists represent a promising therapeutic strategy for acute pancreatitis. (J GASTROINTEST SURG 2006;10:1120–1130)

KEY WORDS: Pancreatitis, peroxisome proliferator-activated receptor, cerulein, inflammation

Acute pancreatitis is a major health care problem that is associated with a significant morbidity and mortality.[1,2] There are many etiologies responsible for acute pancreatitis, with alcohol and gallstones causing 80% of cases. Although several observations have been made regarding the mechanisms leading to acinar cell damage during acute pancreatitis, including colocalization of zymogen granules with lysosomes, alterations in intracellular trafficking, premature activation of digestive enzymes, and recruitment of inflammatory cells, little is known regarding the early gene-mediated events responsible for regulating pancreatic acinar cell homeostasis.[3–8]

PPARs are ligand-inducible transcription factors that are members of the class II nuclear hormone receptor superfamily. Three subtypes have been identified: PPAR-α, -γ, and -β/δ. The anti-inflammatory properties of PPAR-γ agonists, including 15d-PGJ_2 and the thiazolidinediones, have been demonstrated by their reduction of proinflammatory cytokine

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From the Departments of Surgery (M.D.R., S.S., M.A.F., B.H.E., B.J.H., H.H.J., J.D.J., S.J.M., R.E.G.) and Pathology (L.L.E., D.T.Y.), University of Utah School of Medicine, Salt Lake City, Utah.

Reprint requests: Robert E. Glasgow, M.D., University of Utah, Department of Surgery, 30N 1900E, Salt Lake City, UT 84132. e-mail: robert.glasgow@hsc.utah.edu

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production in monocytes,[9] the reduction of colonic inflammation in a mouse model of inflammatory bowel disease,[10] and the reduction of intestinal tissue damage after ischemia/reperfusion injury.[11] Long-term treatment with agonists has shown improvement in arthritis[12] and the fibrosis, edema, and inflammation associated with chronic pancreatitis.[13,14] PPAR-γ deficient macrophages demonstrated increased baseline and induced NO production compared with PPAR-γ competent controls, suggesting that endogenous PPAR-γ plays a role in modulating the inflammatory response.[15] In addition, PPAR-γ independent mechanisms for the anti-inflammatory activity of PPAR-γ agonists have also been identified. $15dPGJ_2$, in addition to binding and activating PPAR-γ,[16] also inhibits NFκB-directed gene expression through covalent modifications of IκB kinase and the DNA-binding domains of NFκB subunits.[17] Furthermore, synthetic agonists, including two thiazolidinediones, were still capable of inhibiting iNOS expression in mesangial cells in which PPAR-γ function was disrupted.[15] Thus, the potent anti-inflammatory properties of PPAR-γ agonists may involve PPAR-γ dependent and PPAR-γ independent mechanisms.

In this study, we evaluated the role of PPAR-γ in the regulation of acute pancreatic inflammation by using a cerulein hyperstimulation model of acute pancreatitis in mice. The effect of cerulein pancreatitis on PPAR-γ and pancreatic tissue inflammatory cytokine expression was used to correlate the relationship between acute inflammation and PPAR-γ expression and function. We evaluated the role of PPAR-γ agonists in ameliorating the severity of acute pancreatitis in both a prophylactic and therapeutic context. The results of this study demonstrate PPAR-γ agonists may have therapeutic potential in preventing acute pancreatitis and treating established acute pancreatitis.

METHODS

Animals

Male C3H/HeN mice, 2–4 months old, were used throughout this study. Mice were maintained in a temperature-controlled room on a 12/12-hour light/dark cycle with free access to food and water. Animal procedures were approved and monitored by the University of Utah Institutional Animal Care and Use Committee.

Materials

$15dPGJ_2$ and troglitazone were purchased from BIOMOL Research Laboratories (Plymouth Meeting, PA). Cerulein was obtained from Research Plus (Manasquan, NJ). Rabbit anti-mouse polyclonal antibody raised against a C-terminal region of PPAR-γ was from Affinity BioReagents (Golden, CO). Fluorescein isothiocyanate (FITC) conjugated anti-rabbit IgG antibody was obtained from Calbiochem (San Diego, CA). All other reagents were obtained from Sigma-Aldrich (St. Louis, MO) unless indicated.

Induction of Acute Pancreatitis

Mice were fasted for the 12-hour period before induction. Pancreatitis was induced at the beginning of photophase (6 A.M.) by using three hourly intraperitoneal (IP) injections of cerulein (100 μg/kg per dose). Sham-treated control mice were given similar volumes of carrier (0.1% bovine serum albumin [BSA] in phosphate buffered saline [PBS]). After completing the injections, mice were given free access to food and water.

Treatment with PPAR-γ Agonists

Pretreatment with $15dPGJ_2$ (100 μg/kg in DMSO) was administered by IP injection 15 minutes before the first cerulein injection,[12] whereas troglitazone (5 mg/kg in DMSO) was given by intraperitoneal injection 30 minutes before induction of pancreatitis. Sham mice received intraperitoneal injections of a similar amount of the drug delivery vehicle (10% DMSO). There were four control and experimental groups. The first group received pretreatment with vehicle (sham) and three hourly intraperitoneal injections of 0.1% BSA in PBS (sham). The second group received pretreatment with sham and three hourly IP injections of cerulein (100 μg/kg). A third group received pretreatment with agonist and sham. The final group received pretreatment with agonist and cerulein. Treatment with troglitazone after induction of pancreatitis was carried out in a similar manner, except troglitazone or carrier was administered either as a single dose 3 hours after the final cerulein injection or as multiple doses 3, 4, and 5 hours after the final cerulein injection. Serum glucose levels were measured by a clinical pathology laboratory.

Serum Amylase Activity

Whole blood samples were obtained from the inferior vena cava. The serum amylase activity for each sample was determined in a starch hydrolysis assay. Absorbance at 405 nm was monitored and recorded at 1 minute and 2 minutes after initial mixing. Activities were determined in triplicate for each sample. Serum amylase activity was expressed in U/L as defined by standard curves.

Pancreas Fixation and Tissue Preparation

A local perfusion of the pancreas was performed by ligating the abdominal aorta above the celiac artery and below the renal vessels and perfusing 10 ml of PBS followed by 10 ml of a 4% paraformaldehyde solution (pH 7.0–7.5) into the abdominal aorta. Blood and perfusate were allowed to escape through a venotomy in the inferior vena cava. Approximately half of the pancreas from each mouse was placed in formalin for paraffin fixation and half in Tissue-Tek OCT cryotomy compound at −80° C for storage until cryosectioned for immunofluorescent staining.

Immunofluorescence

Ten μm pancreatic cryosections were stained with rabbit anti-PPAR-γ antibody added in a 1:250 dilution with 0.1% BSA and PBS. Slides were incubated in a moist dark chamber overnight.[12] After washing in PBS and ethanol, slides were incubated with a 1:200 dilution of FITC conjugated secondary antibody in 0.1% BSA and PBS. The slides were incubated in a moist dark chamber for 30 minutes, then rinsed with PBS. Slides were counterstained with propidium iodide. Antifade (Molecular Probes, Eugene, OR) was added and coverslips were placed.

Histology

For observation using light microscopy, a section of pancreas was immersed in a 4% paraformaldehyde solution (pH 7.0–7.5) and embedded in paraffin. Hematoxylin and eosin stained pancreatic sections were scored by two pathologists who were blinded to the sample identity. Each section was scored for severity of pancreatitis on a scale of 0–4 (normal to severe) as described.[6] The three categories used to determine pancreatic injury were acinar cell necrosis, vacuolization, and inflammatory cell infiltrate.

Western Blotting

A local perfusion was performed as described above by using 10 ml of Complete protease inhibitor cocktail (Roche Applied Science, Indianapolis, IN) in PBS instead of paraformaldehyde. Pancreata were harvested and placed in ice-cold protein extraction buffer (Complete protease inhibitor cocktail, 1 × PBS, 1% Igepal CA 630, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate [SDS]). Samples were homogenized using a rotor-stator homogenizer followed by two sequential centrifugations at 15,000*g* for 20 minutes at 4° C. The protein concentration of the resulting supernatant was determined using the Bradford assay. For each sample, dilutions corresponding to 0.1, 0.5, and 1 μg of total protein were spotted onto polyvinylidene fluoride [PVDF] membranes in a slot-blot apparatus. Blocked membranes were incubated with a 1:500 dilution of rabbit anti-mouse PPAR-γ polyclonal IgG (Santa Cruz Biotechnology, Santa Cruz, CA) for 1 hour, washed, and stained with a 1:2000 dilution of horseradish peroxidase conjugated goat anti-rabbit secondary antibody for 1 hour. Antibody staining was performed using a nonradioactive detection system (ECL Plus, Amersham Biosciences, Piscataway, NJ). Images were visualized using a phosphoimager and quantified using the National Institutes of Health (NIH) ImageJ densitometry software. Slot densities were normalized to densities of control samples to compare multiple blots within the same time point.

Cytokine mRNA Expression

Pancreata locally perfused with 10 ml of PBS were harvested and placed in RNAlater RNA stabilization solution (Ambion, Austin, TX). Total RNA was extracted using an RNeasy RNA extraction kit (Qiagen, Valencia, CA). Levels of IL-6, TNF-α, and acidic ribosomal phosphoprotein (Arbp) mRNA were quantified using QuantiTect Probe reverse transcription polymerase chain reaction (RT-PCR) kits and the corresponding mouse QuantiTect Assay kits (Qiagen) in a real-time thermocycler (LightCycler System, Roche Applied Science). All procedures were carried out as per manufacturers' recommendations.

Statistical Analysis

Significant differences between groups were determined using one-way ANOVA. For histological severity scoring, comparisons were made using Mann-Whitney analyses. A P value < 0.05 was considered significant. Values are expressed as mean + SEM.

RESULTS

PPAR-γ Agonists Ameliorated the Severity of Acute Pancreatitis in Vivo

Acute pancreatitis was induced in mice by using three hourly injections of cerulein. Serum amylase levels were significantly increased in mice receiving cerulein at 1, 6, 12, and 24 hours after the final cerulein injection ($P < 0.0001$; Fig. 1). Pretreatment of mice before the first cerulein injection with a single dose of a PPAR-γ agonist, either $15dPGJ_2$ or troglitazone, significantly reduced peak serum amylase levels. For the prophylactic doses used, $15dPGJ_2$ only reduced the 6-hour peak amylase levels, whereas troglitazone resulted in reduced amylase

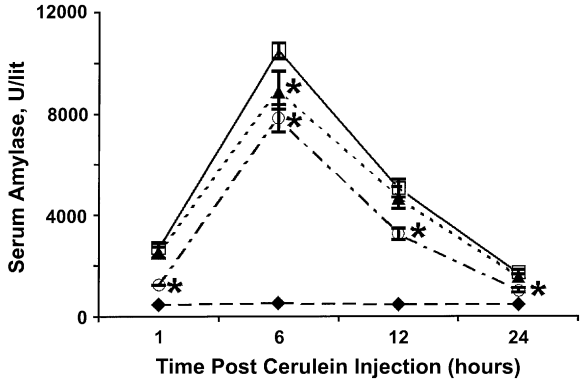

Fig. 1. Effect of prophylactic administration of PPAR-γ agonists on serum amylase levels. Single doses of 100 μg/kg $15dPGJ_2$ in 10% DMSO/PBS (▲) or 5 mg/kg troglitazone in DMSO (○) were administered 30 minutes before induction of pancreatitis with three hourly doses of cerulein (100 μg/kg in 0.1% BSA/saline each dose). Groups of control mice received a 10% DMSO/PBS rather than drug before administration of cerulein (□). Baseline serum amylase activity was determined in mice administered 0.1% BSA/saline carrier rather than cerulein (◆). Serum amylase activity was determined at various times after the last injection. *$P < 0.0003$ versus pancreatitis controls (□) at the indicated time point. n = 3–5 mice per group.

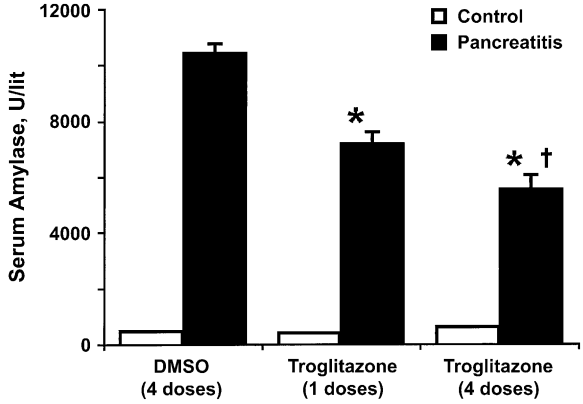

Fig. 2. Troglitazone dose response effect on serum amylase levels. Prophylactic troglitazone was administered 30 minutes before cerulein or carrier control (1 dose), or 30 minutes before and again with each of the three cerulein or carrier injections (4 doses). Serum amylase levels were determined 6 hours after the last cerulein or carrier injection. Black bars represent amylase levels for cerulein-administered groups. Open bars represent groups administered 0.1% BSA in saline carrier. Each troglitazone dose was 5 mg/kg in DMSO. *$P \leq 0.002$ versus DMSO/pancreatitis control. †$P < 0.01$ versus 1 dose of troglitazone. n = 5 mice per group.

release throughout the entire 24-hour time course. Baseline serum amylase activity was determined in mice administered 0.1% BSA/saline carrier rather than cerulein. $15dPGJ_2$ or troglitazone in the absence of cerulein yielded virtually the same serum amylase levels as these baseline levels (data not shown). Amylase activities in cerulein-treated groups were significantly higher than corresponding baseline levels ($P < 0.0001$) at all time points. A further decrease in peak serum amylase levels was seen after increasing the number of troglitazone injections from one to four (Fig. 2), demonstrating the dose-dependent effect of the drug. Serum amylase activity was routinely measured in all experiments to monitor the pancreatitis phenotype. Because sustained administration of troglitazone has a hypoglycemic effect, glucose levels in serum were also monitored. In all cases, serum glucose levels were within the normal range for mice when measured with the human assay (106–278 mg/dL, data not shown), indicating that the relatively low doses of troglitazone administration did not significantly alter glucose metabolism.

The severity of pancreatitis was also examined by histological evaluation (Fig. 3). Cerulein-induced cell damage was evident in sections from pancreata harvested at 6 (Fig. 3, *A*), 12, and 24 (data not shown) hours after the final cerulein injection. Cell damage was decreased in pancreata from mice pretreated with PPAR-γ agonists (Fig. 3, *A*). Pathological scoring of cell damage demonstrated that cerulein treatment resulted in significant increases in inflammatory cell infiltration, necrosis, and vacuolization relative to controls (Fig. 3, *B*). Pretreatment of mice with troglitazone reduced the severity of acinar cell damage during pancreatitis as measured by inflammatory cell infiltration, necrosis, and vacuolization, although significant reductions in vacuolization were only seen with multiple doses (Fig. 3, *B*). Similarly, reductions in inflammatory cell infiltration and necrosis (but not vacuolization) were seen when mice were pretreated with $15dPGJ_2$ (Fig. 3, *B*).

Pretreatment With Troglitazone Inhibited the Cerulein-Induced Increase in Cytokine Expression

To characterize the effects of PPAR-γ agonists on expression of proinflammatory cytokines, we first determined the effect of cerulein pancreatitis on the time course of IL-6 and TNF-α mRNA expression. Peak pancreatic tissue expression of IL-6 and TNF-α was seen 3 hours after the last cerulein injection (Fig. 4). IL-6 expression increased 22-fold, and TNF-α expression increased 18-fold relative to controls. We then determined the effect of a single prophylactic dose of troglitazone (5 mg/kg) on peak cytokine expression (Fig. 5). Pretreatment with troglitazone completely abolished the cerulein-induced increase in IL-6 and TNF-α expression. Troglitazone pretreatment alone had no significant effect

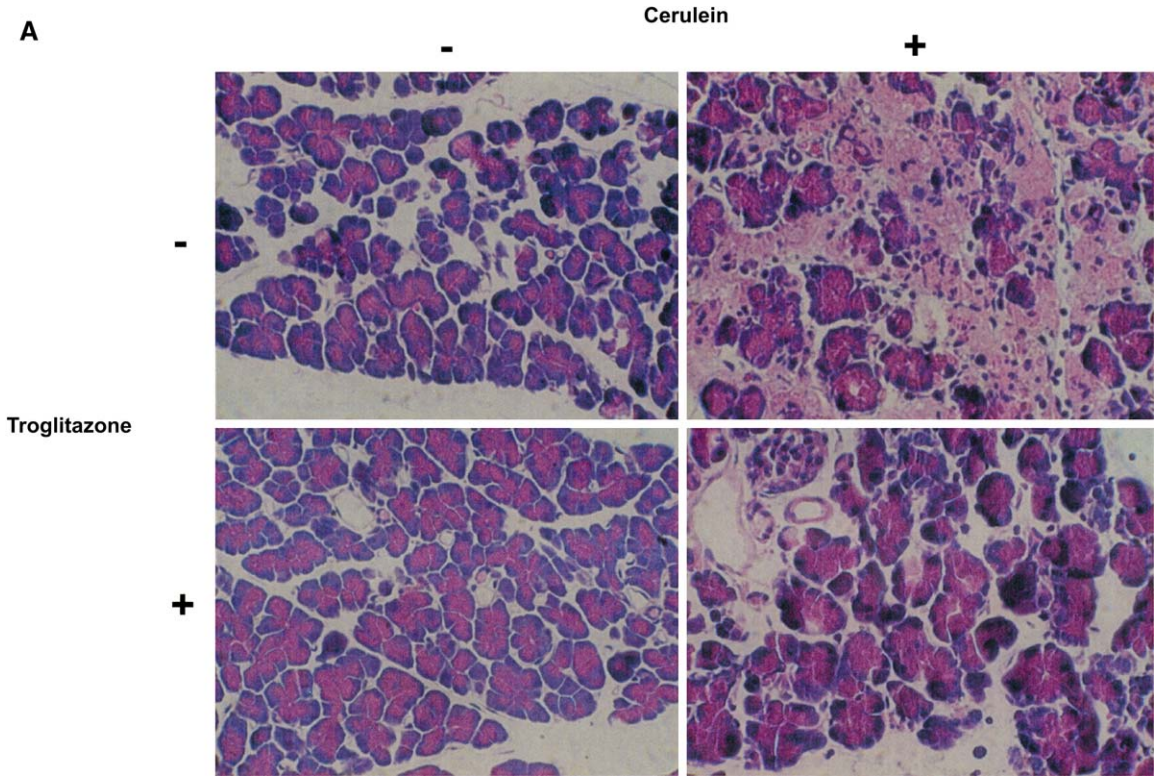

Fig. 3. Histological evaluation of pancreatic sections. (**A**) Representative hematoxylin and eosin stained pancreatic sections of tissue from mice harvested 24 hours after the last injection. Mice administered troglitazone received a single dose (5 mg/kg) 30 minutes before administration of cerulein (+) or carrier (−). Original magnification ×400. (**B**) 15dPGJ$_2$, troglitazone, or drug carrier (DMSO) was administered 30 minutes before cerulein or carrier control (1 dose) or 30 minutes before and again with each of the three cerulein or carrier injections (4 doses). Pancreata were harvested 6 hours after the last cerulein or carrier injection. Hematoxylin and eosin stained sections were evaluated for inflammatory cell infiltration, necrosis, and vacuolization as described in Methods. Black bars represent scores for cerulein-administered groups (pancreatitis). Open bars represent groups administered 0.1% BSA/saline carrier (control). *$P < 0.03$ versus corresponding control. $^{\dagger}P < 0.03$ versus DMSO/pancreatitis control. n = 3–8 mice per group.

on cytokine expression in the absence of inflammatory stimuli (Fig. 5).

PPAR-γ Expression Was Reduced by Cerulein Treatment, but Was Sustained by PPAR-γ Agonists During Acute Pancreatitis

Hyperstimulation with cerulein reduced PPAR-γ expression by 60% as measured by Western slot-blot analysis of total pancreatic protein 3 hours after the last injection (Fig. 6, *A*). Immunofluorescent staining performed on pancreatic cryosections recovered at the same time point confirmed this result. In sections of pancreata from control mice, PPAR-γ staining was cytoplasmic and within the apical region of acinar cells (Fig. 6, *B*). Staining specificity was established by preabsorption with the epitope used to generate the primary antibody, which completely abolished staining (data not shown). Furthermore, no staining was evident by using secondary antibody alone (data not shown). No PPAR-γ specific staining was evident in pancreata isolated from mice treated with cerulein (Fig. 6, *B*). A single prophylactic treatment with either 15d-PGJ$_2$ or troglitazone prevented the cerulein-induced decrease in PPAR-γ expression (Fig. 6, *A*). Drug pretreatment alone had no effect on PPAR-γ (data not shown).

Troglitazone is an Effective Treatment After the Development of Pancreatitis

To determine the effect of PPAR-γ agonists on the severity of pancreatitis after induction, troglitazone was administered to mice either as a single 5 mg/kg dose 3 hours after the last cerulein injection or as multiple 5 mg/kg doses at 3, 4, and 5 hours after the last cerulein injection. Both dosing regimens significantly reduced peak serum amylase levels relative to mice receiving cerulein alone (Fig. 7). Furthermore, multiple doses of troglitazone resulted in

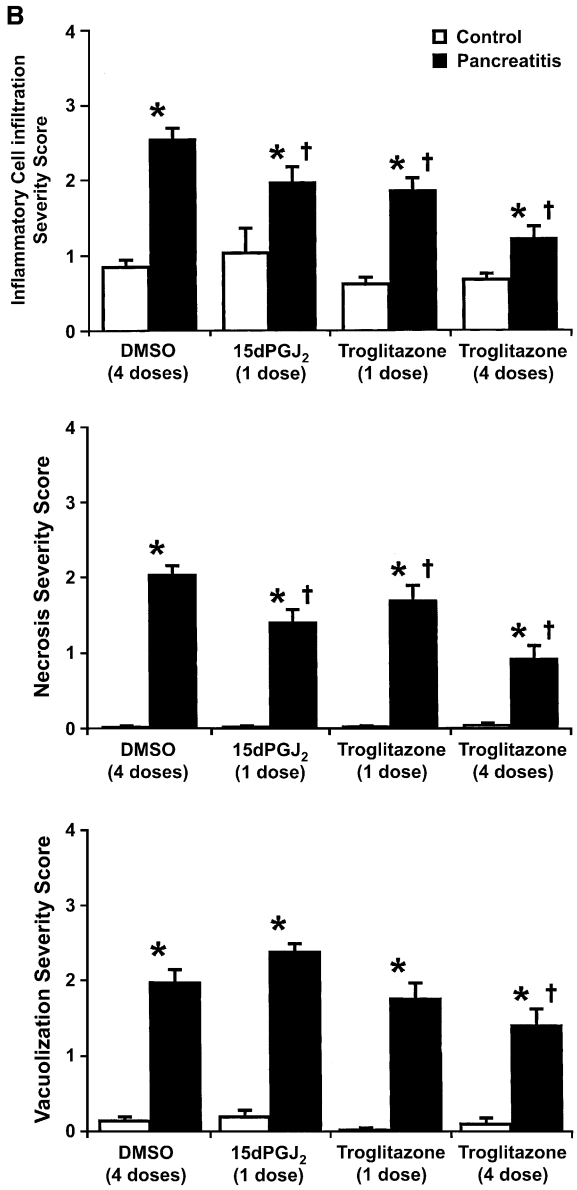

Fig. 3. (Continued)

a greater reduction in serum amylase activity relative to a single dose. Unlike mice receiving prophylactic troglitazone, histological scoring of pancreata from mice given therapeutic troglitazone after the induction of pancreatitis showed no statistically significant improvement relative to controls, although the scores trended lower (data not shown).

DISCUSSION

Prophylactic administration of 15d-PGJ_2[18] or the thiazolidinediones—pioglitazone and rosiglitazone[19]—reduces the severity of acute pancreatitis in mice. In this study, we extend these findings by demonstrating that the thiazolidinedione, troglitazone, and the PPAR-γ agonist, 15d-PGJ_2, reduced the severity of acute pancreatitis in a dose-dependent manner. Consistent with the idea that PPAR-γ activation results in reduced inflammation, we show that the agonists decreased inflammatory cell infiltration within the pancreas and inhibited expression of the proinflammatory cytokines, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). In an attempt to determine the direct participation of PPAR-γ during acute pancreatitis, we examined the effect of cerulein and the agonists 15d-PGJ_2 and troglitazone on PPAR-γ expression. We found that cerulein-induced pancreatitis resulted in a loss of PPAR-γ expression. Prophylactic administration of the agonists sustained PPAR-γ expression, thus linking the cellular levels of PPAR-γ with the reduction in pancreatitis severity and proinflammatory signals.

For this study, we used the cerulein hyperstimulation model of acute pancreatitis. Cerulein stimulation produces pancreatic cell injury and inflammation consistent with the clinical picture of mild, interstitial acute pancreatitis. The magnitude of pancreatic tissue damage can be modulated by cerulein dose and frequency of administration. The dosing regimen of three hourly injections of 0.1 mg/ml cerulein reported in the present study was chosen because it produced an intermediate response, allowing measurement of potential increases and decreases in severity in response to the treatments tested. One goal of this study was to measure early molecular events within the pancreas during acute pancreatitis, which could be obscured by a longer dosing regimen. Delivering cerulein over an 8-hour period, Hashimoto and coworkers[18] demonstrated maximal serum amylase levels 1 hour after the last injection, with a gradual return to baseline levels over the following 16 hours.[18] Similarly, our results using three hourly injections (Fig. 1) showed peak serum amylase activity 6 hours after the last cerulein injection (8 hours after the first cerulein injection). Using a shorter duration injection series allowed measurement of both a gradual increase to peak levels as well as the gradual recovery to baseline amylase levels. Histological evaluation of pancreata from cerulein-treated mice indicated that a significant increase in cellular damage was evident at 6 hours and persisted through 24 hours. Thus, for the dosing regimen used in this study, the initial time course of pancreatitis can be divided into an initial injury stage measured by serum amylase activity that culminates at 6 hours, followed by a recovery stage as amylase levels return to baseline.

Previous studies have demonstrated that the initial injury during acute pancreatitis results in the release

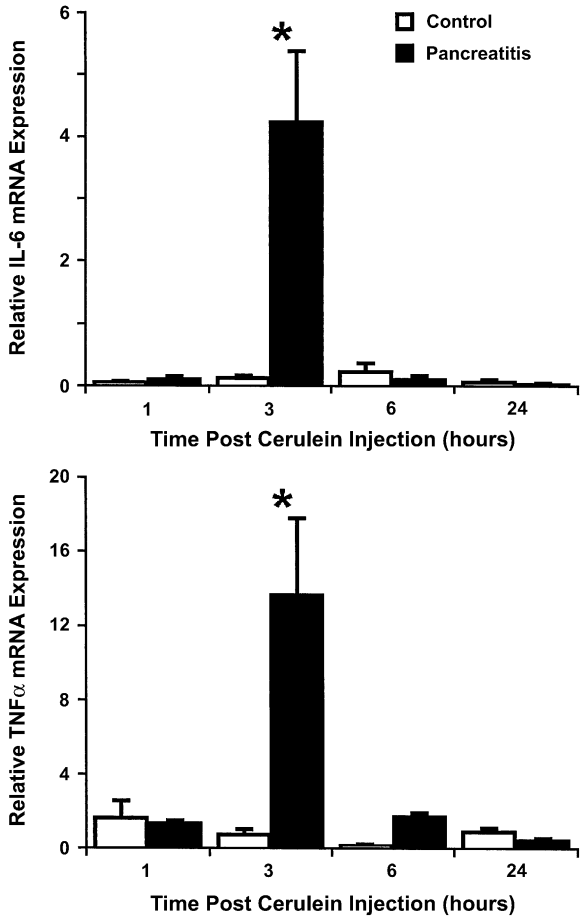

Fig. 4. IL-6 and TNF-α expression time course during acute pancreatitis. Expression levels of IL-6 and TNF-α mRNA were determined using quantitative RT-PCR and normalized to expression of the housekeeping gene, Arbp. Values are mean ± SEM. *$P < 0.0001$ versus all other data points (only significant comparisons). n = 4–5 mice per group.

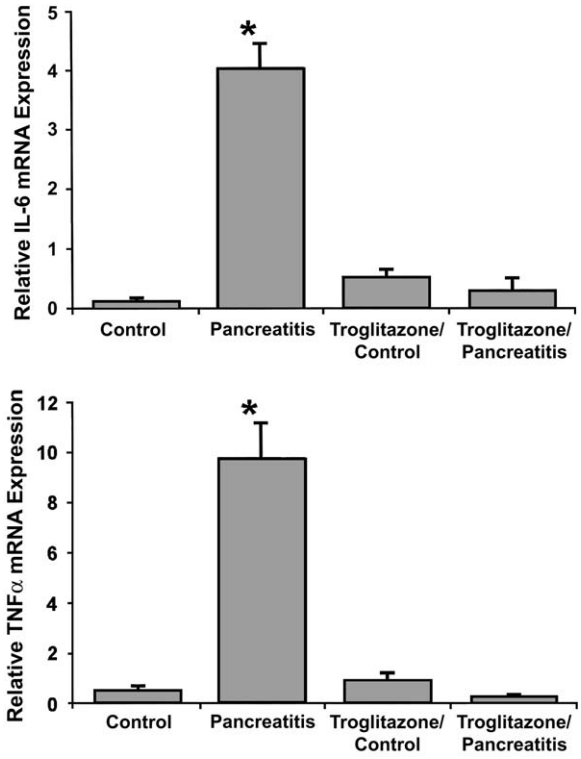

Fig. 5. Effect of troglitazone pretreatment on peak cytokine expression. Expression of IL-6 and TNF-α mRNA was determined in pancreata for the indicated treatment groups 3 hours after the last injection of cerulein. Values are mean ± SEM relative to Arbp expression. *$P < 0.0001$ versus all other data points (only significant comparisons). n = 4–5 mice per group.

of proinflammatory cytokines directly from pancreatic acinar cells,[20,21] which could affect the recruitment and activation of leukocytes and tissue myeloid cells. Our experiments showed a 3-hour peak for both IL-6 and TNF-α expression. These results were consistent with the timing of TNF-α expression previously demonstrated in rats.[21] In fact, with the dosing regimen used here, 3-hour expression was the only significant change in expression seen for both cytokines. This antecedent expression of proinflammatory cytokines correlated well with the subsequent recruitment of inflammatory cells into the pancreas, which reached a plateau at 6 hours. Although cytokine expression from resident myeloid cells may have contributed to the levels of IL-6 and TNF-α mRNA in the pancreas, the magnitude of the increase (18–22-fold), as well as the fact that less than 1% of cells in hematoxylin and eosin sections of pancreata from untreated mice were myeloid, suggests that the majority of the increased cytokine expression was from pancreas cells.

Prophylactic administration of either $15dPGJ_2$ or troglitazone significantly reduced amylase release, inflammatory cell infiltration, and tissue damage in a dose-dependent manner, and completely inhibited the cerulein-induced increase in IL-6 and TNF-α expression. These results are consistent with the various reports indicating that PPAR-γ ligands reduce the inflammatory response via down-regulation of proinflammatory cytokine expression,[9,12,22–29] including in acute pancreatitis[18,19] Both $15dPGJ_2$ and troglitazone bind to PPAR-γ with high affinity and activate PPAR-γ dependent transcription.[16,30] Ligand activation allows the interaction of PPAR-γ with the retinoic acid receptor, and the resulting heterodimer is competent to bind the PPAR response element in the promoter region of various genes, including genes relevant to control of inflammation. DNA-dependent transcriptional repression can thus occur through recruitment of corepressors to the promoter site. DNA-independent transrepression

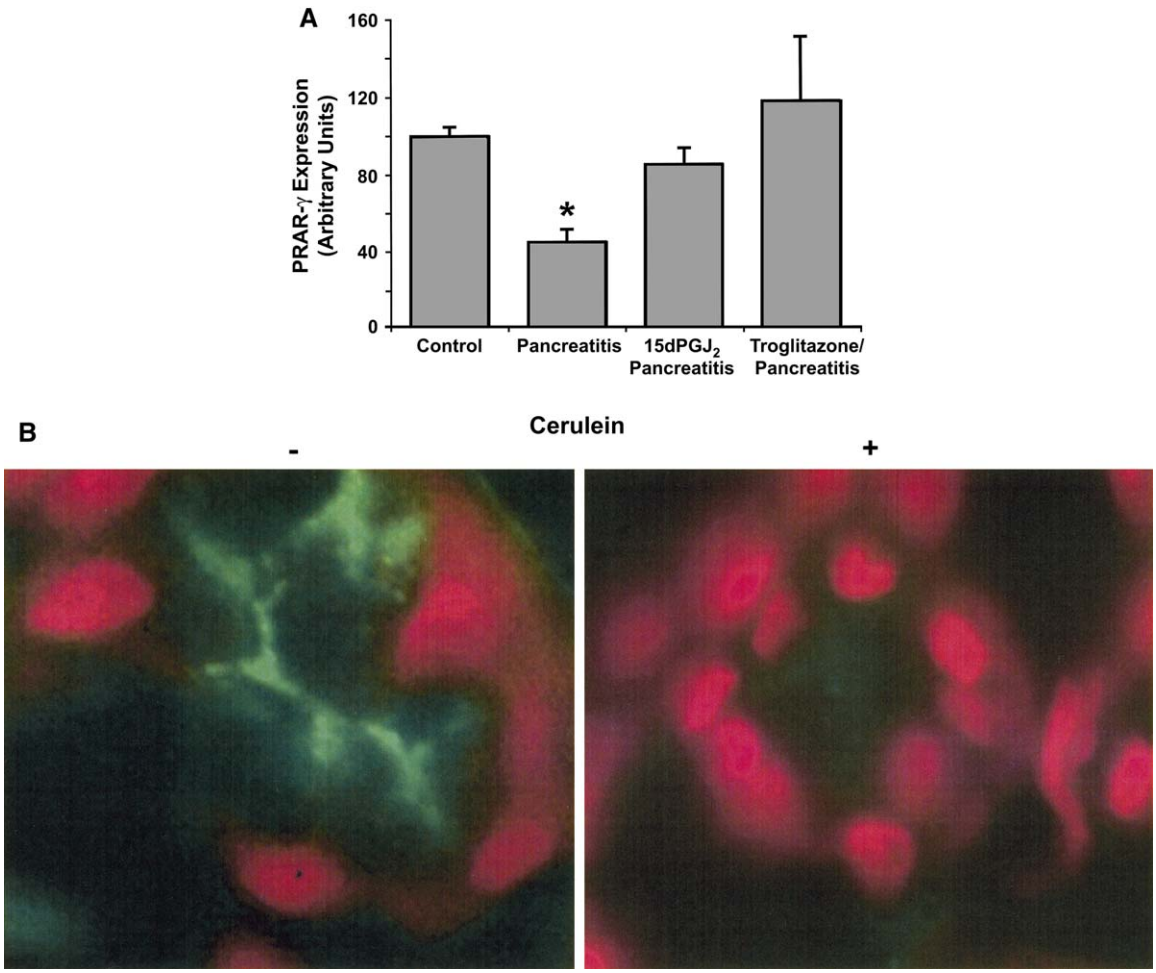

Fig. 6. PPAR-γ protein expression. (**A**) PPAR-γ protein levels were determined in pancreata from mice treated with cerulein alone (pancreatitis), and in mice administered prophylactic 15dPGJ$_2$ or troglitazone before cerulein administration by Western slot-blot analysis. Total cellular protein was extracted from pancreata 3 hours after the last injection, and equal amounts of protein were loaded in each slot. Mice in the control group received carrier. Data represents densitometric evaluation of multiple blots. *P = .03 versus all other groups (only significant comparison). n = 5 mice per group. (**B**) Immunofluorescence staining of pancreas sections from control mice or mice administered cerulein 6 hours after the last injection are shown. Sections were stained with anti-PPAR-γ antibody, visualized with FITC-conjugated secondary antibody (green), and counterstained with propidium iodide (red). Images are representative of staining performed on pancreata from six control and six cerulein-treated mice. Original magnification ×400.

can also occur upon PPAR-γ activation via direct competition for transcriptional coactivators,[31] direct binding of PPAR-γ to transcription factors,[32,33] or inhibition of intracellular signaling cascades.[34]

Despite the clear link between PPAR activation and the repression of inflammatory mediators, mounting evidence suggests that the ligands may function in an anti-inflammatory manner independently of PPAR-γ.[15–17,35] To investigate the dependence of PPAR-γ during acute pancreatitis, we tested the hypothesis that direct participation of PPAR-γ would be reflected in changes in protein expression. In our studies, induction of acute pancreatitis resulted in a 60% reduction in PPAR-γ protein levels in pancreata 3 hours after the last cerulein injection, corresponding to peak expression of the proinflammatory cytokines, TNF-α and IL-6. This suppression of PPAR-γ expression in pancreata was completely blocked by prophylactic treatment with either 15-dPGJ$_2$ or troglitazone. Hashimoto and coworkers[18] demonstrated increased expression of PPAR-γ during acute pancreatitis; however, the

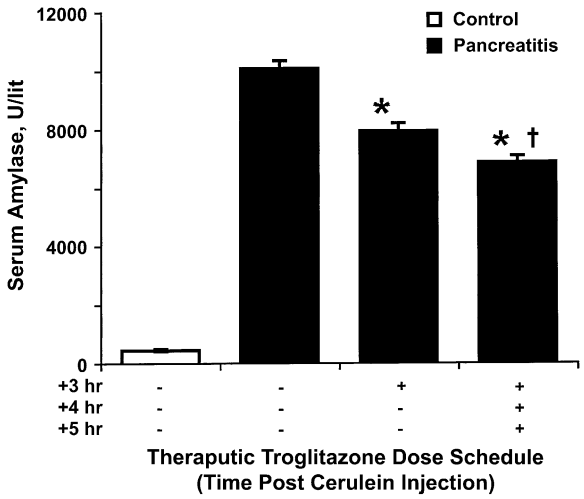

Fig. 7. Effect of therapeutic troglitazone treatment on serum amylase activity. Black bars represent amylase levels for cerulein-administered groups. Open bar represent levels in mice administered 0.1% BSA in saline carrier. Troglitazone was administered at the times indicated after the last cerulein injection. $^{*}P < 0.0001$ versus untreated cerulein injected group. $^{\dagger}P < 0.002$ versus single dose at +3 hours. n = 5 mice per group.

discrepancy with our study is likely explained by their examination of a later time point after recruitment of inflammatory cells into the pancreas. PPAR-γ expression is increased in activated macrophages and monocytes.[36–38] Down-regulation of PPAR-γ expression has been observed in most other tissues examined, including heart and lung after induction of endotoxic shock[29,39] and colon after induction of colitis.[24] As in our study, decreased PPAR-γ expression caused by the administration of the inflammatory cytokines TNF-α, IL-1β, and IL-6[40] was completely reversed by treatment with troglitazone in adipose tissue.[41] Because treatment with 15-dPGJ$_2$ or troglitazone completely inhibited the cerulein-induced peak in TNF-α and IL-6 expression in pancreata, these results suggest that the proinflammatory cytokines released during the initial injury phase of acute pancreatitis correlate with reduction of intracellular PPAR-γ. Maintenance of PPAR-γ expression, then, provides the opportunity for attenuation of the inflammatory response through transcriptional corepression and/or DNA-independent transrepression by ligand-activated PPAR-γ. Given the concomitant repression of proinflammatory cytokines in the pancreas, it is possible that the anti-inflammatory effects of PPAR-γ ligands can function, at least in part, through disruption of a positive feedback loop. Regardless of mechanism, the cerulein-induced loss and the ligand-induced maintenance of PPAR-γ expression imply the direct participation PPAR-γ during ligand-induced decrease in amylase release, inflammatory cell infiltration, and acinar tissue damage during acute pancreatitis.

In the clinical setting, rarely do patients present before pancreatitis, and intervention strategies for established pancreatitis are lacking. We have shown that therapeutic administration of troglitazone in the mouse reduced the severity of pancreatitis in a dose-dependent manner, as measured by serum amylase levels. These data suggest that the thiazolidinediones may provide an effective means for limiting the severity of clinical pancreatitis. The fact that multiple doses of troglitazone were more effective in reducing (or delaying) specific markers of pancreatitis may indicate that turnover was relatively rapid in our system. Higher doses or continuous dosing may ameliorate pancreatic symptoms further. The relatively low doses of troglitazone used in this study were chosen to stay well below the effective hypoglycemic dose, because alteration of glucose metabolism was an unwanted and potentially confounding factor. Additional experimental studies will be required to further elucidate the potential therapeutic benefits of PPAR-γ agonists as therapeutic tools in the treatment of acute pancreatitis. Thus, PPAR agonists may prove beneficial in both preventing acute pancreatitis in clinical situations where this is possible, like endoscopic retrograde cholangiopancreatography prophylaxis, and in the early treatment of established acute pancreatitis.

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Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy

Sari Räty, M.D., Juhani Sand, M.D., Eila Lantto, M.D., Isto Nordback, M.D.

The aim of this study was to prospectively analyze the possible association of delayed gastric emptying and postoperative pancreatic complications after pancreaticoduodenectomy. Although hospital mortality after pancreaticoduodenectomy is minimal, morbidity is still high; delayed gastric emptying is one of the most frequent complications. Thirty-nine consecutive patients undergoing pancreaticoduodenectomy were included in this study: 14 females and 25 males (median age 65 years; range, 7–82). Delayed gastric emptying was defined as the need for a nasogastric tube or recurrent vomiting that prevented normal feeding on the 10th postoperative day. Blood analysis was performed on postoperative days 4, 6, and 10; Gastrografin examination on day 6; CT scan on days 2 and 5; and drain amylases were measured on day 5. Pancreatitis was defined as pancreatitis changes in CT scan interpreted by an experienced radiologist without knowing other data. Pancreatic fistula was defined according to the recent international recommendations. We had no mortality. Twelve patients (31%) developed delayed gastric emptying. Surgical (9/12 vs. 5/27; $P = 0.001$) but not medical complications occurred more often in the delayed gastric emptying group. Of the single complications, postoperative CT-detected pancreatitis (6/12 vs. 4/27; $P = 0.03$) and postoperative pancreatic fistula (5/12 vs. 1/27; $P = 0.0007$) were significantly associated with delayed gastric emptying compared with the patients without delayed gastric emptying. This pancreatitis was already detected in CT scan on day 2 in most patients (6/10, 60%). In delayed gastric emptying patients, the only parameters in blood analysis that differed significantly from patients without this complication were serum amylase activity (mean ± SEM, 715 ± 205 vs. 152 ± 70 IU/L; $P = 0.02$), blood leukocyte count (16 ± 2 vs. 9 ± 0.6 × 10^9/L; $P = 0.007$) and serum C-reactive protein (CRP) concentration (144 ± 28 vs. 51 ± 14 mg/L, $P = 0.01$). Postoperative pancreatic (subclinical) fistula was also associated with postoperative pancreatitis (6/10 vs. 0/29; $P = 0.003$). Preoperative coronary artery disease (OR = 16; 95% CI, 1.0–241; $P = 0.05$) and soft pancreatic texture at operation (OR = 9; 95% CI, 1.4–52; $P = 0.02$) were significant risk factors for the development of postoperative pancreatitis. The diagnosis of delayed gastric emptying after pancreaticoduodenectomy often follows postoperative pancreatitis. Delayed gastric emptying is also associated with postoperative pancreatic fistula, for which this pancreatitis seems to be a risk factor. Preoperative coronary artery disease and soft texture of the pancreas are significant risk factors for postoperative CT-detected pancreatitis. (J GASTROINTEST SURG 2006;10:1131–1139)

KEY WORDS: Pancreaticoduodenectomy, complications, postoperative pancreatitis, pancreatic fistula, delayed gastric emptying

Postoperative mortality after major pancreatic resection such as pancreaticoduodenectomy has decreased well below 5% in the past 10–15 years in expert centers.[1–5] Morbidity, however, has remained high. In most studies, morbidity has still been between 30%–40%.[4–6] The most common complications are delayed gastric emptying, fluid collections, pancreatic fistula, biliary fistula, and acute postoperative pancreatitis. Delayed gastric emptying has been reported to occur in 20%–40% of patients.[6–9]

Delayed gastric emptying is very seldom caused by obstruction of gastrointestinal anastomosis.

From the Departments of Gastroenterology and Alimentary Tract Surgery (S.R., J.S., I.N.), and Radiology (E.L.), Tampere University Hospital, Tampere, Finland.
Supported by the Medical Research Fund of Tampere University Hospital, Pirkanmaa Hospital District, Finland (S.R.).
Reprint requests: Isto Nordback, M.D., Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, P O Box 2000, FIN 33521 Tampere, Finland. e-mail: isto.nordback@pshp.fi

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Pylorus-preserving pancreaticoduodenectomy (PPPD) was initially reported to be associated with a higher incidence of delayed gastric emptying compared with the standard Whipple procedure with antrectomy,[10,11] but this claim was later revoked.[6,12] Several factors have been suggested to play a role in the pathophysiology of delayed gastric emptying: disruption of the gastrointestinal neural connection, ischemic injury, and imbalance in gastrointestinal peptides as a consequence of removing the duodenum.[13–16] The role of gastrointestinal peptides in the etiology may be supported by the finding that erythromycin, a motilin receptor agonist, is helpful in this complication.[7]

Delayed gastric emptying may also be a consequence of other complications.[17] Intra-abdominal abscess due to postoperative pancreatitis, pancreatic fistula, or anastomotic leakage may influence gastric motility. Furthermore, increased risk for developing postoperative pancreatic fistula is associated with soft pancreas, the rate being more than 20% compared with virtually 0% with hard pancreatic texture.[18–22]

In our clinical work, we observed that other complications were also frequently found in our patients with delayed gastric emptying. To study this hypothesis in more detail, we conducted this prospective study to analyze upper abdominal changes after pancreaticoduodenectomy with CT and serum markers and to monitor their possible association with delayed gastric emptying. To our knowledge, such prospective studies have not been previously reported on this topic.

MATERIAL AND METHODS

In this prospective study, we initially included 47 patients admitted to Tampere University Hospital for pancreatic head resection. Eight patients were excluded from the final analysis, because the tumors were not resectable for cure. Thus, in the final analysis, there were altogether 39 patients 14 females and 25 males, with a median age of 65 years (range, 7–82 years). The operative method was PPPD in 34 patients and standard pancreaticoduodenectomy with antrectomy (standard PD) in five patients. The surgical team always consisted of at least two out of our three pancreatic surgeons (I.N., J.S., S.R.). The final histopathologic diagnosis was pancreatic ductal adenocarcinoma in 17 patients, ampullary carcinoma in four patients, bile duct carcinoma in three patients, adenocarcinoma of the duodenum in one patient, carcinoid tumor in one patient, cystic neoplasm in four patients, benign adenomatosis of the distal bile duct in one patient, and chronic pancreatitis in eight patients. The pancreatic resection margin at the site of transsection was studied for acute pancreatitis changes. Such change was observed in none of the patients.

Delayed gastric emptying was defined as the need for a nasogastric tube or as daily vomiting still preventing full enteral nutrition on the 10th postoperative day. All patients underwent Gastrografin examination on the sixth postoperative day.

End-to-end invaginated pancreaticojejunal anastomosis (retrocolic) was performed, hand-sewn in two layers by monofilament absorbable polyglactin material. We routinely placed two drains after the resection: one inserted beside the pancreaticojejunal anastomosis and the other beside the hepaticojejunal anastomosis. No external tube drainage of the pancreatic duct was used. Drains were left in place for at least 5 days. Drain output was measured, and its amylase activity was analyzed day 5 after the operation; fluid of 50 ml or more within the past 24 hours with amylase activity more than three times over the upper normal serum level (normal serum level <300 IU/L) was defined as a fistula. Fistulas were also graded into grades A, B, or C according to the recent consensus statement based on the clinical severity of a fistula.[23] The texture of the pancreas was defined as soft by the operating surgeon when the gland was entirely normal at the transsection site and the pancreatic duct was not dilatated.

The diagnosis of postoperative pancreatitis was based on the CT scan, which was performed both on days 2 and 5, and also later when clinically indicated. CT scans were performed with a multidetector row (16 slice) CT before and after administration of iodinated contrast material. Additionally, 600 ml of oral contrast was administered 1 hour before imaging. Scanning started 50 seconds after injection of nonionic contrast agent (300 mg iodine per ml, 1.5 ml per kg of body weight, at a rate of 4 ml/s). Scanning parameters were 1.25 mm slice thickness and image reconstruction at 0.6 mm intervals. The scans were evaluated for the presence of focal or diffuse enlargement, contour irregularities, and nonhomogeneous attenuation and enhancement of the pancreatic remnant and inflammatory changes in the left anterior pararenal space (Fig. 1). The radiologist who performed the CT scan was not aware of the clinical picture of the patient.

Blood measurements (hemoglobin concentration, white cell count, platelet count, C-reactive protein (CRP) concentration, alanine aminotransferase activity, aspartate aminotransferase activity, alkaline phosphatase activity, bilirubin concentration, albumin concentration, amylase activity, and creatinine concentration) were taken preoperatively and on

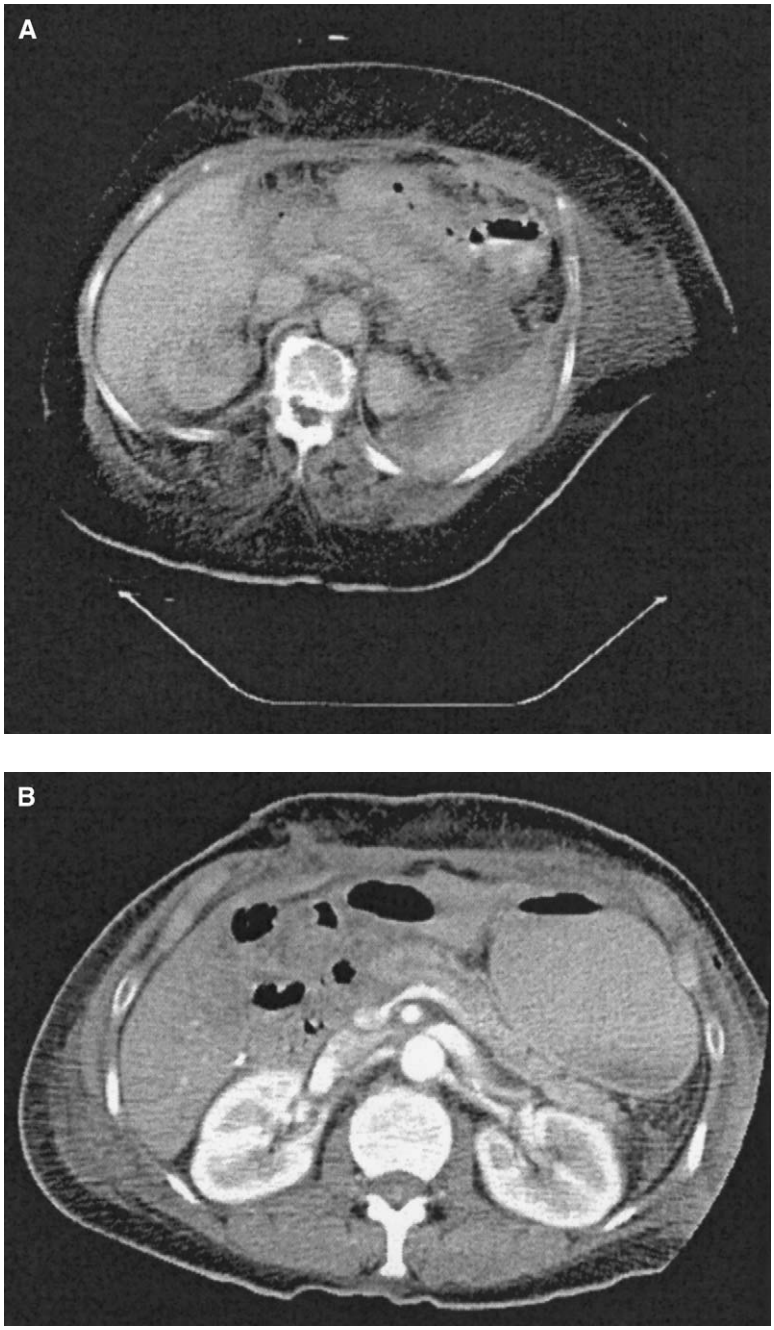

Fig. 1. (**A**) Patient with postoperative pancreatitis. (**B**) Normal postoperative CT.

the 4th, 6th, and 10th postoperative days, and also later when clinically indicated.

Eighteen patients (39%) were jaundiced when diagnosed, 10 of them underwent endoscopic biliary drainage, and eight underwent percutaneous transhepatic biliary drainage preoperatively. Each patient received antimicrobial prophylaxis (III generation cephalosporin and metronidazole), one dose just before the operation, and antithrombotic prophylaxis (subcutaneous low molecular weight heparin injections). None of the patients received somatostatin analogues as a prophylaxis. Postoperatively, all patients received prophylactic proton pump inhibitors daily for 1 month, starting on the first postoperative day. No erythromycin or other prokinetics were given for 1 preoperative week, nor during the first 10 postoperative days.

The patients were divided into two groups: (1) patients with delayed gastric emptying and (2) patients without delayed gastric emptying. When it became

obvious that subclinical pancreatitis was associated with delayed gastric emptying, another analysis was made comparing data between the pancreatitis patients and the other patients.

Statistics

The Fisher exact test, Mann-Whitney *U* test, nonparametric *t* test (1-way ANOVA), and backward stepwise multiple logistic regression analysis were used to compare differences between the study groups. $P < 0.05$ was considered significant.

Ethical Aspects

The study was conducted according to the Helsinki Declaration. The study was approved by the Tampere University Hospital Ethical Committee.

RESULTS

According to the criteria applied, 12 patients (31%) developed delayed gastric emptying, resulting in extended hospital stay (28 ± 4 vs. 11 ± 5 days, $P = 0.001$). We had no hospital mortality. None of the patients with gastrojejunal or duodenojejunal anastomosis had leakage according to Gastrografin examination. One patient who had undergone PPPD procedure had partial obstruction in the Gastrografin examination. This was treated successfully with endoscopic dilatation. Preoperative demographics of the patients are presented in Table 1, and the preoperative and postoperative laboratory values and the operative data in Table 2.

Table 1. Preoperative patient characteristics

	Delayed gastric emptying n = 12	Nondelayed gastric emptying n = 27	*P* value
Age	65 ± 15	58 ± 16	0.21*
Gender (male/female)	6/6	14/13	0.67†
Preoperative history			
Hypertension	1	2	0.68†
Diabetes	2	6	0.79†
Previous cancer	0	2	1.00†
Coronary artery disease	3	1	0.08†
Atrial fibrillation	1	0	0.31†
Pancreatitis	0	2	1.00†
Jaundice preoperatively	5	13	0.76†
Jaundice still at operation	2	2	0.40†

*Mann-Whiney *U* test.
†Fishers exact test.

The overall complication rate was significantly higher in the delayed gastric emptying group compared with the nondelayed gastric emptying group (Table 3). Surgical complications were increased in the delayed gastric emptying group, whereas medical complications did not differ between the study groups (Table 3). Only two patients in the delayed gastric emptying group did not have any other complication detected. Of the 12 patients who developed surgical complications (Table 3), two patients needed a reoperation (one anastomotic leakage in the hepaticojejunal anastomosis and one leakage in the pancreaticojejunal anastomosis).

When the subgroup of patients with surgical complications was studied in more detail, we found that patients with postoperative pancreatitis and patients with postoperative pancreatic fistula developed delayed gastric emptying significantly more often than the remaining patients (Table 3). Of the postoperative laboratory parameters, only the inflammation markers (white blood cell count and CRP concentration) and amylase activity were significantly increased in the delayed gastric emptying group compared with the nondelayed gastric emptying group (Table 2).

Because it became obvious that postoperative pancreatitis was significantly associated with delayed gastric emptying, we studied those patients in more detail. In six patients, pancreatitis changes were already found in CT on the second postoperative day, but in the remaining four patients not until the fifth postoperative day. This pancreatitis would have remained obscure in 9 of the 10 patients without the study CT, because only one patient who needed the reoperation for septic dehiscence of the pancreaticojejunal anastomosis pancreatitis was also seen in laparotomy. Clinically, the patients did not suffer from pain because of epidural analgesia. Furthermore, they were the patients with CT-detected postoperative pancreatitis who had the increased white blood cell count, CRP concentration, and amylase activity (Table 2 and Figs. 2–4). The patients with postoperative pancreatitis had soft texture of the pancreas more frequently (Table 2). It was found that preoperative coronary artery disease (3/10 vs. 1/29; $P = 0.04$) was detected more frequently in those developing postoperative CT-detected pancreatitis than in those not developing postoperative pancreatitis. In multivariate analysis, both the coronary artery disease (OR = 16; 95% CI, 1.0–241; $P = 0.05$) and soft pancreatic texture (OR = 9; 95% CI, 1.4–52; $P = 0.02$) were independent significant risk factors for the development of postoperative pancreatitis.

Table 2. Preoperative variables, operative information and post-operative variables

	Delayed n = 12	Nondelayed n = 27	*P* Value	Pancreatitis n = 10	No pancreatitis n = 29	*P* value
Preoperative laboratory values						
HGB (mmol/L)	13 ± 4	123 ± 5	0.40‡	129 ± 5	125 ± 4	0.58‡
WBC ($\times 10^9$/L)	9.0 ± 0.4	8.5 ± 0.7	0.30‡	9.3 ± 1	8.3 ± 0.5	0.32‡
PLT ($\times 10^9$/L)	363 ± 44	338 ± 17	0.35‡	341 ± 35	347 ± 21	0.88‡
CRP (mg/L)	13 ± 8	19 ± 6	0.52‡	19 ± 10	16 ± 5	0.74‡
ALT (IU/L)	77 ± 32	73 ± 21	0.89‡	39 ± 9	90 ± 24	0.18‡
AST (IU/L)	61 ± 26	53 ± 7	0.73‡	57 ± 19	56 ± 9	0.95‡
PHOS (IU/L)	508 ± 116	520 ± 103	0.95‡	473 ± 167	534 ± 86	0.72‡
Bilirubin (μmol/L)	39 ± 13	36 ± 8	0.95‡	27 ± 12	41 ± 9	0.37‡
Albumin (g/L)	40 ± 1	38 ± 1	0.40‡	40 ± 2	38 ± 1	0.33‡
Amylase (IU/L)	210 ± 44	135 ± 64	0.42‡	186 ± 42	145 ± 77	0.65‡
Creatinine (mmol/L)	69 ± 5	66 ± 3	1.00‡	70 ± 5	66 ± 3	0.53‡
operation information						
Soft texture of pancreas	6	8	0.19†	7	7	0.22†
Operative time (h)	4.8 ± 0.2	4.9 ± 0.2	0.36*	4.7 ± 0.2	4.9 ± 0.1	0231*
Blood loss (ml)	1540 ± 227	1394 ± 134	0.99*	1328 ± 268	1499 ± 150	0.34*
Postoperative laboratory values						
HGB (mmol/L)	103 ± 4	101 ± 2	0.70‡	98 ± 4	104 ± 2	0.20‡
WBC ($\times 10^9$/L)	16 ± 2.3	9 ± 0.6	0.01‡	16 ± 3	10 ± 1	0.01‡
PLT ($\times 10^9$/L)	264 ± 31	241 ± 15	0.46‡	259 ± 34	244 ± 15	0.65‡
CRP (mg/L)	144 ± 28	51 ± 14	0.01‡	141 ± 44	64 ± 11	0.03‡
ALT (IU/L)	33 ± 5	50 ± 7	0.09‡	67 ± 17	126 ± 46	0.33‡
AST (IU/L)	96 ± 39	56 ± 8	0.34‡	87 ± 47	69 ± 17	0.70‡
PHOS (IU/L)	351 ± 58	286 ± 63	0.50‡	330 ± 67	359 ± 56	0.75‡
Bilirubin (μmol/L)	17 ± 4	14 ± 4	0.54‡	14 ± 3	18 ± 5	0.51‡
Albumin (g/L)	20 ± 2	23 ± 2	0.30‡	20 ± 3	22 ± 2	0.43‡
Amylase (IU/L)	715 ± 205	153 ± 70	0.02‡	747 ± 197	121 ± 42	0.01‡
Creatinine (mmol/L)	59 ± 7	78 ± 4	0.93‡	70 ± 8	62 ± 4	0.31‡

HGB = hemoglobin; WBC = white cell count; PLT = platelet count; CRP = C-reactive protein; ALT = alanine aminotransferase; AST = asparate aminotransferase; PHOS = alkaline phosphatase.
*Mann-Whitney *U* test.
†Fishers exact test.
‡*t* test (ANOVA), values means ± SEM.

Because postoperative pancreatitis was clearly associated with delayed gastric emptying, we also studied its association with pancreatic fistula, the other important complication after pancreatic resection. In patients with pancreatitis, there was a fistula rate of 6/10 (60%) compared with 0/29 (0%) in patients without pancreatitis ($P = 0.0001$). Of the six patients who had fistulas coinciding with pancreatitis, there were three (50%) patients whose pancreatitis was already diagnosed by CT on the second postoperative day. Half of these six fistula patients had a subclinical grade A fistula (50%), two (33%) had a grade B fistula, and one (17%) had a grade C fistula.[23]

DISCUSSION

In many series, delayed gastric emptying seems to be the most common complication after pancreaticoduodenectomy.[6,16,17,24] The pathophysiology of this complication has been obscure. Failure in gastrointestinal or duodenojejunal anastomosis seldom explains delayed gastric emptying. The operative method of pancreaticoduodenal resection is not associated with this complication.[6,12,18,24] Some evidence has previously been published supporting the association between delayed gastric emptying and postoperative complications. Miedema et al.,[6] in their retrospective study, found an association between delayed gastric emptying and pancreaticojejunal anastomotic leakage: 54% in patients with delayed gastric emptying compared with 17% in patients without delayed gastric emptying. Furthermore, Riediger et al.,[17] in another retrospective study, found an association between delayed gastric emptying and postoperative overall complications, both medical and surgical. Pancreatitis was not described in these studies. Contrary to these earlier investigations, the present study was performed prospectively.

Table 3. Complications of the patients inthe study group

	Delayed gastric emptying n = 12 (31%)	Non delayed gastric emptying n = 27 (69%)	*P* value*
All complications	10/12 (83%)	6/27 (22%)	0.0005
Surgical complications	9/12 (75%)	5/27 (19%)	0.001
Pancreatitis	6/12 (50%)	4/27 (15%)	0.03
Fistula	5/12 (42%)	1/27 (4%)	0.0007
Abscess	1/12 (8%)	0/27 (0%)	0.31
Spleen necrosis	1/12 (8%)	0/27 (0%)	0.31
Wound infection	1/12 (8%)	3/27 (11%)	0.79
Stenosis of gastrojejunal anastomosis	1/12 (8%)	0/27 (0%)	0.31
Medical complications	4/12 (33%)	3/27 (11%)	0.12
Myocardial infarction	1/12 (8%)	0/27 (0%)	0.31
Atrial fibrillation	1/12 (8%)	0/27 (0%)	0.31
Pulmonary embolism	1/12 (8%)	1/27 (4%)	0.53
Pneumonia	2/12 (17%)	1/27 (4%)	0.22

*Fishers exact test.

In the present study, the rate of delayed gastric emptying (31%) was fairly high but within the range of previously published studies,[6–9] but lower incidences of this complication have been also described.[25,26] However, in the study of Jimenez et al.,[25] the diagnosis of the patients was chronic pancreatitis, which is known to associate with an early complication rate that is not as high as that of the soft pancreas. We found a strong association between delayed gastric emptying and overall complications, explained by surgical but not medical complications, with postoperative pancreatitis and postoperative pancreatic fistula being significant risk factors associated with delayed gastric emptying. Interestingly, the patients with postoperative pancreatitis had coronary artery disease more frequently in the history, which might suggest ischemic factors or factors such as hyperlipidemia or decreased glucose tolerance as the mechanism behind these complications. Soft texture of the pancreas has been well recognized as a risk factor for fistula development after pancreatic resection.[18–22] This study shows that soft pancreas was also a risk factor for postoperative pancreatitis.

The diagnosis of postoperative pancreatitis is difficult. The diagnostic criteria for postoperative pancreatitis after pancreatic resection have not been defined. Amylase measurement may not be sensitive enough for the diagnosis of postoperative pancreatitis, whereas CT—as the gold standard for the diagnosis of acute pancreatitis—should at least detect the severe cases.[27] In the present study, a specialist in pancreatic radiology evaluated the CT scans without knowing the clinical course of the patients. We based the diagnosis of postoperative pancreatitis on the CT scans, because after pancreatic resection, the accuracy of biochemical factors in detecting pancreatitis is not well described. Normal and pathological postoperative findings in CT after pancreaticoduodenectomy have been described by some authors.[27–31] In normal postoperative CT, the pancreatic remnant should have morphological findings similar to those seen in preoperative imaging. In the present study, we used the commonly accepted CT criteria for pancreatitis.[32] CT could detect the pancreatitis in 6 out of 10 cases on day 2. This speaks for the very early onset of postoperative pancreatitis. The detection of pancreatitis in CT in four cases not until day 5 does not necessarily indicate it started then, because there usually is a delay of at least 1–2 days in other etiologies before the pancreatitis changes can be observed in CT.[33] This delay may be even longer in the mild cases.[34]

It was found that pancreatitis very significantly associated with the development of delayed gastric emptying. Interestingly, Murakami et al.[35] found an association with delayed gastric emptying and acinar cell necrosis, lobular fibrosis, and inflammatory cell infiltrations in pancreatic specimens taken during the PPPD operation. These are typical histopathologic changes in acute or chronic pancreatitis.[36] Our margin specimen did not show acute pancreatitis during resection. Thus, it might be possible that pancreatitis, either persisting from the preoperative period, starting postoperatively, or during the operation right after transecting the pancreas with the release of multiple local and systemic mediators of inflammation is the trigger that later influences the gastric motility. In fact, poor gastric motility is a well-recognized condition during pancreatitis.[37] Postoperative pancreatitis might be one important reason for the induction of delayed gastric emptying.

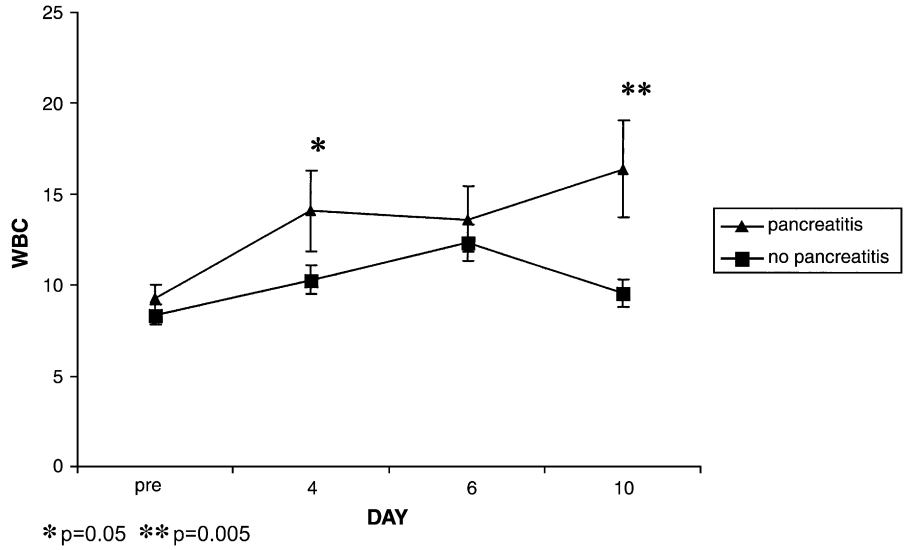

Fig. 2. Mean white blood cell count (WBC $\times$ 10^9) in patients with and without postoperative pancreatitis.

In the present study, we found postoperative pancreatic fistula in 15% of patients, which is much more than Seiler et al.[38] found (3%). When compared with a wider spectrum of studies about pancreatic head resection, the rate of the pancreatic leakage in the present study was within the published range.[6,19,39] Most fistulas were subclinical, did not need any therapy, and were managed with having the drain in place longer. One patient needed a reoperation, giving a symptomatic severe fistula rate of 2.6%, which is comparable to that observed by those who do not use a routine peripancreatic drainage.[40] Of the many criteria used for subclinical fistula (the definition effects the fistula rate), postoperative pancreatic drainage of more than 50 ml of amylase-rich fluid (more than three times above the upper normal level in serum) during the first postoperative week has, until now, been one of the most often applied.[20,22] According to the new definition of postoperative pancreatic fistula—based more on the clinical influence of a fistula during recovery—half of the fistula patients in the present study developed clinical fistulas: two grade B fistulas and one grade C fistula.[23]

Pancreatic fistula was also associated, similar to delayed gastric emptying, with postoperative pancreatitis. It is difficult to prove whether pancreatitis

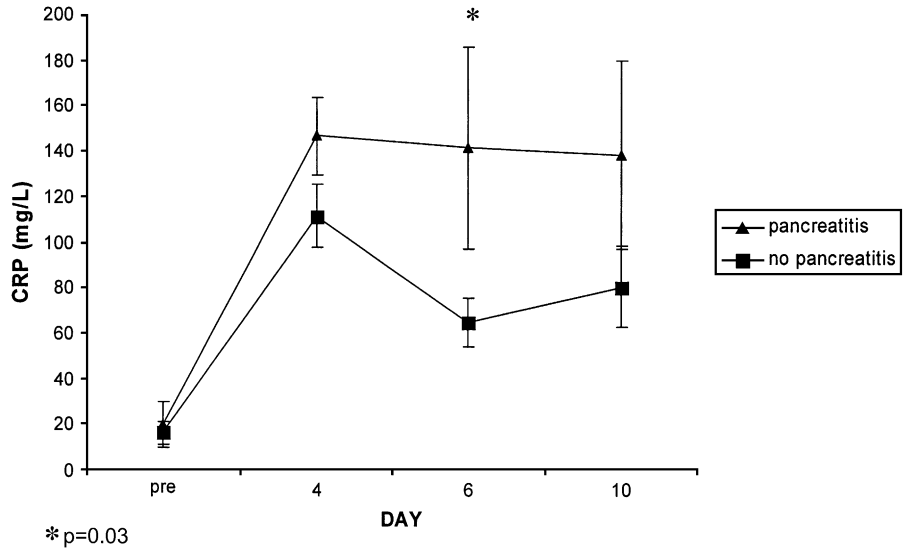

Fig. 3. Mean C-reactive protein (CRP) concentration in patients with and without postoperative pancreatitis.

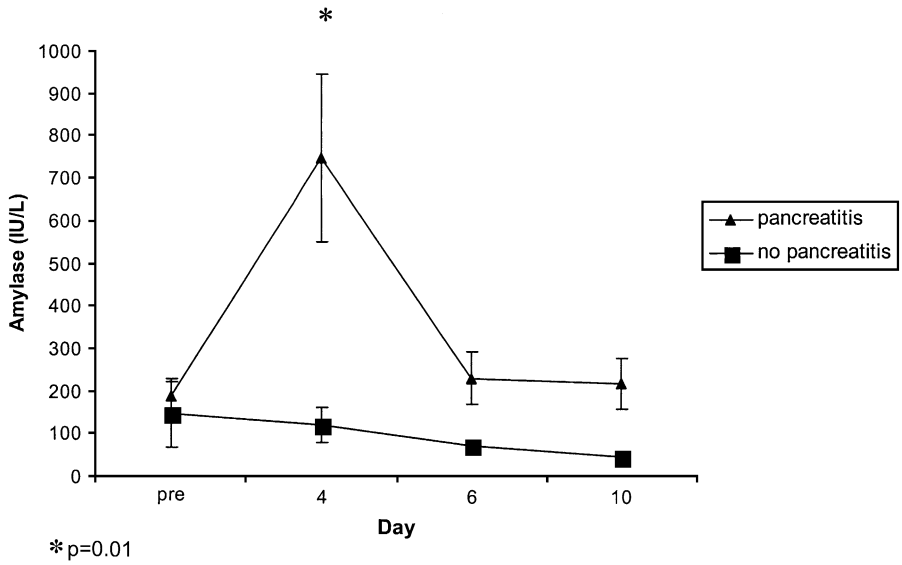

Fig. 4. Mean serum amylase level in patients with and without postoperative pancreatitis.

induced the fistula or vice versa. In the present study, four patients with certain pancreatitis but without any signs of fistula might speak for the fact that, at least in some patients, it is the pancreatitis that induces the fistula, perhaps due to the impaired healing of the anastomosis.

In conclusion, this prospective study showed that postoperative pancreatitis detected in CT scan is a risk factor for the development of postoperative delayed gastric emptying after pancreaticoduodenectomy. This pancreatitis was also significantly associated with postoperative pancreatic fistula. Soft pancreas and preoperative diagnosis of coronary artery disease were the two risk factors for the development of postoperative pancreatitis (Fig. 5).

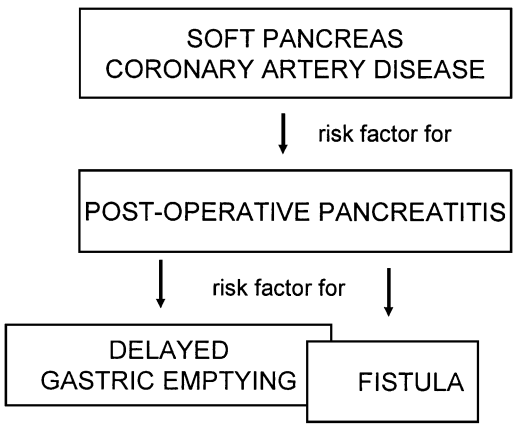

Fig. 5. Hypothesis of the mechanism behind delayed gastric emptying and pancreatic fistula after pancreatic resection.

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Carcinoma of the Papilla of Vater: Are Endoscopic Appearance and Endoscopic Biopsy Discordant?

Michelle Lucinda DeOliveira, M.D., Tarcisio Triviño, M.D., Ph.D., Gaspar de Jesus Lopes Filho, M.D., Ph.D.

Carcinoma of the papilla of Vater is classified as periampullary cancer representing 5% of all gastrointestinal tract malignancies. Early and accurate diagnosis is important for those patients with a tumor of the papilla, as the prognosis is more favorable than in other periampullary neoplasms. Endoscopically obtained biopsies from suspicious papillae can detect an early tumor, although even for skilled pathologists it is often difficult to differentiate carcinomas from noninvasive lesions on the basis of forceps biopsies. The purpose of this study was to assess the preoperative diagnostic accuracy of duodenoscopy appearance and biopsy in all cases with suspicion of tumor. Thirty patients with suspicion of carcinoma of the papilla of Vater and with final diagnosis established by pancreatoduodenectomy were included in this retrospective study. In each case, a comparison was made between endoscopic biopsy and duodenoscopic appearance. Duodenoscopic appearance sensitivity and accuracy for malignancy were 86% and 83%, respectively, whereas endoscopic biopsy sensitivity and accuracy were 65% and 67%, respectively. Although preoperative diagnosis of carcinoma of the papilla of Vater is useful for making therapeutic decisions, the diagnostic value of the endoscopic appearance was superior to endoscopic biopsy in this series. (J GASTROINTEST SURG 2006;10:1140–1143)

KEY WORDS: Endoscopic biopsy, digestive endoscopy, carcinoma, tumors of the papilla of Vater

Carcinoma of the papilla of Vater represents about 1% of all epithelial malignancies and 5% of all carcinomas in the gastrointestinal tract. In clinical practice, four types of tumors are described as periampullary neoplasms, namely carcinoma of the papilla of Vater, cancer at the head of the pancreas, cancer of the distal bile duct, and cancer of the duodenum.[1] As in the colon, it seems that carcinomas of the papilla of Vater arise from precancerous lesions. Many reports have demonstrated the premalignant nature of adenomas and the high rate of association with focal cancer.[2,3] The neoplasm in the papilla of Vater can be diagnosed early, and unlike other periampullary neoplasms, has a good prognosis after surgical therapy.[4,5] However, an accurate preoperative diagnosis is essential to select patients for the most appropriate treatment,[6] because after a complete surgical resection, the 5-year survival rate can be expected to be approximately 60%.[7–9] Endoscopically obtained biopsies from suspicious papillae can establish an early and immediate preoperative diagnosis, although even for skilled pathologists it is difficult to differentiate carcinomas from noninvasive lesions on the basis of forceps biopsies.[10–12] The purpose of this study was to assess the preoperative diagnostic accuracy of duodenoscopic appearance and endoscopic biopsy in all cases with a suspicion of tumor at the papilla of Vater.

PATIENTS AND METHODS

Patients

Thirty patients with suspicion of carcinoma of the papilla of Vater and with final diagnosis established by Whipple's procedure were included in this retrospective study. In each case, a comparison was made

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From the Department of Surgery, Division of Gastrointestinal Surgery, University Federal of São Paulo, Escola Paulista de Medicina, São Paulo, SP, Brazil.
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Reprint requests: Michelle L. DeOliveira, M.D., Hospital São Paulo, UNIFESP, Division of Gastrointestinal Surgery, Rua Napoleão de Barros 715, 2° andar, Vila Clementino, São Paulo-SP Brasil 04039-002. e-mail: michellelgo@uol.com.br

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between endoscopic biopsy and duodenoscopic appearance. The final diagnosis was established on the basis of the surgical specimen. All endoscopically obtained biopsies of the papilla of Vater were performed at the Hospital São Paulo, University Federal of São Paulo between June 1981 and October 2002. This study was approved by the local ethics committee of the University Federal of São Paulo.

Methods

Endoscopic procedures were carried out at the Endoscopy Unit of the Hospital São Paulo, University Federal of São Paulo. The examinations were done using a video duodenoscope with a lateral vision (Pentax Medical Company MD International, Inc., Miami, FL). In the presence of papilla alteration, such as irregularity of mucosa, discoloration of the mucosa, areas of granulation, ulceration or vegetation, a biopsy was carried out removing about five fragments, preferably from the edges and center of the lesion. Then, the collected material was fixed in formalin, identified, and sent for assessment by the pathologists. A papillotomy was performed selectively in cases of jaundice and elevated cholestatic enzymes or when the patient developed cholangitis.

The material obtained from the endoscopic biopsy and from the surgical specimen were stained with hematoxylin-eosin and examined by two pathologists responsible for the evaluation of histological degree and final diagnosis. These two independent observers were not informed about the clinical data of the patients. The diagnoses were established on the basis of criteria generally used in pathological anatomy. To determine the diagnosis of malignancy in lesions of the major duodenal papilla, neoplastic invasion of the wall, presence of nuclear atypia, disturbance of the architecture, and lymphatic and/or perineural invasion were considered.

Results obtained by duodenoscopy and endoscopic biopsy were analyzed to determine the accuracy, agreement, and disagreement between both approaches. The accuracy and sensitivity of the diagnostic methods were evaluated for malignancy. In addition, we calculated the concordance and discordance of diagnostic methods by Kappa's test and by McNemar's test, respectively. The level of statistical significance was $P < 0.05$.

RESULTS

In the comparative analysis of duodenoscopic appearance and surgical specimen diagnosis of cancer of the papilla, the duodenoscopic appearance was suggestive of cancer in 26 (87%) of the 30 cases. This diagnostic tool provided false-positive information in one patient, and it was false-negative for cancer in four (13%) patients (Table 1). Analysis of the results from duodenoscopic appearance revealed a sensitivity of 86% and a false-negative rate of 14%, yielding a positive predictive value of 96% and accuracy of 83%. The disagreement between duodenoscopic appearance and surgical specimen diagnosis did not reach statistical significance (McNemar, $P = 0.37$).

In this comparative analysis between endoscopic biopsy and surgical specimen diagnosis for cancer of the papilla, the endoscopic biopsy provided a true positive test for cancer in 19 (63%) patients, whereas the test was negative in 11 (37%) patients. In fact, the test was false-negative in 10 patients and a true negative in only one patient (Table 1). The analysis of the results from endoscopically obtained biopsy revealed a sensitivity of 65%, a false-negative rate of 35%, and accuracy of 67%. The disagreement between endoscopic biopsy and surgical specimen diagnosis was significant (McNemar, $P = 0.002$).

In the comparative analysis of agreement and disagreement of the diagnostic tests (Table 2), agreement was evaluated according to the Kappa test, resulting in agreement of 50% between duodenoscopic appearance and endoscopic biopsy for cancer ($K = 0.243$; $P = 0.102$). In addition, distribution of disagreement of these tests was evaluated according to the McNemar test ($P = 0.1$).

The comparative analysis of interobserver variability (pathologists) was evaluated regarding the endoscopic biopsy and surgical specimen. The

Table 1. Comparison of duodenoscopy and endoscopic biopsy to final diagnoses

	Duodenoscopy appearance (cancer)			Endoscopic biopsy (cancer)		
Surgical specimen (cancer)	**Positive**	**Negative**	**Total**	**Positive**	**Negative**	**Total**
Present	25	1	26	19	10	29
Absent	4	0	4	0	1	1
Total	29	1	30	19	11	30

Table 2. Agreement and disagreement between duodenoscopy appearance and endoscopic biopsy

	Duodenoscopy appearance					
	Cancer		Nontumor lesion		Total	
Endoscopic biopsy	n	%	n	%	n	%
Cancer	15	50.0	4	13.3	19	63.3
Nontumor lesion	11	36.7	0	0.0	11	36.7
Total	26	86.7	4	13.3	30	100.0

agreement regarding to the endoscopic biopsy results was considered good by the Kappa test ($K = 0.77$; $P < 0.001$), whereas distribution of disagreement of interobserver was not significant (McNemar, $P = 0.5$). For the surgical specimen, the interobserver variability was excellent ($K = 1$; $P < 0.001$), as the pathologists agreed in all cases.

DISCUSSION

Cancer of the papilla, when diagnosed at an early stage, is associated with higher resectability and survival rates than with other malignancies of the pancreas and biliary tree.[8,10] Pancreaticoduodenectomy (PD) is a procedure with low mortality and reasonable morbidity at experienced centers. It is the treatment of choice for invasive carcinoma and large benign ampullary lesions with suspicion of malignancy.[8,13–16]

In clinical practice, surgeons seek a definitive preoperative diagnosis to justify a PD; however, the availability of convincing histopathologic diagnosis is often lacking before surgery.[6,17,18] Until the 1980s, most tumors of the papilla were either diagnosed during laparotomy or even at autopsy.[19] Nowadays, the wide use of upper endoscopy in many centers has changed the approach of abnormal findings at the papilla.[18,20,21] Several attempts have been made to improve the diagnosis accuracy of endoscopically guided biopsy; for example, biopsies through a snare resection approach were shown to improve the sensitivity, but are associated with increased rates of complications such as hemorrhage,[21] pancreatitis, and papillary stenosis.[22] Previous sphincterotomy may also impair the value of the biopsy. Bourgeois et al.[23] pointed out that biopsies done after sphincterotomy often provide necrotic and inconclusive material. In a prospective study, Menzel et al.[6] observed that endoscopic biopsies obtained from tumors of the papilla of Vater before and after sphincterotomy do not allow for adequate diagnosis, and they emphasize that biopsies should be carried out on tumoral lesions of the papilla both on the surface and in the depth. In the presence of a negative biopsy with duodenoscopic evidence of tumor, it has been suggested that other more sophisticated examination like intraductal ultrasonography[6,24,25] or immunostaining techniques of the tissue biopsy [26,27] should be used to better define the diagnosis.

Previous reports have suggested that endoscopic appearance and histopathology of the endoscopic biopsy can be discordant with a diagnostic accuracy, ranging between 45%–82%.[11,12,19,25,28] In the present study, we found that appearance on duodenoscopy offered better accuracy for the diagnosis of cancer of the papilla than with endoscopic biopsy (83% vs. 67%). The false-negative rate and sensitivity of the duodenoscopic appearance were 14% and 86%, respectively. These results had a significant impact on our clinical practice in our service, as we still found ourselves with the same problem as reported by others[5,17,18]; for example, we performed surgery in 10 patients with a final diagnosis of cancer, whereas the histopathologic examination at the preoperative endoscopic biopsy failed to show a malignancy. Only one patient underwent PD without cancer in the surgical specimen.

Taken together, this study shows that despite the development of sophisticated endoscopic techniques,[5,24–26] the accuracy of endoscopic biopsy in establishing the diagnosis of cancer remains limited. This shortcoming may result in an error in the interpretation of the diagnostic instrument, yielding inadequate patient treatment.

CONCLUSION

In conclusion, although preoperative diagnosis of carcinoma of the papilla of Vater is crucial for making optimal therapeutic decisions, endoscopic biopsy was less accurate than endoscopic appearance in the preoperative diagnosis of carcinoma of the papilla of Vater. Thus, currently decision for PD may be justified only on the basis of a suspicious appearance at endoscopy.

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Management and Outcome in Patients With Klatskin-Mimicking Lesions of the Biliary Tree

Dirk Uhlmann, M.D., Marcus Wiedmann, M.D., Frank Schmidt, M.D., Regine Kluge, M.D., Andrea Tannapfel, M.D., Frieder Berr, M.D., Johann Hauss, M.D., Helmut Witzigmann, M.D.

The preoperative and even intraoperative differentiation between benign and malignant strictures at the hepatic hilum remains difficult. The aim of this study was to assess clinical, radiologic, intraoperative, and histopathologic findings; surgical treatment; and outcome of patients with Klatskin mimicking benign lesions. Of 49 consecutive patients who were operated on the initial preoperative radiologic diagnosis of hilar adenocarcinoma (Klatskin tumor), 7 (14%) had benign conditions after final histopathologic diagnosis. Pretreatment work-up, therapy, and outcome of these patients were analyzed. Based on preoperative clinical symptoms, imaging assessment, and CA19-9 values, all seven patients were classified as having malignant neoplasms. At laparotomy, the tumors of six patients were judged to be malignant. Five patients underwent hilar resection and concomitant liver resection, and two patients underwent hilar resection alone. There were no operative deaths. The definitive histopathologic examination showed severe cholangitis with extensive periductal fibrosis in all patients. After a median follow-up of 32 months, all patients are well. Clinical presentation and imaging assessment were similar for Klatskin tumors and benign fibrosing disease; therefore, an aggressive resectional approach is justified in any patient with suspicious obstruction of the liver hilum. (J GASTROINTEST SURG 2006;10:1144–1150)

KEY WORDS: Extrahepatic bile duct, stricture, benign, Klatskin-mimicking

Cholangiocarcinomas comprise less than 2% of all cancer diagnoses and approximately 60% of all cases involve the biliary confluence (hilar cholangiocarcinoma).[1] Therefore, relevant clinical experience in managing hilar cholangiocarcinoma has been limited to a few referral centers.

It is still very difficult to confirm the diagnosis of malignancy prior to resection. False-positive preoperative diagnosis of malignancy has been reported in 9–15% of resected tumors.[2–4] By combining brush cytology and biopsy specimens, a positive histology and cytology is obtained in 40–70% of patients.[5] Frozen section analysis of biliary tree malignancies is known to be difficult and somewhat unreliable.[6,7] Consequently, in a significant number of patients the definitive diagnosis is established only after histologic examination of the resected specimen.

Ultrasonography (US), magnetic resonance imaging (MRI)/magnetic resonance cholangiograhpy (MRC)/magnetic resonance angiography (MRA), and endoscopic retrograde cholangiography (ERC) combined with intraductal ultrasound examination (IDUS) allow detection of a lesion in the liver hilum and estimation preoperatively of its extent into liver and vessels. However, it is still very difficult to confirm the diagnosis of malignancy prior to its removal. Positron emission tomography (PET) with [^{18}F]fluoro-2-deoxy-D-glucose (FDG) has been successfully used for diagnostic evaluation of various malignant primary and recurrent tumors[8–12] and has shown to be highly sensitive and specific for the detection and localization of hilar cholangiocarcinomas.[13,14]

Surgical resection of Klatskin tumors comprises extrahepatic suprapancreatic bile duct resection and hepatic resection combined with resection of the portal vein and caudate lobe and lymph node dissection. In studies using this aggressive approach, in-hospital mortality rates from 7.5% to 18% and

From the Departments of Surgery II (D.U., J.H., H.W.), Internal Medicine II (M.W.), Diagnostic Radiology (F.S.), and Nuclear Medicine (R.K.) and the Institute of Pathology (A.T.), University of Leipzig, Leipzig, Germany; and the Department of Internal Medicine, Paracelsus University of Salzburg, Austria (F.B.).
Reprint requests: PD Dr. Med. D. Uhlmann, 2nd Department of Surgery, University of Leipzig, Liebigstr. 20, 04103 Leipzig, Germany. e-mail: uhld@medizin.uni-leipzig.de

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complication rates from 19% to 85% were observed.[15–19] However, this procedure is an overtreatment for patients with Klatskin-mimicking benign bile duct lesions.

In the present study, we analyzed pretreatment work-up data, therapeutic strategy, and outcome of seven patients with benign lesions of the biliary tree.

PATIENTS AND METHODS

Between January 1998 through May 2004, 49 consecutive patients (22 women and 27 men) underwent resection for suspected hilar cholangiocarcinoma. Of the 49 patients, 7 had Klatskin-mimicking benign lesions of the biliary tree. The results of the 42 patients with hilar cholangiocarcinoma were published elsewhere.[19]

Transabdominal duplex US, computed tomography (CT), MRI/MRC/MRA, and ERC were performed in all seven patients. IDUS was applied in two patients, and percutaneous transhepatic cholangiography (PTC) and digital subtraction angiography (DSA) were applied in two other patients. The location and longitudinal extent of the tumor according to the modified Bismuth-Corlette classification[20] were assessed by ERC and MRC and, if available, also by PTC. The depth of tumor infiltration was measured by CT and MRI and facultatively by IDUS. Biopsy samples from the stenosis were taken during ERC in five of the seven patients; two patients had brush cytologies only. Biliary drainage using at least two 9 or 11.5 F endoprostheses was performed in four patients.

An intraoperative decision was made about the extent of tumor resection. Follow-up of all patients was undertaken in our outpatient department.

RESULTS

Clinical Presentation

No patient had a relevant previous medical history. Painless jaundice was present in five patients. The median serum bilirubin level at admission was 49.5 μmol/L (range, 13.4–194 μmol/L; normal value, <25 μmol/L) (Table 1). Four patients had upper abdominal pain. Three patients had weight loss of 2–10 kg (mean, 5 kg). Elevated levels of CA19-9 were seen in five patients with a median value of 51.36 U/ml (range, 8.5–121 U/ml; normal value, <22 U/ml).

US, CT, MRI, and PET

The results of the pretreatment work-up are summarized in Table 1. CT scan described a cholestasis

Table 1. Preoperative findings in seven patients with Klatskin-mimicking lesions

Patient	Age (yr)	Bilirubin at admission (μmol/L)	CA 19-19 (U/ml)	US tumor size	ERC/PTC	CT scan	MRI/MRC	Biopsy/brush cytology
A.B. (female)	61	43.3	29.7	3 cm	Stenosis both hepatic ducts	Cholestasis	Tumor liver hilum	No malignancy (brush)
G.R. (female)	68	194	20.3	Not visible	Stenotic tumor left hepatic duct	Cholestasis	Tumor liver hilum	Chronic inflammation, no malignancy
C.Z. (male)	68	13.4	88	Not visible	Stenosis left hepatic duct	Cholestasis	Stenosis right hepatic duct	Indefinite of dysplasia/ intraepithelial neoplasia (brush)
H.L. (male)	69	72.3	8.5	3 cm	Stenotic tumor above cystic duct	Cholestasis	Stenosis bifurcation	Fibrosis, no malignancy
S.K. (male)	59	115	55.1	Not visible	Stenosis above cystic duct	Cholestasis	Tumor liver hilum	No malignancy
B.A. (female)	43	49.5	36.1	Not visible	Stenosis above cystic duct	Cholestasis	Stenosis liver hilum	Fibrosis, no malignancy
H.N. (male)	57	21	121.4	Not visible	Stenosis bifurcation	Cholestasis	Stenosis liver hilum	No malignancy

US = ultrasonography; ERC = endoscopic retrograde cholangiography; PTC = percutaneous transhepatic cholangiography; CT = computed tomography; MRI = magnetic resonance imaging; MRC = magnetic resonance cholangiography.

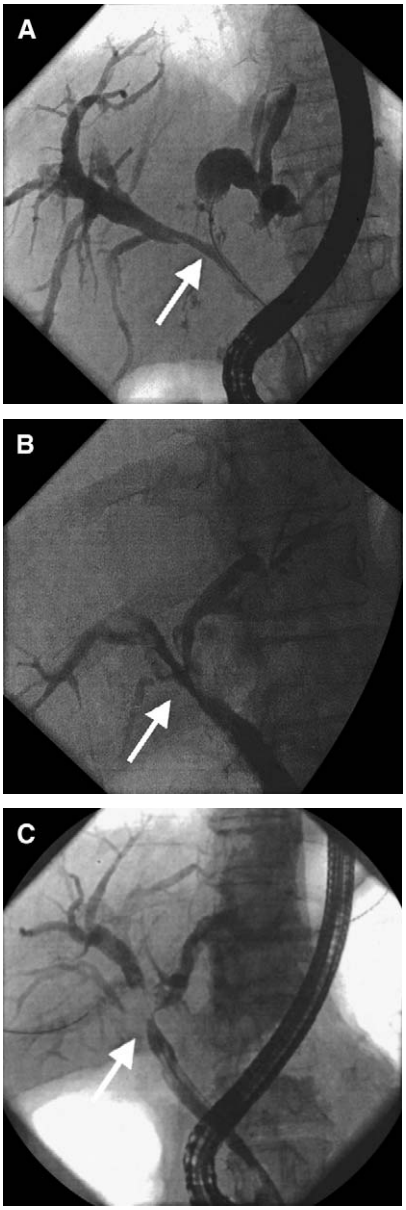

Fig. 1. (*A*) ERC suggesting a Klatskin tumor. Histology revealed a Klatskin tumor. (*B*, *C*) ERCs suggesting a Klatskin tumor. Histology revealed fibrosing cholangitis after resection in both patients (H.L. and A.B.).

without a tumor mass in all seven patients. MRI showed a tumor mass in three patients (Fig. 2, *A*, *B*). In only one of these patients, this mass was also seen on US. FDG-PET was performed in two patients and showed suspicion of a Klatskin tumor in both patients (Fig. 3). The results of CT, MRI, US, and PET did not correlate.

ERC and PTC

In six patients, ERC findings were typical for Klatskin tumors. One patient who underwent PTC had suspicious images, too. In total, all cholangiographs were considered as suspicious for cholangiocarcinoma (Table 1, Fig. 1, *A–C*).

Biopsy/Brush Cytology

Biopsy revealed atypical cells in one patient and bile duct epithelia without atypia in four patients. In one patient, the diagnosis of "indefinite of dysplasia/intraepithelial neoplasia" was made cytologically. The other patient with brush cytology showed no atypical cells (Table 1).

Additional Diagnostics: Mini-laparoscopy, IDUS, DSA

Diagnostic mini-laparoscopy was performed in two patients (A.B., G.R.). There was suspicion of multiple liver metastases in one patient. During surgery, these lesions were histologically assessed as mini-abscesses. In the other patient, no tumor and no metastases were observed. In two patients (A.B., B.A.) only, IDUS was performed and revealed a mass lesion at the stenosis. A small area with irregular vessel structure at the liver hilum suspicious for a Klatskin tumor was described in one patient with DSA (H.N.).

Overall Result of Reassessments

Taking together the reassessments of clinical presentation, CT, MRI/MRC, FDG PET, ERC, PTC, US, mini-laparoscopy, and biopsy/brush cytology, all seven patients were classified as having suspicious lesions by at least one of these diagnostic methods. According to the Bismuth-Corlette system, one patient was classified as type II, three patients as type III, and the remaining three patients as type IV (Table 2).

Surgery, Histology, and Outcome

The results are shown in Table 2. At laparotomy, an obviously suspicious tumor was found in all except one (H.N.) patient. Two patients underwent hilar resection alone. In one patient (H.N.), hilar resection alone was performed due to the benign aspect, which was confirmed by frozen-section examination. In the other patient, limited resection was performed because of the reduced general condition of the patient. Five patients underwent hilar resection and concomitant liver resection. The postoperative morbidity rate was 28%. There was no operative mortality.

During operation, no biopsy specimens for frozen-section examination were taken before resection to avoid spread of tumor cells in the operative field.

Fig. 2. (*A*) MRC suggesting a Klatskin tumor. Coronal thick-slab (∞/1200) images show a lengthy stricture (arrow) with irregular margins and a tumor at the liver hilum. Histology revealed a Klatskin tumor after complete resection. (*B*) MRC suggesting a Klatskin tumor. Coronal thick-slab (∞/1200) images show a lengthy stricture (*arrow*) with a small tumor at the liver hilum. Histology revealed a fibrosing cholangitis after trisegmentectomy, partial portal vein resection, and complete resection of the extrahepatic biliary tree (G.R.).

Frozen-section examination of the surgical margins was performed to ensure a radical resection. In all patients, definitive histopathologic examination of the specimens showed fibrosis with nonspecific chronic inflammation. All patients are well after a follow-up of 1–7 years. Two patients have recurrent cholangitis.

DISCUSSION

It is important for the clinician to realize that there is a remarkably high number of patients with presumed Klatskin tumors that turn out to be benign fibrosing cholangitis after resection. The clinical presentation and preoperative radiologic studies led us to the false-positive diagnosis of malignant bile duct strictures in seven patients. Even intraoperatively, in six of the seven patients, the tumor was considered to be malignant.

There is a general agreement that any localized extrahepatic bile duct obstruction coexisting with intrahepatic bile duct dilatation should be considered to be malignant until proved otherwise.[3,4,6,7] This agreement arose because of the difficulty in obtaining a histopathologic diagnosis in patients with obstructive jaundice caused by a bile duct stricture. The lack of histopathologic evidence might result in some patients being inappropriately treated for malignant disease when a benign stricture was present, and vice versa. In the study of Gerhards et al.,[3] a false-positive preoperative diagnosis of malignancy resulted in a 15% resection rate of benign lesions in patients with suspicious hilar strictures.

A lack of clinical constitutional symptoms such as body weight loss and elevated tumor markers may implicate a possible benign entity of the disorder. Benign, segmental, nontraumatic inflammatory strictures of the biliary tract were infrequently reported with the exception of primary sclerosing cholangitis.[3,17,21,22] Many benign nontraumatic inflammatory strictures of the common bile duct have been generally considered to be a variant of primary sclerosing cholangitis. However, Standfield et al.[23] described 12 cases of benign strictures of unknown etiology and differentiated them from the localized form of sclerosing cholangitis. Inflammatory conditions of the common bile duct that are potential etiologic factors included bacterial or viral infections, parasite infestation, abdominal trauma,

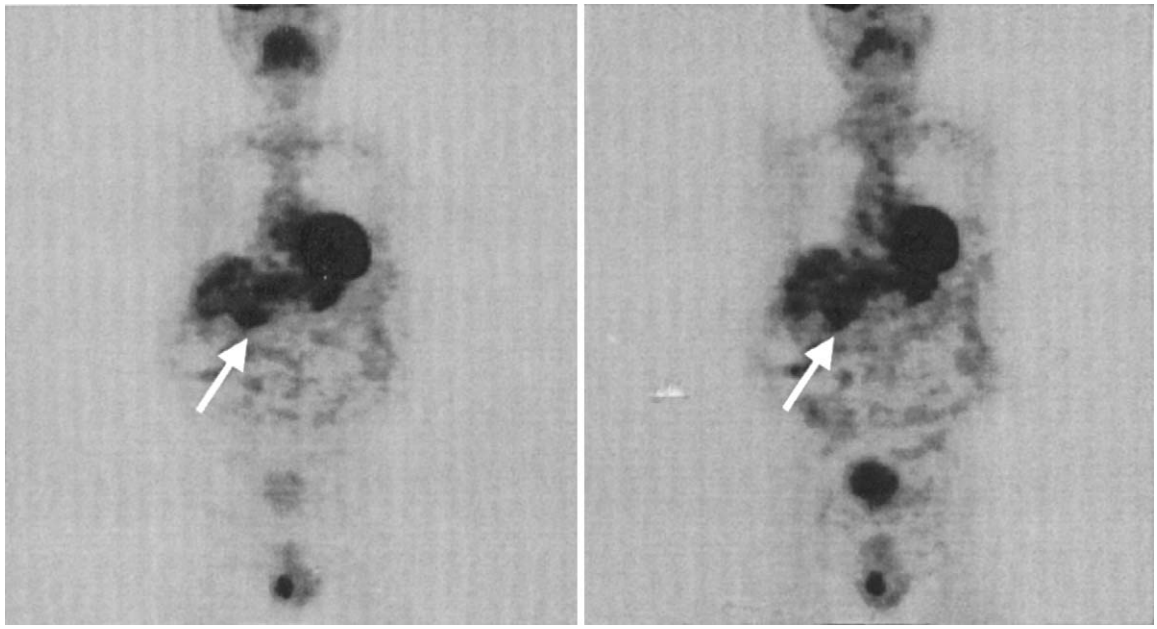

Fig. 3. FDG PET showing a suspicious lesion at the liver hilum mimicking a Klatskin tumor (H.L.).

congenital abnormality,[24] inflammatory pseudotumors,[25] and complication of chemotherapy.[26]

The current state of diagnostic imaging fails to deliver a reliable discrimination between benign and malignant hilar lesions. All clinical and imaging features in our patients were quite compatible with a malignant tumor in the liver hilum. Application of improved diagnostic methods, such as thin-section spiral CT, MRI/MRC, and PET, can potentially increase the diagnostic accuracy, but neither could reliably differentiate malignant from benign lesions.[27,28] A recent study using FDG-PET for diagnosing hilar cholangiocarcinoma could not demonstrate any significant benefit in the differentiation between cholangiocarcinoma and Klatskin-mimicking tumors.[29] However, only two patients with Klatskin-mimicking lesions were included into this study. In the initial staging of patients with extrahepatic bile duct cancer, ^{18}F-FDG-PET offers additional value in relation to CT in evaluating both the primary tumor and regional lymph nodes.[14] In contrast, our group showed that PET can be helpful in the diagnosis of distant metastases but is not suitable for the detection of regional lymph node metastases.[13] A recent study emphasized ^{18}F-FDG-PET/CT for determination of the benign or malignant character of extrahepatic bile duct strictures. All patients with cholangiocarcinoma presented with focal increased uptake in the liver hilus with an standardized uptake value of 6.8 $\pm$ 3.3 (range, 3.9–15.8), compared with 2.9 $\pm$ 0.3 (range, 2.5–3.3) in patients with benign causes of strictures ($P < 0.003$).[30]

Preoperative histologic or cytologic examination by means of biopsy or brush cytology is liable to false-negative results with low sensitivity and carries a potential risk of needle tract metastases.[31,32]

Careful review of all preoperative information and radiologic images of our seven patients yielded the initial diagnosis of a Klatskin tumor, although postoperative histopathologic examination revealed only inflammation and fibrosis. The decision to undertake resection of the strictures in these patients should not be considered an error of judgment. Analogous to lesions of the pancreatic head, resection of the lesion is still the most reliable way to rule out malignancy. Therefore, resection of a benign stricture mimicking a malignant lesion in the extrahepatic bile duct cannot be avoided completely. Most benign segmental strictures of the extrahepatic bile duct reported in the literature are located at the hilum or the distal common bile duct.

In conclusion, there are no reliable diagnostic methods to distinguish Klatskin tumors from benign lesions in patients without histologically confirmed adenocarcinoma. Therefore, in the presence of hilar obstruction, potentially resectable lesions should always be explored and resected to offer patients with a Klatskin tumor the chance for cure.

An important differential diagnosis in patients with suspect hilar strictures is primary sclerosing cholangitis (PSC). The prevalence of PSC is

Table 2. Preoperative staging and postoperative findings in seven patients with Klatskin-mimicking lesions

Patient	Preoperative Bismuth-Corlette classification	Intraoperative evaluation	Treatment	Histology	Follow-up
A.B.	IV	Malignant	Left hemihepatectomy	Chronic cholangitis with fibrosis	Well after 37 mo
G.R.	IIIb	Malignant	Left hemihepatectomy, caudate lobe resection	Chronic cholangitis	Well after 14 mo
C.Z.	IIIa	Malignant	Right trisegmentectomy, portal vein resection	Fibrosis	Well after 20 mo, recurrent cholangitis
H.L.	IV	Malignant	Hilar resection	Fibrosis	Well after 12 mo
S.K.	IIIa	Malignant	Right hemihepatectomy	Fibrosis	Well after 15 mo
B.A.	IV	Malignant	Right trisegmentectomy, portal vein resection	Fibrosis	Well after 21 mo, recurrent cholangitis
H.N.	II	Benign stenosis	Hilar resection	Fibrosis	Well after 7 yr

uncertain, but it probably lies between 3 and 8 per 100,000 population. The reported prevalence of cholangiocarcinoma in PSC patients is wide, ranging from 4.8% to 36.4%. The carcinoma often develops at bile duct bifurcation. Therefore, adequate diagnostics, including liver biopsies or an exploration, need to be considered to clarify the diagnosis. In these patients, liver transplantation should be offered, even though the survival rate in patients with incidental cholangiocarcinoma in PSC is up to 20% less than that for tumor-free PSC patients. Furthermore, there is a wide global range in the prevalence of inflammatory bowl disease (IBD) in patients with PSC, varying from 21% reported from Japan to 71% in the United States and to as high as 80% in Sweden. The overall prevalence of colorectal cancer in any patient with IBD was 3.7% in a meta-analysis.[37] Thus, colonoscopy should be performed in this patient to exclude IBD or even colorectal cancer. However, there is no consensus about surgical treatment of IBD prior to or in combination with a planed orthotopic liver transplantation (for a review, see Cullen and Chapman[33]).

In the near future, the recently described methods of digital imaging analysis, fluorescence in-situ hybridization, and analyses of p16(INK4A) and p14 ARF methylation in bile duct fluid may further improve sensitivity of the diagnosis.[34–36]

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Hepatic Vein Injury During Laparoscopic Cholecystectomy: The Unappreciated Proximity of the Middle Hepatic Vein to the Gallbladder Bed

Chad G. Ball, M.D., M.Sc., Anthony R. MacLean, M.D., F.R.C.S.C., Andrew W. Kirkpatrick, M.D., F.R.C.S.C., Oliver F. Bathe, M.D., F.R.C.S.C., Francis Sutherland, M.D., F.R.C.S.C., Estifanos Debru, M.D., F.R.C.S.C., Elijah Dixon, M.D., F.R.C.S.C., F.A.C.S.

Uncontrollable hemorrhage during laparoscopic cholecystectomy occurs in 0.1% to 1.9% of all cases, with 88% originating from the gallbladder bed. The anatomical proximity between major branches of the middle hepatic vein and the gallbladder bed, and hence the risk of intraoperative bleeding, is unclear. CT scans of 20 random patients were retrospectively reviewed to identify the closest distance between branches of the middle hepatic vein and the gallbladder bed. The vein diameter was also recorded. Risk factors for intraoperative bleeding during laparoscopic cholecystectomy were also retrospectively reviewed. Large branches (mean diameter = 2.1 mm) of the middle hepatic vein are directly adjacent to the gallbladder bed in 10% of patients. An additional 10% of cases also possess branches within 1 mm of the gallbladder bed. Chronically scarred and contracted gallbladder disease may increase the risk of significant bleeding, requiring conversion. Twenty percent of all cases will display a large branch of the middle hepatic vein adherent or immediately adjacent to the gallbladder fossa. These patients are at increased risk for intraoperative bleeding. Furthermore, contracted gallbladders with evidence of chronic disease may be at increased risk for significant hemorrhage. (J GASTROINTEST SURG 2006;10:1151–1155)

KEY WORDS: Laparoscopic cholecystectomy, hepatic vein, hemorrhage

Uncontrollable hemorrhage during laparoscopic cholecystectomy occurs in 0.1% to 1.9% of all cases.[1,2] In 88% of these incidents, bleeding originates from the gallbladder bed.[2] Although the middle hepatic vein or its branches are often implicated as the source of hemorrhage, only recently has this proposed association been evaluated objectively by using color Doppler ultrasound.[3–6] Unfortunately, various investigating groups have come to very different conclusions regarding the precise anatomical relationship between major branches of the middle hepatic vein and the gallbladder bed. Although three groups[3–5] identified middle hepatic veins that were completely adherent to the gallbladder bed in 10% to 15% of healthy volunteers, Kebudi and colleagues[6] observed a vessel-to-bed distance of 6 to 29 mm, with a mean of 17 mm. It is unclear if these dramatic differences are due to the study cohorts themselves, or to the technology used to evaluate this anatomy.

In the past 22 months, four patients at our institution have required emergent conversions from laparoscopic to open cholecystectomy because of profuse bleeding from the gallbladder bed. Each was a direct result of a lacerated superficial branch of the middle hepatic vein. As a result of these cases, as well as the ongoing dispute within the literature, our aim was (1) to identify the precise proximity of the middle hepatic vein, and/or its branches, to the gallbladder bed by using CT technology, and (2) to identify potential risk factors for significant gallbladder bed hemorrhage during laparoscopic cholecystectomy.

From the Department of Surgery, Foothills Medical Centre (C.G.B., A.R.M., A.W.K., O.F.B., F.S., E.D.); and Peter Lougheed Hospital (E.D.), Calgary, Alberta, Canada.

Reprint requests: Elijah Dixon, M.D., F.R.C.S.C., F.A.C.S., Assistant Professor of Surgery, Oncology, and Community Health Sciences, Divisions of General Surgery and Surgical Oncology, Faculty of Medicine, University of Calgary, Tom Baker Cancer Center, 1331 29th Street NW, Calgary, Alberta, T2N 2N4, Canada. e-mail: Elijah.Dixon@CalgaryHealthRegion.ca

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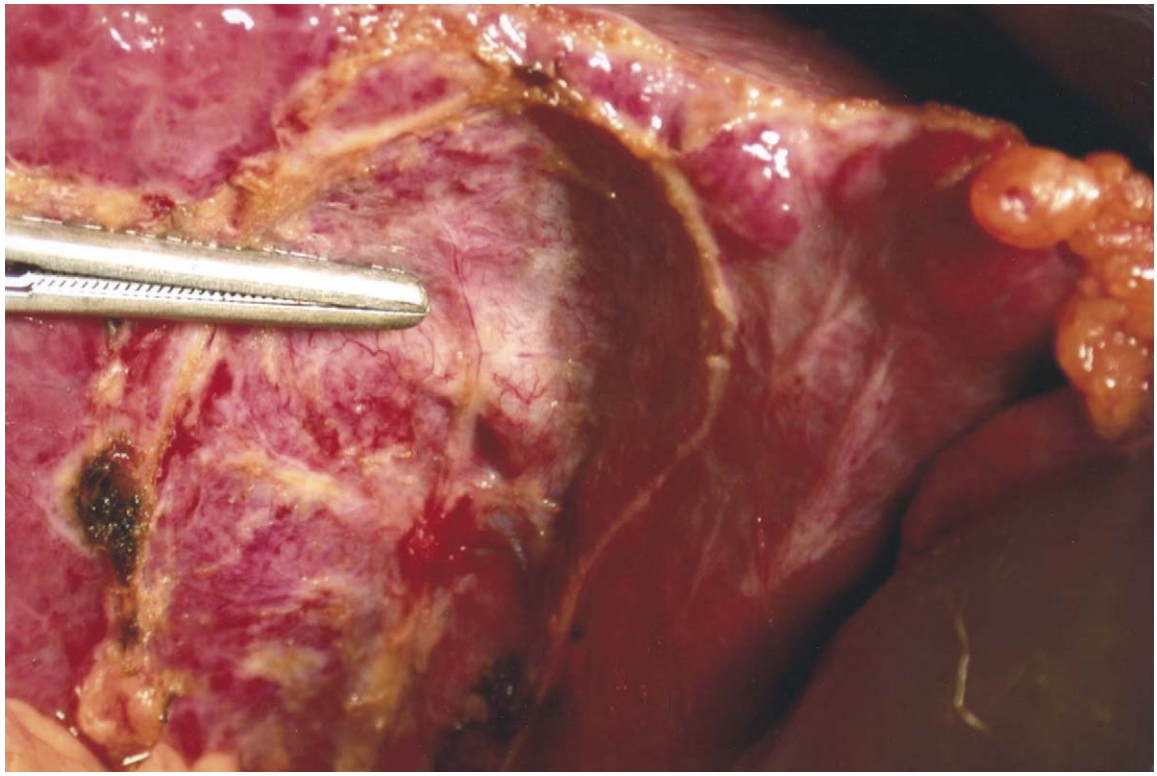

Fig. 1. Intraoperative picture of a superficial middle hepatic vein after removal of gallbladder from the gallbladder bed.

MATERIAL AND METHODS

The anatomical proximity between major branches of the middle hepatic vein and the gallbladder bed was retrospectively obtained by randomly selecting 20 patients, with varying diagnoses, from a busy hepatobiliary practice. Each patient had undergone a CT scan for diagnostic purposes unrelated to this study. This practice is based in an academic, tertiary care hospital with a catchment population of approximately 1.5 million people. Institutional review board ethics approval was obtained prior to commencement. CT scans for each of patient were reviewed concurrently by two experienced hepatobiliary surgeons to identify the closest distance between the vessel and the gallbladder bed. The diameter of the vein at the site of closest proximity to the gallbladder bed was also recorded.

All scans were contrast-enhanced, multiphase examinations designed to evaluate the abdomen and pelvis. Contrast administration consisted of 100 to 150 ml (titrated to weight of the patient) of ioversol (Optiray 350; Mallinckrodt Medical, St Louis, MO) injected intravenously at a rate of 2 ml/sec with a power injector (OP 100; Medrad, Pittsburgh, Pa).

Each exam was viewed on a picture archiving and communication system workstation (Impax; AGFA Technical Imaging Systems, Richfield Park, NJ). On-screen computerized measuring calipers were used for all measurements.

A retrospective chart review of four patients with major intraoperative hemorrhages during laparoscopic cholecystectomy was also completed to identify any similarities between cases. Patient, imaging, operative technique, and anatomical factors were compared.

RESULTS

CT scan confirmed that the majority of patients displayed a well-developed separation of the major branches of the middle hepatic vein and the gallbladder bed. The median separating distance was 6.1 mm. The range, however, was 0 to 47 mm.

Two of 20 (10%) patients possessed middle hepatic vein branches immediately adjacent to the gallbladder bed. An additional two (10%) patients displayed major branches within 1 mm of the gallbladder bed (Figs. 1 and 2). The mean diameter of these veins was 2.1 mm, with a range of 0.9 to 3.2 mm.

Among the four laparoscopic cholecystectomy cases that required emergent conversion for major hemorrhage, the mean patient age was 59 years

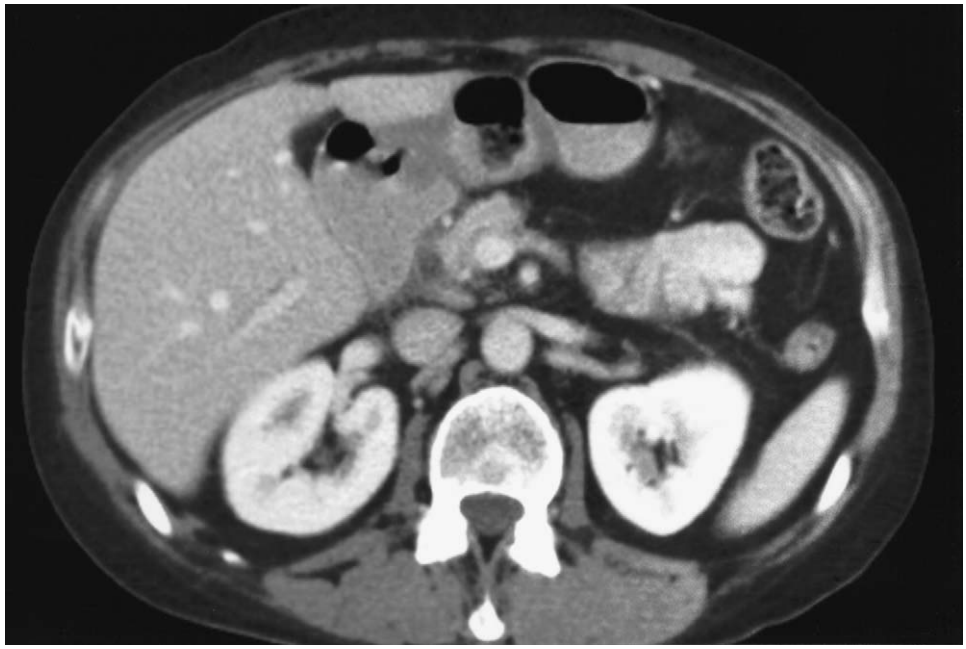

Fig. 2. CT scan of a hepatic vein adjacent to the gallbladder plate.

(range, 52 to 75 years), and the diagnosis was exclusively acute cholecystitis. Comorbidities included type II diabetes mellitus, hypertension, osteoarthritis, and class I angina. Preoperative ultrasound confirmed significant gallbladder wall thickening and gallstone(s) in each patient. Liver enzymes were normal. Initial laparoscopy in all patients revealed a contracted gallbladder with extensive and chronic scarring. In each case, the surgeon felt they were operating in the correct plane between the gallbladder and liver and that no particular technical fault had occurred. Electrocautery was utilized in the separation of the gallbladder from the liver in all cases. The mean blood loss was 940 ml. In each case, a laceration of a branch of the middle hepatic vein was identified. All were ligated with a nonabsorbable synthetic suture. The gallbladder bed was then sprayed with a thrombin-based synthetic agent in three out of four cases. All four patients were discharged from the hospital within 6 days and had no residual complications at long-term follow-up.

DISCUSSION

Although the incidence of major hemorrhage during laparoscopic cholecystectomy is less than 2%, the consequences can be devastating,[1,2] including death.[7–9] Although the origin of bleeding can include the aorta, inferior vena cava, iliac vessels, portal vein, as well as the hepatic artery, injuries to these structures are extremely rare.[1,2] In the largest reported series outlining laparoscopic cholecystectomy-related complications, Deziel and colleagues[2] reported that 88% of all major bleeding originates from the gallbladder bed itself. In spite of the fact that the presumed source of hemorrhage was from various branches of the middle hepatic vein, it was not until recently that color Doppler ultrasound was employed to objectively measure the distance between the most superficial branches of the middle hepatic vein and the gallbladder fossa.[3–6]

Although it is generally agreed that the majority of healthy volunteers possess a substantial distance between the branches of the middle hepatic vein and the gallbladder bed, investigators differ with respect to the incidence of cases where these two structures are immediately adjacent to one another. Three publications[3–5] have identified middle hepatic veins that were completely adherent to the gallbladder bed in 10% to 15% of healthy Asian volunteers. Kebudi et al.,[6] however, did not observe any vessel-to-bed distances of less than 6 mm. It is unclear if these dramatic differences are due to the study populations themselves, or to the technology used to evaluate this anatomy.

As a result of this discordance in defining the true anatomical relationship between branches of the middle hepatic vein and the gallbladder bed by using color Doppler ultrasound, we employed CT technology. Not only is CT imaging less reliant on operator experience, but it has been proven to be extremely effective and accurate in delineating precise

hepatic vessel anatomy in patients with a variety of hepatobiliary diagnoses.[10–12] Using CT imaging, we identified a median distance of 6 mm between the most superficial branch of the middle hepatic vein and the gallbladder bed. The range of distances was 0 to 47 mm. Although these values correspond very well with those of Misawa et al.[3] and Shen et al.,[5] who displayed mean distances of 5.3 and 5.0 mm respectively, we also observed a small group of patients with extremely concerning anatomy. The percentage of patients with hepatic vein branches completely adherent to (0 mm) or immediately adjacent to (<1 mm) the gallbladder bed was 10% and 10%, respectively, in our series. This observation supports literature by Misawa et al.,[3] Zhang et al.[4] and Shen et al.,[5] which outlines 10%, 15%, and 15% of patients, respectively, with complete vein adherence to the gallbladder fossa, as well as an additional 6%, 7%, and 11%, respectively, with middle hepatic vein branches coursing within 1 mm of the gallbladder bed.

Although measurements across studies show remarkable consistency, it is unclear why the data of Kebudi et al.[6] did not support these values. On the basis of our series, however, it certainly appears that close anatomical proximity between the middle hepatic vein and the gallbladder bed is not infrequent and does extend to a typical North American population.

Although direct pressure to the gallbladder bed via a laparoscopic instrument arrested the hemorrhage in two of four (50%) patients in the series of Misawa et al.,[3] this maneuver was not sufficient in our bleeding patients. As a result, all four patients required conversion to an open procedure with a primary sutured liver repair. Although it is impossible to compare the severity of the injuries between different case series, we are unsure if our more than double volume of blood loss compared with that of Misawa et al.[3] was related to a more significant injury, or simply represents ongoing bleeding during the conversion itself.

In addition to the close proximity of the middle hepatic vein branches, the size of the vessels themselves was also surprising. In our series, the mean diameter of the adjacent vessels was 2.1 mm. The range however, was 0.9 to 3.2 mm. These values again compare favorably to the other series.[3–5] Interestingly, the closest point between the middle hepatic vein and the gallbladder bed was most often (43%) located on the right side of the longitudinal axis of the gallbladder.[5] Three of the four cases of hemorrhage in our series were also on the right side.

Although no other published series discusses the impact of a chronically scarred and contracted gallbladder on intraoperative hemorrhage, we believe this may lead to an increase in the proximity of an already close branch of the middle hepatic vein. In each of our four cases, the surgeon felt they were operating in the correct plane, yet the hemorrhage was both acute and severe. Hook electrocautery was used to separate the gallbladder from the liver in the standard fashion. Furthermore, the experienced operator felt that no obvious technical error had occurred. Although there appeared to be no other unique factors among these four patients, when informally compared with the thousands of laparoscopic cholecystectomy cases performed in our hospital each year, the chronic scarring and contraction was notable. Although superficial hepatic veins would normally be bypassed in a typical, nonchronically scarred dissection, we propose this increased proximity between the vein and gallbladder fossa increases the risk of injury. Our lack of confirmatory preoperative CT imaging in these four patients represents a limitation of the study.

As a result of the close anatomical proximity of some hepatic veins, as well as the significant consequences of any associated bleeding, some groups[3] have advocated the routine use of preoperative ultrasound to evaluate middle hepatic vein anatomy. We have not attempted this at our institution.

CONCLUSION

In otherwise normal patients, between 10% and 15% of all cases will display a large branch of the middle hepatic vein adherent to the gallbladder fossa, and hence to the dissecting plane, during a laparoscopic cholecystectomy. An additional 6% to 15% of patients also possess substantially sized veins within 1 mm of the gallbladder bed. These patients are at increased risk for intraoperative bleeding. Furthermore, contracted gallbladders with evidence of chronic disease may be at increased risk for significant hemorrhage from the gallbladder bed, and therefore, for conversion to open cholecystectomy on an emergent basis.

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Retroperitoneal Paraganglioma: Single-Institution Experience and Review of the Literature

Steven C. Cunningham, M.D., Hyun S. Suh, M.D., Jordan M. Winter, M.D., Elizabeth Montgomery, M.D., Richard D. Schulick, M.D., F.A.C.S., John L. Cameron, M.D., F.A.C.S., Charles J. Yeo, M.D., F.A.C.S.

Paragangliomas are rare tumors arising from extra-adrenal chromaffin cells. We examined the clinical characteristics of all patients at our institution having paragangliomas resected from 1984 through 2005. Of 253 resections, 22 (9%) were retroperitoneal and were selected for further study. The ratio of males to females was 1.3:1, and the median age was 39 years. The average size, rate of metastasis (i.e., malignancy), and rate of function was 7.4 cm, 9.5%, and 57.1%, respectively. Tumors larger than 7 cm were more likely to require adjacent organ resection ($P = 0.01$). The overall 5-year survival was 73%. Survival was significantly worse after metastasis ($P = 0.0023$) but did not depend on the tumor diameter, the secreting function of the tumor, the status of surgical margins of resection, or status of the resected lymph nodes. (J GASTROINTEST SURG 2006;10:1156–1163)

KEY WORDS: Retroperitoneal, paraganglioma, surgery, survival

Paragangliomas (sometimes referred to as extra-adrenal pheochromocytomas) are rare tumors arising from extra-adrenal chromaffin tissue, that is, the paraganglia, which are widely distributed near or within the autonomic nervous system in a variety of retroperitoneal sites and in the sympathetic ganglia of various viscera; all paragangliomas are believed to derive from the neural crest and can synthesize and store catecholamines.[1] They represent 10% to 20% of all chromaffin tissue-related tumors (the remaining majority being adrenal), and of those, approximately 10% are retroperitoneal (the remaining majority being located in the head and neck).[2] Because of their rarity, little information is available regarding the natural history of these tumors and patient outcome after resection. We present a review of our 21-year institutional experience with resected retroperitoneal paragangliomas and review the relevant literature.

PATIENTS AND METHODS

Approval from the Johns Hopkins University Institutional Review Board was obtained. From May 1984 through July 2005, 253 patients with paragangliomas (also referred to as extra-adrenal pheochromocytomas) underwent resection at the Johns Hopkins Hospital. Of those, 22 (9%) had retroperitoneal paragangliomas. One patient's tumor was a microscopic incidental finding and was excluded from further analysis. Demographics, presenting signs and symptoms, complications, survival time, tumor functional status, margin status, and other relevant data were extracted from hospital records. Patient confidentiality was ensured in all cases.

For the purpose of this study, morbidity was defined as a complication, that is, a disease or disorder that occurred as a result of tumor resection, and operative mortality was defined as death occurring during or within 30 days of the operation. Functioning tumors were defined as those tumors in patients with elevated urine or serum catecholamine levels attributable to the presence of the tumor. Malignant tumors were defined as those associated with identified lymph node metastases or distant metastases. R0 resections were defined as those leaving behind no gross or microscopic tumor, R1 as those leaving behind microscopic tumor, and R2 as those leaving

From the Departments of Oncology (S.C.C.), Pathology (E.M.), and Surgery (J.M.W., R.D.S., J.L.C., C.J.Y.), The Johns Hopkins Medical Institutions, Baltimore, Maryland; Department of Surgery, University of Maryland Medical System (S.C.C.), Baltimore, Maryland; The Johns Hopkins University School of Medicine (H.S.S.), Johns Hopkins University, Baltimore, Maryland.
Reprint requests: Richard D. Schulick, M.D., F.A.C.S., Department of Surgery, Rm. 442, Cancer Research Building, 1650 Orleans Street, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD 21231-1000.
e-mail: rschulick@jhmi.edu

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behind gross tumor. Complications were graded according to the Clavien classification.[3]

Data analysis was performed using Stata version 7.0 (Stata Corporation, College Station, TX). Categorical variables were compared using the Fisher exact test. The Kaplan-Meier method was used to calculate survival.[4] The Social Security Death Index[5] was used to determine the status of patients (alive or dead) who were lost to follow-up. Survival rates were compared using log-rank tests. Significance was accepted at $P < 0.05$.

RESULTS

Patient Characteristics

Patient and tumor characteristics are shown in Table 1. The median age of the 21 patients at the time of diagnosis was 39 years (range, 18–79). Twelve patients were men and nine were women. The most common presenting symptoms were hypertension (43%), a palpable mass (29%), diaphoresis (19%), palpitations (19%), pain (19%), and panic or anxiety (14%). One patient (patient 13) was known to have multiple endocrine neoplasia type 2A, and another patient (patient 19) with pediatric erythrocytosis and multiple paragangliomas likely had von Hippel-Lindau disease type 2A.[6]

Tumor and Operative Characteristics

All 21 tumors were found to arise from the retroperitoneum. The average maximal diameter of the tumors was 7.4 cm. Three (14%) tumors were malignant and were operated upon predominantly for

Table 1. Clinical characteristics of 21 patients with retroperitoneal paragangliomas

Patient No.	DOS	Age	Max cm	Function	Signs and symptoms	Met	LN	Margins*	Other organ presection	Complications
1	11/24/1992	33	9.0	No	Mass	No	0/1	R0	None	0
2	3/24/1994	43	7.4	Yes	HTN	Yes	0/1	R0	Aorta	V
3	9/1/1994	79	17.0	No	Mass	No	0/0	R1	None	V
4	12/14/1994	25	9.2	Yes	HA, HTN, pain	No	0/2	R1	Aorta	IIIb
5	4/29/1997	19	7.5	Yes	HTN, HA, panic attacks	No	0/6	R0	L kidney	Fasciotomy
6	8/8/1997	45	5.5	No	Mass	No	0/8	R0	Whipple	0
7	9/8/1999	63	3.0	No	Leg weakness	No	0/0	R0	None	0
8	2/10/2000	51	8.0	Yes	HTN, palpitation, HA, diaphoresis	No	0/1	R0	None	0
9	4/13/2000	35	8.0	Yes	Diaphoresis, flushing	No	0/4	R1	None	0
10	6/20/2000	43	7.5	No	Pain, nausea Paroxysmal	No	0/15	R0	R colon	0
11	3/28/2001	31	6.0	Yes	HTN, Diaphoresis, Dyspnea, anxiety	No	0/0	R0	None	0
12	4/17/2001	65	2.0	No	Pain	Yes	1/10	R0	Whipple	0
13	8/21/2001	24	3.0	Yes	HA, HTN, palpitations, diarrhea	No	0/0	R0	Spleen	0
14	2/20/2003	47	5.2	Yes	HTN, reflux	No	0/0	R0	None	0
15	6/30/2003	33	9.0	Yes	Preeclampsia, HTN	No	0/0	R0	IVC well	0
16	8/12/2003	39	15.0	No	Mass	Yes	6/29	R0	R colon Whipple	0
17	3/10/2004	37	5.5	Yes	Mass	No	0/0	R0	None	0
18	9/3/2004	36	5.0	Yes	HTN, HA palpation, diaphoresis	No	0/0	R0	None	0
19	11/9/2004	18	4.2	Yes	Palpitations, chest pain, anxiety	No	0/0	R0	None	0
20	6/1/2005	63	8.5	No	Mass	No	0/0	R1	R kidney	0
21	9/16/2005	73	1.1	No	Pain, jaundice	No	0/0	R0	Whipple	0
	Mean or Percent	40.2	7.4	57.1%	NA	9.5%	N/A	19.0%	NA	14.3%

DOS = date of surgery; Met = metastasis; LN = lymph nodes; HTN = hypertension; HA = headache; L = left kidney; R = right; IVC = inferior vena cava; R = right.
*See text foe explanation of margins.

palliation. Surgical margins of resection were positive for microscopic disease (R1 resection) in four (19%) patients. Three of the 21 tumors were resected via a pancreaticoduodenectomy: two of those were likely arising from the duodenal wall (patient 6 and patient 12); one of those (patient 21) was a 1.1 cm paraganglioma found incidentally within the Whipple specimen resected for pancreatic ductal adenocarcinoma—a cancer known to be associated with a markedly different 5-year survival compared with paraganglioma—and was therefore excluded from survival analyses. Of the remaining cases, adjacent organ resection was required in 41% of cases, excluding patient 13, in whom splenectomy was performed, not because of tumor size but rather to increase exposure to a 3 cm tumor in a patient with chronic pancreatitis, previous cystgastrosomy, and significant portal varices. By a Fisher exact test, adjacent organ resection was more likely to be required for tumors greater than 7 cm in greatest diameter ($P = 0.01$).

Most (12/21; 57%) of the tumors in this series were functional. Not surprisingly, patients with functional tumors were more likely to have presented with hypertension, diaphoresis, or palpitations than patients with nonfunctioning tumors, who were more likely to present with nonspecific symptoms such as a mass or pain ($P = 0.00003$). Excluding the 1.1-cm incidental tumor (patient 21), nonfunctional tumors had a larger greatest diameter on presentation (average, 8.4 cm) than functional tumors (average, 6.5 cm; $P > 0.05$).

Adjuvant Treatment for Malignant Disease

Of the three patients in our series with malignant disease, one (patient 2) received four cycles of preoperative systemic chemotherapy, one (patient 16) received postoperative radiation, and one (patient 15) was lost to follow up, but according the Social Security Death Index,[5] died 2.7 years after resection at the age of 68.

Morbidity and Mortality

Morbidity and mortality are shown in Table 1. There was one patient with complications and two perioperative deaths. One death was due to a massive pulmonary embolism and the other to pneumonia. The patient with complications (patient 4) had a 9.2 cm tumor adherent to the aorta. The infrarenal abdominal aorta was therefore resected en bloc with the tumor, followed by reconstruction with an aorto-bi-iliac bypass graft. On postoperative day 1, the patient developed compartment syndrome of the leg requiring four-compartment fasciotomy.

Survival and Recurrence

Five-year survival was calculated for the study population as a group, and as stratified by tumor size (<7 cm vs. >7 cm), tumor functional status (functional vs. nonfunctional), margin status (R0 vs. R1/2), status of resected lymph nodes (positive vs. negative), and distant malignancy (present vs. absent metastasis). The overall 5-year survival was 73%. Survival correlated significantly with malignancy, that is, the presence of metastasis ($P = 0.0023$; Fig. 1), but not with size ($P = 0.69$), functional status ($P = 0.84$), margin status ($P = 1.0$), or nodal status ($P = 0.15$; Fig. 2).

The recurrence rate for patients with a median follow-up of 2 years was 14%, eliminating patients with follow-up times less than 1.5 months and two

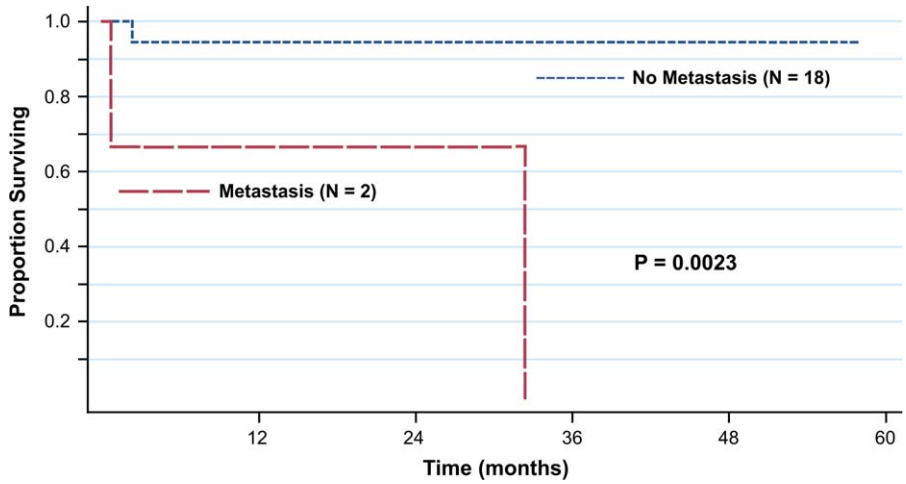

Fig. 1. Survival of patients undergoing resection of retroperitoneal paraganglioma, stratified by metastasis.

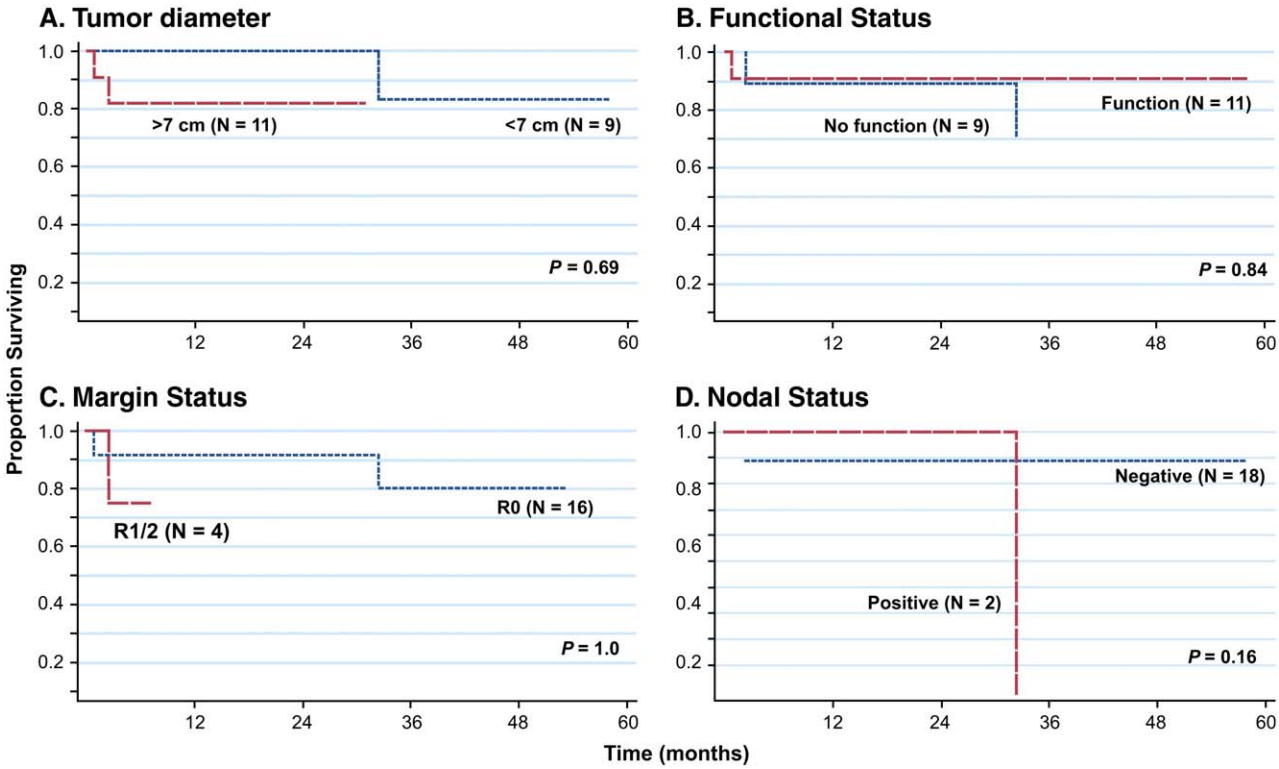

Fig. 2. Survival of patients undergoing resection of retroperitoneal paraganglioma stratified by (**A**) size, (**B**) functional status, (**C**) margin status, and (**D**) nodal status.

patients with von Hippel-Lindau disease and multiple endocrine neoplasia.

DISCUSSION

Paragangliomas may occur anywhere paraganglia are found, from the base of the skull to the floor of the pelvis. In addition to the rare sites reported from the Mayo Clinic, including heart, pancreas, bladder, prostate, and sacrum,[2] others have reported paragangliomas arising from the bronchus,[7] the thoracic spine,[8] the vagina,[9] and the ovary.[10] Our current report includes only retroperitoneal extra-adrenal tumors—the most common retroperitoneal location—in our series and elsewhere,[2] being periaortic and pericaval. As shown in Fig. 3, tumors in this location may displace or adhere to adjacent organs. Contrast-enhanced computed tomographic scanning reveals typical heterogeneous appearance with peripheral enhancement (Fig. 3).

The low incidence of this tumor accounts for the wide variation in the observed rates of malignancy and functionality. For example, reported rates of malignancy vary from 0%[11] to 50%,[12,13] and reported rates of functioning tumors range from 0%[14] to 100%[13] (Table 2). The extra-adrenal location of the tumors in our series is consistent with the observation that none of the patients with functioning tumors had elevated epinephrine, because the enzyme required to convert norepinephrine to epinephrine, phenylethanolamine N-methyltransferase, is known to be active in the adrenal medulla but not in extra-adrenal tumors.

The extra-adrenal paraganglion system is composed predominantly of chief (type 1) cells, arranged in compact nests (zellballen), and peripheral to these nests, sustentacular (type 2) cells (Fig. 4). The diagnosis of a paraganglioma historically relied on electron microscopy and silver staining techniques to detect neurosecretory granules in paraganglioma cells. Now, a wide array of antibodies for immunohistochemistry has simplified the diagnosis. Antibodies detecting neuron-specific enolase and chromogranin are among the most sensitive for chief cells (nearly 100% accuracy when used in combination), and anti-S100 antibodies are most commonly used to detect sustentacular cells.[21]

The traditional teaching for pheochromocytomas has been that approximately 10% are bilateral, 10%

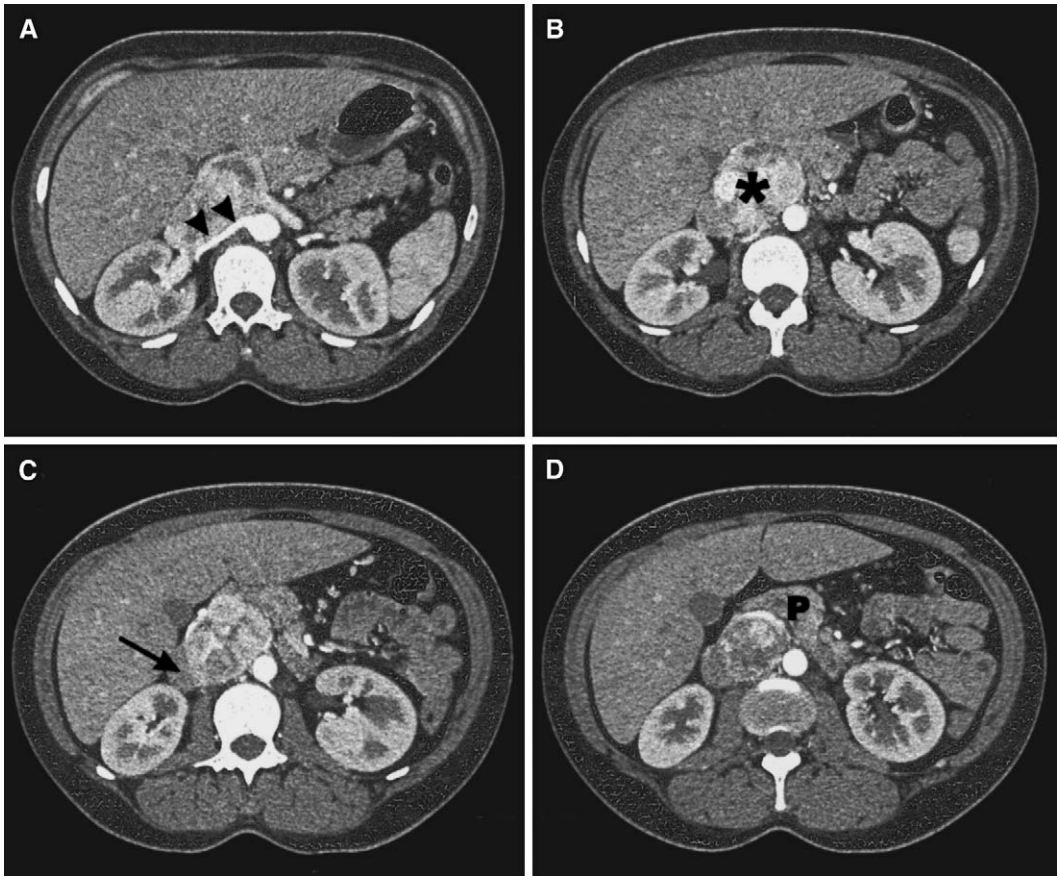

Fig. 3. Representative CT scan (patient 15). (**A–D**) Serial slices through tumor at ~2 cm intervals, from cephalic to caudal extremes. The tumor (**B,** *asterisk*) displaces the inferior vena cava (**C**, *arrow*), the right renal artery (**A**, *arrowheads*), and the head of the pancreas (**D**, *P*). Resection required including a ~1 cm section of caval wall en bloc, but was otherwise uncomplicated and yielded a mass 9.0 × 6.0 × 4.5 cm. All margins were negative for tumor. Preoperative, immediate postoperative, and 1-month follow-up serum total catecholamine levels were 2397, 1019, and 204 pg/ml, respectively (normal, 123–671 pg/ml). The patient is free of disease at 2-year follow-up.

are malignant, 10% are extra-adrenal (i.e., are paragangliomas), 10% are hereditary, and 10% are not associated with hypertension. However, this classic teaching has recently been challenged given that (1) a greater proportion are discovered in normotensive patients during imaging performed for other reasons, (2) the risk of malignancy well exceeds 10% in patients with extra-adrenal pheochromocytomas or with associated germline mutations (e.g., in a succinate dehydrogenase gene), and (3) up to a third of patients are now recognized to carry a germline mutation in a gene predisposing to tumorigenesis.[22] The findings of the current series and review are consistent with most of these points. For example, only 43% of patients in our series had hypertension and 24% of patients in our review had malignancy. However, the rarity of this disease, which decreases the accuracy of such estimates, is evidenced in the wide range of reported rates of malignancy and functionality among series in the literature.

Patient 15 was pregnant when she first presented with symptoms of her paraganglioma, although the correct diagnosis was not appreciated by the referring hospital until after delivery of the infant, highlighting the importance of maintaining a high index of suspicion for active neuroendocrine tumors in hypertensive pregnant patients. Although hypertension is the most common medical complication of pregnancy, and paraganglioma in pregnancy is rare, it has been suggested that, in any pregnant woman with hypertension or with otherwise clinically unexplained symptoms, the routinely performed fetal ultrasound be extended to the upper

Table 2. Reported series of retroperitoneal paraganglioma

First author	Institution	Time period	N	Size (cm)*	Functional(%)	Malignant(%)†
Sclafani, 1990[12]	MSKCC	1949–1990	22	10.5	36	50
Hayes, 1990[15]	AFIP	1979–1989	28	8.6	64	14
Melicow, 1977[16]	Columbia	1926–1976	9	NR	89	22
Golstein, 1999[17]	Vanderbilt	1950–1998	26	NR	27‡	23
Van Heerden, 1982[18]	Mayo§	1971–1980	20‖	NR	NR	40
Altergott, 1985[13]	Loyola	1972–1983	4	9.0	100	50
Kryger-Baggesen, 1985[14]	Denmark¶	1948–1983	38	NR	0	29
Glenn 1976[19]	Cornell¶	NR¶	28	NR	NR	31
Erickson, 2001[2,#]	Mayo§	1978–1998	57	5.6**	92	0 (5)††
Somasundar, 2000[11,#]	WVU	1986–1996	5	NR	80	0
Present series	JHU	1984–2005	21	7.4	57	10
Weighted average	All	—	238	—	53.9%	24.2%

MSKCC = Memorial Sloan-Kettering Cancer Center; AFIP = Armed Forces Institute of Pathology; WUV = West Virginia University School of Medicine; JHU = Johns Hopkins University; NR, not reported.
*Greatest dimension.
†Generally defined as metastasizing.
‡A seven patient subset of this series published in 1982[20] reported that all seven patients had functional tumors, but the functional rate in the current series is not reported.
§These two Mayo series overlap by 2 years.
‖Includes 3 extraabdominal tumors.
¶Predominantly a review of the literature as opposed to an institutional series.
#Excluding nonretroperitoneal cases.
**Greatest dimension calculated from reported volume of 94.1 cm^3 for tumors below the neck (including thoracic tumors), assuming a sphere.
††Five percent of 249 patients screened had malignant tumors and were excluded from this study of benign tumors.

abdomen, because 90% of all catecholamine-secreting neuroendocrine tumors are typical pheochromocytomas, that is, are adrenal in location.[23]

Surgical resection offers the only chance for a cure in these patients and is associated with improved survival. In a series of 22 cases of extra-adrenal retroperitoneal paraganglioma from Memorial Sloan-Kettering Cancer Center (MSKCC), the 5-year survival for tumors not resected was 19% compared with 75% after complete resection.[12] This is consistent with our postresection 5-year survival rate of 73%.

Because paragangliomas are rare tumors, all series, including our own, have limited power to detect significant differences. For example, in Fig. 2 the low numbers do not allow detection of significant differences if they exist. Our significant finding in Fig. 1, on the other hand, has a known chance (0.02) of representing a type I (false positive) error.

Recurrences after resection are possible, and the rate of recurrence is likely underestimated in most series because different surgeons may treat the primary and recurrent tumors. The reported rate of local recurrence in the MSKCC series was 50% of resected cases. Despite our lower rate of recurrence, we agree with others who have recommended that follow-up be lifelong for these patients, given that metastases have been observed as late as 7 years after paraganglioma[12] and local recurrence as late as 13 years after resection of pheochromocytomas.[24] The greater proportion of metastases in the MSKCC series (50%) is consistent with the lower overall survival in that series compared with the current series (5-year survival of 60% vs. 73%). However, the MSKCC series began in 1949, allowing for longer follow-up. Furthermore, the recognition and treatment of this disease has evolved significantly over the ensuing period.

As is true concerning its more common adrenal counterpart, pheochromocytoma, large or functioning paragangliomas require careful preoperative preparation, such as aggressive appropriate blood pressure control, sufficient planned operative time, collaborative operative support (such as preparation for possible en bloc resection or vascular reconstruction, as was required in 41% of our cases), and sufficient blood-replacement products. Control of elevated blood pressure caused by elevated catecholamines in the preoperative period should include α-blockade and intravenous hydration, followed by β-blockade only after α-blockade had been optimized. Perioperative anesthesia management of patients with pheochromocytomas and paragangliomas has been recently reviewed.[25] When the

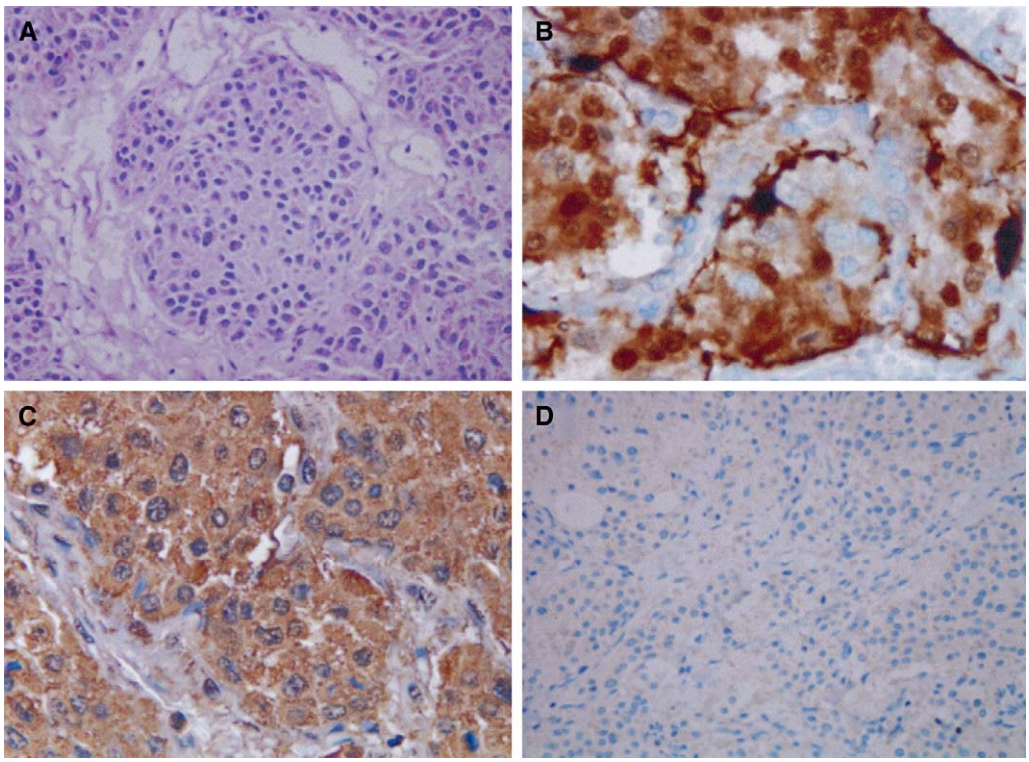

Fig. 4. Histologic diagnosis of paraganglioma. (**A**) Hematoxylin-eosin stain of chief (type 1) cells arranged in one of the typical cell nests, or zellballen (×60). (**B**) Peripheral to the cell nests are the stellate sustentacular (type 2) cells, intensely brown after S-100 immunolabeling (×100). (**C** and **D**) Also classic for paragangliomas, chromogranin immunolabeling is strongly positive (×100 in **C**), and cytokeratin immunolabeling is negative (×60 in **D**).

hospital, patient, and surgeon are adequately prepared, even very large tumors may be safely resected.

CONCLUSION

Retroperitoneal extra-adrenal paragangliomas are rare tumors whose optimal management requires the surgeon to be highly attentive to the disease course, from diagnosis of functioning or nonfunctioning lesions, through operative treatment that may require adjacent organ resection, to lifelong follow-up for recurrences. Because of their rarity, these tumors are not well studied. In our series, size greater than 7 cm was predictive of adjacent organ resection, a finding that may prove useful in preoperative planning.

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Bile Duct Growing Factor: An Alternate Technique for Reconstruction of Thin Bile Ducts After Iatrogenic Injury

Miguel Ángel Mercado, M.D., Héctor Orozco, M.D., Carlos Chan, M.D., Carlos Quezada, M.D., Alexandra Barajas-Olivas, M.D., Daniel Borja-Cacho, M.D., Norberto Sánchez-Fernandez, M.D.

A variant of bilioenteric anastomosis, laterolateral hepatojejunostomy, is described in which the opened anterior aspect of the common hepatic duct and left hepatic duct is anastomosed to a Roux jejunal limb. This technique is specially designed for thin, injured bile ducts in which a conventional anastomosis is difficult due to the small diameter of the ducts. A wide anastomosis is obtained, leaving the posterior wall as a conduit for bile, ensuring an adequate anastomotic diameter. (J GASTROINTEST SURG 2006;10:1164–1169)

KEY WORDS: Hepatojejunostomy, bile duct, iatrogenic injury

The surgeon involved in the treatment of bile duct injuries related to laparoscopic cholecystectomy can face several scenarios. In some instances, the patient arrives stable, with jaundice, history of cholangitis, and dilated extrahepatic bile ducts, fully visible on ultrasound. In this condition, a bilioenteric anastomosis is easy to create. Unfortunately, there are patients who arrive with systemic inflammatory response or a biliary fistula with or without biliary peritonitis. Another scenario is when the injury has been recognized in the index operation, allowing identification of the severed duct, which is usually small and thin.

It is a technical challenge to create an enteric anastomosis to a small and thin hepatic duct. It has been emphasized that in many instances, it is wiser to delay the surgery for several weeks in order to operate on a stable injury.

Placement of a percutaneous catheter into the bile ducts allows drainage of all the segments of the liver with subsequent diversion of bile. This maneuver, which is necessary to treat cholestasis and cholangitis and to prevent liver function deterioration related to obstruction, does not always result in dilation of the biliary tree. On the other hand, it is very difficult to predict which patient is going to dilate and which is not.

It is extremely important to create the bilioenteric anastomosis to a healthy, noninflamed, nonscarred, nonischemic duct. Stabilizing the injury limits ischemic damage to the duct. It has been suggested that a larger injury has to be presumed whenever there is ischemic damage.[1]

Our group has proposed a high repair to warrant an anastomosis to healthy, nonischemic ducts. At first, we did it only in the acute cases (when the injury is repaired during the same operation in which the injury occurred); later we started creating it routinely in all cases in order to obtain a low-risk bilioenteric, Roux-en-Y hepatojejunostomy.[2]

By creating the anastomosis under these conditions, we believe we prevent a nonischemic stenosis in the postoperative period, although it does not offer a wide duct for the anastomosis. The

From the Department of Surgery, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán," Tlalpan, Mexico.
Reprint requests: Miguel Ángel Mercado, M.D., Department of Surgery, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán," Vasco de Quiroga No. 15, Tlalpan 14000 Mexico, D.F. e-mail: mercadiazma@yahoo.com

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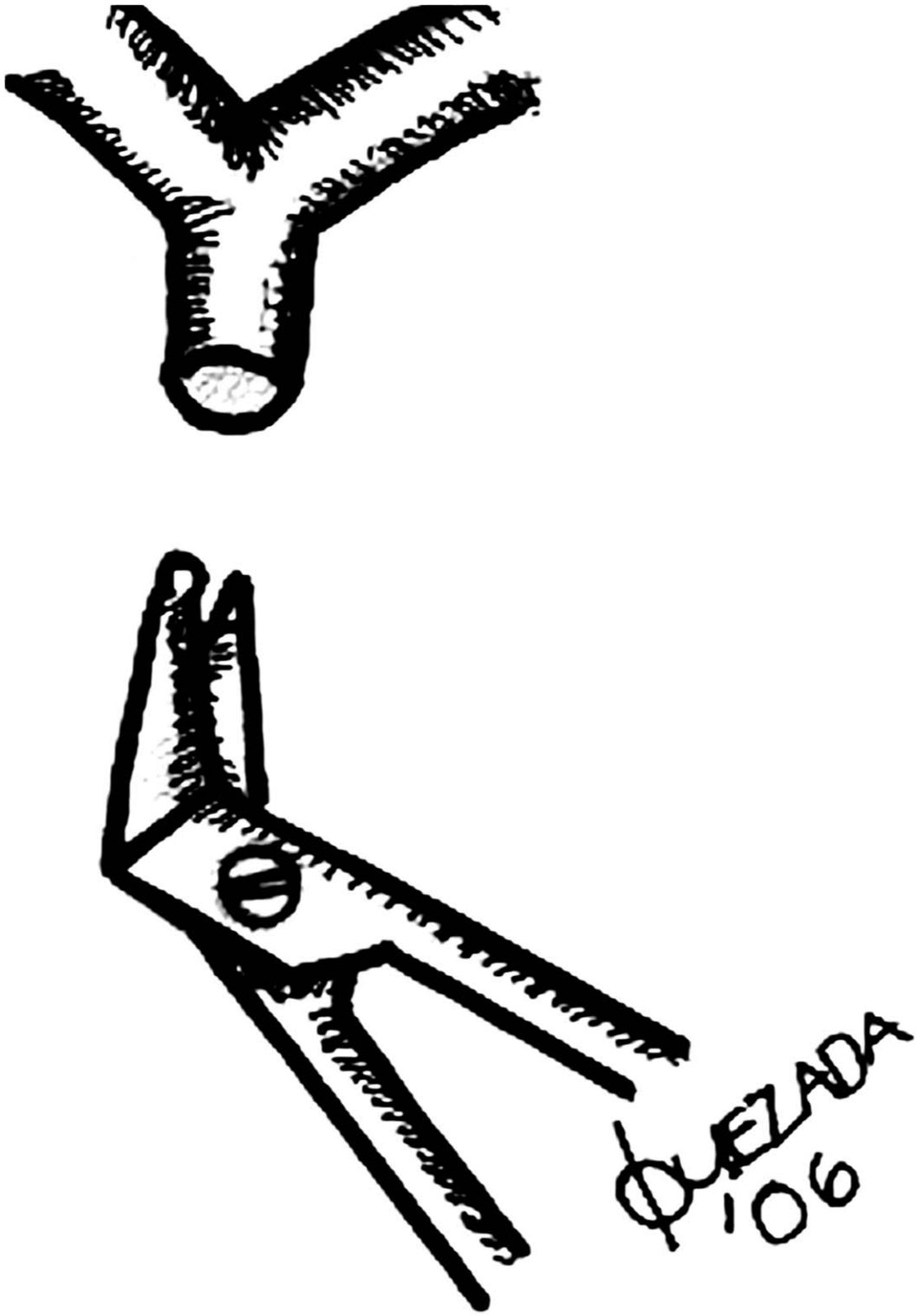

Fig. 1. The severed thin duct is shown with preserved junction. Fine Potts scissors are used for the anterior cut.

Fig. 2. The anterior aspect of the duct is opened with a fine Potts scissors, with the cut directed to the left duct in order to preserve the lateral vessels.

Fig. 3. Complete opening of the common and left duct. To reach this level, iy is necessary to remove the hilar plate and, if necessary, the adjacent portions of hepatic segments IV and V.

Hepp-Couinaud approach with Jarnagin and Blumgart modifications is an excellent alternate for laterolateral hepatojejunostomy.[3] Partial removal of segments IV and V also promotes better exposure of the ducts with adequate placement of the jejunal limb.[2]

A high-quality anastomosis is one that is done to nonischemic, noninflamed, and/or nonscarred bile ducts. The use of absorbable monofilament sutures contributes to the goal by reducing the inflammatory reaction at this level.

Most surgeons create the anastomosis when they find a healthy duct. When a thin duct is found, less than 4 mm in diameter, a technically difficult anastomosis is to be expected. Sometimes the anastomosis allows the placement of only a few stitches, and some surgeons advise the placement of transanastomotic tubes.

Herein we describe an alternate easy technique for anastomosis in the common hepatic duct in which its diameter is small (less than 4 mm).

Starzl et al.[4] described a technique for small vascular anastomosis in which a wide lumen was obtained after placing a continuous polypropylene suture, calling it the "growth factor." Paraphrasing this, we refer to this technique as the "bile duct growing factor."

TECHNIQUE

After careful liberation of all adhesions (if the patient had a previous operation), the porta hepatis is completely dissected. All of the hepatic arterial branches are carefully preserved. When the duct is found (the lumen in the acute injury or a scar in the delayed repair), removal of the duct has to be done up to a level at which a healthy duct is found.

There is no need to dissect the duct more when its main vessels are found. If the duct is thin, we open its anterior aspect with the help of Potts scissors (Figs. 1 and 2). Fine absorbable sutures are placed in the border of the duct to control bleeding from the edges (Fig. 3). These types of sutures are preferred to electrofulguration, in order to limit the duct damage. The anterior opening is dissected, if necessary, into the left duct, until a 1.5-cm opening is achieved. For the left duct, we sometimes require dissection of the hilar plate and, on some occasions, even partial resection of segment IV. After this maneuver, the foramen of secondary biliary branches can be identified with the help of thin dilators. During the dissection, the posterior wall and the lateral aspects of the ducts are not dissected.

After the Roux-en-Y jejunal limb has been prepared, the laterolateral anastomosis is done. Beginning in the upper angle, a fine stitch is placed (knot outside) and additional stitches are placed (out-in, in-out) along the medial border of the duct (Figs. 3 and 4). Afterward, we start the complete medial posterior row (out-in, in-out) at the upper angle. After one third of the anterior row is placed, knotting is started. Placement of stitches in the upper

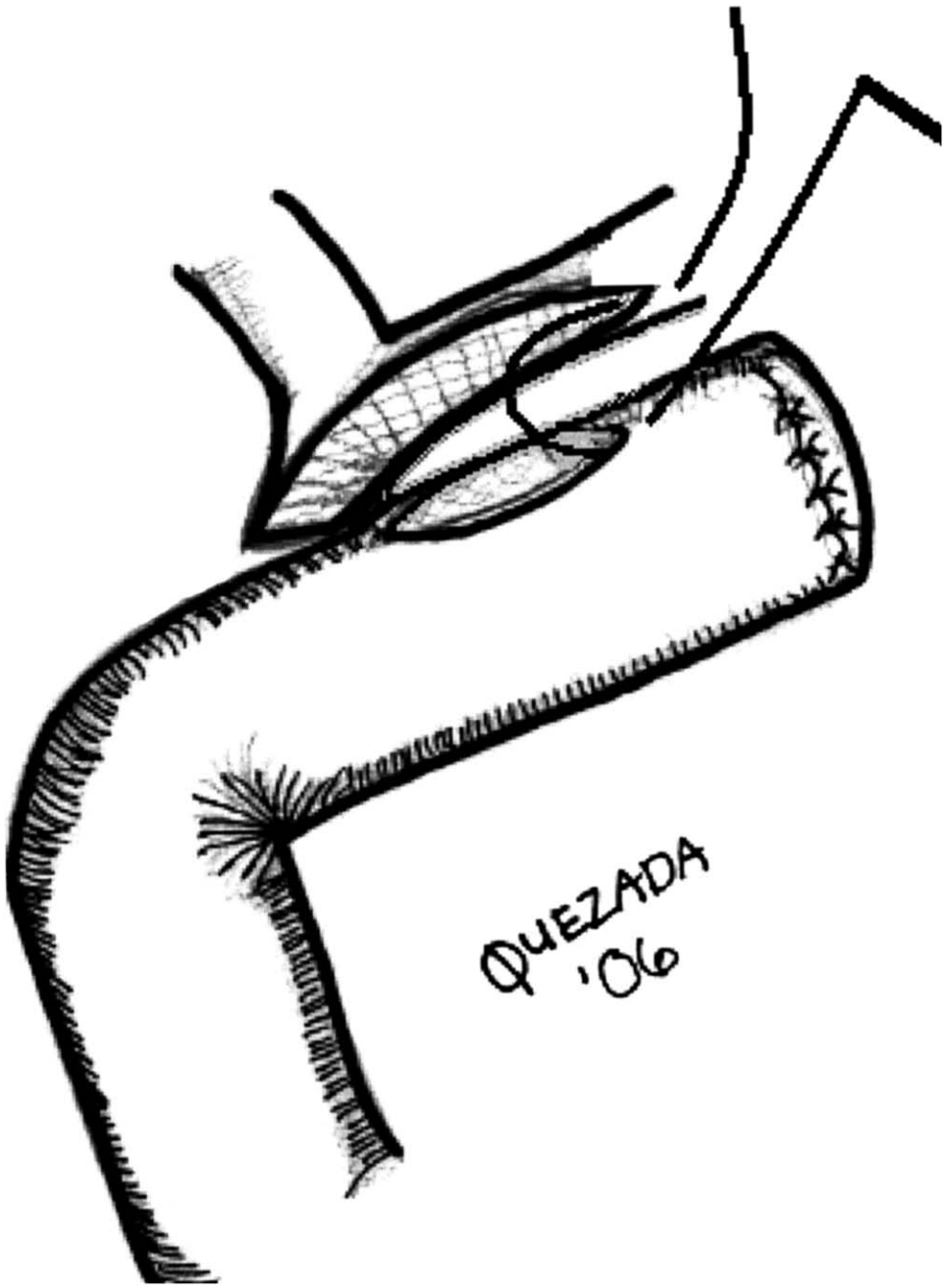

Fig. 4. Laterolateral hepaticojejunostomy. Everting stitches (5-0 absorbable monofilament) are used in order to leave the knots outside.

angle is critical because of the very small lumen found of the duct. They have to be placed when the limb is separated, so that no occlusion of the lumen occurs.

Bile from the secondary ducts flows along the posterior wall (slide effect) and then through the wide opening to the jejunal limb.

This approach can also be used when leaving a small scar in the distal stump of the common hepatic duct. This scar is not included in the anastomosis; if it were, it would represent only a small portion of the anastomosis.

RESULTS

Among 355 cases of bile duct reconstruction, this technique has been used in 32 cases in which a small lumen has been found and the probability of postoperative occlusion of an anastomosis has been

a concern. All of the injuries were classified as Strasberg E1 or E2.[5] Two reconstructions of bile ducts in patients with a liver transplant have also been done with this technique when a failure of the primary anastomosis and dehiscence occurred. No operative deaths have resulted, and the postoperative course of the patients has been uneventful.

After a follow-up of more than 48 months, no cases of cholangitis have been reported, and no patient needed either radiologic instrumentation or a new operation.

These types of injuries (Strasberg E1 or E2) have the best results in all reviews. We have shown that a preserved confluence of the bile ducts after the injury has the best outcome, when a high-quality anastomosis can be created.[6,7]

Although in many instances a small-lumen, high-quality anastomosis has a good prognosis, a wide anastomosis enhances the chance of an excellent outcome. A wide anastomosis (1.5–2 cm) usually results in no dysfunction. Technically, it is easier to do, because it allows correct positioning of the stitches.

Also, postoperative early dysfunction of the anastomosis (probably secondary to anastomotic edema, mainly on the intestinal side) is prevented. Also, avoiding posterior and lateral dissection of the ducts prevents further ischemic injury and makes an easier technical approach, even in an anatomical complex hilus. The laterolateral anastomosis preserves the posterior aspect of the bile ducts, the posterior wall of the common and left hepatic ducts, the anterior aspect, and the limb lumen, resulting in adequate drainage.

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Review Article

Biliary Pancreatitis

George Sarosi, M.D., Robert V. Rege, M.D.

Acute pancreatitis is a common, potentially life-threatening disease that presents with acute abdominal pain. The term *acute pancreatitis* comprises a wide spectrum of disease ranging from a mild, quickly resolving problem manifest only by increased serum amylase and lipase with edema of the gland to a severe, life-threatening disease with pancreatic necrosis, multi-organ failure, and secondary infectious complications.

Although high-quality data on temporal trends are limited, it appears that the incidence of pancreatitis is increasing.[1–3] However, the incidence varies widely, from 5−50 cases per 100,000 populations, between different countries.[4] The reasons for the geographic variation are not entirely clear. Although associated with a myriad of causes, the incidence of the acute pancreatitis largely reflects the incidence of alcohol abuse and prevalence of gallstones, the two leading causes of acute pancreatitis in the population. In most reports, gallstone disease is the leading cause being responsible for roughly 30−50% of cases of acute pancreatitis.[1] Despite the relatively high prevalence of gallstones in Western populations, the lifetime risk of developing biliary pancreatitis in a given individual with gallstones is low (8−11%).[5] It is more frequent in women than in men, and frequency increases with age.[4] But despite being more common in the elderly, there is little evidence that gallstone-induced pancreatitis is of greater severity than other causes of pancreatitis. Most patients have a brief course of mild to moderately severe pancreatitis that resolves promptly with passage of the gallstone.

PATHOGENESIS OF BILIARY PANCREATITIS

The diverse list of conditions associated with acute pancreatitis suggests a multitude of causes that may trigger the event, such as direct damage to the pancreas and/or pancreatic duct by trauma, toxic effects of alcohol and drugs on pancreatic acinar cells, and genetic defects present in familial pancreatitis. The following discussion will specifically address the events that trigger acute pancreatitis in patients with gallstones. Once acute pancreatitis is established, the resulting pathological changes and cellular dysfunction that ensues is similar, regardless of cause. A multitude of factors then determine the severity of the episode and whether there will be systemic consequences. The pathological events that result in severe pancreatitis will also be reviewed.

Biliary pancreatitis was the first form of pancreatitis in which the causative event was recognized. In 1901, Opie[6] observed and reported impaction of a gallstone at the ampulla of Vater at autopsy in a patient who died of pancreatitis. His suggestion that the impacted gallstone lying distal to the junction of the bile and pancreatic duct resulted in increased pancreatic duct pressure and reflux of bile into the pancreatic duct became known as the "common channel theory" of pancreatitis. The common channel theory was rapidly accepted and it was thought that both increased pancreatic ductal pressure and the toxic effects of bile in the duct led to disruption of ductal mucosal integrity with subsequent damage to the gland.

Variations of the common channel theory dominated the theories of pathogenesis of biliary pancreatitis during most of the twentieth century and led to most of the animal models of pancreatitis studied in the laboratory. However, many of models examining the effects of increased pressure and toxic effects of bile salts were nonphysiological. For example, forceful injection pressures greatly exceeded the pressure that actually occurs during obstruction of the duct in vivo. Such studies must be viewed critically. Moreover, a large number of patients with acute

From the Division of Gastrointestinal/Endocrine Surgery (G.S.), Department of Surgery (R.V.R.), University of Texas Southwestern Medical Center, Dallas, Texas.
Reprint requests: Robert V. Rege, M.D., Department of Surgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9031. e-mail: robert.rege@utsouthwestern.edu

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pancreatitis do not have gallstones, let alone impacted gallstones, in their common bile duct at operation. In addition, the anatomy of the ampulla of Vater is quite variable and, in many patients, an impacted gallstone cannot anatomically cause common channel obstruction with bile reflux. For example, Jones and colleagues[7] showed that one third of patients with acute pancreatitis have separate bile duct and pancreatic duct openings on intraoperative cholangiography. In others, the channel is so short that the pancreatic duct will be directly obstructed by the stone negating bile reflux into the pancreatic duct. In short, the common channel theory does not explain a large number of cases of acute biliary pancreatitis.

The lack of impacting stones in patients was later explained by the observations of Acosta and Ledesma in 1974.[8] They screened the stools of 36 patients with gallstones and acute pancreatitis and compared them to 36 patients with gallstones but no evidence of pancreatitis. Thirty-four of the 36 patients with, but only 3 of 36 patients without, pancreatitis were found to have gallstones in their feces. Moreover, calculi retrieved from stools were identical to gallstones later removed at cholecystectomy. These findings strongly suggested that an episode of acute pancreatitis was associated with passage of a gallstone through the common bile duct into the intestine. The authors suggested that acute pancreatitis is frequently caused by "transient blockage of the ampulla of Vater by migrating gallstones." In 1980, Acosta, Pellegrini, and Skinner[9] examined the role of gallstones in acute pancreatitis in 78 patients with acute gallstone pancreatitis. They found impacted common bile duct stones in 49 patients, choledocholithiasis without impaction in 8 patients, gallstones in the duodenal lumen during a transduodenal exploration in 2 patients, and gallstones in the feces of 9 patients without common duct stones who were screened postoperatively. The remaining 10 patients with only gallbladder stones did not undergo postoperative screening of their stools. The authors concluded that acute biliary pancreatitis is caused by obstruction of the common bile and pancreatic ducts, but the obstruction might only be transient. They also theorized that pancreatitis would be mild if obstruction of the ampulla was relieved within 48 hours but more severe with persistent obstruction.

It must be understood that although it is now generally accepted that impaction of a gallstone in, or passage through, the distal common bile duct triggers acute pancreatitis, not every patient who passes stones or has choledocholithiasis develops pancreatitis. Moreover, it is also recognized that passage of "sludge" or "microlithiasis" through the bile duct may trigger an episode of acute pancreatitis. It is difficult to understand how sludge and small stones lead to ductal obstruction.[10,11] Therefore, theories of transient obstruction still do not fully explain all cases of biliary pancreatitis. Some authors have suggested that passage of stones through the common bile duct into the intestine causes inflammation and edema of the ampulla of Vater[12] with functional obstruction of the pancreatic duct or that a dilated sphincter of Oddi allows reflux of duodenal juice into the bile and pancreatic ducts.[13]

Joehl and coworkers[14] studied an obstruction-induced model of acute pancreatitis in conscious rats. Rats were prepared with sham operation, bile duct ligation alone, or combined bile and pancreatic duct ligation. The ligatures were placed on the bile duct so that bile could not reflux into the pancreatic duct. Bile duct obstruction alone did not induce acute pancreatitis, but it did increase circulating cholecystokinen (CCK) levels above normal. Combined bile-pancreatic duct ligation resulted in markedly elevated serum amylase, edema of the pancreas, and very significant increases in circulating CCK levels. The marked elevations of circulating CCK raised the possibility that acinar cell stimulation plays a role in the pathogenesis of obstruction-induced pancreatitis, especially since another model of pancreatitis utilizes high does of cerulean, a CCK agonist.[15–18] Interestingly, shunting of bile and/or pancreatic juice back into the duodenum of rats with combined bile and pancreatic duct ligation decreased circulating CCK levels and ameliorated acute pancreatitis. These findings strongly indicated that both increased pancreatic ductal pressure and exclusion of bile/pancreatic juice from the duodenum are important in the pathogenesis of obstruction-induced acute pancreatitis.[19–21] Obstruction not only increases pancreatic duct pressure but also increases acinar cell stimulation, since circulating CCK is increased by exclusion of bile and pancreatic juice from the duodenum. Examination of the zymogen-enriched subcellular fraction of rat pancreas homogenates demonstrated that amylase synthesis is increased by acinar cells during an episode of acute pancreatitis indicating that acinar cell hypersecretion is indeed playing an important role in acute pancreatitis.[21] The link between elevated circulating concentrations of CCK and acute pancreatitis was further studied by pretreating rats with the somatostatin analog octreotide to eliminate CCK release or the specific CCK antagonist L-364,718 to block its effects on the acinar cell and then inducing pancreatitis in the combined bile-pancreatic duct model. Both somatostatin and octreotide limited the severity

of acute edematous pancreatitis in rats with combined bile and pancreatic duct obstruction. As predicted, octreotide limited the increase in circulating CCK levels.[22]

Ligation of the bile and pancreatic ducts in the rat causes only edematous, not severe, necrotic pancreatitis. Although edematous pancreatitis in rats is quite similar to the mild edematous pancreatitis found in 70–80% patients with acute pancreatitis, the rat model does not mimic the severe gallstone pancreatitis observed in the remainder of patients. On the other hand, bile and pancreatic duct ligation in opossums results in severe acute necrotizing pancreatitis that uniformly leads to death within 14 days. The morphological features of early pancreatitis in these two species are almost identical, indicating that the triggering events are likely similar in both models and that the events triggering early pancreatitis are likely pertinent to both species. Other factors determine if pancreatitis will progress to necrosis.[23,24]

Our current understanding of the pathogenesis of biliary pancreatitis begins with passage of a gallstone into the common bile duct and often into the duodenum. The stone may cause obstruction or transient obstruction, inflammation of the sphincter of Oddi, and/or reflux of duodenal contents into the bile and pancreatic ducts. Exclusion of bile and pancreatic juice from the duodenum also stimulates release of CCK into the circulatory system and acinar cell hyperstimulation. Acinar cell hypersecretion against elevated pancreatic duct pressure results in acinar cell dysfunction, release of pancreatic enzymes into serum, edema of the gland, and, under certain conditions, severe cellular damage leading to cell death. During an episode of pancreatitis, pancreatic enzyme synthesis, transport, and secretion appear to be disturbed,[15–18,25] changes that are detected very early after pancreatic duct obstruction. The progression of the disease after acinar cell dysfunction is probably very similar in all types of pancreatitis.

Normally, digestive enzymes are secreted from acinar cells as inactive zymogens. Enterkinase in the brush border of the intestine activates trypsin, which in turn activates zymogens to functional digestive enzymes. Pancreatitis results when early activation of digestive enzymes occurs in the cells or in the parenchyma of the pancreas.[26,27] As they pass through the Golgi apparatus, digestive enzymes are separated from lysosomal enzymes, protecting against inadvertent intracellular activation of enzymes. One theory, the co-localization theory, hypothesizes that activations occurs when digestive enzymes in dysfunctional cells are abnormally transported to lysosomes after synthesis. In fact, co-localization of digestive and lysosomal enzymes has been demonstrated during acute pancreatitis.[16,17,25] It is hypothesized that co-localization results in intracellular activation of digestive enzymes, cell damage, cell death, and leakage of activated enzymes into the pancreatic parenchyma causing more damage. Cell damage induces edema and inflammation. The inflammatory response is mediated both by cytokines and by immune cells, especially macrophages. Release of free radicals causes peroxidation of cellular membranes. Early inflammation leads to increased blood flow, but later increasing cell damage, edema, and systemic effects of pancreatitis such as hypovolemia decrease pancreatic blood flow, causing further ischemic damage to the gland.

The cellular immune response to pancreatitis may be the key factor for systemic effects of the disease. Indeed, blocking of macrophage activity with gadolinium in experimental hemorrhagic pancreatitis in mice decreased lung injury but did not alter the local severity of pancreatitis.[28] Moreover, activated enzymes and inflammatory agents gain access to the circulation resulting in multiorgan dysfunction and the systemic effects of acute pancreatitis. The inflammatory response to pancreatitis can be so intense that patients exhibit systemic responses indistinguishable from sepsis, although they do not necessarily have an infected pancreas (pancreatic abscess). This syndrome, termed systemic inflammatory response syndrome (SIRS), is similar to that reported after significant trauma and burns and clearly contributes to multiorgan failure. Of course, secondary infection may occur in the necrotic pancreas leading to true sepsis, further complicating the disease. The differentiation between SIRS and pancreatic abscess is often problematic.

DIAGNOSIS OF BILIARY PANCREATITIS

A diagnosis of acute pancreatitis should be entertained in any patient presenting with acute-onset epigastric abdominal pain, nausea, and vomiting. The pain typically begins as moderate to severe pain that increases in intensity over several hours to a few days, often radiates to the back or flanks, and is typically boring and constant in character, not colicky. In more severe cases, pain may be diffuse rather than localized to the epigastrium. In addition, fever or chills are commonly associated with pain in acute pancreatitis, and abdominal tenderness of varying degrees is a major physical finding associated with pancreatitis. Diffuse peritonitis may be present and indistinguishable from other disorders, causing a surgical abdomen. Therefore, acute pancreatitis

may be difficult to distinguish from biliary colic, acute cholecystitis, or perforated viscus.

Because the clinical presentation of acute pancreatitis is relatively nonspecific, a variety of biochemical and imaging studies are necessary to confirm the diagnosis. Measurements of serum amylase and lipase are the primary means of confirming a diagnosis of acute pancreatitis. Elevation of the serum amylase occurs rapidly in the course of acute pancreatitis, and because this biochemical marker is available in nearly all health care settings, it remains the primary supplemental diagnostic test to confirm the diagnosis of acute pancreatitis. However, the relatively low specificity of amylase, which can be elevated from a large variety of causes due to extrapancreatic sources of amylase, results in specificities as low as 70% and a sensitivity of 80−90% and limits its utility. Up to 20−30% of patients with pancreatitis have a normal amylase level at presentation, and since amylase rapidly normalizes, its sensitivity decreases at time points greater than 24 hours after an attack begins.[29,30] Elevated serum lipase, the other biochemical marker used to confirm the diagnosis of acute pancreatitis, is just as sensitive as and more specific than amylase, primarily because there are fewer extrapancreatic sources of lipase. Lipase levels also remain elevated longer after the onset of acute pancreatitis.[29] Interestingly, despite the different limitations of amylase and lipase in the diagnosis of acute pancreatitis, it does not appear that using both markers improves diagnostic accuracy.[31]

Serum markers may be helpful in distinguishing biliary pancreatitis from other causes of pancreatitis, because amylase levels tend to be markedly elevated (>1000 IU/L) in biliary pancreatitis. Such elevations are rare in alcoholic pancreatitis.[32] However, although a high serum amylase value suggests a biliary cause, the specificity of serum amylase alone in distinguishing between the etiologies of pancreatitis is poor. Determinations of serum liver biochemistries such as ALT, AST, alkaline phosphatase, and bilirubin have also been advocated as aids to discriminate between pancreatitis etiologies. Interestingly, while elevations in all of the liver biochemistries support the diagnosis of biliary pancreatitis, elevation of ALT greater than 3-fold the normal value has the highest positive predictive value for biliary pancreatitis.[33]

Imaging studies are important adjuncts in the diagnosis of pancreatitis and play a critical role in identifying gallstones as the etiologic agent in pancreatitis. Although trans-abdominal ultrasound is accurate in the diagnosis of pancreatitis, gaseous bowel distention can limit pancreatic imaging in the setting of acute abdominal emergencies.[34] Ultrasound, however, is highly accurate in diagnosing gallstones or sludge in the gallbladder and the most useful test for establishing gallstones as the etiology of acute pancreatitis. It detects cholelithiasis in 70−80% of patients with biliary pancreatitis, and is superior to computed tomography (CT) in detection of choledocholithiasis and biliary dilation.[35]

CT scanning is the most accurate imaging study to confirm, and may be the gold standard for, the diagnosis of acute pancreatitis.[36] CT accurately demonstrates swelling of the gland, peripancreatic inflammation (Fig. 1) and, late in the disease, pancreatic fluid collections and/or pancreatic necrosis (Fig. 2). However, it is expensive and not always necessary. In patients in whom biliary pancreatitis is suspected by biochemical profiles but have a negative trans-abdominal ultrasound, endoscopic ultrasound should be considered to confirm the diagnosis. Although the evidence is evolving, it appears to be as accurate as endoscopic retrograde cholangiopancreatography (ERCP) without the risks associated with ERCP.[37] Magnetic resonance cholangiopancreatography (MRCP) is another new noninvasive method for assessing biliary anatomy. Although the exact role of MRCP in biliary pancreatitis is still being defined, it appears to be nearly as sensitive as ERCP for the diagnosis of common bile duct stones.[38] The choice between MRCP and EUS as a noninvasive adjunct in the diagnosis of biliary pancreatitis depends on institutional expertise in these operator-dependent techniques.

MANAGEMENT: ASSESSMENT OF SEVERITY

One of the initial management challenges in caring for a patient with gallstone pancreatitis is assessing the severity of the attack. The majority of patients have a mild self-limited course of edematous pancreatitis, with a low risk of mortality or complications. Roughly 20% of patients progress to severe pancreatitis with associated necrosis. In severe pancreatitis, the risk of major complications and death may be as high as 20−30%. Significant resources are required to care for patients with complicated pancreatitis.[39] The ability to accurately and promptly stratify the severity of patients with pancreatitis allows physicians to avoid excessive use of scarce medical resources in mild cases or undertreatment of severe cases. Multiple approaches have been used to assess severity in acute pancreatitis, including simple clinical assessment, multiple factor−scoring systems, and image- or laboratory-based studies. The ideal method for predicting severity of an attack of pancreatitis should accurately detect patients with severe pancreatitis within a few hours of

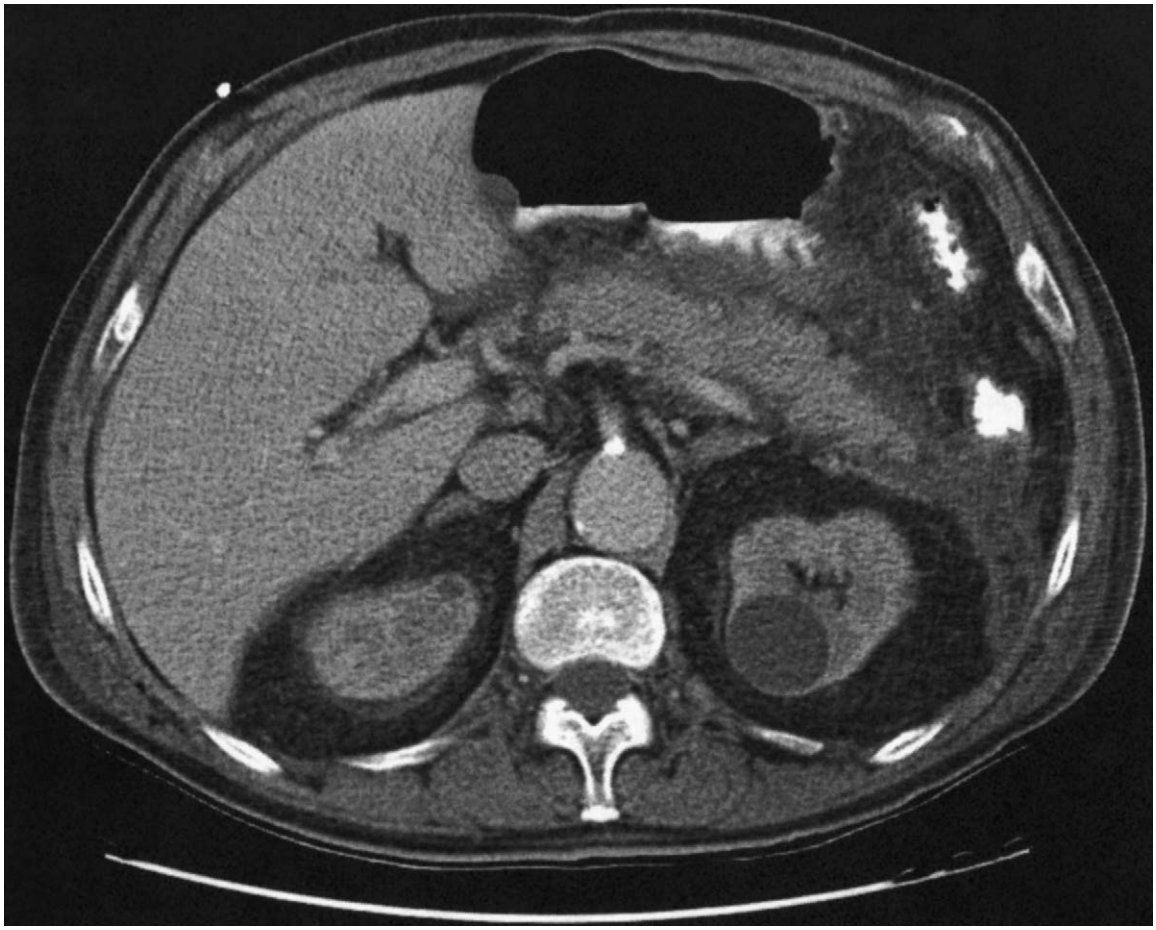

Fig. 1. Illustrates edematous pancreatitis. Note the loss of pancreatic definition and edema, the peripancreatic stranding, and the stranding in the perinephric space. All of the pancreatic parenchyma is perfused. (Image courtesy of Jorge Lopez, M.D., Dallas VAMC.)

hospitalization, use readily available noninvasive tests, and be inexpensive. Unfortunately, the presence of a wide variety of approaches demonstrates that an ideal method is yet to be developed.

Clinical assessment, especially by experienced observers, is very good at identifying mild pancreatitis, but sensitivity is poor early in the course of the disease with accuracies as low as 34%.[40] Therefore, Ranson in the early 1970s and Imrie (Glasgow score) in the late 1970s proposed multiple factor−scoring systems specific for pancreatitis. Both systems combined clinical and laboratory factors over the first 48 hours of care. A score of 3 or more factors is predictive of severe pancreatitis and associated with increased mortality.[41,42] Both systems have been modified but remain common clinically used tools for assessing pancreatitis severity (Table 1). Glasgow or Ranson's criteria are 70−80% accurate at predicting an episode of severe pancreatitis at 48 hours.[39] Despite the widespread use, both systems are limited by the 48-hour delay to achieve optimal accuracy and incomplete data collection can reduce their predictive value.

To address limitations of scoring systems, investigators in the 1980s applied the nonspecific disease severity score, APACHE II, to pancreatitis.[43] APACHE II is a multiply factor−scoring system based on physiologic and laboratory parameters, patient age, and comorbid conditions. Unlike disease specific scores, APACHE II score has good prognostic value at admission, uses physiologic and medical history data, is less likely to be limited by incomplete information, and may be recalculated daily to identify worsening patients. An admission APACHE II score of 8 or higher is roughly 70% sensitive and specific in predicting severe pancreatitis. A score greater than 10 at 48 hours is as accurate as Glasgow or Ranson's score in severity assessment.[39,43,44] Despite impressive performance of the APACHE II score, it is cumbersome and time consuming to calculate and has not achieved the popularity of the Ranson and Glasgow scores.

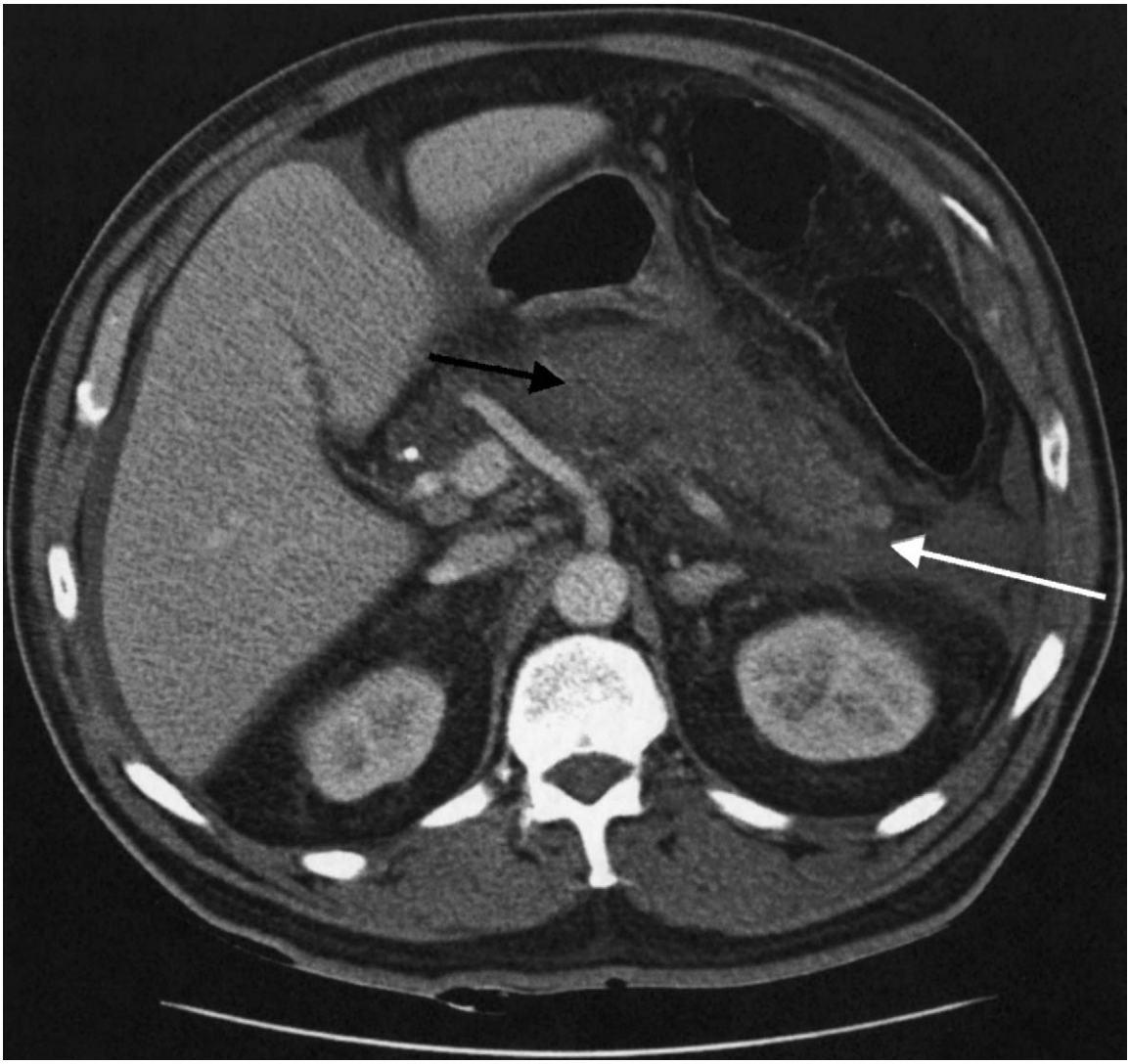

Fig. 2. Illustrates necrotizing pancreatitis. Only the tail of the pancreas enhances (*white arrow*). The central portion of the pancreatic body does not enhance and is necrotic (*black arrow*). (Image courtesy of Jorge Lopez, M.D., Dallas VAMC.)

Because of its central role in the pathophysiology of severe pancreatitis, early identification of pancreatic necrosis would seem to be an alternative for identifying patients with severe pancreatitis. In the early 1980s, several investigators used CT scanning to assess pancreatitis severity. In 1985, Balthazar and colleagues correlated a CT grading system based on the appearance of the pancreas on CT with outcome.[45] Their modified grading system with refined ability to detect pancreatic necrosis through the use of improved intravenous contrast techniques and thinner imaging cuts (Table 2) displayed excellent correlation with complications and mortality[46] with an accuracy at least equal to the Ranson and APACHE systems[47] (Table 3). Accurate CT detection of necrosis is optimal at 48−72 hours after the onset of an attack, and the delay in detection and requirement for iodinated contrast represent major limitations of CT grading of pancreatitis severity.

MANAGEMENT: INITIAL CARE

Supportive care is the initial management of patients with biliary pancreatitis. Because patients with pancreatitis have significant pain, analgesia with patient-controlled analgesia using narcotics should be given for pain relief. Accurate management of fluid and electrolytes with balanced electrolyte solutions is essential since patients with pancreatitis develop significant capillary leak and fluid sequestration. A urinary catheter is essential to verify adequate resuscitation. Patients with

Table 1. Criteria for Ranson's and Glasgow Pancreatitis Severity Scores

	Ranson's	Glasgow
Age	>70	—
White blood cell count	>18,000/mm^3	>15,000
Blood sugar level	>220 mg/dl	>10 mmol/L
Serum LDH	>250 U/L	>600 U/L
Serum AST	>250 U/L	>200 U/L
Hematocrit fall	>10%	—
BUN	Increase of >2 mg/dl	>16 mmol/L
Serum calcium	<8 mg/dl	<2 mmol/L
Arterial PO_2	—	<60 mm Hg
Base deficit	>5 mEq/L	—
Estimated fluid sequestration	>41	—
Serum albumin	—	<32 g/L

LDH = lactose dehydrogenase; AST = aspartase transferase; BUN = blood urea nitrogen.
For Ranson's criteria, the first five are assessed at admission and the last six at 48 hours after admission. For the Glasgow criteria, all are assessed at 48 hours after admission. The presence of three or more criteria with either system predicts a severe attack of pancreatitis.

predicted severe pancreatitis, evidence of organ failure, or greater than expected fluid requirements require intensive care unit with invasive monitoring of central venous pressures. Although high-quality evidence is scant, case series suggest that failure to reduce admission hematocrit in the first 24 hours is much more common in patients with necrotizing than interstitial pancreatitis,[48] suggesting that aggressive fluid resuscitation, and adequate perfusion of the inflamed pancreas, may reduce the risk of developing necrotizing pancreatitis. Although a number of specific therapies for pancreatitis have been studied, including protease inhibitors and antisecretory therapy with octreotide, randomized trials[49,50] have not shown benefit.

Table 2. Pancreatitis scoring system

	Finding	Points
Grade	A: Normal pancreas	1
	B: Pancreatic enlargement	2
	C: Pancreatic or peripancreatic inflammation	3
	D: Single peripancreatic fluid collection	4
	E: Two or more fluid collections or peripancreatic air	5
Necrosis	<30%	+2
	30–50%	+4
	>50%	+6

Table 3. Correlation of computed tomography (CT) severity score with morbidity and mortality

CT severity index	Morbidity	Mortality
0–3	8%	3%
4–6	35%	6%
7–10	92%	17%

A persistent area of controversy in management of pancreatitis is the role of antibiotic prophylaxis to prevent infected pancreatic necrosis. The details of the controversy were well addressed in the recent UK consensus recommendations on pancreatitis.[50] Definitive meta-analysis of multiple heterogeneous trials suggests a reduction in infected necrosis and mortality with antibiotic prophylaxis, but this could not be verified in a recent randomized controlled trial.[51,52] At this point, we currently provide 14 days of Imipenem therapy to our patients with severe gallstone pancreatitis.

Given the pivotal role of gallstones in triggering the cascade of events leading to biliary pancreatitis, a logical, specific therapy for gallstone-induced pancreatitis is early removal of the stone and elimination of obstruction at the ampulla of Vater. Initial attempts to accomplish this goal with early cholecystectomy and operative bile duct exploration demonstrated increased morbidity and mortality compared with standard delayed treatment.[53] At this time, operative clearance of impacted stones does not appear beneficial.

With the development of ERCP in the 1980s, investigators applied this new technique to patients with biliary pancreatitis. Three randomized trials comparing early ERCP and endoscopic sphincterotomy with standard supportive therapy have been performed. The first two single-institution trials demonstrated significant reduced morbidity in patients predicted to develop severe pancreatitis with ERCP performed within 24−72 hours of presentation.[54,55] In addition, the study from Hong Kong showed a strong trend toward reduced mortality in patients with severe pancreatitis. In contrast, a multicenter European trial showed no benefit with early ERCP, and in fact severe complications increased with early ERCP.[56] The discrepant results in these trials created significant confusion prompting secondary and meta-analysis.[57,58] Essentially, the trials showing benefits included patient with jaundice and biliary obstruction, while those that did not excluded such patients. Thus, urgent ERCP is recommended in patients with suspected or documented biliary obstruction and pancreatitis. In contrast, ERCP and sphincterotomy do not

alter the course of biliary pancreatitis without evidence of biliary obstruction.[49,50]

MANAGEMENT: DEFINITIVE CARE

The long-term treatment goal of gallstone pancreatitis is prevention of further episodes of pancreatitis. A recent paper suggests that recurrent pancreatitis can be more severe than the initial bout.[60] The standard approach is performance of cholecystectomy and cholangiography to remove stones in the gallbladder and exclude common bile duct stones. Cholecystectomy is effective: the recurrence of gallstone pancreatitis secondary to retained or primary bile duct stones occurs in less than 3% of patients after cholecystectomy.[59] Patients who do not undergo a cholecystectomy have a recurrence rate of pancreatitis between 20% and 60% over the 2–3 months. Because high early recurrence rates, it is recommended that surgically fit patients undergo cholecystectomy at their index hospitalization, as soon as pancreatitis has resolved.[49,50]

However, many authors question whether poor surgical candidates should undergo cholecystectomy. ERCP with sphincterotomy theoretically prevents further episodes of pancreatitis by decreasing the risk of stone impaction at the ampulla of Vater and can be performed with a low procedural risk. Although no randomized trials exist that compare the risks of cholecystectomy to those of endoscopic sphincterotomy with gallbladder in situ in pancreatitis patients, multiple trials have examined this question in patients with choledocholithiasis. Recurrent pancreatitis after endoscopic sphincterotomy occurs in 3–6% of patients over at least a 2-year follow-up period,[61,62] and there appears to be a 20–40%

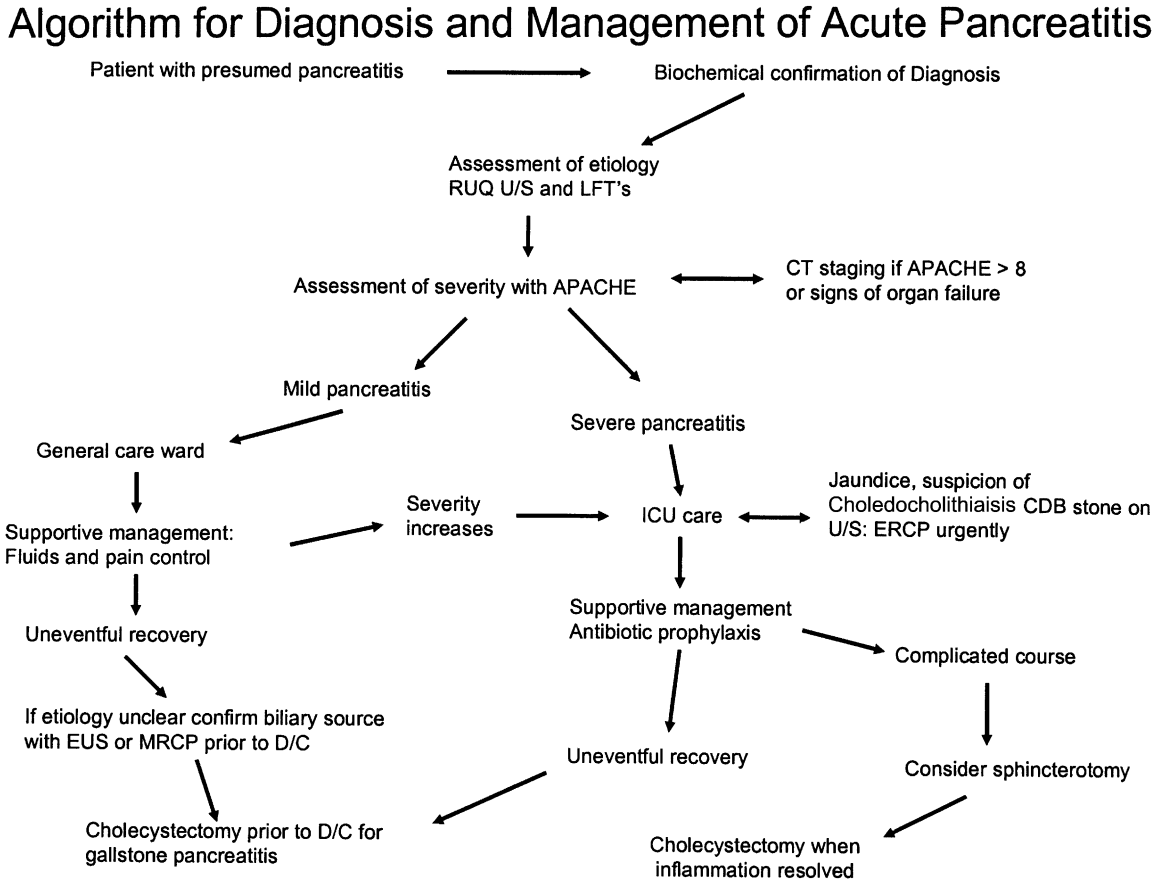

Fig. 3. Presents an algorithm for the diagnosis and treatment of patients with acute gallstone pancreatitis. Since the long-term goal of treatment is prevention of further episodes, cholecystectomy is should be done as soon as it is safe. The exact timing of the operation however depends on the severity of pancreatitis and whether the patients developed complication of acute pancreatitis. RUQ = right upper quadrant of abdomen, U/S = ultrasound, LFTs = liver function tests, CT = computed tomography, ICU = intensive care unit, CBD = common bile duct, ERCP = endoscopic retrograde choleangiopancreatography, EUS = endoscopic ultrasound, MRCP = magnetic resonance choleangiopancreatography, D/C = hospital discharge, APACHE = scheme for assessing severity of illness.

risk of developing other biliary tract complications, which may result in the need for later cholecystectomy over a 2- to 3-year period. These complications may be severe (cholecystitis, cholangitis, and jaundice) in up to 15% of patients.[63–65] Given these data, endoscopic sphincterotomy leaving the gallbladder in situ after biliary pancreatitis appears to be an acceptable option in poor-risk patients.

Patients with severe necrotizing pancreatitis also should not undergo cholecystectomy prior to discharge from their index pancreatitis presentation. They are at an increased risk for pancreatic infectious complications and conversion to open surgery if they are operated on early in their postpancreatitis course.[66] Based on these observations, it seems appropriate to delay cholecystectomy until their acute illness is resolved. Given the ability of ERCP plus endoscopic sphincterotomy to reduce the risk of recurrent pancreatitis, it seems prudent to recommend endoscopic sphincterotomy in any patient who will have a delayed cholecystectomy.

An algorithm for diagnosis and management of acute gallstone pancreatitis is summarized and illustrated in Figure 3.

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Transverse Colon Herniation Through the Foramen of Winslow Presenting With Unusual CT Findings

Luigi Maria Pernice, M.D., Maurizio Bartolucci, M.D., Valentina Mori, M.D., Luca Ponchietti, M.D., Alessandro Tedone, M.D.

Bowel herniation through the foramen of Winslow is among the rarest of internal hernias, accounting for less than 0.8%. In its origin, a pivotal role is played by some anatomic variations, or anomalies such as the increased mobility of the right transverse colon, and maybe the exceedingly large bore of the foramen itself. The first case of hernia through the foramen of Winslow was reported by Blandin in 1834. Since then, no more that 200 new cases have been described. Diagnosis usually is established during surgery while treating a bowel obstruction. Only in an exceedingly small group of patients is diagnosis achieved preoperatively on the basis of radiological findings. We describe a preoperatively diagnosed case of transverse colon herniation through the foramen of Winslow, showing a portal vein narrowing and periportal lymphedema at computed tomography (CT). To the best of our knowledge, only a few cases of preoperative CT diagnosis of Winslow foramen hernia have been described in the past. None had the abovementioned CT findings. (J GASTROINTEST SURG 2006;10:1180–1183)

KEY WORDS: Winslow foramen, internal hernia, computed tomography, bowel obstruction, halo sign

CASE REPORT

A 45-year-old female was admitted to the hospital after a 5-hour history of diffuse abdominal pain, especially intense at the epigastria, with nausea and vomiting. The symptoms started acutely while the patient was sleeping. The pain was only partially relieved by the knee-chest position. The patient's past medical history was unremarkable. Upon admission, blood pressure was 100/60 mmHg and heart rate was 76 beats/minute. Serum amylase (29 U/L), electrolyte concentrations (Na^+ 136 mEq/L, K^+ 3.6 mEq/L), liver enzymes (ALT 18 U/L and AST 29 U/L), total bilirubin (1.0 g/L), and white blood cell count (8.08×10^9 L) were all within normal limits. On clinical examination, the abdomen was soft but severely tender in the epigastria. There was no palpable mass. Bowel sounds were hypoactive. The patient's last bowel movement was from the day before. Standard abdominal roentgenograms in the supine and upright positions showed no relevant findings. Ultrasound examination (US) showed the portal vein displaced forward by a mass behind it that narrowed it, and an ectasia of the splenic vein. In addition, circumferential ipoechoic zones were present around the portal vein as well as around the segmental and subsegmental portal venous branches. The US findings showed evidence of portal vein that was at first ascribed to a partial circumferential portal vein thrombosis associated with an expansive mass close to the hepatic hilum.

Subsequently, the patient underwent unenhanced and biphasic contrast enhanced computed tomography (CT). Images in the arterial and portal phases

From the Departments of Medical and Surgical Critical Care (L.M.P., V.M., L.P., A.T.) and Clinical Pathophysiology - Radiodiagnostica I (M.B.), University of Florence, Firenze, Italy.
Reprint requests: Luigi Maria Pernice, M.D., Associated Professor of General Surgery, Department of Medical and Surgical Critical Care, University of Florence, Sct. Clinica Chirurgica Generale e Discipline Chirurgiche, Viale Morgagni, 85 - 50134 Firenze, Italy. e-mail: pernice@unifi.it

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were acquired 25 seconds and 70 seconds, respectively, after intravenous contrast medium (iopromide) administration. The arterial dominant phase showed a transient hepatic attenuation difference involving the lateral segments (i.e., segments II and III) of the left lobe, with good evidence of row through the left hepatic artery. The portal vein was stretched, displaced forward, and narrowed because of an ab extrinseco compression due to transverse colon herniated through the foramen of Winslow. A circumferential hypodensity "halo" was confirmed at the site of portal narrowing. It reached the peripheral branches of the portal vein (Fig. 1). This sign was interpreted as a periportal lymphedema due to the compression of anterior pillar of Winslow's foramen.

At operation, the herniation of transverse colon through the foramen of Winslow was confirmed; the foramen was enlarged enough to allow the introduction of three fingers. The gastrohepatic ligament was so stretched by the herniated colon that it appeared almost transparent. We were able to reduce the hernia by delicate manipulation. The viscus then appeared perfectly viable. Finally, we reduced the size of Winslow's foramen with nonabsorbable stitches between the anterior and the posterior foramen pillars, so that it allowed only a single finger to pass. We did not perform a colopexy. We left no drains.

After operation, the patient did well and was discharged 5 days later. CT control performed 4 days after operation showed complete disappearance of the alterations previously described (Fig. 2).

DISCUSSION

The foramen of Winslow allows communication between the peritoneal cavity and the lesser sac. Bowel herniation through the foramen of Winslow is among the rarest of internal hernias, accounting for less than 0.8%.[1] Three types of internal hernias are described according to the segment of bowel involved in the hernia (small intestine, cecum, and right colon or transverse colon). Hernia of the small intestine is the most common, whereas that of the transverse colon is the rarest.[2]

Moynihan[3] was the first to systematically study the disease. He suggested that this particular internal

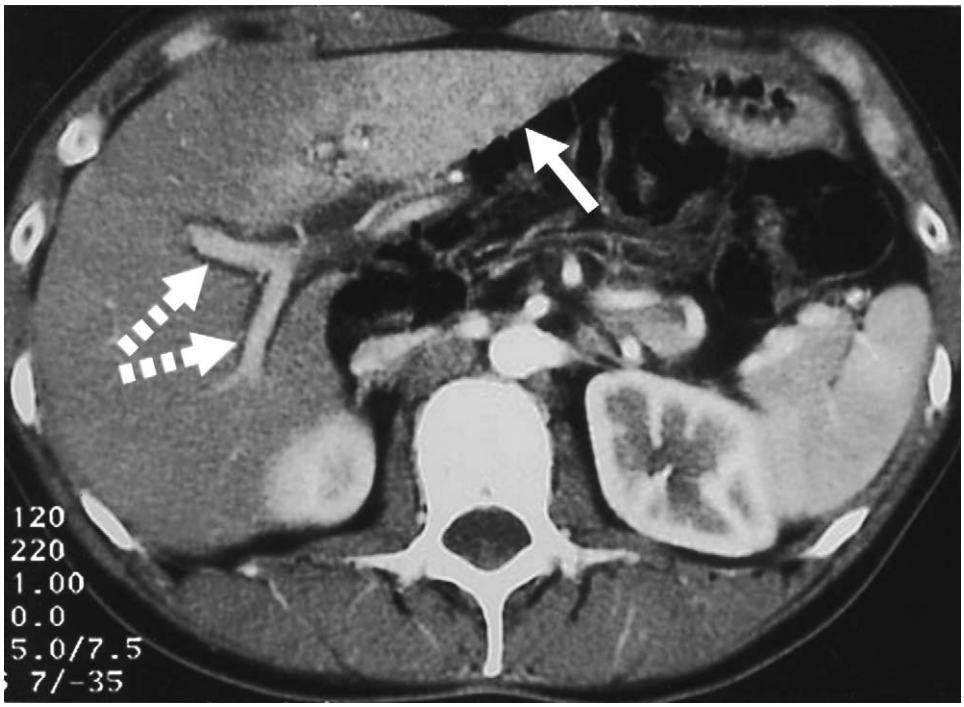

Fig. 1. Contrast-enhanced CT in arterial phase showing the portal vein stretched, displaced forward, and narrowed because of an ab extrinseco compression due to the transverse colon herniated through the Winslow's foramen. The arterial dominant phase shows a transient hepatic attenuation difference (THAD) involving the lateral segments (i.e., segments II and III) of the left lobe (*white arrow*), with good evidence of flow through the left hepatic artery. A circumferential hypodensity "halo" is present around the peripheral branches of the portal vein (*dotted line arrows*), a sign of portal venous narrowing.

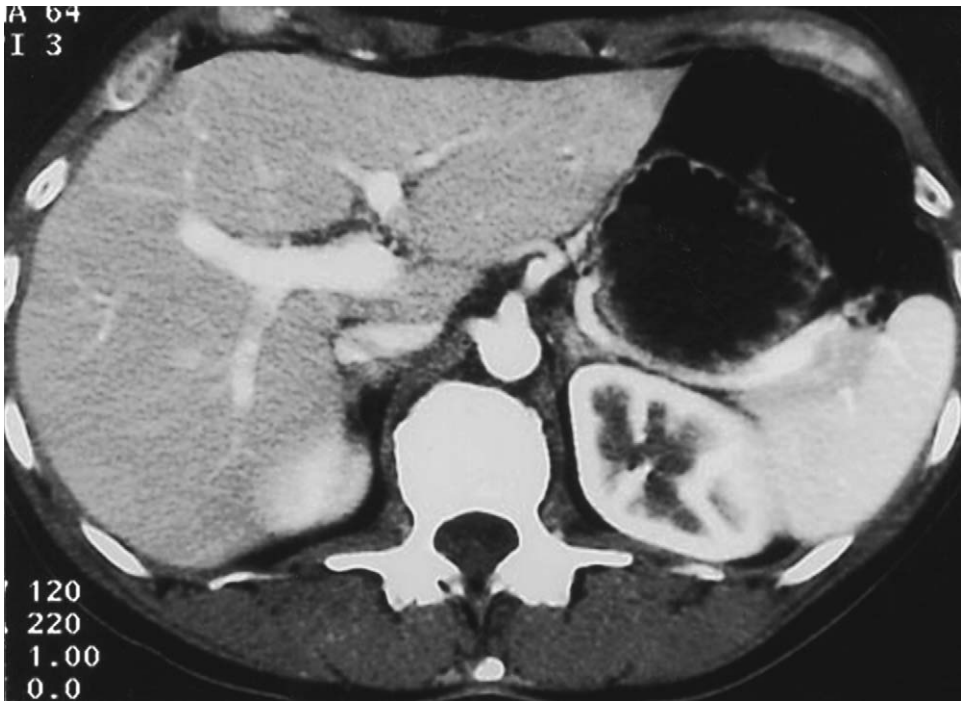

Fig. 2. CT control performed 4 days after operation shows complete disappearance of the previously described alterations.

hernia could depend on congenital abnormalities such as a common mesentery, absence of coalescence of the right primitive mesocolon to the posterior abdominal wall, an abnormally large size of Winslow's foramen, and excessive length of the colonic mesentery. Erskine accepted this hypothesis, stressing that the most important single abnormality should be the increased size of the foramen. In adults, the Winslow foramen approximately ranges between one and two fingers.

Clinical presentation is a common occurrence with acute bowel obstruction. Complications of Winslow hernia are both typical (i.e., strangulation) and atypical. The following complications, which are all due to hepato-duodenal ligament compression, are rarer but quite characteristic: gallbladder ischemia, obstructive jaundice, and Zahn's liver infarct. No laboratory findings are specific or are of value for differential diagnosis from other kinds of intestinal obstruction. Standard X-ray imaging offers few specific signs, such as a round mass containing gas and/or fluid level in the upper abdomen medial to the stomach.[2] An upper gastrointestinal radiographic series using $BaSO_4$ is rarely performed in patients with an acute abdomen, but water-soluble contrast medium can be used to show small intestine herniation, whereas contrast media given as an enema can visualize colon herniation.[2] Despite the above-mentioned typical radiological findings, radiographs are often misinterpreted due to the uncommonness of the disease. The advent of US and CT has improved the diagnosis; US can detect the mass entrapped in the lesser sac and can show a number of indirect signs due to the compression exerted on the gastrohepatic ligament. Actually, CT seems to be the most powerful tool to achieve diagnosis. Its findings are the most conclusive because of the direct identification of the internal hernia and of the viscus involved.[4] In our patient, plain X-Ray of the abdomen was of little value, whereas US was not able to characterize the nature of the mass compressing the gastrohepatic ligament. On the contrary, CT showed the colon entrapped in the lesser sac and additional peculiar and previously undescribed findings. The halo sign is described in a number of hepatic diseases such as acute or chronic rejection and acute hepatitis, but to the best of our knowledge, it has never been described as a consequence of an internal hernia.[5] Its genesis was interpreted as a lymphatic engorgement resulting from the compression of the lymphatic vessels lying along the portal vein and its branches. Arterialization of the left hepatic lobe has never been described in Winslow's hernia. In our opinion, it is probably produced by hemodynamic changes in response to diminished portal flow due to the squeezing of the portal trunk.

These aspects must be kept in mind while analyzing CT images from patients with an acute abdomen.

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Book Reviews

Advanced Therapy in Thoracic Surgery, Second Edition:
Edited by Kenneth L. Franco and Joe B. Putnam Jr. Hamilton, Ontario: BC Decker Inc., 2005. Pages: 548. Price: $139.00.

Reviewer: Mark K. Ferguson, M.D.

The explosion of growth in general thoracic surgery in the late 20th and early 21st centuries has engendered renewed interest in the subspecialty. Stimulated by minimally invasive trends in abdominal surgery, many thoracic surgeons now find that almost one third of their procedures are performed using thoracoscopic techniques. Examples of other recent technological advances include gene therapy, self-expanding stents, ECMO, and artificial lungs. Conditions newly managed by thoracic surgeons include end-stage lung disease, for which lung volume reduction surgery and transplantation are now routinely offered, and for which xenotransplantation may be available in the near future.

Given the rapid expansion of the knowledge base necessary to perform thoracic surgery, standard surgical texts are no longer sufficient to adequately cover the breadth of the field. *Advanced Therapy in Thoracic Surgery* is designed to fill the need for more in-depth information on new developments in the specialty. It is a copiously illustrated and heavily referenced resource authored by internationally recognized experts in the field.

That this is a second edition attests to the ongoing need for such a compendium. Owners of the first edition should not be misled by this label, however. Over half of the 44 chapters are on new topics, and of the remaining chapters, 10 are by new authors. The material consists in part of overviews of developments in traditional fields such as unusual pulmonary infections, congenital disorders, and pleural diseases. In addition, many chapters focus in depth on new developments including radiofrequency ablation of lung tumors, advances in diagnostic imaging, blood substitutes and artificial lungs, just to name a few.

There is more material in the second edition on mediastinal disorders, giving additional balance to the topics covered. Of particular interest to the readership of this journal will be authoritative contributions on aspects of esophageal diseases, including motor disorders, management of Barrett's esophagus, use of esophageal stents, and minimally invasive esophagectomy.

Advanced Therapy in Thoracic Surgery will serve as a valuable reference for surgeons who include thoracic surgery as part of their practice. It is readable, portable (the hardcover edition includes a CD of the work), and is good value for the cost.

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Anesthesia for Fetal Intervention and Surgery
Edited by Laura B. Myers and Linda A. Bulich. Hamilton, Ontario: BC Decker Inc., 2005. Pages: 190. Illustrations 42: Price: $149.00.

Reviewer: Dan Ostlie, M.D.

Anesthesia for Fetal Intervention and Surgery is a 190 page book and CD-ROM with multiple contributing authors of appropriate backgrounds that is directed toward physicians participating in the anesthetic care of mothers and their fetuses during and immediately following fetal intervention.

It covers the background of fetal and maternal anatomy and physiology and the limitations in the context of anesthetic concerns that are encountered in the gestational age of the fetal surgical patient. The contribution to the physiology in the book is very good and of appropriate length, although it is clearly meant as an overview for those individuals with a strong background in the maternal/fetal arena.

Two areas of high concern (uterine relaxation and preterm labor) are covered in a very nice overview, including the mechanisms of each, approaches for control based upon those mechanisms, and specific considerations based upon the type of fetal intervention and complications anticipated. An excellent description and review of current techniques and research developments of fetal monitoring is included.

The book then progresses to specific interventions that have been or are currently being pursued in the research arena. Unfortunately, this is where the book loses some of its focus. The chapters have committed significant space to the background and clinical management of the various prenatal congenital anomalies. Given that in all likelihood, most anesthesiologists will find this information less useful than the clinicians performing the surgical intervention or caring for the patients postoperatively, these portions could have been omitted or perhaps utilized for more appropriately focused anesthetic information. However, I do commend the editors for the

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coverage of the most current interventions for fetal diseases.

Finally, the book spends a good deal of time covering the most clinically relevant intervention for all practitioners caring for fetal patients, the EXIT and EXIT to ECMO procedures.

Overall, the book is consistently written with regard to chapter content and outline and covers the intended topic (anesthesia for fetal surgery) well. Its focus audience is very small, and for those clinicians outside of institutions currently performing research-based fetal interventions, it will not likely be of significant value.

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Tissue Adhesives in Clinical Medicine

by James V. Quinn, MD. 2nd ed. Hamilton, Ontario: B.C. Decker, 2005, Pages: 183. Illustrations 53: Price: $99.95.

Reviewer: Kevin E. Behrns, M.D.

J.V. Quinn's second edition of *Tissue Adhesives in Clinical Medicine* is designed to be a comprehensive monograph that addresses the composition of various adhesive materials, the indications for their use, and the appropriate use of tissue adhesives. The text is divided into eight chapters that provide an overview of the topic, historical background, and the composition, use, and pitfalls of cyanoacrylate compounds, fibrin-based hemostatic agents, protein polymers, and bone cements. The book concludes with two chapters that discuss the role of the Food and Drug Administration in the regulation of biochemical materials overall, and specifically tissue adhesives.

The first two chapters provide a history and overview of tissue adhesives, which are defined as compounds that "stick." Following these introductory chapters, the clinical use of cyanoacrylate compounds is discussed. This chapter is quite informative in that it reviews thoroughly the stages of wound healing, and it provides exquisite detail about the indications and clinical use of cyanoacrylate wound closure compounds. In addition, the author provides substantial data and references that demonstrate the equivalence of these compounds to suture material. The author also presents a balanced discussion of the advantages and disadvantages of cyanoacrylate compounds. These adhesives can serve as excellent topical dressings, but seepage of the agent into the wound may retard wound healing.

Subsequent chapters outline the use of fibrin-based hemostatic agents such as Tisseal and other similar compounds. A complete description of specialties and operations in which these materials may have clinical use ensues. The products and the details of the application to the wound are explicitly provided. Similarly, a chapter on protein polymers describes the utility of these adhesives. Finally, a chapter on bone cement discusses the clinical applications of these materials in orthopedic and oral and maxillofacial surgery. The details of the various bone cements are reviewed and the uses and contraindications described.

The book concludes with two chapters that review Food and Drug Administration regulations regarding these compounds. The thorough discussion of the regulatory process for the clinical approval of these compounds delineates the rigorous review process.

The references provided are numerous. In addition, the drawings are useful and clear, and several photographs nicely supplement the discussion in the text. The index is ample and permits easy identification of requested topics. The accompanying CD replicates the text in PDF format.

In summary, this short book contains valuable information that fills a niche in adjuncts to wound closure. Moreover, it contains many pearls that should be known by all clinicians using tissue adhesives.

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Letters to the Editors

To the Editor:

We read with interest the article by Essani and coworkers[1]: in the November-December JOURNAL OF GASTROINTESTINAL SURGERY issue, titled: "Cost-saving effect of treatment algorithm for chronic anal fissure: A prospective analysis." This article outlines the cost-saving effect of a treatment algorithm to manage chronic anal fissure, which first includes nitroglycerin ointment (NTG); then in case of failure at 4 weeks follow-up, type A botulinum toxin (BTX-A) injection of 40 UI, and finally, after 4 weeks, in nonresponders to medical approach, lateral internal sphincterotomy (LIS). To demonstrate the effectiveness and cheapness of this stepwise excalation, the authors perform a cost analysis by calculating the effective and hypothetical total cost of the algorithm and of two alternative models. The first, called the Brisinda approach, is based on the use of BTX-A injection in all cases, leaving surgery for toxin's failures; the second approach, named the Nclson approach, uses LIS to cure all patients.

The statistical examination is based on a prospective trial of 67 patients with chronic anal fissure. NTG application was successful in 46.2% of cases (31/67 patients), three patients then required surgery: subsequently, BTX-A was effective in 84.8% (28/33 patients), whereas surgery was performed in 5/67 patients (11.9%). Based on the above-mentioned rates, the total cost was $33,282, including $290 for NTG treatment, $20,580 for NIG plus toxin, and finally $9,025 for NTG plus BTX plus LIS, considering a toxin vial used for every patient. Based on the same healing rate, the authors underline that using the Brisinda approach (Botox injection in all patients and toxin plus surgery in 15.2% of cases), the total cost rises to $56,688, which means a 70.3% increase comparing with the algorithm approach. On the opposite, considering the price of 40 BTX-A units used for every patient instead of a whole vial that contains 100 U, the total cost of the Brisinda strategy decreases to $45,292, which means an increase of 36% compared to the multistep approach. Besides, the therapeutic effect of different doses of BTX-A in chronic fissure have been recently reported in literature. Recently, we investigated the effect of two different Botox dosage regimens (20 U and 30 U injected anteriorly in the internal anal sphincter) with a completed healing rate of 73% and of 89% in the 20 U group at 1 and 2 month follow-up respectively, and of 87% and 96% in the 30 U group 1 and 2 months after the treatment respectively.[2] Furthermore, five patients in the 30 U group reported mild incontinence of flatus lasting 2 weeks, which spontaneously disappeared. According to these results, to compare efficacy and tolerability of the two BTX-A formulations available today, we randomized 50 patients treated with 50 U of Botox formulation and 50 patients treated with 150 U Dysport formulation, and obtained, at 1 month evaluation, a healing rate of respectively of 82% and 84% in the two groups, with 11 patients of the Botox group and eight patients of the Dysport group temporary incontinent to flatus, which means a 19% rate of incontinence in all patients.[3] Thus, we do not believe that higher doses (50 or 100 U) are necessary, as we are able to produce an adequate effect using 20–30 U of Botox or 60–90 U of Dysport formulation, assuming that with a conversion factor between their potencies of 3, efficacy and tolerability of the two formulations are the same. Considering 20 or 30 of Botox U used for every patient, the total cost of the Brisinda model decreased to $29,300 and $32,837, respectively. In addition, with the use of Dysport formulation the model becomes even more cost-saving, considering that a Dysport vial is enough to treat eight or five patients with 60 or 90 U, respectively. Furthermore, performing one, or if necessary, more rescue treatments with BTX-A instead of surgery, according to our clinical experience, it's possible to cut the high cost of surgery in nearly all patients. The total cost for the surgery, according to Nelson strategy,[4] was $74,973, which means a 125.3% increase when comparing with the multistep approach. Although considerable, this calculation left out additional costs that might result from perioperative time off work, surgical fees, and surgical complications like faecal incontinence, whose rate oscillates in literature between 0 and 45%.[5] What is the cost of the treatment of a case of faecal incontinence? Accordingly, Sierra,[6] in a recent statistical comparison between BTX-A and LIS to treat chronic anal fissure, obtained a result in favour of botulinum treatment, considering the number of patients that benefit from the sphineterotomy versus every patient harmed by the operation—in comparison with botulinum treatment.[6,7]

The multistep approach was developed by Essani and coworkers[1] to obtain an effective, safe, and cost-saving therapy. Although some preliminary trials showed a healing rate with two no donor ointment

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of 88%; subsequently, other studies demonstrated a lower healing rate ranging from 33% to 68%.[8] Besides, as in the use of NTG for angina, moderate-to-severe headaches in up to 84% of patients are a significant side effect of treatment, provoking interruption of therapy in greater than 10% of patients.[8,9]

Aimed to compare efficacy and tolerability of BTX-A and NTG, in recent trial, we randomized 50 patients suffering from chronic anal fissure to receive BTX-A injection of 20 U or 0.2% NTG ointment locally applied twice a day for 6 weeks. At 2 months follow-up, the healing rate was 96% in the BTX-A group and 60% in the NTG group. Resting anal tone at the same time was significantly lower in the BTX-A group than in the NTG arm. Adverse effects were reported only in the NTG group; five patients suffered from moderate-to-severe headache. No relapses were reported during an average of 15 months follow-up.[10]

BTX-A injection is more effective in inducing reduction of sphincter tone and fissure healing than topical nitrate. Furthermore, the injection is not related to the patients willingness to complete treatment, and no complications or side effects were reported after the injection or during the follow-up period.

In conclusion, we believe that BTX-A injection of 20–30 U is an effective, safe, and inexpensive treatment and should be considered the first line therapy for patients with chronic anal fissure.

Giuseppe Brisinda, Federica Cadeddu, Gaia Marniga, and Giorgio Maria
Department of Surgery
Catholic School of Medicine
Rome, Italy

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Author's reply:

I am glad to have stimulated some discussion and appreciate Dr. Brisinda's comments on our recent paper on the cost effectiveness of a treatment algorithm for chronic anal fissures.[1] However, his summary turned out almost longer than the actual paper. While there are numerous studies that have compared two different regimens with each other up to the point of either success of failure, our open algorithm allowed us to treat patients beyond failure. And even though it is undebated that the NTG is not the most successful of all approaches, BTX is not it either.[2] In a disease/condition such as chronic anal fissure, which more often constitutes a chronic annoyance than a risk or handicap, one is not forced in any way to deliver only the most effective treatment at any price.[3] But most importantly, it is the patients themselves, who in the overwhelming majority, opt for a stepwise escalation from the least uncomfortable to the most invasive approach. And not surprisingly, an injection to the anus is not the patients's first choice.

Andreas M. Kaiser, M.D., F.A.C.S.
Associate Professor of Clinical Colorectal Surgery
Department of Colorectal Surgery
Keck School of Medicine
University of Southern California
Los Angeles, California

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Journal of
Gastrointestinal Surgery

Laparoscopic Liver Resections: Extent of Resection Defines Length of Stay

To the Editor:

We enjoyed reading the article by Learn et al.[1] in the March–April 2006 JOURNAL OF GASTROINTESTINAL SURGERY issue, titled: "Laparoscopic Hepatic Resection using, Saline-Enhanced Electrocautery Permits Short Hospital Stays. We at the University of Southern California University Hospital are currently doing over 100 liver resections a year and are one of the leading centers in the country for living donor liver transplantation. To say that saline-enhanced electrocautery reduces the hospital stay delivers the wrong message to the reader base. This is just another technique of cutting the liver and has nothing to do with decreasing the hospital stay. The question this paper should really address is the selection of the patients for laparoscopic liver resection (LLR). How many patients who are seen for resection really lend themselves to a laparoscopic resection? What precludes the remaining patients from being done laproscopically?

As proponents of LLRs ourselves, whether one uses the stapler, harmonic, or saline-enhanced electrocautery, there should be no difference as long as it pertains to wedge or small resections. To say that this is true for all resections is unsafe. Learn et al.[1] state that "no association was found with respect to location or size of the mass." Well, this case series is too small to make such a profound statement. What truly determines hospital stay is the extent of surgery. Even if one does a laparoscopic right lobectomy uneventfully with minimal blood loss, it is ethically and medically unsafe to send this patient home on postoperative day 1. In fact, there is a dramatic drop in the phosphorus levels, which directly correlate to postoperative complications.[2] Clinical consequences of severe hypophosphatemia include impaired diaphragmatic contractility, ventricular irritability, myocardial depression, and insulin depression. Pomposelli et al.[3] observed life-threatening hypophosphatemia in liver donors, which was managed by replacing the phosphate intravenously. On an average, the inorganic phosphate begins to drop on the second postoperative day and ends around the fifth postoperative day.[2] Moreover, at the present time there is no literature that correlates specifically the extent of the resection and the degree of hypophosphatemia, but the fact is that it occurs with major liver resections. Whether this electrolyte disturbance is a function of increased metabolic and synthetic demands of the regenerating liver or whether this is secondary to renal hypophosphaturia[4] is a moot point. However, this in itself should be caution enough to not send the patient home prematurely.

Laparoscopic liver resections are rapidly coming to be a way of main stream practice, and a plethora of papers are beginning to flood the literature; however, length of stay needs to be weighed in perspective to the extent of resection and not the modality used to cut the liver. Discharging patients in 24 hours after doing a LLR can sometimes be inappropriate and may even be fatal; therefore, caution needs to be exercised with the authors' recommendations.

Singh Gagandeep, M.D., F.A.C.S.
Division of Hepatobiliary & Pancreatic Surgery
Department of Surgery
Keck School of Medicine
University of Southern California University Hospital
Los Angeles, California

Rick Selby, M.D.
Division of Hepatobiliary & Pancreatic Surgery
Department of Surgery
Keck School of Medicine
University of Southern California University Hospital
Los Angeles, California

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Author's reply:

I would like to thank Drs. Singh and Selby for their comments and offer this reply. I would agree that sending a patient home 1 day after major hepatic resection would not be medically safe. All the comments in relation to major hepatic resection and hypophosphatemia are very sound, and I empirically add phosphate to the postoperative fluid management of major resection patients. In our manuscript, we dealt with a different population of patients, and the comments were related only to this group. In this small initial series, we were looking at limited resections that do not have the same physiologic risks as major hepatic resections. For these patients, pain

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Division of Hepatobiliary & Pancreatic Surgery
Department of Surgery
Keck School of Medicine
University of Southern California University Hospital
Los Angeles, California

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Division of Hepatobiliary & Pancreatic Surgery
Department of Surgery
Keck School of Medicine
University of Southern California University Hospital
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management would generally dictate the hospital stay, more so than the systemic effects of significant parenchymal resections. It also showed that patients with more systemic problems as related to ASA category were more likely to have a longer stay. However, this is probably more of a bias on the part of the physicians not wanting to send this group of patients home early.

A short hospital stay for a major hepatic resection would probably be considered 5 days. Because the majority of complications that would keep patients in the hospital longer for major liver resections are systemic problems, it seems difficult to imagine that even laparoscopic technique would significantly impact this length of stay. With the advent of more advanced laparoscopic procedures, caution and judgment do need to be exercised. We are using significantly more expensive technology and need to be able to justify its use to impact patient outcomes. I would be cautious in saying that laparoscopic liver resections are coming into the main stream, especially lobar resections. This article is about a specific group of patients. The comments within were not meant to be expanded to dissimilar patient populations.

Kevin T. Watkins, M.D.
Assistant Professor of Surgery
Department of Surgery, School of Medicine
Health Sciences Center
State University of New York
Stony Brook, New York

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More On: What's in a Name, of and around the Pancreas?

To the Editor:

I read with interest and pleasure the insightful and thought-provoking letter by Professor Kapoor entitled "Pancreas: What is in a Name?"[1] The author should be congratulated for raising awareness of some inconsistencies and lack of precision regarding our widely used clinical nomenclature. Despite my general agreement with the discussion of nearly all terms, I take the liberty to propose one dissenting opinion and some short additions.

One would agree that use of the term "periampullary cancer" is highly variable. However, the recommendation to differentiate periampullary from pancreatic cancers based on differences in management and prognosis can be questioned. The term "periampullary" specifically describes an anatomic location "around the ampulla" (e.g., papilla of the terminal pancreatobiliary duct channel).[2] It therefore appears sensible to use this term as an anatomic descriptor of tumor location, not of disease prognosis. Even among nonpancreatic periampullary tumors, prognostic differences exist between biliary, duodenal, or ampullary cancers, and both operative as well as adjuvant treatment may differ based on stage and risk assessment. With proper imaging, the majority of these lesions can in fact produce a detectable mass lesion and are often enough difficult to differentiate from head of pancreas cancers, irrespective of location within or extension beyond the suggested 1 cm distance from the ampulla.

Operative therapy (not surgery!) of periampullary cancers commonly involves resection of the pancreatic head, duodenum, and distal bile duct. The grammatically correct term for this procedure would be "pancreatoduodenectomy,"[2] not "pancreaticoduodenectomy". The term "pancreatico-" denotes a relationship to the pancreas or the pancreatic duct ("ductus pancreaticus"), but not the pancreas as such. Hence, pancreaticojejunostomy or pancreaticogastrostomy are appropriate ways of reconstruction after pancreatectomy (not "pancreaticeatomy") or pancreatotomy (not "pancreaticotomy"), especially if the pancreatic duct is involved. Aside from pancreatoduodenectomy "pancreatology," or "pancreatolysis" would be other examples of comparable terms relating to the pancreas proper and not requiring the "ic" insertion. At any rate, both scientific terms for the Whipple-Kausch resection appear to have their followers; a Medline title word search yielded 574 results for pancreaticoduodenectomy, compared to 451 for pancreatoduodenectomy. Is there an opportunity for the grammatically conscious to do better?

All surgeons strive to achieve minimized morbidity after pancreatic resections, especially avoiding treatment-related deaths. An increasing number of clinical series proudly state that there was "no mortality," when in fact the mortality (a rate, not an event) was zero, since there were no lethal events (or "fatalities")—an enviable result!

Finally, much hope has been placed on novel multimodality treatment strategies to improve survival after pancreatic cancer resection. While benefits of postoperative, "adjuvant" (i.e., aiding or assisting the operative effects) therapy forms continue to be debated, many centers are evaluating preoperative chemotherapy or chemoradiation. Although this strategy is no longer novel at all, the misnomer "neoadjuvant" (i.e., "new" form of adjuvant treatment) therapy prevails, largely due to not sensible reasons.[3] If we already have to consider any preoperative treatment to truly serve as adjuvant, the sequence would be properly described as "protoadjuvant," indicating that the

management would generally dictate the hospital stay, more so than the systemic effects of significant parenchymal resections. It also showed that patients with more systemic problems as related to ASA category were more likely to have a longer stay. However, this is probably more of a bias on the part of the physicians not wanting to send this group of patients home early.

A short hospital stay for a major hepatic resection would probably be considered 5 days. Because the majority of complications that would keep patients in the hospital longer for major liver resections are systemic problems, it seems difficult to imagine that even laparoscopic technique would significantly impact this length of stay. With the advent of more advanced laparoscopic procedures, caution and judgment do need to be exercised. We are using significantly more expensive technology and need to be able to justify its use to impact patient outcomes. I would be cautious in saying that laparoscopic liver resections are coming into the main stream, especially lobar resections. This article is about a specific group of patients. The comments within were not meant to be expanded to dissimilar patient populations.

Kevin T. Watkins, M.D.
Assistant Professor of Surgery
Department of Surgery, School of Medicine
Health Sciences Center
State University of New York
Stony Brook, New York

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More On: What's in a Name, of and around the Pancreas?

To the Editor:

I read with interest and pleasure the insightful and thought-provoking letter by Professor Kapoor entitled "Pancreas: What is in a Name?"[1] The author should be congratulated for raising awareness of some inconsistencies and lack of precision regarding our widely used clinical nomenclature. Despite my general agreement with the discussion of nearly all terms, I take the liberty to propose one dissenting opinion and some short additions.

One would agree that use of the term "periampullary cancer" is highly variable. However, the recommendation to differentiate periampullary from pancreatic cancers based on differences in management and prognosis can be questioned. The term "periampullary" specifically describes an anatomic location "around the ampulla" (e.g., papilla of the terminal pancreatobiliary duct channel).[2] It therefore appears sensible to use this term as an anatomic descriptor of tumor location, not of disease prognosis. Even among nonpancreatic periampullary tumors, prognostic differences exist between biliary, duodenal, or ampullary cancers, and both operative as well as adjuvant treatment may differ based on stage and risk assessment. With proper imaging, the majority of these lesions can in fact produce a detectable mass lesion and are often enough difficult to differentiate from head of pancreas cancers, irrespective of location within or extension beyond the suggested 1 cm distance from the ampulla.

Operative therapy (not surgery!) of periampullary cancers commonly involves resection of the pancreatic head, duodenum, and distal bile duct. The grammatically correct term for this procedure would be "pancreatoduodenectomy,"[2] not "pancreaticoduodenectomy". The term "pancreatico-" denotes a relationship to the pancreas or the pancreatic duct ("ductus pancreaticus"), but not the pancreas as such. Hence, pancreaticojejunostomy or pancreaticogastrostomy are appropriate ways of reconstruction after pancreatectomy (not "pancreaticeatomy") or pancreatotomy (not "pancreaticotomy"), especially if the pancreatic duct is involved. Aside from pancreatoduodenectomy "pancreatology," or "pancreatolysis" would be other examples of comparable terms relating to the pancreas proper and not requiring the "ic" insertion. At any rate, both scientific terms for the Whipple-Kausch resection appear to have their followers; a Medline title word search yielded 574 results for pancreaticoduodenectomy, compared to 451 for pancreatoduodenectomy. Is there an opportunity for the grammatically conscious to do better?

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adjuvant component is being administered first. "Preoperative" or "induction" therapy would, of course, serve the same descriptive purpose equally well. Unfortunately, savages here greatly outnumber the terminologically savvy; the Medline title word search yields 2363 "neoadjuvant" hits since its first use in 1984, compared to only one "protoadjuvant" result! There are 1311 finds for "neoadjuvant chemotherapy," versus 785 for "preoperative chemotherapy."

Can we conclude that in the world of surgical pancreatology, not just the actual state-of-the-art treatment, but even the proper use of descriptive terms can provide significant challenges?

Roderich E. Schwarz, M.D.
Department of Surgery
UMDNJ–Robert Wood Johnson Medical School
New Brunswick, NJ 08903

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To the Editor:

I read with interest the overview on "Management of pain in small duct chronic pancreatitis" published in the January–February 2006 JOURNAL OF GASTROINTESTINAL SURGERY.[1] The authors have highlighted the role of various resection and drainage procedures in small duct disease. However, they have omitted to mention published data in favour of the Frey procedure. We have published in 2003[2] our experience with lateral drainage and head coring for small duct chronic pancreatitis. Forty-five patients with ductal diameters less than 5 mm were treated by ductal drainage with head coring (Frey procedure), with 94% pain relief and preservation of pancreatic function over a minimum follow-up of 30 months.

Ductal drainage, with appropriate coring out of the head parenchyma, depending upon the presence and size of associated head mass, is a viable option in treatment of small duct chronic pancreatitis. It provides relief of pain and avoids resection, thus preserving pancreatic function as far as possible.

H. Ramesh, M.S., M.ch., F.A.C.S., F.R.C.S.
Chief Surgeon & Associate
Director Lakeshore Hospital & Research Center
Cochin, Kerala, India

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Chief Surgeon & Associate
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