"How I Do It" Session: Autoimmune Sclerosing Pancreatitis

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INTRODUCTION

A number of recent publications have increased awareness of autoimmune sclerosing pancreatitis (ASP) as an entity that should be suspected in patients with atypical pancreatic head masses or symptoms of chronic pancreatitis. Most of the series are surgical and derived from retrospective review of patients who were thought to have pancreatic cancer and found to have ASP by the pathologist. Although many unresolved issues remain, the availability of specific tests for its diagnosis and its response to steroid treatment highlight the importance of this entity in the differential diagnosis of a pancreatic mass.

This year's *How I Do It* session of the Pancreas Club dealt with ASP and featured three expert speakers: Andres Gelrud, M.D., who gave the perspective of the gastroenterologist, discussed clinical presentation, pathogenesis, and laboratory and radiologic work-up, as well as treatment of ASP; Greg Lauwers, M.D., who also discussed aspects of pathogenesis, gave an excellent presentation on the histopathology of ASP and brought up the challenging issue of whether the diagnosis can be made with a needle biopsy; and Charlie Yeo, M.D., who gave the perspective of the surgeon, including the added technical difficulties involved in the resection of this entity.

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Autoimmune Pancreatitis

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Autoimmune pancreatitis (AIP) is an increasingly recognized benign condition that is frequently mistaken for pancreatic cancer. Differentiating between the conditions is essential to identify those patients in whom a trial of corticosteroids would be beneficial, avoiding unnecessary pancreatic resection.[1–3] Since Sarles et al.[4] first described a case of pancreatitis with hypergammaglobulinemia more than 40 years ago, more than 350 cases have been reported, particularly in the Japanese literature. This has led to the proposal of AIP as a distinct clinical entity.[5,6]

Clinically, patients with AIP may present with the following features: no symptoms (incidental finding during abdominal imaging), nonspecific abdominal pain, painless jaundice, and, rarely, acute attack of pancreatitis. Multiple serum markers have been studied, but none has a high sensitivity or specificity. The diagnosis is based on the pathology finding, and most of the patients have a dramatic response to treatment with steroids.[3,6–14]

Various terms have been used in reference to this complex syndrome, including lymphoplasmacytic sclerosing pancreatitis,[15,16] idiopathic duct destructive pancreatitis,[16] primary inflammatory pancreatitis, sclerosing pancreatitis,[17,18] nonalcoholic duct destructive chronic pancreatitis,[19,20] chronic inflammatory sclerosis of the pancreas, primary chronic pancreatitis,[20] and, most recently, idiopathic tumefactive chronic pancreatitis.[16] As mentioned in an editorial by DiMagno,[21] "The field needs simplification of terms" and the diagnosis should be based on pathologic findings.

AIP is occasionally seen in association with other autoimmune disorders, most commonly primary sclerosing cholangitis,[12,22,23] Sjögren's syndrome,[24–27] and type 1 diabetes mellitus.[7,28–30] Acute tubulointerstitial nephritis was described, for the first time, as a renal complication in association with AIP.[31,32]

To unify criteria and terminology, Pearson et al.[33] and Okazaki[34] suggested that primary or secondary AIP be classified on the basis of the absence or presence of other autoimmune diseases, although it is unclear whether the pathogenic mechanisms differ from each other.

PATHOGENESIS

Cavallini[35] first described the development of antibodies against an antigen in the epithelium of the pancreatic ducts, with secondary inflammatory infiltration around the main and/or secondary pancreatic ducts followed by the development of an obliterating periductal fibrosis. Kawa et al.[36] found a close association between AIP and the HLA *DRB1*0405-DQB1*0401* haplotype (Japanese population), suggesting that the specific peptide presented by these HLA molecules trigger the pathologic process of the autoimmunity. Kino-Ohsaki and colleagues[37] demonstrated the presence of antibodies to carbonic anhydrase II, an enzyme present in the epithelium of the pancreatic and biliary ducts and the gastrointestinal tract.[38] Carbonic anhydrase II is thought to be a target antigen, but it has not been fully confirmed. Elevated concentrations of IgG_4 are closely associated with AIP and disease activity,[17] although the exact role of the high serum IgG_4 is not entirely understood. Other nonspecific autoantibodies that have been associated with AIP include anti-lactoferrin antibody, antinuclear antibody, and rheumatoid factor.[39]

CLINICAL PRESENTATION

Patients with AIP may present with a wide spectrum of clinical symptoms (Table 1), including vague abdominal pain, weight loss, jaundice, night sweats, and, occasionally, hyperglycemia and steatorrhea. Confirmatory diagnosis of AIP in the absence of tissue relies on clinical and radiographic features, particularly a history of other autoimmune disorders, the presence of a diffusely enlarged pancreas, or a discrete mass that is often mistaken for a pancreatic malignancy by abdominal imaging.

Okazaki,[40] from Japan, described 21 patients with AIP. Fourteen had no associated autoimmune diseases, 7 had other systemic conditions, and 17 had concomitant lesions of the bile ducts. Eleven of the

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Table 1. Relevant features of autoimmune pancreatitis

No symptoms or only mild symptoms, usually without acute attacks of pancreatitis
Male predominant
Age usually greater than 50 years
Increased levels of serum gamma globulins, IgG, or IgG_4
Presence of serum autoantibodies
Diffusely enlarged pancreas
Diffusely irregular or isolated narrowing of the main pancreatic duct
Rare pancreatic calcification or cyst
Response to steroid therapy
Lymphocytic infiltration with fibrotic changes

17 patients with bile duct strictures had distal common bile duct stenosis in the intrapancreatic portion and 6 had upper biliary stenosis resembling primary sclerosing cholangitis. Nine patients had diabetes mellitus (45%), three with sialoadenitis (15%), three (15%) with retroperitoneal fibrosis, and two (10%) with renal dysfunction. Serum levels of IgG_4 were elevated in 68% of the cases. Interestingly, all patients with biliary involvement showed increased IgG_4 levels, suggesting that IgG_4 may be a good marker for AIP with biliary involvement.

Kim et al.,[3] from Korea, recently published their experience with 17 patients who were diagnosed and treated with AIP. The predominant features were jaundice or nonspecific gastrointestinal symptoms, elderly and male, elevated IgG levels in 8 (47%) of 17 patients, and presence of autoantibodies in 6 (35%) of 17 patients. Diabetes mellitus was present in 13 of 17 patients. One patient had primary sclerosing cholangitis, and a second patient had Sjögren's syndrome. Thirteen patients showed histologic findings of lymphoplasmacytic infiltration and fibrosis, and one showed predominant infiltration of eosinophils. Fifteen patients had radiologic images of diffuse swelling of the pancreas. All of the features improved with steroid treatment.

DIAGNOSTIC WORK-UP

The diagnosis of AIP should be based on a combination of clinical and laboratory findings, pancreatic imaging, and other conditions having been ruled out (Table 2). Histologic examination remains the diagnostic gold standard. Briefly, the histologic features include periductal inflammation, periphlebitis, lymphoplasmacytic infiltration of the pancreas, and interstitial fibrosis. When tissue is obtained via fine needle aspiration, a predominance of inflammatory cells is present with relatively few epithelial cells that lack atypia. However, the sensitivity and specificity of fine needle aspiration in differentiating AIP from neoplasia are unknown.

LABORATORY INVESTIGATION

Patients with AIP frequently exhibit serologic markers of autoimmunity, including positive antinuclear antibody, anti-smooth muscle antibody, antibodies to carbonic anhydrase II, and lactoferrin. Patients usually have a mild elevation of amylase and lipase. Elevated levels of gamma-globulin are occasionally seen. Hamano et al.[17] demonstrated that patients with AIP have elevated levels of the immunoglobulin IgG_4 (Table 3), a subtype capable of activating the classic complement pathway by binding C1q, and that the values are closely associated with disease activity. IgG_4 has been suggested as a simple serologic test that can be performed preoperatively in patients with a pancreatic mass who have a history of autoimmune disease or who do not fit the classic imaging pattern of having a pancreatic malignancy.[15] It is unclear whether IgG_4 levels are elevated in patients of other races or ethnic groups. In our experience with small numbers of patients, all of whom are white, IgG_4 has been either normal or mildly elevated.

Another clinical feature strongly supportive of the diagnosis of AIP is the dramatic response to steroids.[3,6–14]

IMAGING STUDIES

In general, pancreatic calcifications or pseudocysts are rarely seen. Abdominal computed tomography findings include a diffusely enlarged hypoechoic pancreas or a discrete mass often mistaken for a pancreatic malignancy.[41,42] An additional feature is the presence of a low-density capsule-like rim that may correspond to an inflammatory process involving peripancreatic tissues.[42,43] Magnetic resonance imaging reveals a diffusely diminished signal intensity and delayed enhancement on dynamic scanning.[43,44]

Endoscopic retrograde cholangiopancreatography findings are characterized by segmental or diffuse

Table 2. Differential diagnosis of autoimmune pancreatitis with a diffusely enlarged pancreas

Pancreatic cancer
Malignant lymphoma
Plasmacytoma
Metastatic tumor

Table 3. Differential diagnosis of elevated IgG_4

Pemphigus
Bronchial asthma
Atopic dermatitis

From Hamano et al.[17]

irregular narrowing of the main pancreatic duct, usually accompanied by a stricture of the distal common bile duct.[45] On occasion, a double duct sign (concomitant presence of distal common bile duct and distal pancreatic duct stricture, thought to be pathognomonic of pancreatic cancer) may be present, suggesting a tumor in the head of the pancreas.

Endoscopic ultrasound with fine needle aspiration in the diagnosis of AIP has not been well characterized. The high-resolution imaging of endoscopic ultrasound has been shown to be an effective imaging modality in the diagnosis of pancreatic malignancy, particularly for the detection of small pancreatic lesions.[46] Endoscopic ultrasound has the additional advantage of obtaining tissue in a minimally invasive way.

TREATMENT

Corticosteroids is the principal treatment, particularly for patients who are symptomatic with either chronic abdominal pain, jaundice (secondary to distal common bile duct compression from the pancreas), steatorrhea, or, to a lesser degree, diabetes.[7,9,13,29] When primary sclerosing cholangitis is associated with AIP, the efficacy of steroid treatment is poor.[9]

The recommended starting dose is 30 to 40 mg of prednisone/day (or 0.6 to 0.8 mg/kg/day) until symptoms improve, followed by a slow taper of 5 to 10 mg. The overall efficacy of steroid therapy in patients, especially outside of Japan, is unknown.

Other second-line treatments[9] that have been used with unclear results include proton pump inhibitors at the usual dosages, $histamine_2$ receptor antagonists at the usual dosages, atropine sulfate (1.5 mg/day orally in divided doses), and scopolamine hydrobromide (1.2 to 2.4 mg/day). Gabexate mesilate (a protease inhibitor available in Italy and Japan) has been also used at a dosage of 100 to 300 mg/day intravenously in divided doses. Limited experience is available with the use of ursodeoxycholic acid, but it was recently postulated as an alternative therapy.[47]

Surgical treatment is rarely indicated. Patients with jaundice and distal common bile duct strictures unresponsive to corticosteroids may need surgical bypass to prevent cholangitis or repeated endoscopic retrograde cholangiopancreatograms for stent exchange. Other indications include inability to differentiate AIP from a malignant process or persistent symptoms.[9]

Success of treatment is measured by improvement of symptoms and laboratory abnormalities, recovery of pancreatic endocrine and exocrine function, and marked improvement in the imaging studies.[34,45] Patients with quiescent disease do not require pharmacologic treatment.[9]

PROGNOSIS

AIP is a relatively new condition, for which long-term prospective studies are lacking. Based on the available published data, the overall prognosis is very favorable.

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Histopathology of Autoimmune Pancreatitis: Recognized Features and Unsolved Issues

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Autoimmune pancreatitis (AIP) is a chronic fibroinflammatory condition affecting the pancreatic gland. Reflecting the numerous clinical and pathologic aspects of this process (or processes), this condition has been variably reported in the literature as *primary sclerosing pancreatitis*,[1] *sclerosing cholangitis*,[2] *nonalcoholic duct destructive chronic pancreatitis*,[3] *lymphoplasmacytic sclerosing pancreatitis*,[4] and *autoimmune pancreatitis*.[5]

The original description is attributed to Sarles and colleagues,[6,7] who reported, in the 1960s, several cases of chronic pancreatitis in patients with hyper–gamma globulinemia. As discussed by Gerlud and Freedman,[8] one of the characteristic features of this immune-mediated process is its frequent association with fibroinflammatory conditions affecting other organ systems. Consequently, AIP has been classified as either primary or secondary whether it appears singly or in association with systemic autoimmune/inflammatory disorders.[9]

The clinical and surgical aspects of AIP are exhaustively reviewed by Gerlud and Freedman[8] and Yeo.[10] Thus, we comment herein only on the histopathologic aspects of AIP. Until recently, AIP was included in the larger group of chronic idiopathic pancreatitis, a heterogeneous group of lesions representing 30–40% of chronic pancreatitis.[11] In recent Japanese series, the incidence of AIPs (with or without biopsy) ranges between 1.86% and 6.6% of chronic pancreatitis.[12–14] A North American surgical series report that AIP represent 21–34% of cases with Whipple resections for benign conditions.[15,16]

GROSS FEATURES

As highlighted by imaging studies, AIP may be diffuse and involve the entire pancreas, or in some cases preferentially involve the head of the pancreas.[5,17–19] On gross examination, the pancreas has an unremarkable external appearance but is usually firm at palpation.[20] Despite the tumefactive nature of AIP, importantly, no dominant mass or well-circumscribed nodules are found on examination. Rarely, multiple masses have been reported.[21] Sections through the gland reveal a fibrotic parenchyma, although pancreatic lobulation is usually retained to some extent.[4] Stenosis of the pancreatic duct and intrapancreatic segment of the common bile duct, which may not be probed, is frequent.[3,22]

MICROSCOPIC FEATURES

The cardinal features of AIP include a dense lymphoplasmacytic infiltrate of the pancreatic gland with secondary fibrosis and absence of changes associated with chronic alcoholic pancreatitis (Fig. 1). The inflammatory infiltrate is preferentially centered around the main pancreatic duct and medium-sized interlobular ducts.[3,4] Lymphocytic exocytosis (i.e., infiltration of lymphocytes into the ductal epithelium) with epithelial damage is also present[3,4] (Fig. 2). Although the infiltrate is predominantly composed of lymphocytes, sometimes forming lymphoid follicles, plasma cells as well as eosinophils and neutrophils can be numerous.[3] Secondary to the ductal damage, periductal "onion-skin" fibrosis (similar to primary sclerosing cholangitis) and occasional scars representing destroyed ducts can be seen. In addition, periphlebitis and obliterative phlebitis are frequently detected[3,4,15,23] (Fig. 3). Perineural lymphocytic aggregates are also reported, although this is not a specific finding.[23] Concurrently, the pancreatic parenchyma shows evidence of progressive acinar atrophy with acute and chronic inflammation.[3] Aggregates of foamy histiocytes may be present, sometimes in vaguely granulomatous arrangements, but epitheloid granulomas, that can be observed in lymph nodes, are rarely seen in the pancreas.[4,24] In place, pancreatic parenchyma may essentially be replaced by dense fibrosis with scattered islets of Langerhans, which are rarely completely destroyed. Another feature of AIP is a patchy

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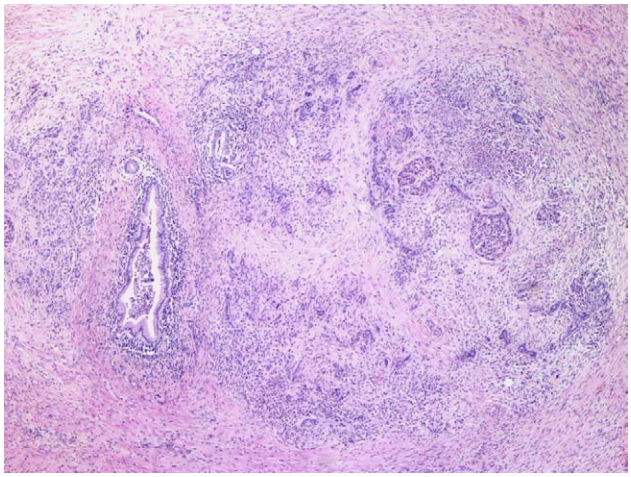

Fig. 1. Low-power view showing marked interstitial fibrosis with atrophy of the exocrine pancreas. Chronic inflammation is noted throughout the section with periductular accentuation. Residual endocrine islets are seen.

distribution of the parenchymal damage with neighboring acini that may reveal a normal histology. An important aspect of this condition is the absence of features usually associated with alcoholic chronic pancreatitis such as duct dilation with mucoprotein plugs, pseudocysts, autodigestive necrosis, and calcifications.[3,4]

PATHOGENESIS

The pathogenesis of AIP remains unknown. Immunologic evaluation of the patients usually reveals

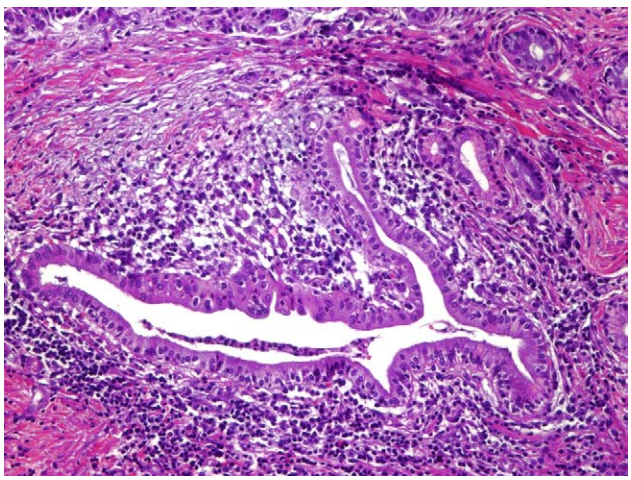

Fig. 2. Medium-size interlobular pancreatic duct cuffed by a brisk lymphoplasmacytic infiltrate. Lymphocytic exocytosis (i.e., infiltration of lymphocytes into the ductal epithelium) is present.

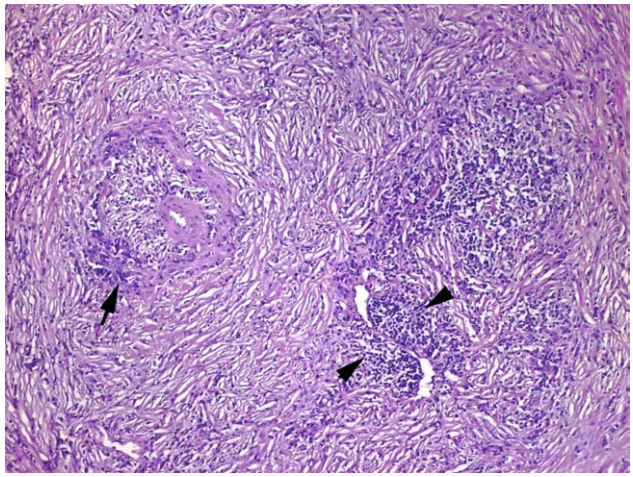

Fig. 3. Phlebitis (*arrowheads*) and obliterative arteritis (*arrow*) are observed in this section. Note the absence of residual exocrine pancreatic tissue replaced by a dense fibrosis.

the elevation of IgG and/or gamma-globulin in the majority of cases as well as IgE.[5,14,25]

The lymphocytic population is predominantly composed of T lymphocytes, but B cells are consistently present. Most cells are $CD4^+$ (55%), although others report a predominance of $CD8^+$ T cells.[3,12,13,21] It is advanced that cytokines released by T lymphocytes upregulate the aberrant expression of HLA class II molecules by the duct epithelial cells.[3,21,26] Antibodies to carbonic anhydrase II antigens (30–59% of the cases) and lactoferrin (present in 50–76% of the cases) that are present on the ductal and acinar cells, respectively, might be responsible for the Th2-type antibody-mediated immune reaction and the ensuing lymphocytic infiltrate.[12,14,26–28] Other antibodies, including rheumatoid factors, perinuclear anti-neutrophil cytoplasmic (pANCA), anti-nuclear (ANA), anti-smooth muscle (ASMA), anti-mitochondrial (AMA), anti-thyroglobin, and anti-microsomal antibodies, have been variably reported, although none are consistently positive.[5,12,14,27] In patients with concurrent Sjögren syndrome, anti–SS-A and anti–SS-B antibodies can be detected.[28] In a retrospective study, Hamano et al.[29] found that AIP patients had high levels of IgG_4, the least common of IgG subclasses. Although apparently more frequent in Japanese patients, the same finding has been observed in a white patient and an African American patient.[30] Also, Kamisawa et al.[31] recently noted the infiltration of IgG_4^+ plasma cells not only in the pancreas but also in multiple organs.

UNSOLVED ISSUES

Despite a growing body of knowledge, several issues, some specifically related to histopathology of AIP, can be highlighted.

Preoperative Diagnosis

In most cases, the distinctive features found on evaluation of a resected pancreas are sufficient to suggest the diagnosis of AIP even in the absence of associated clinical conditions. Alternatively, whether a preoperative tissue diagnosis of AIP is possible remains a challenging issue. In patients with well-established systemic conditions, the detection of a tumor-like lesion in the pancreas should raise clinical suspicions of a concurrent AIP. However, the findings on fine-needle aspiration cytology are not specific enough to support the diagnosis. The possibility of preoperative diagnosis is even more challenging when a good clinical history or the presence of associated conditions is lacking. One may be critical of the reports of AIPs on needle biopsy specimens lacking the histologic hallmark of AIPs seen only on resected specimens. The role of lymphocyte subtyping and detection of IgG_4^+ plasma cells for preoperative diagnosis on biopsies has yet to be explored.[31]

Effect of Steroid Therapy

Despite clinical and biologic evidence of reversibility—at least partial—of diabetes and exocrine insufficiency under steroid therapy, little is known of the modulation of the inflammation and glandular damage under treatment.[13,14,26] Some claim a restoration of the parenchyma after therapy.[17] However, the claim is based only on needle biopsy specimens, and the issue of sampling error and heterogeneity of the process was not addressed. Although one can expect improvement of the inflammatory infiltrate, effacement of the fibrosis is less likely.

Uniformity of Diagnosis

There is a real possibility that several conditions, all having in common an autoimmune trait, are lumped together, and as pointed out by DiMagno,[32] there is a need for uniformity in the diagnosis and classification of AIP. As discussed by Gelrud and Okazaki in this issue,[8,33] the case has already been made for dividing AIP between sporadic primary disease and the one associated with a systemic condition. With regard to the diagnosis, many authors, particularly in Japan, have often diagnosed AIP on the basis of radiologic findings, clinical data, and response to steroid therapy without histologic evaluation.[5,14,19] In others, the report of the pathologic findings is limited to fibrosis with lymphocytic infiltration but no ductal exocytosis or obliterative venulitis mentioned.[1,14,20,33] Whether characteristic pathologic features should be included in diagnostic criteria, as suggested by some, needs to be evaluated.[32]

Anatomic Distribution of Limited AIP

As discussed exhaustively elsewhere, AIP can be associated with systemic disorders including "multifocal idiopathic fibrosclerosis" and various autoimmune conditions (primary biliary cirrhosis, collagenous disorders, etc.).[3,22,33–38] However, these associations are noted in only approximately 34–60% of patients, and therefore in a significant number of cases the inflammatory process is apparently limited to the pancreas.[3,25,33–38] Even in the latter group of patients with primary AIP, two types of anatomic distribution are noted: those with a pancreaticocentric lesion and those with a pancreaticobiliarycentric condition that extends to the bile duct and/or gallbladder.[4,15,23,33] Morphologically, the involvement of the common bile duct is similar to the inflammation surrounding the main pancreatic ducts. Interestingly, Hirano and colleagues[13] recently showed that the development of bile duct alterations, which were originally absent, could be observed in 50% of patients (four of eight) during mean follow-up of 4 years when no steroid therapy was initiated. This finding obviously raises the question of whether these patients represent a subset of AIP or whether it is an indication of the natural history of the disease.

Histologic Variation

The histologic features of AIP vary from one patient to another.[14] Recently, researchers from the Mayo Clinic argued that two morphologic types of AIP can be observed.[39,40] *Lymphoplasmacytic sclerosing pancreatitis* (LPSP) corresponds to the case reported by Kawaguchi et al.,[4] whereas the second type, *idiopathic duct centric chronic pancreatitis* (IDCP) resembles more closely the cases originally reported as nonalcoholic duct-destructive chronic pancreatitis by Ectors et al.[3] LPSP is characterized by diffuse poorly circumscribed fibrosis replacing the exocrine pancreas. Lymphoid follicles are common along with a dense lymphoplasmacytic infiltrate centered on the main pancreatic duct and its interlobular branches, and phlebitis is constantly present. However, lymphocytic exocytosis within the epithelium is not prominent. In IDCP, a dense mixed inflammatory infiltrate with numerous neutrophils involves the lobules, whereas inflammation in the fibrotic areas and the surrounding peripancreatic tissue is limited. Neutrophils are constant and particularly dense around the intralobular ducts, which may be plugged by microabscesses. Phlebitis is not a common pattern of this subtype. No significant clinical difference was noted between LPSP and IDCP, if not a more common tendency of jaundice in LPSP.[39] The significance of moderate to marked eosinophilia noted in 20%

of cases and sometimes associated with a noticeable eosinophilic infiltrate in the biliary tract while a subgroup of patients has a significant clinical history of allergic or atopic manifestation (41% according to one study) remains to be investigated.[41] Whether this represents a subset of AIP or another entity with overlap of clinical and histologic features remains to be determined. Finally, in some patients, the parenchyma is replaced by a dense cellular proliferation of spindle cells or myofibroblasts, collagen, and varying amounts of lymphoplasmacytic infiltrate.[15,23,42] These lesions can arise independently or in the background of a more classic AIP.[15] They are similar to the lesions reported in pseudotumors of the liver and spleen.[42] Whether it represents a late stage in the evolution of AIP, in which the active inflammation is replaced by mature fibrous tissue, remains to be determined.[23]

Since the original recognition of AIP by Sarles and colleagues, significant advances have been achieved in the clinical diagnosis, management, and, more recently, the understanding of pathogenesis of this condition. However, with the wealth of information and the desire to rationalize the knowledge may have come the error of lumping together conditions, which, despite significant overlap, may not be similar. Pathologic analysis (which is not always performed), in correlation with clinical characteristics and biologic features, could help in a better categorization of pancreatitis with autoimmune mechanisms.

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Autoimmune Sclerosing Pancreatitis: The Surgeon's Perspective

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The role of the surgeon in the management of patients with autoimmune sclerosing pancreatitis (ASP) is controversial and in evolution.[1–17] On the one extreme are those who believe that surgical intervention or resection for this entity is not indicated, as there are data to suggest that this is a nonsurgical disease. On the other extreme are those who believe that surgical intervention for ASP can benefit patients by unquestionably providing a definitive diagnosis and excellent symptom palliation and by avoiding the use of corticosteroids with their side effects. For the purposes of this discussion, the terms *autoimmune sclerosing pancreatitis* and *lymphoplasmacytic sclerosing pancreatitis* (LPSP) are used interchangeably. The features suggestive of this entity are listed in Table 1.

THE PROBLEM IN PERSPECTIVE

In recent years, a spectrum of clinically underrecognized inflammatory conditions of the pancreas and biliary tree that simulate pancreatic and peripancreatic malignancy, but had been previously reported as "chronic pancreatitis," were recognized. Abraham et al.[18] recently reported a retrospective review of 442 pancreaticoduodenectomy specimens at The Johns Hopkins Hospital from January 1999 through June 2001. Various clinical characteristics, radiologic findings, and operative reports were examined, and the final pathologic diagnosis was carefully reviewed. Of the 442 Whipple resections, a total of 47 specimens (10.6%) were negative for benign or malignant neoplasms. In reviewing the clinical history, 40 of these resections were performed because of a clinical suspicion of a malignancy, whereas in the remaining seven cases the resection was performed for non-neoplastic disease. These 40 resections may be considered as "false positives," and they represent 9.2% of the resection specimens. The clinical presentation in these 40 "false positives" included the presence of a mass lesion in 67%, obstructive jaundice in 50%, a common bile duct stricture in 40%, and some form of suspicious cytology in 12%. Importantly, the final pathologic diagnoses in these 40 patients included ASP in 28%, alcohol-associated chronic pancreatitis in 12%, gallstone-associated chronic pancreatitis in 10%, chronic pancreatitis of unknown etiology in 10%, isolated benign common bile duct stricture in 10% and sclerosing cholangitis in 7%. The 11 patients in this series with ASP had a mean age of 57 years, including 8 men and 3 women, and all of their resection specimens were characterized by a dense lymphoplasmacytic infiltrate, periductal fibrosis, and acinar atrophy. None of these patients had a history of alcohol abuse or primary sclerosing cholangitis, and only two patients had a history of ulcerative colitis. An important conclusion from this study recognizes that the diagnosis of "chronic pancreatitis" includes several genetic, environmental, and autoimmune conditions that yield, as a final finding, parenchymal fibrosis. Importantly, chief among these non-neoplastic entities in this series was ASP.[18]

A follow-up study by Abraham et al.[19] evaluated the coexistence of lymphoplasmacytic chronic cholecystitis and biliary tract disease in patients with LSP. The authors studied 20 gallbladders from patients with LPSP and compared the findings with those for 20 gallbladders removed from patients with primary sclerosing cholangitis, 20 gallbladders from patients with chronic cholelithiasis, and 20 gallbladders from patients with benign (non-LPSP) pancreatic disease. By evaluating various parameters (such as degree and composition of gallbladder mucosal inflammation, lymphoid nodules, metaplasia, and fibromuscular hypertrophy), the authors noted that 60% of the gallbladders in patients with LPSP contained moderate or marked inflammatory infiltrates and lymphoid nodules, similar in frequency to gallbladders removed from patients with primary sclerosing cholangitis but significantly more common than in gallbladders from patients with chronic cholelithiasis and benign pancreatic disease. These findings suggested that the inflammatory pathology seen in patients with LPSP

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Table 1. Suggestive features of autoimmune sclerosing pancreatitis

Parameter	Findings
Clinical findings	Jaundice, abdominal pain, reversible exocrine insufficiency, diabetes, other "autoimmune diseases"
Serum tests	Hypergammaglobulinemia, eosinophilia, tumor markers, anti-nuclear antibodies, anti-carbonic anhydrase antibodies, anti-lactoferrin antibodies, serum trypsinogen
CT/MRI	Diffusely enlarged pancreas, absence of hypodense lesions, compression of SMV-portal vein confluence, presence of a low density capsule-like rim
Percutaneous ultrasonography	Hypoechoic diffuse pancreatic swelling (sausage-like pancreas)
EUS/IDUS	Hypoechoic diffuse pancreatic swelling, concentric wall thickening of the distal common bile duct and main pancreatic duct
ERP/MRCP	Diffuse narrowing of the main pancreatic duct with irregular thumbprint-like marks
Response to	Corticosteroids (prednisone 30 to 40 mg/day with tapering), ursodeoxycholic acid

CT = computed tomography; MRI = magnetic resonance imaging; EUS = endoscopic ultrasound; IDUS = intraductal ultrasound; ERP = endoscopic retrograde pancreatography; MRCP = magnetic resonance cholangiopancreatography.

represents a spectrum of inflammatory diseases that affects not only the pancreas but also the biliary tract and the gallbladder. These findings have been further corroborated by Hirano et al.,[20] who confirmed the findings of extrapancreatic bile duct changes in patients with ASP. Further, Hyodo and Hyodo[21] confirmed biliary findings in ASP patients, verifying that distal common bile duct strictures can be imaged by endoscopic ultrasonography, intraductal ultrasonography, and contrast-enhanced ultrasonography.

REVIEW OF RECENT SURGICAL SERIES

Two large series of patients who underwent resection for ASP have recently appeared in the literature: reports by Weber et al.[22] from the Memorial Sloan-Kettering Cancer Center in New York City and by Hardacre et al.[23] from The Johns Hopkins Hospital in Baltimore.

Weber et al.[22] reviewed a total of 1287 pancreatic resections between 1985 and 2001 at the Memorial Sloan-Kettering Cancer Center. Of these patients, 159 (12%) had benign disease at pathologic evaluation. Of these, 29 were identified as having ASP in the resection specimen, whereas 2 additional patients were identified from the pathology database who were thought to have unresectable ASP pseudotumors. These 31 patients form the overall study population. The patient characteristics included a median age of 62 years, with 68% of the patients being male, 68% presenting with jaundice, 29% having abdominal pain, and only 19% having an "autoimmune disease" association. The operations performed included 23 pancreaticoduodenectomies, 4 distal pancreatectomies, 2 total pancreaticoduodenectomies, and, as noted previously, 2 patients with "unresectable" disease. The disease was thought to be unresectable in both cases because of superior mesenteric artery and portal vein encasement. A most interesting feature of this report includes the observation that 8 of the 29 resected patients (28%) had "recurrences" of their disease following resection. Importantly, 3 of the 4 patients with distal resection developed postresection jaundice, 4 of 23 patients undergoing pancreaticoduodenal resection developed jaundice (3 had multiple intrahepatic strictures and 1 had a biliary-enteric anastomotic stricture), and 1 of 23 patients undergoing pancreaticoduodenal resection developed pancreatitis from pancreatic ductal strictures. The authors pointed out that in the time period of the study, it proved extremely difficult to differentiate preoperatively between pancreatic cancer and ASP, and nearly one third of their patients had some form of a "recurrence" after resection, mandating close follow-up.[22]

An experience with many similarities, and some differences, was reported by Hardacre et al.[23] from Johns Hopkins. In this report, 1648 pancreaticoduodenal resections were reviewed from 1992 through 2002. Of these resections, 176 (11%) were for chronic pancreatitis, and 37 of these patients (21%) were found to harbor ASP. Importantly, all patients with ASP were suspected of harboring pancreatic cancer preoperatively, and all underwent resection. The patient characteristics included a mean age of 62 years, with 64% being male, 84% presenting with jaundice, 54% presenting with abdominal pain, and only 24% of patients having an "autoimmune disease" association. The operations performed included 26 pylorus-preserving pancreaticoduodenectomies and 11 classic pancreaticoduodenectomies. In this report, several interesting features arose: first, the observation that patients with ASP, in contrast to patients with pancreatic cancer, typically had diffusely firm or hard glands; second, ASP patients often had evidence of very difficult separation of the Whipple specimen from the visceral vessels; and third, ASP patients tended to

have greater intraoperative blood loss and longer operative times. At 3-year follow-up in this study, 48% of patients had gained weight, 37% had developed glucose intolerance, and 35% had occasional diarrhea, but there was no evidence of recurrence of jaundice (perhaps in part because all patients had pancreaticoduodenectomy), and none had undergone subsequent distal pancreatectomy.[23]

HOW TO PERFORM THE DIFFICULT PANCREATICODUODENAL RESECTION

As we gain knowledge and experience with the entity of ASP, and learn more about its appropriate management, it can be hoped that the number of patients undergoing pancreatic resection for what ultimately proves to be this non-neoplastic entity will decline in number. Nonetheless, in the absence of a 100% accurate means of preoperative diagnosis, there will likely remain patients who undergo pancreatic resection with the final pathology revealing ASP. It is important to recognize that pancreatic resection for this entity can be far more challenging and dangerous than resections performed for, for example, small periampullary neoplasms without evidence of vascular encasement and peripancreatic inflammation.

As the experience from Hardacre et al.[23] indicates, pancreatic resection for ASP may be particularly challenging because of the peripancreatic inflammation, lack of normal tissue planes, difficulty in separating the pancreaticoduodenectomy specimen from the visceral vessels, and the potential for a lengthy surgical procedure. For such difficult resections, it is important that the surgeon avoid the predictable problems of venous bleeding, arterial injury, and margin positivity.

Venous Bleeding

It is not overly dramatic to consider the superior mesenteric vein (SMV)–portal vein axis to represent a "friable tiger." The average hepatopedal blood flow in this venous structure approximates 1 L/min, and the thin walls of the SMV–portal vein axis make venous injuries extremely troublesome and dangerous. In those cases with SMV–portal vein "encasement," it is best to leave the venous separation as one of the last steps in the pancreaticoduodenal resection. In these cases, it is best to divide the bile duct, duodenum, and jejunum first and perform the difficult venous separation only when ready, avoiding efforts at creating a tunnel dorsal to the pancreatic neck at a point in the operation where rapid control cannot be obtained of the SMV and portal vein. In fact, in extremely difficult resectional situations it is possible, and may be recommended, to separate the Whipple specimen (uncinate process) from the SMA, before attempts at SMV–portal vein/specimen separation. Of course, in cases of pancreatic neoplasia with tumor infiltration into the SMV or the portal vein, venous resection and reconstruction may be required.

Arterial Injury

In the face of a difficult pancreaticoduodenal resection, it is best to always assume that the arterial anatomy is abnormal, being watchful of such entities as a replaced right hepatic artery off of the superior mesenteric artery (SMA), a replaced common hepatic artery off the SMA, or proximal celiac artery stenosis with proper hepatic artery flow to the liver via the SMA side of the gastroduodenal artery. As should be routine, it is always wise to test clamp the suspected gastroduodenal artery before dividing it. Further, always assume that any large vessel to the patient's right of the common bile duct serves as the sole arterial inflow to the liver. Maintain awareness that the safest plane for separation of the uncinate process may be the plane right adjacent to the SMA. Additionally, it is always wise to have a Doppler flow probe at hand, to confirm arterial signals in tubular structures that should not be divided!

Margin Positivity

Although not a critical issue in the case of ASP, it is important to mark all of the surgical margins for the pathologist, doing it the same way every time, so that the pathologist can proceed to gross and microscopic inspection of the specimen in a standard fashion. Importantly, one should endeavor never to do an anastomosis to the bile duct or to the pancreas without first confirming that the respective margin is negative for neoplasia.

ASP is a relatively newly described entity that can mimic pancreatic neoplasia. To diagnose this entity, you must have knowledge of it and bring this knowledge to the patient's bedside. In the proper clinical setting, ideally with confirmatory laboratory findings, and with the requirement for confirmatory pathologic findings, the entity of ASP, at least in the reports of small series, appears to respond to corticosteroid therapy. This is certainly not the case in patients with pancreatic cancer. Like other management algorithms, one must be willing to alter the treatment if the expected therapeutic response is not observed.

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A National Comparison of Surgical Versus Percutaneous Drainage of Pancreatic Pseudocysts: 1997–2001

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Case series results indicate that a surgical approach is superior to percutaneous drainage of pancreatic pseudocysts. To determine if this surgical advantage is persistent, national outcomes for both approaches were compared from 1997 through 2001. The National Inpatient Sample, a 20% sample of all nonfederal hospital discharges, was searched for patients who had a pancreatic pseudocyst diagnosis, an *ICD-9* diagnosis code 577.2, and an *ICD-9* procedure code of 52.01 for percutaneous drainage (PD) or 52.4 and 52.96 for the surgical approaches. Variables were compared by using either *t* test or χ^2 analysis. Confounding variables were controlled for by linear or logistic regression models. No clinically significant demographic, comorbidity, and disease-specific severity-of-illness differences existed between the two groups. Significant differences in complications, length of stay (15 ± 15 versus 21 ± 22 days, $P < 0.0001$), and inpatient mortality (5.9% versus 2.8%, $P < 0.0001$) favored the surgical approach. In addition, endoscopic retrograde cholangiopancreatography use had a protective effect on mortality (odds ratio, 0.7), whereas percutaneous drainage had an increased risk of mortality (odds ratio, 1.4). This population-based study suggests that surgical drainage of pancreatic pseudocysts, particularly when coupled with use of endoscopic retrograde cholangiopancreatography, leads to decreased complications, length of stay, and mortality in comparison with percutaneous drainage. (J GASTROINTEST SURG 2005;9:15–21)

KEY WORDS: Pancreas, pseudocyst, percutaneous, database, surgery

Pancreatic pseudocysts (PPs) are a serious, common complication of both acute and chronic pancreatitis. Diagnosis of PPs has increased over the past decade with the advent of more sensitive imaging modalities, including the increased use of computed tomography (CT), endoscopic ultrasonography, and magnetic resonance cholangiopancreatography.[1] During the past two decades, the management of PPs has also evolved to include several strategies. Current therapeutic options include observation, percutaneous drainage (PD), endoscopic drainage, and surgical drainage (SD) of PPs. The confluence of both increased diagnosis and different treatment options has given focus to determining the optimal application of treatment options.

Formerly, traditional management of PPs included observation for 6 weeks, followed by SD for persistent pseudocysts.[2] Recent natural history studies demonstrate that observation is a safe option for small asymptomatic pseudocysts, challenging older dogma.[1,3–5] Newer treatment options of PD and endoscopic drainage have been recently introduced with

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varying rates of PP recurrence and complications.[6–8] SD of PPs, however, has remained a time-honored, safe, effective, and enduring treatment.[3] Unfortunately, no prospective comparisons for the differing treatment options exist. All current comparison studies have been small, retrospective, and single institution.[3,4,9]

Observation of small pseudocysts has been shown to be an effective treatment option in selected cases based on pseudocyst size and patient symptoms. Expectant management for asymptomatic cysts less than 4.5–6 cm has demonstrated low morbidity, recurrence, and need for further intervention. Selection criteria do limit uniform application of this treatment strategy. PD of PPs has been shown to be an effective short-term treatment modality but has been associated with increased complications, PP recurrence, and need for further intervention. Short-term success rates from 70% to 90% for PD engendered early enthusiasm that has been tempered by follow-up studies demonstrating lower long-term success rates of 25–42%.[3,6,7] PD does remain a viable option for PP patients who are a major operative risk or have an infected PP. Recently, endoscopic drainage of PPs has been offered as a minimally invasive therapeutic option.[8] Initial success rates have been appealing, but long-term outcomes are still unknown. Endoscopic management of PP is acutely dependent on favorable anatomic opposition of the PP and gastrointestinal lumen, conditions that have limited its application. Clinical expertise is also requisite in performing this advanced procedure, again potentially limiting its use.

The most established treatment of PPs is SD, which has been long shown to be effective with success rates of 88–92%.[3,4] Despite concern for surgical adverse events, surgical treatment in comparison to PD has been demonstrated to be safe, resource efficient, and associated with low recurrence rates.

Selecting between treatment options may be guided by imaging modalities, particularly CT and ERCP. CT may help distinguish acute from chronic pancreatitis, a key distinction in choosing a treatment option, whereas ERCP may demonstrate pancreatic duct changes that suggest a favorable outcome via a particular treatment approach.[4,10,11] Main pancreatic duct size and continuity may help predict success for differing treatments.

The aim of this study was to examine population-based outcomes between the two primary treatment options for PPs, namely, PD and SD. A secondary aim was to identify predictive factors of outcomes between the two treatment modalities.

METHODS

Data Source

The National Inpatient Sample (NIS) is maintained by the Agency for Healthcare Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project.[12] The NIS is a 20% representative sample of all hospital discharges in the United States, stratified by geographic region, hospital size, urban versus rural location, and teaching versus nonteaching status. Teaching status of the hospital was determined by hospital affiliation with either a medical school or an ACGME residency program. Hospital size, which is divided into small, medium, and large, had a range for large hospitals of greater than 100–450 beds, depending on urban/rural and teaching status. The NIS is the largest, all-payer U.S. administrative database that incorporates discharge data from approximately 1000 hospitals and 5–7 million discharges annually. The NIS 20% sample is based on a stratified probability sample of all U.S. hospitals, to provide a national estimate of inpatient health services. Only inpatient data found in a discharge abstract are available in the NIS. The NIS does not have unique patient identifiers, and as a result, patients cannot be followed longitudinally. Further information regarding the NIS is available from the AHRQ, which administers the database as part of the Healthcare Cost and Utilization Project.

Case Identification

In this retrospective cohort study, cases were identified by *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis code for PP, 577.2, and by procedure code 52.01 for PD and codes 52.4 and 52.96 for SD of PPs. No specific *ICD-9* procedure code exists for endoscopic drainage. To ensure homogeneity of the two comparison cohorts, cases with *ICD-9* diagnoses codes for gastrointestinal malignancies (150–159 inclusive) were excluded and only cases with patient age of greater than 17 years were included. Furthermore, cases that had procedure codes for both SD and PD were excluded because primary treatment could not be established temporally. The period studied was from January 1, 1997, through December 31, 2001; this period was chosen on the basis that both treatment modalities were mature in this timeframe and the results would be sufficiently recent to avoid secular trend bias.

Patient Characteristics

Patient age, gender, admission type, accompanying diagnoses, and comorbidities were examined. The Deyo modification of the Charlson Comorbidity Index (0–3, with 3 indicating greatest comorbidity) was calculated for each patient based on *ICD-9* diagnosis codes.[13] Specific accompanying *ICD-9* diagnosis codes included acute pancreatitis (577.0), chronic pancreatitis (577.1), other pancreas diagnoses (577.8,

577.9), biliary tract disorders (574–576 inclusive), diabetes (250 inclusive), and alcoholic liver cirrhosis (571.0–571.3). The association of these diagnoses with each PP case permits risk stratification by a general severity of illness scale (Charlson Comorbidity Index) and a disease-specific scale of accompanying diagnoses (pancreatitis, biliary tract, diabetes, and cirrhosis).

Structures and Processes of Care

To adjust for potential differences in delivery of care that might bias outcomes of PD or surgical management, structure and processes of care were analyzed. Structure of care was examined by noting each case's payor status and hospital size and teaching status. In addition, processes of care, namely number of procedures performed, use of CT scan (*ICD-9* procedure code 88.01), and ERCP utilization (*ICD-9* procedure codes 51.10, 51.11, 52.13, 52.93, 52.94, and 52.97), were inspected to determine their impact on outcomes of care.

Outcomes

Patient outcomes after either PD or SD of PPs were examined. Outcomes assessed include complication rates, length of stay (LOS), disposition, and inpatient mortality. Specific complications included intra-abdominal abscess, bleeding, pulmonary embolus, pneumonia, other pulmonary complications, deep venous thrombosis, urinary tract infections, cardiac arrhythmias, myocardial infarction, and cerebrovascular accidents (specific *ICD-9* codes available on request).

Statistical Analyses

Dichotomous and continuous variables were examined by Student's t test and χ^2 analyses. Linear and logistic regression analyses were applied to LOS and mortality variables to correct for potential confounders.[14] A P value of <0.05 was set as significant. The statistical program SAS (Version 8.1; SAS Institute, Cary, NC) was used for database analysis.

RESULTS

Review of the database revealed that a total of 27,533 admissions for PP were made between 1997 and 2001. Of these 27,533 admissions, 14,914 (54%) PPs were either surgically or percutaneously drained within the study period of 1997–2001. Of these 14,914 PPs, 8,121 (56%) were drained percutaneously and 6,409 (44%) were surgically drained.

Patient Demographics

Surgically treated patients, in comparison with PD patients, were male, younger, and admitted less frequently on an emergency basis (Table 1). On the basis of the Charlson Comorbidity Index, surgically treated patients had a significantly lower mean score (0.32 ± 0.71 versus 0.40 ± 0.84, $P < 0.0071$), although the majority of patients in both groups had a Charlson score of 0, indicating few comorbidities, whereas a small percentage of patients had the highest Charlson score of 3 (Table 1). Differences were noted on accompanying diagnoses between both groups: surgically treated patients had significantly less frequent diagnoses of acute pancreatitis, both acute and chronic pancreatitis, diabetes, and cirrhosis but had significantly more frequent diagnoses of chronic pancreatitis, biliary tract disorders, and other pancreatic diseases (Table 2).

Structure and Processes of Care

Surgically treated patients had a higher rate of ERCP and CT use and private insurance status than PD. A difference in teaching status was also noted between the two groups, with surgically treated patients being cared for in teaching hospitals at a less frequent basis than patients who underwent percutaneous drainage (Table 3).

Outcomes

Assessment of complications by treatment-specific complications and multisystem complications demonstrated that patients treated by PD had a consistently higher complication rate than those treated by

Table 1. Patient demographics

	Percutaneous drainage (n = 8121)	Surgical drainage (n = 6409)	*P* value
Age (yr)	53 ± 16	51 ± 15	0.006
Gender (% male)	58	59	0.05
Emergency admission (%)	50	29	0.0001
Charlson Comorbidity Index (mean)	0.40 ± 0.84	0.32 ± 0.71	0.0071
0 (%)	77	79	0.0001
1 (%)	12	15	0.0001
2 (%)	5	3	0.0001
3 (%)	6	4	0.0001

$P < 0.05$ significant.

Table 2. Disease-specific severity of illness markers for pancreatic pseudocysts treatment

Associated diagnosis (%)	Percutaneous drainage (n = 8121)	Surgical drainage (n = 6409)	*P* value
Diabetes	17.4	16.7	0.27
Cirrhosis	3.63	3.28	0.24
Biliary	15.9	23.8	0.0001
Pancreatitis, acute (A)	50.7	22.1	0.0001
Pancreatitis, chronic (C)	13.7	26.4	0.0001
Pancreatitis, both A + C	6.01	50.3	0.0001

$P < 0.05$ significant.

surgical management (Table 4). As a result, LOS in the PD group was significantly higher, at 21 ± 22 days, than in the surgery group, at 15 ± 15 days ($P < 0.0001$). A significantly higher percentage of surgically treated patients were discharged to home versus percutaneously drained patients: 80% versus 56%, respectively ($P < 0.0001$). The mortality rate was significantly higher in the PD group than in the SD group: 5.9% versus 2.8%, respectively ($P < 0.0001$) (Table 5).

The data were also analyzed to adjust for confounding variables, and we found that a statistically significant difference between the two groups did not persist for LOS after correction with linear regression analysis. Before correction, the difference in LOS, PD versus SD, was 6 days, but after adjustment for confounding variables, a difference in LOS of 1 day was not statistically or clinically significant. These confounders were selected for the model on the basis of statistical significance between the two groups and included ERCP use, emergency admission, acute pancreatitis diagnoses, biliary diagnoses, Charlson Comorbidity Index score, CT scan use, and teaching hospital status. Of interest, the estimates for the effect of independent variables found that the use of ERCP decreased LOS by 2.2 days (95% CI, −3.97 to −0.008), whereas an emergency admission increased LOS by 7.3 days (95% CI, 5.56 to 8.98). In addition, a diagnosis of acute pancreatitis increased LOS by 12.8 days (95% CI, 11.1 to 14.4), and a biliary tract disorder increased LOS by 3.6 days (95% CI, 1.89 to 5.37).

Adjusted mortality differences between the two groups did persist after correction for potential confounders by logistic regression analysis. Confounders, as noted previously, were chosen for model inclusion based on statistically significant differences between the two groups and then were excluded from the model by backward elimination procedure. Of note, the percutaneous approach for PP in comparison with SD increased the odds of in-patient mortality by 1.37-fold (95% CI, 1.12–1.68). Furthermore, both emergency admission status and acute pancreatitis diagnoses significantly increased odds of inpatient mortality, 2.45 (95% CI, 1.87–3.20) and 2.36 (95% CI, 1.89–2.96), respectively. However, ERCP use did

Table 3. Structure and process of care for pancreatic pseudocyst drainage

Structure/process of care (%)	Percutaneous drainage (n = 8121)	Surgical drainage (n = 6409)	*P* value
ERCP	13	14	0.0007
CT	17	6	0.0001
Commercial insurance	46	49	0.0001
Teaching hospital	63	59	0.8394
Large hospital	66	65	0.3467

ERCP = endoscopic retrograde cholangiopancreatography; CT = computed tomography.
$P < 0.05$ significant.

Table 4. Complications for pancreatic pseudocyst treatment

Complication (%)	Percutaneous drainage (n = 8121)	Surgical drainage (n = 6409)	*P* value
Intra-abdominal abscess	6.80	4.54	0.0001
Bleeding requiring transfusion	9.64	8.96	0.157
Pulmonary embolism	0.65	0.23	0.0002
Pneumonia	7.86	3.89	0.0001
Other pulmonary complications	11.3	5.09	0.0001
Deep venous thrombosis	4.99	3.25	0.0001
Urinary tract infection	6.15	4.42	0.0001
Cardiac arrhythmias	8.49	5.30	0.0001
Myocardial infarction	1.25	0.59	0.0001
Cerebrovascular accident	0.29	0.09	0.006

$P < 0.05$ significant

Table 5. Outcomes for pancreatic pseudocyst treatment

	Percutaneous drainage (n = 8121)	Surgical drainage (n = 6409)	*P* value
Length of stay (mean days)	21 ± 22	15 ± 15	0.0001
Disposition, home (%)	56.3	79.6	0.0001
Inpatient mortality (%)	5.9	2.8	0.0001

yield a protective effect on inpatient mortality with an odds ratio of 0.68 (95% CI, 0.51–0.9).

DISCUSSION

These data from the NIS database represent the largest group of patients with PPs that underwent either PD or SD. These data demonstrate that SD results in fewer in-patient complications and mortality than PD even after correction for potential confounders such as comorbidities and disease severity. In addition, these data show the increased LOS and mortality prompted by a diagnosis of acute pancreatitis. Of note, ERCP use may render an important protective mortality benefit and decreases LOS.

This study demonstrates the power of population-based analyses incorporating 14,530 PP patients treated by either SD or PD. The largest comparative series before our study had a study population of 253 patients.[4] In addition to vastly increasing the number of patients available for review, this population-based analysis effectively avoids selection bias by including the entire national population for review. Furthermore, our study period allows for a contemporaneous examination of both interventions at a point in their use beyond any learning curve and free of any secular trend bias. In this particular circumstance, where interventions are already disseminated without randomized trial evidence, a retrospective, population-based cohort analysis may represent an advantage over a randomized clinical trial (RCT). However, that single advantage of the retrospective cohort analysis is diminished in comparison to the power engendered by randomized trial in assigning causality.

Ideally, an RCT could help determine a rational approach to choosing which drainage modality to use. However, an RCT would be difficult to achieve given that new treatment modalities are already in effect and that accruing sufficient patients would be difficult even in a multi-institutional study, as noted in a previous attempt at a national cooperative pseudocyst trial in the early 1990s. Moreover, this analysis assesses outcomes of interventions in their "natural" state, that is, in a nonstudy environment. Recognition of this "efficacy-versus-effectiveness" phenomenon is critical in determining the true impact of an intervention in practice, particularly once it has disseminated without the benefit of randomized trial evidence.

In addition to demonstrating the strengths of population-based analysis using administrative databases, this study also demonstrates the weaknesses of this approach. The NIS database is composed of administrative, hospital discharge data with the potential for miscoding. Also, no anatomic or physiologic data are available for review in this study. The impact of biochemical markers and pseudocyst characteristics on drainage outcomes cannot be analyzed in this study. It is also difficult to assess the temporal order of complications from these data. It is possible that complications before treatment may have influenced the choice of treatment. Furthermore, the NIS database has the specific limitation of being unable to follow patients longitudinally. As a result, long-term results for either drainage modality are not available. This limitation is of particular import for patients who underwent PD given the propensity of that modality for pseudocyst recurrence and need for subsequent intervention.[3,19]

Our study has demonstrated in a national population that SD has lower rates of in-patient complications and mortality than PD. This study also displays the benefit of ERCP on both LOS and mortality. Adverse surgical outcomes in this study may be overestimated given that PD often requires "salvage" surgery, in up to 87% of cases.[3,4,19] It is also known that surgical intervention in the setting of previous PD carries higher morbidity.[19,20] As a result, some of the adverse events noted in the surgical group may be attributed to previous PD. In contrast, morbidity and mortality of PD may be underestimated in this study given our inability to follow patients longitudinally. As mentioned previously, this limitation has real significance for PD given its rate of recurrence and need for further intervention. It is also important to note that drainage modality outcomes may reflect treatment strategies and processes of care beyond that of drainage modality.

A rational approach for using the different PP drainage modalities is essential. Recent literature points to emerging strategies. First, multiple studies have shown that observation is safe and effective for small, asymptomatic cysts.[3–5] Second, because pseudocysts arising from acute or chronic pancreatitis have a distinct pathophysiology, it is critical to determine the etiology given that PD in chronic pancreatitis is usually met with failure.[3,4,15] Third, ERCP use can predict treatment success and, in our study, rendered a protective mortality effect.[4] Concerns regarding exacerbating existing pancreatitis were not borne out in this study, as ERCP use decreased both LOS and mortality. Accumulating evidence suggests that more emphasis should be given to ductal anatomy than cyst characteristics. Studies have confirmed that main pancreatic duct complete obstruction is a poor prognostic factor for PD.[4,10,11] The benefit of ERCP may be both diagnostic and therapeutic given the ability to endoscopically stent the main pancreatic duct. Caution should be exercised in stenting chronic pancreatitis given the strong potential for

numerous stent exchanges over the long course of the disease. ERCP use likely should be increased given its benefit and low use, as shown in this study and others.[3,4] Increased use of ERCP should be tempered by the potential for adverse events associated with ERCP use, particularly at an institutional or a provider level. In addition, the advent of MRCP may address anatomic status of the pancreatic duct while avoiding some of the adverse events associated with ERCP. Last, SD of PPs should be used more frequently. This study is the latest in a series demonstrating that SD of a PP is safe, effective, and enduring.[3,4] Clear indications for SD remain large or multiple cysts; cysts with adjacent organ involvement, particularly splenic involvement[16]; biliary pancreatitis[17]; and chronic pancreatitis.

The clinical circumstances in which either PD or endoscopic drainage should be used remain unclear.[18] Potentially, PD could be used as a "bridge" procedure for patients who have an infected pseudocyst, are malnourished, or are a poor surgical risk. Clear end points for failure of PD are necessary. More data are needed to fully assess the role of endoscopic drainage, which we were unable to study here. Endoscopic drainage may have specific clinical application in PPs in the head of the pancreas or small persistent PPs.

This large sample of patients with PPs treated by percutaneous or surgical methods demonstrates that surgically treated patients have decreased LOS and lower morbidity and mortality. These results must be tempered by the fact that the comparison is retrospective and derived from administrative data. In addition, the use of ERCP is associated with improved outcomes and suggests that evaluation of the pancreatic duct is an integral process in the application of appropriate treatment strategies for patients with PPs.

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Discussion

Dr. Andrew Warshaw (Boston, MA): I have a couple of questions. One is, there seems to be a major selection bias in your two different groups: that is, the difference between predominance of acute pancreatitis versus chronic pancreatitis. Those are very different conditions, and I could propose that acute pancreatitis by itself would account for all of your findings of increased difficulties. That also would

relate to the timing of the procedure, how soon after admission or original acute pancreatitis the procedure was performed.

Second, you have left out the potential use of endoscopic drainage. I wonder if you have any comments there.

Third, what is the contribution of ERCP? Why should that make any difference at all? Are you defining those who have a communication with a pseudocyst or not?

Dr. Santhi Swaroop Vege (Rochester, MN): I would like to emphasize the same comment that Dr. Warshaw made, that acute pancreatitis may probably account for the differences.

And one more thing is that some "pseudocysts," in acute pancreatitis, may be necrotic collections, so-called "necromas" or "organized pancreatic necrosis." CT cannot distinguish them from pseudocysts, and those patients usually have worse outcomes. That may be another reason why there is a significant difference between the two groups presented by you, if one group had more necrotic collections than the other, which is not clear from the data.

Dr. Richard Prinz (Chicago, IL): There are some aspects of the presentation that I think raise a number of questions. Can you tell me why you excluded the combination drainages, since I think a lot of information can be gleaned from them? We very often will go to the opposite type of treatment if we have had a failure with either percutaneous surgical drainage. Do you have any idea about the number of pseudocysts that were infected and how they were treated in this series? Also, do you know if any of the percutaneous drainage procedures were actually endoscopic drainings, since there is no approved billing code for the latter?

Dr. Morton: In response to some of Dr. Warshaw's questions regarding selection bias for acute pancreatitis, I think that is a very valid point. I would like to point out that as part of our regression analysis correction for some of the changes that we saw, we did include the status of pancreatitis as part of that correction. So even though more patients who were percutaneously drained had an accompanying diagnosis of acute pancreatitis, they still had a higher mortality rate after we corrected for that diagnosis. So that was taken into account.

Regarding endoscopic drainage, one reason we excluded it is that there is no single diagnosis code or procedure code that fits endoscopic drainage, and, as a result, we were not able to study it in this particular setting.

I think the last point Dr. Warshaw made was a very important one, and that is—what role does ERCP play? And the question there is, "Do you have more of a therapeutic or diagnostic benefit from ERCP?" And I think both approaches are valid in that diagnostically it can tell you if there is a cutoff of the main pancreatic duct, if there is some sort of cutoff that will not allow resolution percutaneously, we are aware of that, and so I think in that circumstance diagnostically an ERCP might help. Therapeutically it might help by stenting the duct. That is something else that could occur.

In response to the gentleman from Rochester regarding acute pancreatitis and pseudocyst formation, I think that is a question that I have answered earlier for Dr. Warshaw. I think sometimes pseudocysts in the acute setting may or may not be pseudocysts. They may be acute fluid collections as well.

And the last question was what to do with the combination of procedures. We did look at those procedures, but we found that they were fairly small in comparison to this series, it was something less than 1%, and we did not feel we could get any really meaningful data from looking at such a small sampling.

I would like to point out that quite often a lot of these surgically drained patients have had prior percutaneous drainage; in fact, salvage procedures sometimes incorporate up to 87% of percutaneously drained pseudocysts. So, if anything, I think the study actually overestimates some of the adverse events associated with surgical drainage. Some of the surgical drainage adverse events may be in part attributed to previous percutaneous drainage.

Thank you very much.

F-18-Fluorodeoxyglucose Positron Emission Tomography in Differentiating Malignant From Benign Pancreatic Cysts: A Prospective Study

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The differential diagnosis between benign and malignant pancreatic cystic lesions may be very difficult. We recently found that F-18-fluorodeoxyglucose positron emission tomography (18-FDG PET) was useful for the preoperative work-up of pancreatic cystic lesions. This study was undertaken to confirm these results. From February 2000 to July 2003, 50 patients with a pancreatic cystic lesion were prospectively investigated with 18-FDG PET in addition to helical computed tomography (CT) and, in some instances, magnetic resonance imaging (MRI). The validation of diagnosis was based on pathologic findings after surgery (n = 31), percutaneous biopsy (n = 4), and according to follow-up in 15 patients. The 18-FDG PET was analyzed visually and semiquantitatively using the standard uptake value (SUV). The accuracy of FDG PET and CT was determined for preoperative diagnosis of malignant cystic lesions. Seventeen patients had malignant cystic lesions. Sixteen (94%) showed increased 18-FDG uptake (SUV >2.5), including two patients with carcinoma in situ. Eleven patients (65%) were correctly identified as having malignancy by CT. Thirty-three patients had benign tumors: two patients showed increased 18-FDG uptake, and four patients showed CT findings of malignancy. Sensitivity, specificity, positive and negative predictive value, and accuracy of 18-FDG PET and CT in detecting malignant tumors were 94%, 94%, 89%, 97%, and 94% and 65%, 88%, 73%, 83%, and 80%, respectively. 18-FDG PET is accurate in identifying malignant pancreatic cystic lesions and should be used in combination with CT in the preoperative evaluation of patients with pancreatic cystic lesions. A negative result with 18-FDG PET may avoid unnecessary operation in asymptomatic or high-risk patients. (J GASTROINTEST SURG 2005;9:22–29)

KEY WORDS: Pancreas, cystic lesions, intraductal papillary mucinous tumor, mucinous cystadenoma, serous cystadenoma, positron emission tomography, benign pancreatic cysts

Pancreatic cystic tumors include a variety of lesions with different biological behavior from benign to premalignant or borderline and to frankly malignant neoplasms.[1] Aggressive resection has been advised for most of the pancreatic cystic lesions, but this attitude is now changing for several reasons: (1) not all of these tumors require resection, and some patients have comorbid conditions that increase surgical risk, (2) increasing incidental detection of pancreatic cystic lesions in asymptomatic patients has been reported,[2] and (3) limited pancreatic resections are performed with increasing frequency for benign or borderline cystic lesions. Therefore, a correct preoperative identification is crucial for the appropriate management of these lesions.

Preoperative evaluation of pancreatic cystic lesions currently includes abdominal sonography, helical computed tomography (CT), and magnetic resonance imaging (MRI).[3–5] Recently, percutaneous[6,7] or endoscopic ultrasonography (EUS)[8,9] aspiration cytology and cyst fluid tumor marker determination have been proposed as useful tools helping in the differential diagnosis. However, conflicting results and pitfalls have been reported.[10,11]

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Positron emission tomography with F-18-fluorodeoxyglucose (18-FDG PET) shows an expanding role in the evaluation of many solid tumors, including pancreatic adenocarcinoma.[12,13] 18-FDG PET is based on the increased incorporation and metabolism of glucose by tumor cells compared with normal cells: so, a focal uptake likely suggests malignancy. Recently, we have reported in a preliminary study[14] that 18-FDG PET was very accurate in discriminating between malignant and benign cystic lesions.

The purpose of this prospective study was to confirm our preliminary data with PET in a cohort of patients with pancreatic cystic lesions and its relevance on clinical management of these patients.

MATERIAL AND METHODS

From February 2000 through July 2003, 50 patients with suspected cystic tumor of the pancreas (n = 33) or intraductal papillary mucinous tumors (IPMTs) (n = 17) were prospectively investigated with 18-FDG PET. All patients underwent helical CT scanning and serum CA 19-9 tumor marker determination (RIA; Centocor Inc., Malvern, PA; serum reference <37 U/mL). The preoperative evaluation also included MRI (n = 25) when the CT findings were not clear or when an IPMT was suspected. 18-FDG PET images were obtained using a dedicated tomograph (Siemens ECAT EXACT 47) with a field of view of 16.2 cm. After an overnight fast, 444 MBq (12 mCi) of 18-FDG was injected intravenously to each patient. To avoid interferences due to hyperglycemia, blood glucose level was checked just before the procedure and lowered to less than 120 mg/dL with insulin administration whenever necessary. Two transmission scans of the abdomen, for 15 minutes each, were obtained with 68 Ge rod sources before the FDG administration to obtain cross sections for attenuation correction of the emission images. Then, two emission scans, 15 minutes each, were acquired starting 60 minutes after FDG administration. The reconstruction was performed in a 128 × 128 matrix with Hanning filter 0.3 cutoff. Transaxial, coronal, and sagittal sections were obtained for visual analysis. To perform a quantitative analysis, the standardized uptake value (SUV) was calculated in the suspected neoplastic foci (SUV = tissue tracer concentration per injected dose per body weight). For the SUV analysis, a circular region of interest was placed over the area of maximal focal FDG uptake suspected to be a neoplastic focus, and the mean radioactivity values were obtained. Based on a previous study,[14] a focal uptake with an SUV of at least 2.5 was considered positive. The PET scan was interpreted by a single observer (F.C.) without knowledge of the CT scan results. Each CT scan was also interpreted by a single reader (G.L.), and the diagnosis of malignancy was based on general rules and on criteria suggested for IPMTs.[15] Validation of diagnosis was based on the pathologic findings of resected specimen, biopsy, or follow-up. Pathologic classification of the pancreatic tumors was made according to World Health Organization (WHO) histologic typing.[1] Sensitivity, specificity, positive and negative predictive value, and accuracy of 18-FDG PET and CT scan in differentiating malignant from benign lesions were evaluated. Our policy in the clinical management of patients with pancreatic cystic lesions was to resect, whenever possible, all of the symptomatic, or PET-positive, cystic lesions. For PET-negative cystic lesions, surgery was performed only when clinical and radiologic features suggested mucinous tumors (cystadenomas or IPMTs). Standard resection was the operation of choice for malignancies, whereas more conservative surgery-sparing pancreatic parenchyma or spleen, was reserved for benign lesions. Follow-up was considered for those asymptomatic PET-negative patients, with high surgical risk or lesions located in the head of the pancreas.

RESULTS

The distribution of patients according to pathology is summarized in Table 1. The final pathologic diagnosis was obtained after surgery in 31 patients and after percutaneous biopsy in 4. Fifteen PET negative

Table 1. Distribution of patients based on pathology

Type of lesion	No. of patients
Malignant lesions	17
IPMT	8
Cystadenocarcinoma	5
Solid-cystic tumor	2
Endocrine	1
ACCD	1
Benign lesions	33 (15)
Serous cystadenoma	10 (6)
Mucinous cystadenoma	5 (4)
IPMT	8 (4)
Pseudocyst	5 (1)
Endocrine	1
Single cyst	1
Others*	3

IPMT = intraductal papillary mucinous tumor; ACCD = adenocarcinoma with retention cyst. Values in parentheses = diagnosis of patients in follow-up based on morphologic appearance.
*Left adrenal lymphangioma, cystic dysplasia of the duodenum, pancreatic localization of Tangiers's disease.

cystic lesions were put on follow-up (median, 12 months; range, 8–44 months). None of these lesions developed changes in radiologic appearance or malignancy. There were 17 men and 33 women, with a mean age of 58.1 years (range, 14–87 years). Thirty-one patients (62%) were symptomatic: the most common symptoms and signs were pain (n = 23), dyspepsia (n = 5), jaundice (n = 1), and palpable abdominal mass (n = 2). Twelve patients had one or more attacks of acute pancreatitis. Nineteen patients (38%) were asymptomatic and the pancreatic lesion was incidentally discovered during investigations for unrelated disease. Mean tumor diameter was 3.5 cm (range, 1.0–10.0 cm). Fourteen patients had multiple pancreatic cystic lesions.

Seventeen patients had malignant lesions: five cystadenocarcinomas, two solid-papillary carcinomas, one endocrine carcinoma, one adenocarcinoma with retention cyst, and eight IPMTs (intraductal papillary mucinous carcinoma, two in situ and six invasive types, according to WHO classification). Thirty-three patients had benign lesions.

Malignant Tumors

There were 11 women and 6 men with a mean age of 58.3 years (range, 14–87 years). Fourteen patients (82%) were symptomatic: nine had abdominal pain; two, dyspepsia; two, palpable mass; and one, jaundice. One patient underwent cystojejunostomy for presumed pancreatic pseudocyst before referral to our department; another patient was admitted with a diagnosis of chronic pancreatitis and cholangitis. Three patients experienced one or more attacks of acute pancreatitis. Three patients were asymptomatic and their lesion was incidentally found during investigation for other disease (chronic hepatitis in two and breast cancer in one). Four patients had diabetes.

The CT scan showed a solitary cystic mass (n = 11) with internal septa (n = 6) or multiple cysts (n = 5) or a dilated main pancreatic duct (n = 5). In one patient, CT scan showed liver metastases, and in four patients, encasement of the superior mesenteric vein. Mean tumor size was 4.3 cm (range, 1.5–10.0 cm). Clear CT features of malignancy were found in 11 patients (65%). PET scan was positive in 10 of them. Sixteen of the 17 patients (94%) showed 18-FDG PET uptake with an SUV range of 2.5–7.0. An isolated focal uptake was found in 10 patients, and a peripheral uptake with central absence of metabolism was found in 6 patients (Fig. 1). Both patients with IPMT and carcinoma in situ showed 18-FDG uptake with an SUV of 2.5 and 5.0, respectively (Fig. 2). In three patients, 18-FDG PET showed liver metastases: these were detected by CT scan in one of them. In two other patients, PET detected lymph node metastases that were confirmed at laparotomy.

Twelve patients underwent resection (pancreaticoduodenectomy in six, total pancreatectomy in one, distal pancreatectomy and splenectomy in five), and two underwent bypass operation (both for vascular involvement). Three patients did not undergo surgery because of multiple liver metastases (n = 2) or mesenteric vein involvement (n = 1); in these patients, the diagnosis was confirmed by percutaneous fine-needle biopsy.

Among them, the single patient who showed normal 18-FDG uptake was a woman with well-differentiated cystadenocarcinoma of the head of the pancreas that was treated with pancreaticoduodenectomy. This tumor recurred 13 months later in the peritoneum, and 18-FDG PET showed multiple foci of pathologic uptake in the abdomen. Chemotherapy

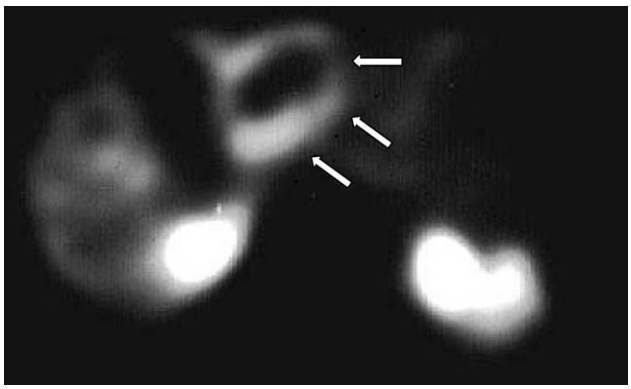

Fig. 1. Positron emission tomography scan (transaxial projection). Peripheral F-18-fluorodeoxyglucose uptake in the wall of a large pancreatic head cystic lesion (*arrows*). Malignant intraductal papillary mucinous tumor.

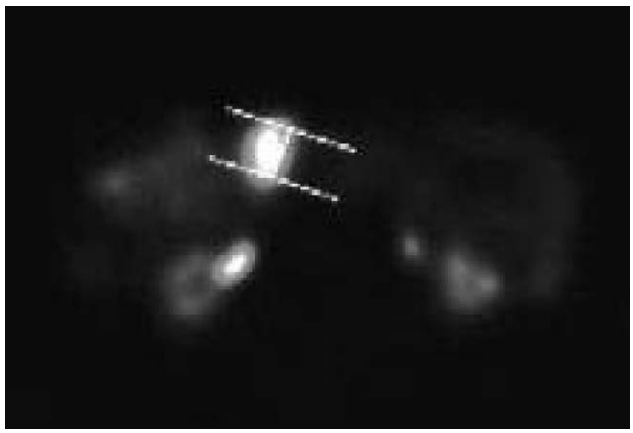

Fig. 2. Positron emission tomography scan (transaxial projection). Isolated focal F-18-fluorodeoxyglucose uptake in the pancreatic head. Malignant intraductal papillary mucinous tumor (carcinoma in situ).

was started and the patient is still alive 19 months after primary operation.

An additional four patients had one or more PET scans during the follow-up after resection; three had tumor recurrence in the liver, liver and peritoneum, and para-aortic lymph nodes, respectively. CT identified only liver metastases in two patients, while 18-FDG PET correctly showed all sites of tumor relapse. One of these patients had a successful resection of lymph node recurrence.

Benign Tumors

Among the patients with benign tumors, there were 22 women and 11 men with a mean age of 58.0 years (range, 17–86 years). Five patients (15%) had a pseudocyst (in two cases, multiple pseudocyst) with CT features resembling a cystic tumor, without history of acute or chronic pancreatitis. Seventeen patients (52%) were symptomatic: the most common complaints were abdominal pain (n = 14) and dyspepsia (n = 3). In nine patients, there was a history of one or more bouts of acute pancreatitis, and five had diabetes. Sixteen patients (48%) were asymptomatic and their lesion was incidentally found during investigations for unrelated disease.

CT showed a solitary cystic mass in 25 patients (with internal septations in 10) and multiple cysts with a dilated main pancreatic duct in 8. The mean tumor size was 3.2 cm (range, 1.0–10.0 cm). Four patients showed CT features suggesting a malignant tumor (Fig. 3). In 31 of 33 patients (94%), no uptake of 18-FDG was shown. Two patients showed a peripheral uptake with a central area of absent tracer concentration: a malignant cystic tumor in the tail of the pancreas was diagnosed and resected. Final pathologic examination showed a pseudocyst opened into the spleen (SUV = 2.6) and a pancreatic localization of Tangier's disease (SUV = 3.0), respectively.

Seven patients underwent distal pancreatectomy (five with spleen preservation) (Fig. 3); three patients, pylorus-preserving pancreaticoduodenectomy; two patients, duodenum-preserving pancreatic head resection; one patient, median pancreatectomy; two patients, tumor enucleation; and two patients, cystojejunostomy. Sixteen patients were not operated on: only one of them underwent percutaneous aspiration biopsy and cyst fluid tumor marker determination without evidence of malignancy (possible serous cystic tumor). All 16 patients had follow-up (median follow-up, 12 months; range, 8–44 months): none of them showed malignancy or changes in radiologic findings of their lesion.

Sensitivity, specificity, positive and negative predictive values, and accuracy of 18-FDG PET in detecting malignant cystic lesions were 94%, 94%, 89%, 97%, and 94%, respectively; these figures for CT were 65%, 88%, 73%, 83%, and 80%, respectively.

DISCUSSION

The differential diagnosis of cystic lesions of the pancreas remains a challenge. Resection has been advocated for all suspected cystic tumors of the pancreas to minimize diagnostic errors.[16] On the other hand, the increasing number of these lesions seen in the clinical practice[17] and the large number of studies concerning pancreatic cystic tumors require some considerations. First, more asymptomatic patients with pancreatic cystic mass are now detected, as in our experience (nearly half of the patients) and in other reports.[2,18] Second, some pancreatic cystic lesions are invariably benign[16]; so, it is unlikely that asymptomatic patients experience benefit from tumor removal. Third, pancreatic resection in old, high–surgical risk patients seems to be justified only for malignant or symptomatic tumors. Finally, the resection of tumors located in the head of the pancreas suggests caution even in younger patients. Therefore, we need a simple, reproducible, noninvasive method able to differentiate malignant from benign cystic lesions. Despite previous descriptions of typical clinical and radiologic features, conventional imaging modalities such as CT and MRI do not reliably distinguish between benign and malignant cystic lesions.[5,19] EUS has an expanding role in the preoperative evaluation of patients with pancreatic tumors.[20,21] EUS also has been advocated for the evaluation of pancreatic cystic masses,[8,22–24] but EUS alone seems not to improve CT results in distinguishing malignant from benign pancreatic cystic lesions.[9,25] Fine-needle aspiration cytology and cyst fluid analysis for enzyme and tumor marker determination appear to be logical adjunctive tests to better define a cystic mass of the pancreas.[9,25,26] However, cytology often shows false-negative or inconclusive results, and the wide overlap of tumor marker values makes the differentiation difficult.[9,10,25] Mucin determination in the aspirated cyst fluid seems to improve accuracy in detecting mucinous tumors,[25] but puncture of the cyst is an invasive method with a risk, although low, of complications also during EUS examination.[9,25]

In recent years, 18-FDG PET imaging has been increasingly used in the diagnosis, staging, and post-treatment surveillance of many types of malignancy.[27] During the process of malignant transformation, the majority of cells become avid glucose scavengers, with increased glucose transport and utilization. The enhanced glucose uptake explains why 18-FDG PET

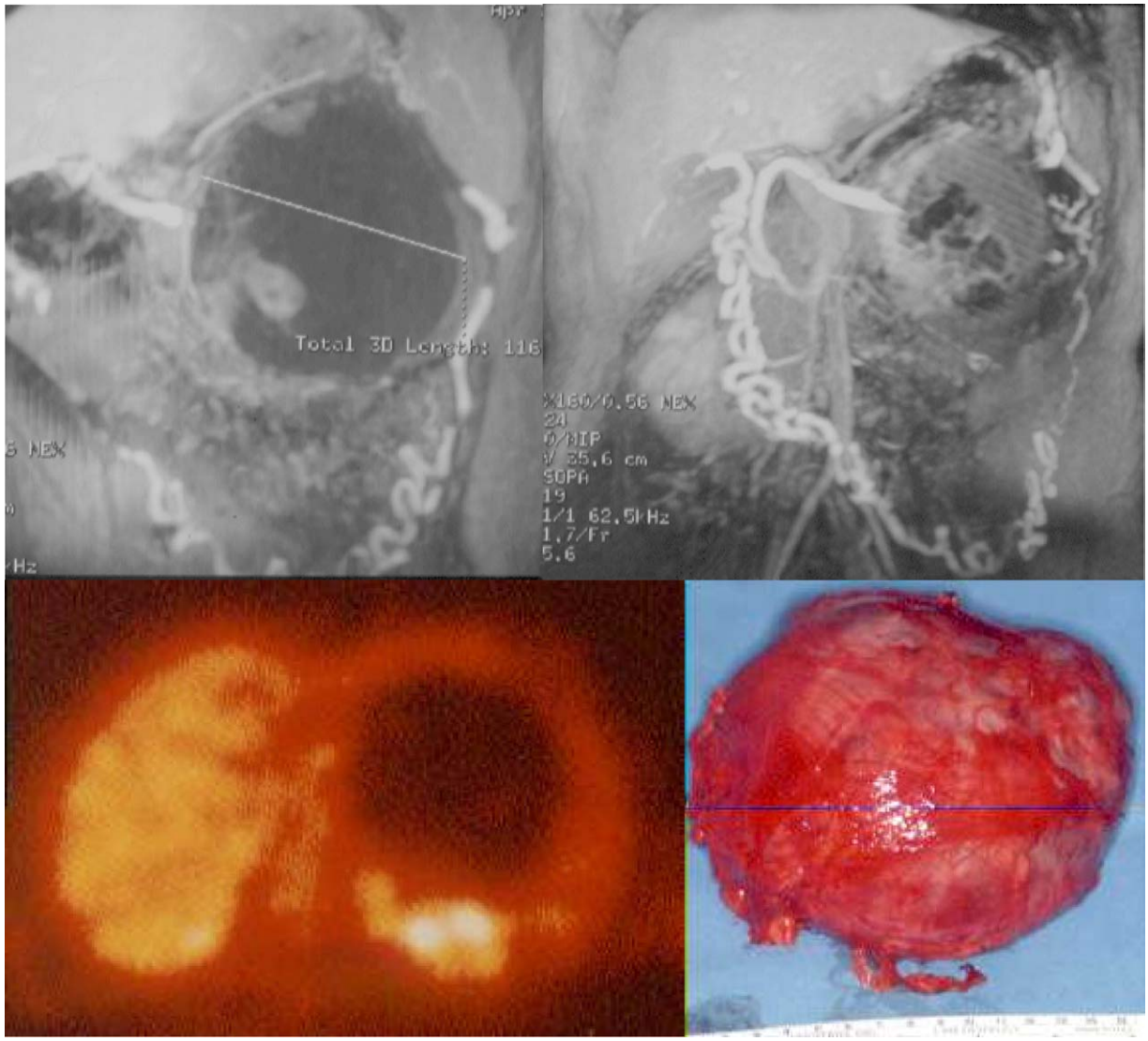

Fig. 3. *Top right and left*, Magnetic resonance image of a suspected cystadenocarcinoma of the body-tail of the pancreas in a 32-year-old woman. The large collateral veins draining the spleen suggest the obstruction of the splenic vein. *Bottom left*, Positron emission tomography scan is negative for malignancy. *Bottom right*, Borderline mucinous cystadenoma resected with a spleen-preserving procedure.

can functionally identify malignant tissues. This principle led us to verify in 2001 a possible role of 18-FDG PET in the differential diagnosis of cystic lesions of the pancreas, particularly in distinguishing malignant from benign pancreatic cystic lesions.[14] This preliminary study in 56 patients with suspected pancreatic cystic tumors showed that PET correctly identified 16 of 17 malignant and 38 of 39 benign cystic lesions with a specificity, positive and negative predictive value, and accuracy of 97%, 94%, 97%, and 96%, respectively, in detecting malignant tumors. Since then, we have continued to use 18-FDG PET, whenever possible, in the preoperative work-up of all patients with suspected cystic tumor of the pancreas. To our knowledge there are few reports dealing with PET imaging and cystic diseases of the pancreas. Yoshioka et al.[28] reported a high 18-FDG uptake in two patients with IPMT and invasive carcinoma. On the other hand, McHenry et al.[29] found that EUS fine-needle aspiration was more accurate (71%) than PET scan (50%) in detecting malignant cystic lesions. However, this study included only 13 valuable patients, suggesting further experiences are necessary to assess the role of 18-FDG PET in cystic lesions of the pancreas. Our current study results confirm the excellent results that we previously reported[14]: 18-FDG PET was able to detect 16 of 17 malignant cystic lesions (sensitivity of 94%) with a specificity of 93%. Interestingly, PET imaging showed increased uptake of 18-FDG, also in both patients with IPMT

and carcinoma in situ, in whom CT and MRI did not show any sign of malignancy. The identification of initial malignant transformation in the course of carcinogenesis is obviously crucial for the treatment of neoplasms, especially for those lesions that represent potentially curable tumors. Some[30] emphasized the importance of EUS biopsy in detecting malignant IPMTs, with an accuracy of 91% for invasive cancers. However, only 40% of noninvasive cancers (e.g., carcinoma in situ) were detected by examination of biopsy specimens.

Furthermore, in our series, 18-FDG PET added new information about tumor extension in 3 of 17 patients, showing liver and lymph node metastases not detected by traditional imaging. The single false-negative result occurred in a patient with cystadenocarcinoma of the head of the pancreas, correctly identified by CT. Thirteen months after resection, PET scan showed peritoneal recurrences that were not detected by CT scan. The false-positive results in our series occurred in a patient with pseudocyst partially invading the spleen and in a patient with a very rare pancreatic localization of Tangier's disease mimicking a malignant cystic tumor. A false-positive result of FDG PET in acute inflammations is a well-known event[31]; the false-positive result in such a rare metabolic disease (Tangier's) is explained by abundant infiltration of hystiocytes and macrophages and their 18-FDG incorporation, like inflammatory granulomas.[32] Thirty-one of 33 benign tumors (94%) showed no FDG uptake. On the basis of previous experience,[14] PET-negative cystic lesions were regarded as benign. Therefore, they were resected in low-risk patients when a premalignant tumor was diagnosed or when disabling symptoms were present. Furthermore, a negative PET scan prompted a more conservative pancreatic resection (n = 7) or avoided unnecessary splenectomy (n = 5). According to this policy, 16 asymptomatic patients underwent follow-up. Although the follow-up is relatively short, all non-operated patients were checked at 6 months and thereafter once a year. None showed changes in cyst diameter or appearance (all patients underwent abdominal sonography and/or CT or MRI; three patients had PET repeated). A limitation of 18-FDG PET remains the inability of this functional imaging modality to replace anatomic imaging in the assessment of tumor resectability; thus, 18-FDG PET is a sensitive and specific adjunct to CT in the differential diagnosis of cystic tumors of the pancreas. In the near future, when the PET-CT scan[33] becomes widely available, a single procedure probably can provide more precise information, both functional and morphologic, simultaneously.

CONCLUSION

18-FDG PET is a very useful technique for the preoperative work-up of patients with suspected cystic tumors of the pancreas. The high FDG uptake suggest a malignant tumor that require aggressive resection, whereas a negative PET scan likely identifies a benign tumor that may be treated with more conservative surgery or simple follow-up. The importance for the clinical management, especially in asymptomatic high-risk patients, is clearly relevant.

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Discussion

Dr. Nathaniel Soper (Chicago, IL): Did you look at any other modalities that have been reported for differentiating between benign and malignant lesions, such as aspiration techniques and assessing cyst fluid for CA 19-9, etc.? And second, did you find any differences between this prospective study compared to the retrospective study that you previously published in the *Annals of Surgery?*

Dr. Pedrazzoli: As to the first question, we worked for several years trying to find a specific marker for malignancy for a differential diagnosis but could not find such a reliable marker. The problem is also that when you do aspiration, if you have a malignant lesion, you can also seed malignant cells. So it is not safe when you have a suspected malignancy and you need to decide the feasibility or not. So that if you do a PET, it is a noninvasive modality.

About the difference between the first study and the second study, the accuracy was the same, exactly the same. In the first study, we decided to have histology in all patients. In the second study, after the first few patients, 16 patients had only follow-up, and most of them are asymptomatic patients who were followed up from 12 months to 4 years, without any change.

Dr. Henry Pitt (Milwaukee, WI): This analysis was very nice and you are to be congratulated for finding a way to differentiate the benign and malignant tumors. Clearly, we have not had anything as accurate as PET. It was interesting to me, however, you had two groups that were benign and malignant; but when you came to your conclusion, you had three groups, benign, premalignant, and malignant. It would be ideal if we had a way of differentiating benign versus premalignant and malignant, because most of us believe that the premalignant lesions should come out before they become malignant. Unfortunately, PET does not give us that additional advantage.

Dr. Pedrazzoli: Unfortunately, I was wrong in my conclusion, but premalignant are still benign lesions,

and should be considered still a benign lesion not yet transformed; for this reason they were included in the benign group. Usually, conventional radiology (CT or MRI) is able to distinguish serous cystoadenomas, always benign lesions, from the other types of tumors. So the differential diagnosis between benign and premalignant and malignant lesions is not so difficult. However, it is important to diagnose a malignant lesion in old patients who need surgical treatment or a benign premalignant lesion in old patients who do not need surgical resection because they are old and they would not die of the disease.

Dr. Stephen Vogel (Gainesville, FL): As you know, many patients with small cystic tumors in this country undergo endoscopic ultrasound with aspiration, and either the endoscopist samples the fluid in his or her hands, finds it sticky, and then makes a diagnosis of mucin or the pathologist will stain for mucin. Now, we are finding small mucin-producing cystic lesions. Do you have a series of small mucin-producing cystic lesions with a negative PET scan that you followed, in other words, you did not operate on, for some period of time?

As you know, our pathologists may not diagnose malignancy in a mucinous tumor. They will just call it a mucinous tumor based on the fact, as Dr. Pitt mentioned, that there is a "potential" for it to become malignant somewhere down the road. So my question is, have you followed small mucin-producing cystic lesions for a period of time with negative PET scans? Thank you.

Dr. Pedrazzoli: I agree with you that a young woman with a small cystic lesion may be better treated with a limited resection. It is easier. If you wait, it becomes larger, and therefore you have to resect more pancreas. We have four PET-negative patients with mucinous cystoadenoma currently on follow-up. But the real problem is the intraductal papillary mucinous tumor, which commonly occurs in the older population. In the older population, if you have a benign or borderline lesion, we would place the patient into follow-up.

I forgot to tell that two patients with carcinoma in situ were PET positive, while old patients with borderline or only low-grade or medium-grade dysplasia were negative.

So I believe that PET scan is one of the best ways to do the differential diagnosis in the uncertain cases, not in all cases. When calculating the cost-effectiveness of PET, we must consider not only the high cost of the procedure, but also the cost of the surgical procedures avoided, thanks to PET's negative results.

Laparoscopic Adjustable Gastric Banding Versus Laparoscopic Gastric Bypass for Morbid Obesity: A Single-Institution Comparison Study of Early Results

Jay C. Jan, M.D., Dennis Hong, M.D., Natasha Pereira, M.D., Emma J. Patterson, M.D.

Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic adjustable gastric banding (LAGB) are common surgical procedures for morbid obesity, but few studies have compared LRYGB and LAGB. All patients who underwent LRYGB and LAGB by a single surgeon at Legacy Health System were identified from a prospectively maintained database. Preoperatively, most patients were allowed to choose between LRYGB and LAGB. Age, sex, body mass index (BMI), complications, mortality, and weight loss were examined. From October 2000 to November 2003, 219 patients underwent LRYGB and 154 patients underwent LAGB. Mean preoperative BMI was 49.5 ± 6.6 and 50.9 ± 9.4 kg/m^2, respectively ($P = 0.10$). Mean age was 42 ± 9 and 47 ± 11 years ($P < 0.001$). The LAGB group had a higher proportion of male patients (21% versus 7%, $P < 0.001$). Patients undergoing LRYGB had longer operative times (134 versus 76 minutes, $P < 0.001$), more blood loss (43 versus 28 ml, $P < 0.01$), and longer hospital stays (2.6 versus 1.3 days, $P < 0.001$). Excess weight loss was 35% for LRYGB versus 19% for LAGB at 3-month follow-up ($P < 0.001$), 49% versus 25% at 6 months ($P < 0.001$), 64% versus 36% at 12 months ($P < 0.001$), 70% versus 45% at 24 months ($P < 0.001$), and 60% versus 57% at 36 months ($P = 0.85$). Major complications occurred in 7% and 6% ($P = 0.58$) and minor complications occurred in 18% and 20% ($P = 0.65$) of patients, respectively. Reoperation occurred in 21 patients (10%) after LRYGB and 31 (20%) patients after LAGB ($P < 0.01$). Of patients undergoing reoperation, eight (38%) LRYGB patients and one (3%) LAGB patient required open laparotomy. One death occurred in each group. Patients undergoing laparoscopic adjustable gastric banding have shorter operative times, less blood loss, and shorter hospital stays compared with laparoscopic gastric bypass patients. The incidence of major and minor complications is similar; however, morbidity after LRYGB is potentially greater and the reoperation rate is higher in the LAGB group. Early weight loss is greater with gastric bypass, but the difference appears to diminish over time. (J GASTROINTEST SURG 2005;9:30–41)

KEY WORDS: Morbid obesity, bariatric surgery, gastric bypass, gastric banding, complications, weight loss

The prevalence of obesity has increased steadily over the past three decades in the United States with the largest proportional increase occurring in the morbidly obese category (body mass index [BMI], ⩾40 kg/m^2).[1–3] Obesity substantially increases morbidity, impairs quality of life, decreases life expectancy, and is associated with many chronic health conditions.[4–6] Currently, bariatric surgery remains the most effective treatment of morbid obesity.[7] The application of new, minimally invasive techniques to bariatric surgery in the past decade has reduced perioperative morbidity and has contributed to a remarkable increase in interest in the surgical treatment of morbid obesity.[8,9]

Two of the most commonly performed surgical procedures for morbid obesity worldwide are Roux-en-Y gastric bypass and adjustable gastric banding. Since the application of laparoscopic techniques to the gastric bypass procedure 10 years ago, laparoscopic gastric bypass has become the standard bariatric

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procedure in many centers in the United States. Laparoscopic gastric bypass has been shown to produce substantial sustained weight loss with resolution of obesity-related comorbid conditions.[10–13] Laparoscopic adjustable gastric banding (LAGB) for morbid obesity has been reported in several large series from Europe and Australia also with good weight loss and improvement in comorbid conditions.[14–16] However, some surgeons in the United States doubt the efficacy of LAGB in the American population.[17,18] Clinical experience in the United States with LAGB is limited, but recent data show promising results that are comparable to the international experience.[19,20]

The purpose of this study was to compare our early results of laparoscopic gastric bypass and laparoscopic adjustable gastric banding (LAGB).

MATERIAL AND METHODS

Study Population

The study population consists of a consecutive series of patients who underwent laparoscopic Roux-en-Y gastric bypass (LRYGB) and LAGB for morbid obesity over a 3-year period by a single surgeon. Operations were performed by a fellowship-trained laparoscopic bariatric surgeon (E.J.P.) in the setting of a comprehensive multidisciplinary program with an established laparoscopic surgery fellowship. All LAGB patients had the Lap-Band System (INAMED Health, Santa Barbara, CA) placed. The surgeon completed mandatory training in a Lap-Band System workshop and subsequent on-site proctoring by a surgeon experienced with LAGB. All patients met criteria for bariatric surgery established by the National Institutes of Health Consensus Development Panel[7]; patients had a body mass index (BMI) $\geq$40 kg/m^2 or $\geq$35 kg/m^2 in the presence of obesity-related comorbidities. All patients had failed to maintain weight loss with supervised dietary programs. Most patients were allowed to choose either LRYGB or LAGB after extensive counseling regarding treatment options for morbid obesity. LAGB was recommended to the highest risk patients, based on surgeon judgment. The first eight LAGB patients in this series were enrolled in a clinical trial ("C" Trial) for the Lap-Band System prior to United States Food and Drug Administration approval of the device in June 2001.

Preoperative Evaluation and Preparation

Patients attended a comprehensive informational session, were evaluated by a clinical psychologist and dietician, and attended support group meetings. Additional specialty consultation was obtained if indicated. All patients were required to undergo overnight polysomnography before surgery. If patients were diagnosed with obstructive sleep apnea, institution of nocturnal continuous positive airway pressure (CPAP) therapy was required before surgery. Patients were given instructions for a low-fat, low-carbohydrate diet and were encouraged to lose 5% of their initial weight before surgery.

Prophylaxis against venous thromboembolism consisted of perioperative lower extremity sequential pneumatic compression devices. Prophylactic intravenous antibiotic administration was routine for all patients. LRYGB patients underwent preoperative bowel cleansing.

Surgical Technique

Laparoscopic Gastric Bypass. Using a 15-ml balloon-tipped orogastric tube (INAMED Health) to size the gastric pouch, multiple loads of a 3.5-mm linear cutting stapler (Endo GIA; U.S. Surgical, Norwalk, CT) were applied, starting at the lesser curvature just caudal to the inflated balloon and proceeding to the angle of His. This created a 15- to 20-ml divided gastric pouch. The anvil of a 25-mm circular stapler (CEEA, U.S. Surgical) was secured to an orogastric tube in a flipped position in a similar technique as described by Matthews et al.[21] The tube was passed orally, anvil side last, by the anesthesiologist and brought out through a small gastrotomy in the pouch staple line, created by the ultrasonic coagulating shears. The greater omentum was divided in the midline with the ultrasonic coagulating shears to the transverse colon to form a channel for the Roux limb to reduce tension on the gastrojejunostomy. The jejunum was divided 100 cm from the ligament of Treitz. The jejunal mesentery was minimally divided (1–2 cm) with the ultrasonic coagulating shears. A gastrojejunostomy with an antecolic, antegastric Roux limb was created with the circular stapler. The anastomosis was evaluated for a leak by using methylene blue administered through an orogastric tube with the Roux limb clamped. A side-to-side jejunojejunostomy was performed with a single fire of a 2.5-mm linear cutting stapler to restore intestinal continuity, creating a 100-cm Roux limb. The common enterotomy at the jejunojejunostomy was closed with intracorporeal suturing. Mesenteric defects were not closed. Concomitant cholecystectomy was performed only for symptomatic gallstone disease.

Laparoscopic Adjustable Gastric Banding. The surgical technique for LAGB is similar to the one described by Fielding and Allen.[22] Blunt dissection and electrocautery were used to separate the angle of His from the left crus. A balloon-tipped orogastric

tube was inserted by the anesthesiologist and inflated with 15 ml of air. The tube was pulled back to the esophageal hiatus to evaluate for the presence of a hiatal hernia. If a hiatal hernia was detected, crural closure was performed. Dissection was carried out by the pars flaccida technique, in which the clear area of the gastrohepatic ligament was divided with electrocautery and the right crus was identified. The peritoneum was incised with electrocautery just anterior to where the left and right crura meet. A blunt atraumatic grasper was inserted gently in a flat trajectory toward the angle of His. The tubing of the band device was grasped and brought through the retrogastric tunnel. The tubing was placed through the buckle of the Lap-Band System and locked. Peritoneum and fat were incised to ensure that the band could freely rotate around the stomach. Three gastrogastric sutures were placed, creating an anterior fundoplication over the band. The first suture was placed high on the greater curvature of the stomach near the angle of His. The gastroesophageal fat pad was routinely excised with cautery. Concomitant cholecystectomy was performed for symptomatic gallstone disease. The band reservoir was left empty at the completion of surgery.

Postoperative Management

Both LRYGB and LAGB patients recovered in a surgical ward experienced in the postoperative care of bariatric patients. Early ambulation on the evening after surgery was strongly encouraged. Patient-controlled analgesia was used for pain management. Water-soluble contrast study was obtained the next morning. If no leak or perforation was demonstrated, liquid diet was initiated. LAGB patients were routinely discharged on the first postoperative day. LRYGB patients were routinely discharged on the second postoperative day.

Postoperatively, LRYGB patients were seen at 3 weeks after surgery, then every 3 months during the first year, every 6 months during the second year, and yearly thereafter. LAGB patients were seen at 3 and 6 weeks, then monthly for the first 6 months, then bimonthly for the next 6 months, then every 3 months for the second year, and then yearly thereafter. At each visit, patients were weighed on the same bariatric scale and stadiometer (Scale-Tronix, White Plains, NY). All patients were started on a daily multivitamin 3 weeks after surgery. If patients had an intact gallbladder, they were started on a 6-month regimen of ursodeoxycholic acid to reduce the risk of gallstone formation. In addition, LRYGB patients were started on lifelong daily vitamin B_{12}, iron, and calcium supplements.

For the LAGB patients, saline was not added to the band reservoir until at least 6 weeks had elapsed after surgery. Early in our experience, band adjustments were performed under fluoroscopy. We now routinely perform adjustments in the clinic. The need for band reservoir adjustment is determined by various factors, including amount of gastric restriction during meals, level of satiety or hunger after meals, and amount of recent weight loss or gain; no strict protocol was used. We typically aim for weight loss of 1 to 2 pounds per week, a meal amount that is less than 1 cup, and sustained satiety between meals. The first adjustment usually involves addition of 1 ml of sterile saline. The second adjustment involves addition of 0.5 or 1 ml of saline. Subsequent adjustments typically require the addition of 0.2 to 0.5 ml.

Data Collection and Statistical Analysis

All data were entered prospectively into a computerized database and reviewed retrospectively. Data measures include patient demographics, obesity-related comorbid conditions, operating time, blood loss, hospital stay, complications, and weight loss. Weight loss was expressed as percent excess weight loss (EWL). *Percent excess weight loss* was defined as the difference between start weight and end weight, divided by baseline excess weight. Excess weight was determined from the ideal body weight, based on sex- and height-adjusted weight for a medium frame according to the 1983 Metropolitan Life Insurance Company tables.[23] *Major complication* was defined as a potentially life-threatening adverse event requiring urgent intervention. *Minor complication* was defined as an adverse event that was not life threatening and was managed by medical therapy or elective intervention. Patients who had their bands removed were excluded from further weight loss analysis. Most of these patients were either converted to another bariatric procedure or were lost to follow-up. Two-tailed Student's t test was used for continuous variables, and Pearson χ^2 test was used for categorical variables. Continuous variables are expressed as mean $\pm$ SD. Post-hoc logistic regression analysis was performed to adjust for differences in patient demographics between groups. Variables in the regression model included age, sex, type of surgery, year of surgery, presence of diabetes, and preoperative BMI. Statistical analysis was performed with SPSS version 11.5 software (SPSS Inc., Chicago, IL). All P values are two-sided and $P < 0.05$ was considered statistically significant.

RESULTS

Overview

Between October 2000 and November 2003, 373 patients underwent attempted LRYGB or LAGB at

Legacy Health System in Portland, Oregon, by the study surgeon. Two hundred nineteen (59%) patients underwent LRYGB, and 154 (41%) patients underwent LAGB. Our procedure volume increased nearly threefold over the 3-year period with 54% of procedures occurring in the third year. In the first year, LAGB represented 19% of procedures. By the third year, LAGB represented 47% of procedures. Mean follow-up was 13.5 ± 8.1 months (range, 1–41). Follow-up data were available for 222 patients at 1 year after surgery, 58 patients at 2 years, and 15 patients at 3 years. All patients underwent primary bariatric procedures except for two patients in the LAGB group; one patient had undergone previous jejunoileal bypass and the other patient had undergone both previous jejunoileal bypass and vertical banded gastroplasty.

Patient Characteristics

Patient demographic and comorbidity data for the LRYGB and LAGB groups are shown in Table 1.

Table 1. Baseline characteristics of the patients, according to treatment group*

Characteristic	LRYGB (n = 219)	LAGB (n = 154)	*P* value
Age (yr)	42 ± 9	46 ± 11	<0.001
⩾60	2 (1)	17 (11)	<0.001†
Gender			
Male	16 (7)	32 (21)	<0.001
Female	203 (93)	122 (79)	<0.001
Race			
White	214 (97)	145 (95)	NS
Black	2 (1)	4 (3)	NS
Hispanic	1 (1)	3 (2)	NS
Asian	3 (1)	1 (1)	NS
BMI, kg/m^2	50 ± 7	51 ± 9	NS
<50	120 (55)	84 (55)	NS
⩾50 and <60	80 (37)	47 (31)	NS
⩾60	19 (9)	23 (15)	NS
Comorbidity			
Hypertension	109 (50)	85 (55)	NS
Diabetes mellitus	66 (30)	50 (33)	NS
Hyperlipidemia	87 (40)	47 (31)	NS
Obstructive sleep apnea	144 (66)	113 (73)	NS
GERD	118 (54)	59 (38)	<0.05
Degenerative joint disease	173 (79)	112 (73)	NS
Depression	135 (62)	80 (52)	NS
Stress urinary incontinence	110 (50)	68 (44)	NS
Menstrual irregularity	62 (28)	35 (23)	NS
Metabolic Syndrome	74 (34)	53 (34)	NS

LRYGB = laparoscopic Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable gastric banding; BMI = body mass index; GERD = gastroesophageal reflux disease; NS = not significant.
*Values in parentheses represent percentages.
†Fisher's exact test.

The LAGB group was significantly older and had a higher proportion of male patients compared with the LRYGB group. Significantly more patients with age ⩾60 years were in the LAGB group. Both groups were similar with respect to mean preoperative BMI and ethnicity. Although not statistically significant, the LAGB group had more patients with BMI ⩾60 kg/m^2 (15% versus 9%; $P = 0.06$). There was no significant difference between the two groups with respect to comorbidity except for gastroesophageal reflux disease, which was more common in the LRYGB group.

Perioperative Data

Three hundred seventy (99%) procedures were successfully completed. LAGB placement was not completed in three patients; two patients had intraoperative bleeding and one patient had gastric perforation identified intraoperatively. Among patients undergoing completed procedures, two patients (0.5%) required open conversion. One patient in the LRYGB group required open conversion because of extensive intra-abdominal adhesions from prior surgery. One open conversion occurred in the LAGB group because of inadequate exposure due to an enlarged liver and inadequate pneumoperitoneum. Patients undergoing LRYGB had significantly longer operative times, more blood loss, and longer hospital stays (Table 2). Forty-one LRYGB patients (19%) underwent 44 concomitant procedures and 33 LAGB patients (21%) underwent 35 concomitant procedures at the time of surgery (Table 3).

Complications

Major complications for LRYGB and LAGB are listed in Tables 4 and 5, respectively. Sixteen major complications (7%) occurred in the LRYGB group and 9 major complications (6%) occurred in the LAGB group ($P = 0.58$). The incidence of major

Table 2. Perioperative data for laparoscopic gastric bypass and laparoscopic adjustable gastric banding*

	LRYGB (n = 219)	LAGB (n = 154)	*P* value
Operative time (min)	134 ± 36	76 ± 32	<0.001
Blood loss (ml)	43 ± 42	28 ± 57	<0.01
Hospital stay (days)	2.6 ± 3.4	1.3 ± 1.3	<0.001
Concomitant procedure	41 (19)	33 (21)	NS
Open conversion	1 (0.5)	1 (0.6)	NS
Death	1 (0.5)	1 (0.6)	NS

LRYGB = laparoscopic Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable gastric banding; NS = not significant.
*Values in parentheses represent percentages.

Table 3. Concomitant procedures with laparoscopic gastric bypass and laparoscopic adjustable gastric banding

LRGYB (n = 219)		LAGB (n = 154)	
Procedure	**n**	**Procedure**	**n**
Hiatal hernia repair	19	Hiatal hernia repair	18
Cholecystectomy	10	Adhesiolysis	13
Adhesiolysis	9	Ventral hernia repair with mesh	2
Paraesophageal hernia repair	2		
Liver biopsy	2	Cholecystectomy	1
Partial omentectomy	1	Liver biopsy	1
Oophorectomy	1		
Total	44		35

LRYGB = laparoscopic Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable gastric banding.

complications with LRYGB is shown in Table 6. One death occurred as a result of LRYGB (0.5%); this early death occurred in-hospital after small bowel perforation secondary to jejunojejunostomy obstruction. There were two late deaths that were unrelated to surgery; one death occurred 4 months after surgery from a probable cardiac cause and the other death occurred 2 years after surgery from pneumonia. One death occurred in the LAGB group (0.6%); this was an intraoperative death from bleeding caused by vascular trocar injury and was not specifically caused by band placement. There were no late deaths in the LAGB group.

To adjust for differences in age and sex between groups, a logistic regression was performed to assess the impact of the type of surgery (LAGB or LRYGB) on major complications. Odds ratio is shown in Table 7. Although not quite statistically significant, the odds of developing a major complication was twofold higher in patients who underwent LRYGB.

Reoperation occurred in 21 patients (10%) after LRYGB and 31 (20%) patients after LAGB ($P < 0.01$). An additional 10 patients (5%) in the LRYGB group required therapeutic endoscopy (10 anastomotic stenosis; 1 anastomotic bleeding). The cause of reoperation in 27 of the 31 LAGB patients was a late complication, most frequently band slippage or port/tubing event; they were all managed laparoscopically or with a local procedure. Eight of the 11 patients in the LRYGB reoperation group (38%)

Table 4. Major complications with laparoscopic Roux-en-Y gastric bypass (N = 219)

Major complication	Cause	Management	Outcome
Early			
Peritonitis	Obstruction at jejunojejunostomy with perforation	Open repair; multiorgan system failure; prolonged hospitalization	Death
Peritonitis	Gastric pouch staple line leak	Attempted laparoscopic repair; open repair; prolonged hospitalization	Resolved
Peritonitis	Gastrojejunostomy leak	Open repair; developed ventral hernia and enterocutaneous fistula; prolonged hospitalization	Resolved
Hemorrhage	Gastrojejunostomy staple line bleeding	Therapeutic endoscopy	Resolved
Hemorrhage	Roux limb staple line bleeding	Laparoscopically oversewn	Resolved
Hemorrhage	Trocar site bleeding	Transfusion 4 units red blood cells	Resolved
Obstruction	Gastric remnant dilatation	Open exploration; gastrostomy	Resolved
Obstruction	Gastric remnant dilatation	Roux limb and gastric necrosis requiring open revision	Resolved
Small bowel obstruction	Adhesive band	Open adhesiolysis with gastrostomy and jejunostomy	Resolved
Respiratory insufficiency	Underlying pulmonary disease	Extended intubation	Resolved
Upper gastrointestinal bleeding	Anastomotic bleeding	Endoscopy	Resolved
Late			
Small bowel obstruction	Stricture at jejunojejunostomy	Open revision of jejunojejunostomy	Resolved
Small bowel obstruction with bowel ischemia	Adhesive band	Laparoscopic converted to open adhesiolysis	Resolved
Perforated ulcer	Marginal ulcer	Laparoscopic repair	Resolved
Perforated ulcer	Duodenal ulcer	Laparoscopic repair; cholecystectomy	Resolved
Thiamine deficiency	Nausea and vomiting	Intensive care unit care; extended hospitalization	Resolved

Total of 16 (7%).

Table 5. Major complications with laparoscopic adjustable gastric banding (N = 154)

Major complication	Cause	Management	Outcome
Early			
Hemorrhage	Trocar insertion injury	Open conversion	Death
Hemorrhage	Liver retractor injury	Open conversion; splenectomy; band not placed	Resolved
Gastric perforation	Creation of retrogastric tunnel	Laparoscopic repair during primary procedure; band placed 1 month later	Resolved
Gastric perforation	Creation of retrogastric tunnel	Laparoscopic band removal and repair	Resolved
Pulmonary embolism	Venous thrombosis	Anticoagulation	Resolved
Gastric perforation	Stoma obstruction	Open repair with removal of band; prolonged hospitalization	Resolved
Late			
Band infection	Seeding from infected port	Laparoscopic removal of band; subsequent laparoscopic gastric bypass	Resolved
Acute gastric prolapse	Blunt trauma/motor vehicle accident	Laparoscopic removal of band	Resolved
Acute gastric prolapse	Acute retching	Laparoscopic revision of band	Resolved

Total of 9 (6%).

required open laparotomy, with 6 occurring in the early postoperative period. On the other hand, only one of the patients in the LAGB reoperation group (3%) required open laparotomy; this occurred in the early postoperative period. Overall, patients requiring early reoperation with open laparotomy had an average of 2.7 ± 2.0 abdominal operations with a median length of hospital stay of 45 days (range, 10–159 days).

Minor complications for LRYGB and LAGB are shown in Table 8. The most common minor complications were anastomotic stenosis, which occurred in 10 (5%) of patients in the LRYGB group, band slippage or pouch dilatation in 14 (9%) of LAGB patients, and port/tubing events in 10 (7%) of LAGB patients. Anastomotic stenosis was managed successfully with endoscopic balloon dilatation in all patients; one patient required three dilatations and one required two dilatations. Band slippage was managed laparoscopically in all patients (12 band revisions; 4 band removals); two patients had recurrent band slippages. Most of the anastomotic stenosis and band slippage complications occurred early in our learning curve.

Table 6. Incidence of major complications with laparoscopic Roux-en-Y gastric bypass (N = 219)

Complication	n (%)
Anastomotic leak	2 (0.9)
Small bowel obstruction	4 (1.8)
Bleeding	4 (1.8)
Gastric remnant dilatation	2 (0.9)
Pulmonary embolism	0 (0)
Death	1 (0.5)

Twelve of the patients who had band-specific complications (band slippage and band erosion) were among the first 34 LAGB patients (35%) in the series, when the suturing technique incorporated fixation to the diaphragmatic crura or the gastric pouch was sized with the calibration balloon. There have been four band-specific complications (3%) in the last 120 LAGB patients.

Nine patients (6%) underwent band removal. Reasons for band removal were band slippage/pouch dilatation (four patients), gastric perforation (one patient), gastric erosion (one patient), band infection (one patient), poor weight loss (one patient), and gastric perforation due to stomal obstruction (one patient). All were performed laparoscopically, except for the patient with the gastric perforation, who underwent open repair at another institution. Four of these patients (44%) subsequently underwent other bariatric procedures (laparoscopic biliopancreatic diversion in three, laparoscopic gastric bypass in one).

Table 7. Predictors of major complications*

Factor	Odds ratio	95% Confidence interval	*P* value
Type of surgery	2.03	0.76–5.42	0.16
Gender	1.91	0.66–5.56	0.23
Year of surgery	0.70	0.41–1.18	0.18
Diabetes	1.21	0.5–2.93	0.67
Age	1.07	1.02–1.12	0.008
Preoperative body mass index	1.02	0.97–1.08	0.50

*Reference levels were the following: type of surgery = laparoscopic adjustable gastric banding; gender = female; year of surgery = first year; diabetes = absent.

Table 8. Minor complications after laparoscopic gastric bypass and laparoscopic adjustable gastric banding

LRYGB (n = 219)		LAGB (n = 154)	
Complication	**n**	**Complication**	**n**
Stenosis	10	Band slippage/pouch dilatation	16
Wound infection	9	Port dislodgement	5
Incisional hernia	7	Port leak	4
Symptomatic cholelithiasis	6	Symptomatic choleithiasis	3
Nausea/vomiting	3	Malposition	2
Marginal ulcer	3	Wound infection	2
Urinary tract infection	2	Band erosion	1
Kidney stones	2	Aspiration	1
Iron deficiency anemia	2	Partial small bowel obstruction	1
Urinary retention	1	Port irritation	1
Thiamine deficiency	1	Tubing disconnect	1
Pain	1	Dehydration	1
Hypoproteinemia	1	Pain	1
Hypocalcemia	1		
Subphrenic abscess	1		
Decubitus ulcer	1		
Total*	51		39

LRYGB = laparoscopic Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable gastric banding.
*51 Minor complications occurred in 40 LRYGB patients (18.3%), and 39 minor complications occurred in 31 LAGB patients (20.1%).

Weight Loss

Figure 1 shows the percent EWL and BMI for LRYGB and LAGB patients at 3, 6, 9, 12, 18, 24, and 36 months after surgery. Total weight loss and EWL were significantly higher and mean BMI was significantly lower with LRYGB at all postoperative intervals except at 3 years of follow-up, when no significant differences in these parameters were seen. Figure 2 compares EWL in superobese (BMI $\geq$50 kg/m^2) and nonsuperobese (BMI $<$50 kg/m^2) subgroups of LRYGB and LAGB patients. There was a tendency for less EWL in superobese patients in the LRYGB compared with nonsuperobese patients; however, this phenomenon was not seen in the LAGB group.

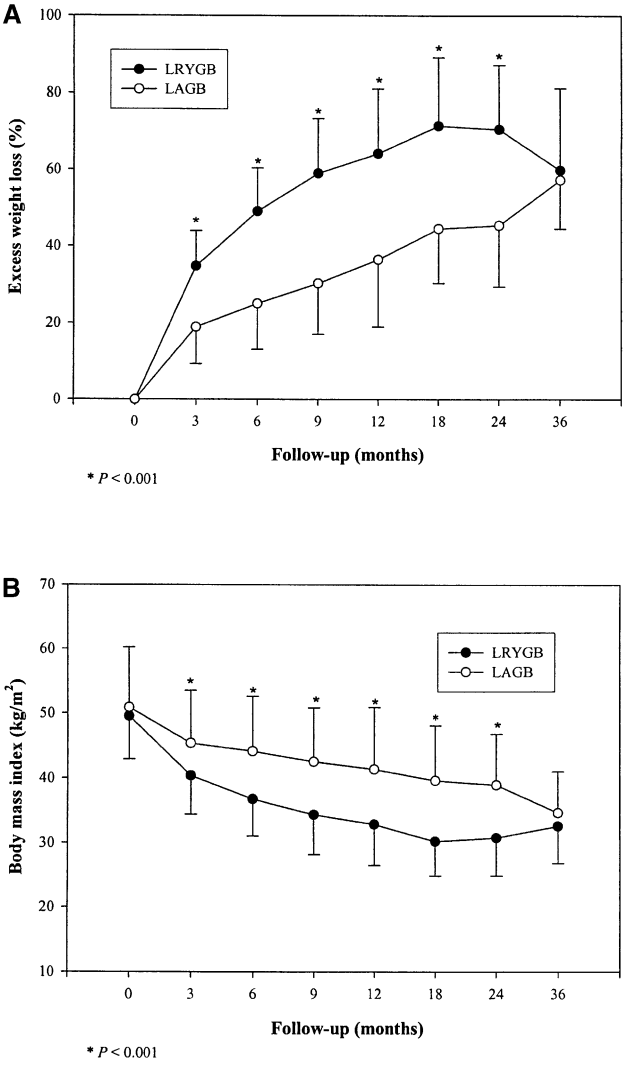

Fig. 1. Comparison of percent excess weight loss (**A**) and change in body mass index (**B**) for laparoscopic gastric bypass and laparoscopic adjustable gastric banding patients. Error bars indicate SD.

DISCUSSION

Since the application of minimally invasive techniques to bariatric surgery more than 10 years ago, the demand for weight loss surgery has increased dramatically.[9] Laparoscopic bariatric surgery is associated with decreased perioperative morbidity and faster recovery with comparable weight loss to open bariatric procedures.[8,24] Laparoscopic approaches have been described for various bariatric procedures, including gastric bypass, adjustable gastric banding, vertical banded gastroplasty, and biliopancreatic diversion with or without duodenal switch. At present, two commonly performed laparoscopic bariatric procedures are LRYGB and LAGB. Although both LRYGB and LAGB cause a decrease in caloric intake and induce satiety, the exact mechanism for weight loss has yet to be completely elucidated. Many studies have demonstrated that both LRYGB and LAGB are safe and effective in the treatment of morbid obesity.[10–15] Both procedures produce sustained weight loss and result in improvement in obesity-related comorbidities.[25,26] For LRYGB, early results range from 56% to 77% EWL.[10–13] EWL with LAGB ranges from 50% to 60% in Europe and Australia.[16,27–32] In the United States, the early experience

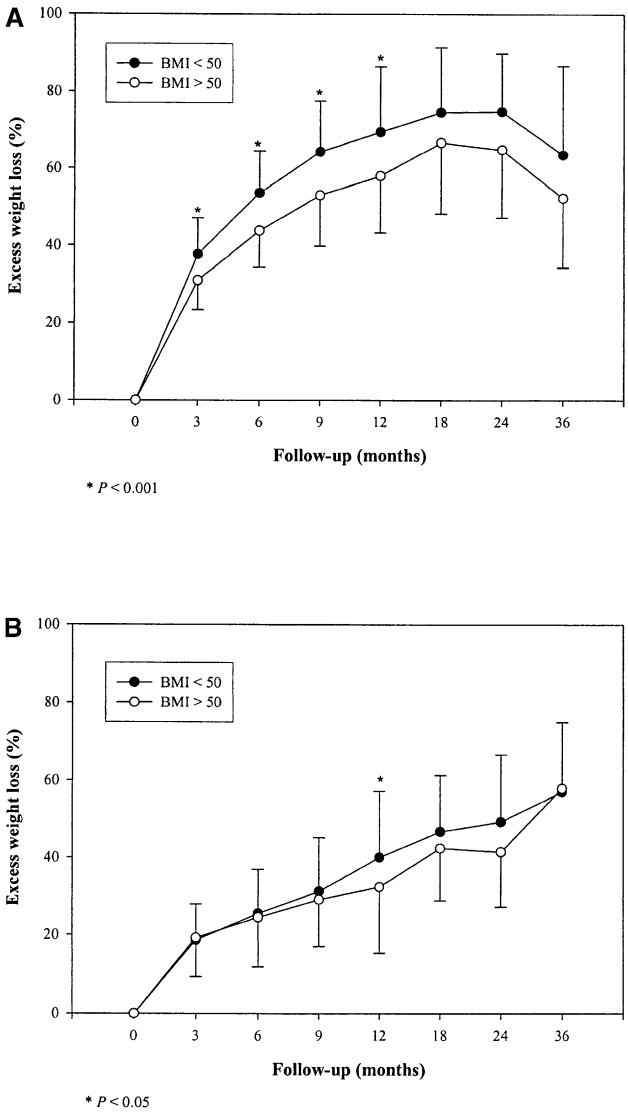

Fig. 2. Comparison of percent excess weight loss in patients with body mass index of 50 kg/m^2 or greater and body mass index less than 50 kg/m^2 for laparoscopic gastric bypass (**A**) and for laparoscopic adjustable gastric banding (**B**) patients. Error bars indicate SD.

with LAGB was less successful,[17] but recent reports parallel the international experience.[19,20] Nevertheless, all of these reports represent individual single-institution case series and no prospective randomized studies have compared the two procedures. Most of the reported LAGB series come from Europe and Australia, whereas most of the LRYGB series originate from the United States. Because of the different patient populations, surgeons, and health care systems, the comparison of these series is not feasible.

Our study is the first single-institution case series to compare LRYGB and LAGB for the treatment of morbid obesity. We report a consecutive series of patients who have undergone LRYGB and LAGB by a single surgeon in the first 3 years of practice after fellowship training. Although most patients were allowed to choose between the two procedures, the highest risk patients were recommended to undergo LAGB, which we thought offered a lower risk of perioperative morbidity and mortality. Patients were subjectively considered high risk if several factors were present, including higher age, male sex, super-superobesity (BMI $\geq$60 kg/m^2), and presence of significant cardiopulmonary disease. As a result of this policy, patients undergoing LAGB were more likely to be older and male and the LAGB group had a higher proportion of super-superobese patients (Table 1). The prevalence of obesity-related comorbidities was relatively similar between the two groups, except for gastroesophageal reflux disease, which was more prevalent in the LRYGB group.

In our series, LRYGB is associated with longer operative time, more blood loss, and longer hospital stay compared with LAGB. Both LRYGB and LAGB are associated with low rates of conversion to open procedures. Reported operative times in the literature vary because of specific technical variations with each procedure and surgeon experience. However, our shorter operative time with LAGB is not surprising when one compares the complexity of the procedures. LRYGB requires multiple precise steps, including division of the stomach and creation of two anastomoses. LAGB, on the other hand, is technically simpler, but significant intraoperative pitfalls remain, specifically when creating the blind retrogastric tunnel.

The comparison of adverse events after LRYGB and LAGB is difficult because each is associated with well-known procedure-specific complications, with little overlap between procedures. The most significant procedure-specific major complication with LRYGB is anastomotic or staple line leak, which can occur in up to 4% of cases.[10,33] Well-known minor complications include stomal stenosis, marginal ulcer and nutrient deficiencies. Adverse events after LAGB are typically device-specific and range from uncommon, but significant, complications such as intraoperative gastric perforation to frequently occurring, minor complications involving band slippage and port/tubing problems. In comparing complication rates between the two procedures, one must also consider the severity of morbidity associated after each adverse event.

There was no significant difference in the number of major complications between patients undergoing LRYGB and LAGB in our series of patients. However, patients who underwent LAGB were older and

had a greater proportion of males. Both of these factors have been shown to potentially increase morbidity and mortality of bariatric surgery.[33–35] Therefore, the difference in patient demographics in our comparative analysis would bias against LAGB. To control for these differences, a post-hoc logistic regression analysis was performed that showed the odds of a major complication was twofold higher in patients who underwent LRYGB. However, this result must be interpreted with some caution because the confidence interval was large. Our practice of recommending LAGB to higher-risk patients may have influenced our anastomotic leak rates in our LRYGB patients. Because both increasing age and male sex have been shown to predict anastomotic leak,[33] many patients at higher risk for anastomotic leak from LRYGB were encouraged to undergo LAGB. As a result, our incidence of anastomotic leak (0.9%) compares favorably to the 3–4% incidence noted in other series.[10,13]

On closer analysis of the major complications in the LRYGB group, six patients in the early postoperative period required open laparotomy, after which they often endured long hospitalizations and frequently required multiple operations. Only one patient in the LAGB group required early open laparotomy and subsequent prolonged hospitalization. The two occurrences of intraoperative gastric perforation from creation of the retrogastric tunnel were both managed laparoscopically without significant sequelae. Therefore, although the incidence of major complications did not differ significantly between the LRYGB and LAGB, we believe that the perioperative morbidity of early major complications after LRYGB is potentially more severe than that after LAGB.

Although the rate of minor complications also did not differ significantly between our LRYGB and LAGB groups, many of the LAGB and LRYGB patients with minor complications required additional procedures. Anastomotic stenosis, band slippages, and tubing/port problems accounted for a significant number of minor complications. All band slippage and port/tubing problems were managed laparoscopically or with a local procedure with minimal morbidity, but these still contributed to the higher reoperation rate in the LAGB group. On the other hand, all LRYGB patients with anastomotic stenosis required endoscopic dilatation; some patients required multiple attempts. The majority of anastomotic stenoses and band slippages occurred early in our series, which probably reflects the learning curve of both procedures.

Our data demonstrate that weight loss is substantial after both LRYGB and LAGB. Patients undergoing LRYGB lose weight more rapidly and have significantly greater weight loss up to 2 years of follow-up. However, the weight loss difference appears to diminish over time, and our analysis of early data at 3-year follow-up demonstrates similar weight loss with LRYGB and LAGB. This same difference and trend in weight loss between the LRYGB and LAGB groups remained after stratifying by preoperative weight (BMI $\geqslant$50 versus BMI $<$50 kg/m^2). However, within the LRYGB group, superobese patients (BMI $\geqslant$50 kg/m^2) had less EWL over the first 2 years compared with patients with BMI less than 50 kg/m^2. This concurs with previous reports that Roux-en-Y gastric bypass is less effective in superobese patients than in nonsuperobese patients.[36,37] Interestingly, the disparity between superobese patients and nonsuperobese patients was not seen in the LAGB group.

We believe that no true "gold standard" exists for weight loss surgery and that both LRYGB and LAGB are viable options. Significant morbidity can occur with either procedure, but perioperative morbidity with LAGB is less severe and LRYGB has a lower reoperation rate. In our practice, we offer both procedures to most patients. In fact, because of the popularity of bariatric surgery, we have found that the majority of our patients are well-informed and have already decided which procedure to pursue before our consultation. Nevertheless, for those patients whom we consider to be at the highest risk, we recommend LAGB.

Certain limitations of our study must be acknowledged when reviewing our data. First, this is a nonrandomized comparison study and selection bias affected the allocation of patients into the treatment groups. The disparity in age and sex reflects bias by the patient and surgeon that increased age and male sex are associated with increased morbidity in LRYGB.[34,35] Second, the classification of complications into major and minor was not determined *a priori*. For example, some surgeons would classify band slips as a major complication of LAGB. Yet, we believe that the vast majority of slips can be treated laparoscopically with relative ease with little morbidity to the patient. Third, our analysis of outcomes is limited by small patient numbers, specifically at 3 years of follow-up. Because the majority of our cases were performed in the last year of our study period, longer follow-up is needed to fully assess trends in weight loss, improvement in comorbidities, and late complications. Last, our analysis did not include other important outcome measures such as resolution of comorbid conditions, cost, or quality of life.

CONCLUSION

In our series, both LRYGB and LAGB produce substantial weight loss with low mortality. Patients

undergoing LAGB have shorter operative times, less blood loss, and shorter length of hospital stay compared with LRYGB patients. The incidence of major and minor complications did not differ significantly; however, morbidity after LRYGB was potentially greater and the reoperation rate was higher in the LAGB group. A randomized trial is needed to clarify which procedure provides the best results.

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Discussion

Dr. Sayeed Ikramuddin (Minneapolis, MN): Thank you and congratulations on presenting a very timely study and thank you for giving me an advance copy of your paper to review ahead of time.

This study is the first single institutional case series to compare gastric banding and laparoscopic Roux-en-Y gastric bypass from the United States. I think its findings support what we have seen so far. Perhaps the mean follow-up of 13.5 months shows a slightly diminished excess weight loss in the gastric bypass group, but what is more important, I think, is the validation of what we have seen in European and other centers throughout the world in a single institutional study. So you are to be commended for that.

Conclusions from this paper must be balanced against the fact that, as you mentioned, it is a nonrandomized study, and there is a significant difference in demographics, particularly the increase in male patients within the banding group, that may have an effect on long-term weight loss. I have three general questions for you.

First, what can you tell us about failures, how do you define failure in this population, and was there a difference in failures between the band and the bypass group? Second, how about the sweets-eaters population? This is a notoriously difficult population to deal with in restrictive procedures. Have you been able to define any differences between the gastric bypass group and the banding group? And finally, I noticed from the paper looking at your follow-up program that you see the banding patients an average of approximately 13 times within the first 3 years for adjustments and so forth, whereas you see the gastric bypass patients approximately nine times. Do you think this type of increased follow-up may lead to increased motivation and may result in some of the results you are seeing?

I want to thank you for an excellent paper, and this certainly calls for a randomized study with longer follow-up. Thank you.

Dr. Jan: Thank you for your kind comments, Dr. Ikramuddin. I will address your questions in order. In terms of failures, we did not define failures in our series. Some have defined failures as not attaining greater than a 50% excess weight loss or a BMI less than 35. Because our early results for gastric bypass and gastric banding demonstrate different weight loss curves, we feel that it's too early to define "failures" in either group. Our gastric bypass patients have greater early weight loss than do gastric banding patients; however, the weight loss difference appears to decrease over time, with continued weight loss for the gastric banding patients and a plateau and some weight regain for gastric bypass patients. We're very interested in following the weight loss trend in our gastric bypass and gastric banding patients over a longer period of follow-up.

With regard to sweets eaters and non–sweets eaters, we did not classify our patients based on dietary habits. We have not noticed a difference in our outcomes based on this; however, we did not focus on this specifically.

And in terms of frequency of follow-up, you bring up a good point. Our early follow-up with the gastric banding patients is more frequent. Typically, we see the gastric banding patients monthly for the first 6 months and every other month for the next 6 months; this allows for the frequent, small band adjustments. The early follow-up for the gastric bypass patients involves visits every 3 months for the first year. Certainly, if patients come to our office more frequently, they may be more inclined to stick with the program and be more motivated, but both groups of patients are encouraged to attend our support group meetings and to visit the dietician postoperatively. This is something that we could look at more closely.

Dr. John Kellum (Richmond, VA): I congratulate you on this effort. I do urge caution, however, in the interpretation of the results, since there was massive selection bias in your study. For example, did your patients who chose to have a gastric banding contact you through the Internet? Having done research, perhaps they were better educated, and more likely to be a compliant group of patients. I think the point about sweets addiction is very important. You should look into that. What were your recommendations as to exercise following both of these procedures? And what was your percentage of African American patients? We found only an 11% loss of initial excess weight in our African American patients having gastric banding. Our patients tend to be sweets addicted, and many of them lost little or no weight. Thank you.

Dr. Jan: With respect to your first question, there was definitely a selection bias in our patients. The people we thought were higher risk tended to undergo gastric banding. Most of the patients who come to see us for bariatric surgery certainly are well-informed, have been on the Internet, have been to support groups, and have talked to each other, but we have not noticed a difference between our gastric

bypass and gastric banding patients. All of them attend a comprehensive information session describing both procedures, and we allow the majority of our patients to choose which procedure they want. By the time they see us in the office, most of them have already decided which procedure they want. Only in the 5% or so that we think are the highest risk do we actually push them more toward gastric banding. It is certainly possible that our gastric banding patients may be more well-informed and compliant, but that is something that we did not look at specifically and we did not select more well-informed patients to undergo a specific procedure.

In terms of our postoperative care and exercise, both the gastric bypass and the gastric band patients routinely attend support groups and they are both part of the same multidisciplinary process. There is no specific exercise regimen; however, we do encourage them to pursue some sort of structured exercise program or increased activity.

With respect to ethnic variations and outcomes, in our program, more than 90% of our patients were white in both gastric bypass and gastric banding groups, and African Americans comprised only 1.6% of our patients. We did not see any significant difference in excess weight loss between gastric bypass and gastric banding among African Americans at 2-year follow-up (64.0% versus 60.1%).

Invited Commentary

The Laparoscopic Adjustable Gastric Band: We Need to Keep an Open Mind—YET STILL

Michael G. Sarr, M.D.

This work by Dr. Emma Patterson's group[1] really is an exciting, carefully done study— especially so to this "non-believer," or maybe better put, this "ongoing skeptic," who is still a non-convert.

Readers (and especially we ongoing skeptics) should be encouraged to give this paper both a fair reading and its due respect. This group in Portland, working in the Legacy Health System, reports their experience in a respectfully objective manner, with a notable lack of the zealotry too often present in this topic. Their results suggest an equivalency of weight loss of laparoscopic adjustable gastric band (LAGB) and laparoscopic Roux-en-Y gastric bypass (LRYGB) (eventually) at 3 years postoperatively, with similar short- and longer-term morbidity. The advantages they claim, however, are shorter OR times, hospitalizations, and probably procedure-related costs, although the latter data (unfortunately) are not reported. The authors end by stating their opinion "that no true 'gold standard' exists for weight loss surgery and that both LRYGB and LAGB are viable options."

LAGB is a theoretically attractive procedure—minimal access approach, short 1-day hospital stay, no anatomic replumbing, gut not opened, it is "adjustable," no gastrointestinal bypass, no global or selective maldigestion/malabsorption, and it is relatively easily (laparoscopically) reversed without need for any replumbing.

YET STILL—this study reports only 3-year follow-up. All bariatric surgeons remember the theoretic attractiveness (at their original introduction) of the jejunoileal bypass, the original loop gastric bypass (and the recent, short-lived mini-gastric bypass), the numerous forms of stapled gastroplasties, and even the vertical banded/ring gastroplasty—however, none have prevailed because of unappreciated side effects or poor durability. The lessons we learned (I hope) are that confident acceptance of a new approach requires long-term study—so I remain a non-convert—YET STILL, we need to keep an open mind.

YET STILL—the LAGB requires the use of a foreign body device around the stomach. We all remember the Angelchik prosthesis—yes, an effective device, but associated with too many problems. Other GI devices, such as those in the perianal region and some around enterostomas, have not been successful; even the bands/rings of the vertical banded/ring gastroplasty can erode, etc. What will the status of these bands be in 5, 10, 20, or even 30 years later? Are they durable, does their need for (eventual) replacement (which this commentator believes to be inevitable—admittedly based only on common sense, not data) negate their value?

YET STILL, isn't the LAGB just another form of "gastroplasty," all of which previously have failed? I agree with the argument that most other stapled gastroplasties have a high incidence of failure secondary to staple line disruption[2]—and that the LAGB has no staple line to disrupt. However, our experience with ⩾10-year follow-up of vertical banded gastroplasty,[3] unlike the initial data causing my original (premature) enthusiasm,[4] was that many patients failed despite an anatomically intact anatomy because of ingestion of calorie-dense sweets that "slid through" the banded stoma leading to maladaptive eating (and, of course, weight regain). The argument that good dietary choices in the LAGB patients will prevent this weight regain is not a realistic argument as witnessed by a previous lifetime of the inability to do so by these patients.

In summary, yes we all (even us skeptics) need to keep an open mind and review the accumulating data on LAGB fairly—YET STILL I would disagree with the authors "that no 'true gold standard' exists." We

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have 7–10+ years' data on durability and efficacy in weight loss maintenance after RYGB, and these are the best data at hand.[5,6] I maintain that these data on RYGB provide the gold standard against which other operations must be compared, and possibly compared in the specific national and racial population to be evaluated. Time will tell. YET STILL, we need to keep an open mind.

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Outcomes of Roux-en-Y Gastric Bypass Stratified by a Body Mass Index of 70 kg/m^2: A Comparative Analysis of 825 Procedures

Ioannis Raftopoulos, M.D., Ph.D., Julie Ercole, Anthony O. Udekwu, M.D., James D. Luketich, M.D., Anita P. Courcoulas, M.D., M.P.H.

We compared the safety, excess weight loss (EWL), and improvement in comorbidities after Roux-en-Y gastric bypass (RYGB) in morbidly obese and superobese patients (body mass index, < 70 kg/m^2 or $\geqslant 70$ kg/m^2). Of 825 patients who underwent RYGB by our group between 1995 and 2003, 79 (9.6%) were superobese (group A) and 746 were morbidly obese (group B). There were significant differences in age (A, 40.8 years; B, 43.2 years; $P = 0.01$), gender (males: A, 40.5%; B, 17.6%; $P < 0.0001$), and type of access (laparoscopic RYGB: A, 4.1%; B, 34.2%; $P < 0.0001$). Sleep apnea (A, 57%; B, 31.4%; $P < 0.0001$) and venous insufficiency (A, 16.5%; B, 2.4%; $P < 0.0001$) were more common in superobese patients. Hospital stay was similar (A, 6.3 days; B, 5.3 days) with adjustment for differences in type of access. Although morbidity was comparable, mortality was higher in the superobese group (A, 2.5%; B, 0.5%; $P < 0.05$). At a comparable follow-up (A, 17.7 months; B, 18.25 months), percent EWL at 1 year was lower in the superobese group (A, 54.6%; B, 64.3%; $P < 0.0001$), but it became similar at 3 years (A, 66.5%; B, 60.7%). Postoperative improvement of comorbidities was equally dramatic in both groups with the exception of venous insufficiency. In conclusion, complications are not increased in the superobese, but they are more often fatal. Superobese patients achieve their maximum weight loss in a longer period of time and reach their nadir at year 3. (J GASTROINTEST SURG 2005;9:44–53)

KEY WORDS: Morbid obesity, superobesity, morbidity, mortality, weight loss, comorbidities

Although superobesity is not officially recognized as a weight category, it has been the subject of intense scrutiny because of reported associations with a higher incidence of comorbid medical conditions and potentially greater health risks,[1] increased technical challenges with higher morbidity and mortality rates,[2] and suboptimal weight loss.[3] *Superobesity* has been arbitrarily defined as either a body weight of greater than 225% of the ideal body weight[4] or greater than 200 pounds of ideal body weight,[5] as well as either a body mass index (BMI) of 60 kg/m^2 or greater[6] or, more commonly, a BMI of 50 kg/m^2 or greater.[7] In our experience, patients with a BMI of 70 kg/m^2 or greater represent a distinct group of patients because of increased technical difficulties, limitations in the preoperative and postoperative diagnostic work-up, and higher intolerance to any adverse events after surgery. The outcome of Roux-en-Y gastric bypass (RYGB) in "extremely" superobese patients with a BMI of 70 kg/m^2 or greater in terms of safety, weight loss, and improvement in obesity-related disorders has not been previously investigated and is the objective of this study.

MATERIALS AND METHODS

This is a retrospective review of 825 morbidly obese patients who underwent RYGB between January 1995 and July 2003. All procedures were performed by one of three surgeons A.O.U. (n = 114), J.D.L. (n = 64),

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and A.P.C. (n = 646). Data regarding gender, age, race, BMI, percent excess weight loss (% EWL), comorbid medical conditions, type of access, length of stay (LOS), complications, and length of follow-up were prospectively collected and recorded in our database. Perioperative complications were recorded by the caring physician and were entered in our database by designated personnel.

All patients met the National Institutes of Health criteria for bariatric surgery[8] and underwent a standard preoperative work-up, which included upper gastrointestinal series (UGI), abdominal ultrasound (unless cholecystectomy had been previously performed), and nutritional and psychiatric evaluation. Based on the individual patient's coexisting medical conditions and risk factors, additional diagnostic testing was selectively performed that included stress test, upper endoscopy, sleep apnea study, lower extremity venous Doppler studies, as well as renal, hematology, or neurology consultation.

Surgical Technique

Before surgery, all patients undergoing RYGB received 5,000 U of heparin subcutaneously and intravenous antibiotics. Open RYGB was performed through a midline subxiphoid incision (Fig. 1). A 15- to 20-ml pouch was created by gastric partitioning with the TA-90 stapler (US Surgical Corp., Norwalk, CT). A 150- to 200-cm Roux limb was constructed in a retrocolic antegastric fashion and was anastomosed to the gastric pouch side-to-side with the 3.5-mm/45-mm linear stapler (EndoGIA II; US Surgical Corp.). The gastrojejunostomy was measured to be 3 cm in diameter. The gastroenterostomy was closed in one layer with interrupted sutures. The jejunojejunostomy was created in a side-to-side fashion with the 3.5-mm/60-mm linear stapler (EndoGIA II). The mesenteric, mesocolic, and Petersen's defects were closed with sutures.

Laparoscopic RYGB was performed through six ports (US Surgical Corp.) as shown in Fig. 2. Abdominal access and pneumoperitoneum was established with the Hasson technique. A 15- to 20-ml gastric pouch was constructed with the 3.5-mm/45-mm linear stapler (EndoGIA II). A 150- to 200-cm Roux limb was constructed in a retrocolic retrogastric fashion and was anastomosed to the gastric pouch side-to-side with the 3.5-mm/45-mm linear stapler (EndoGIA II). The gastrojejunostomy was measured to be 3 cm in diameter. Using the endoscope as a stent, the gastroenterostomy was closed in two layers with interrupted sutures using the Endostitch device (US Surgical Corp.). The jejunojejunostomy was created in a side-to-side fashion with the 3.5-mm/60-mm linear stapler (EndoGIA II). The mesenteric, mesocolic, and Petersen's defects were closed with sutures.

All patients who had laparoscopic RYGB underwent UGI on the first postoperative day and began a clear liquid diet at the same time if the study was negative for leaks. UGI was selectively performed in patients who had an open RYGB only if clinically indicated. A clear liquid diet was started on the second postoperative day. Drains were not routinely used.

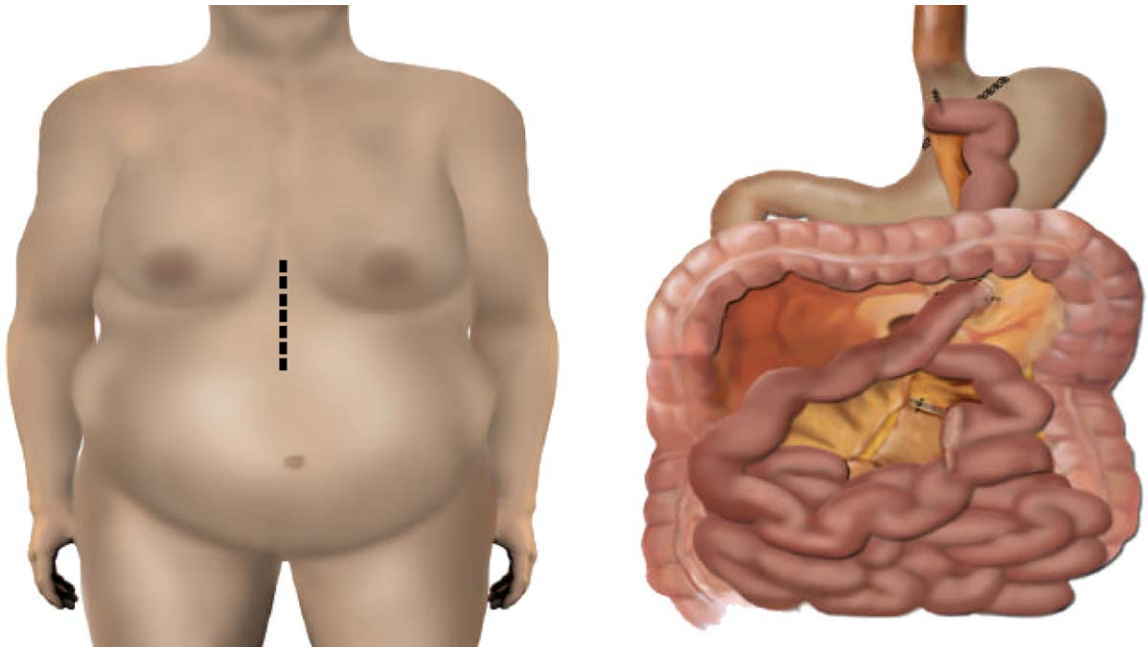

Fig. 1. Technique of open Roux-en-Y gastric bypass.

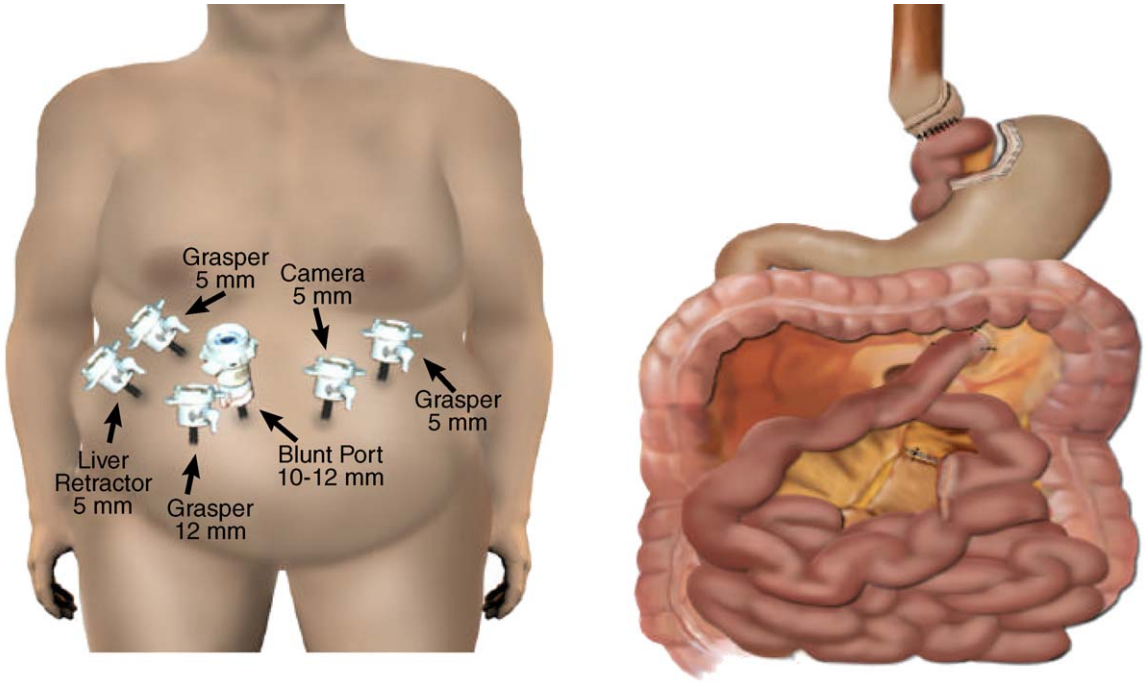

Fig. 2. Technique of laparoscopic Roux-en-Y gastric bypass.

Follow-up

All patients were scheduled for routine postoperative visits at 2 weeks, 6 weeks, every 3 months for the remaining first year, every 6 months for the second year, and annually thereafter. Comorbid medical conditions, including sleep apnea, hypertension, diabetes mellitus, degenerative joint disease, gastroesophageal reflux disease, stress incontinence, depression, asthma, hyperlipidemia, and venous insufficiency, were evaluated preoperatively and at each follow-up visit. The postoperative status of each comorbidity was defined as resolved, improved, or same. The postoperative status of sleep apnea was determined based on the use of C-PAP/BiPAP and pressure requirements before and after surgery. The postoperative status of hypertension, diabetes mellitus, degenerative joint disease, depression, asthma, and hyperlipidemia was assessed based on comparison of the preoperative and postoperative values and dose of medications required. Venous insufficiency was assessed by comparing severity and diuretic requirements before and after surgery. The status of each comorbidity at the most recent follow-up was compared with the preoperative baseline value.

Statistical Analysis

The outcome measures used to assess short-term (<30 days) and long-term (>30 days) outcomes include major and minor complications, LOS, mortality, % EWL, and percent improvement in comorbidities. Morbid obesity was defined as a BMI of less than 70 kg/m^2 and superobesity as a BMI of 70 kg/m^2 or greater. Comparison of continuous and categorical variables was assessed with the Student's t test and the χ^2 test, respectively. A value of $P < 0.05$ was considered significant.

RESULTS

Of the 825 patients, 746 (90.4%) had a BMI of less than 70 kg/m^2 (mean, 51.5 kg/m^2; range, 32.8–69.9 kg/m^2), and 79 (9.6%) had a BMI of 70 kg/m^2 or greater (mean, 79.9 kg/m^2; range, 70.1–133.1 kg/m^2). The mean % EBW was significantly higher in the superobese group. Superobese patients were younger and more often of male gender than morbidly obese patients. There was a trend toward a higher percentage of black patients at the superobese group but the difference was not significant (Table 1). A laparoscopic access was used more often in the morbidly obese group (BMI <70 kg/m^2: n = 255, 34.2% versus BMI ⩾70 kg/m^2: n = 3, 4.1%; $P < 0.0001$).

Based on the preoperative assessment of comorbidities, sleep apnea and venous insufficiency were more common in the superobese group, whereas elevated cholesterol was more frequently encountered in the

Table 1. Patient demographics

Body mass index (kg/m^2)	Age (yr)*	Gender (n)		Race (n)		Excess body weight (%)*	Excess body weight (lb)*
		Female	Male	White	Black		
<70	43.2 ± 9.9	615 (82.4%)	131 (17.6%)	633 (84.6%)	113 (15.4%)	128.5 ± 41.2	176.2 ± 63.7
⩾70	40.8 ± 8.8	47 (59.5%)	32 (40.5%)	61 (77.2%)	18 (22.8%)	254 ± 57.6	359.7 ± 91.8
P	0.01	<0.0001		NS		<0.0001	<0.0001

*Values given as mean ± SD.
NS = not significant.

morbidly obese group. The number of comorbid medical conditions per patient was similar in both groups (BMI < 70 kg/m^2: 3.1 ± 1.4 versus BMI ⩾ 70 kg/m^2: 3.3 ± 1.6). The prevalence of all comorbid medical conditions before surgery is summarized in Table 2.

LOS was significantly longer in the superobese group (Table 3), but when the groups were controlled for type of access, the difference between the two groups was not significant (Fig. 3). The cumulative incidence (Table 3), as well as the incidence of individual early major and minor complications (Tables 4 and 5), was similar in both groups. Mortality was significantly increased in the superobese group. There were four deaths in the morbidly obese group—one from pulmonary embolism, one from complications of small bowel obstruction, one from cardiac arrest of unknown etiology, and one from respiratory failure. There were two deaths at the superobese group, both due to respiratory failure. The results of our statistical analysis with regard to the early major (5.4% versus 6.4% versus 1.4%, $P = 0.25$) and minor (16.1% versus 13.7% versus 20%, $P = 0.38$) complications and mortality (0% versus 1.1% versus 2.5%, $P = 0.17$) did not change when the patients were further subdivided into three BMI groups (<50 kg/m^2, 50–69 kg/m^2, and >70 kg/m^2).

The mean follow-up was similar in the morbidly obese (18.25 months) and superobese (17.7 months) groups. During follow-up, there was no significant difference in the incidence of late major (BMI <70 kg/m^2: 15 of 779, 1.92% versus BMI ⩾70 kg/m^2: 1 of 79, 1.27%) and minor (BMI <70 kg/m^2: 191 of 779, 24.5% versus BMI ⩾70 kg/m^2: 22 of 79, 27.8%) complications between the two groups (Tables 6 and 7).

The mean % EWL at the time of most recent follow-up was similar in the morbidly obese (54.1%) and superobese (51.3%) patients. The % EWL was greater at the morbidly obese group during the first year of follow-up, but the difference between the two groups was not significant at the third year of follow-up (Fig. 4). Although BMI was significantly reduced in both groups, the percentage of patients who continued to have a BMI of greater than 40 kg/m^2 was significantly higher in the superobese group (Table 8). During follow-up, there was a significant improvement in comorbid medical conditions in both groups. With the exception of venous insufficiency that did not improve as much at the superobese group, improvement of comorbidities was similar in the two groups (Table 9).

Table 2. Preoperative prevalence of comorbidities

Comorbidity	<70 kg/m^2	⩾70 kg/m^2	*P*
Sleep apnea	31.4%	57%	<0.0001
Hypertension	50.9%	39.2%	NS
Diabetes mellitus	24.4%	19%	NS
Coronary artery disease	4.5%	6.3%	NS
Degenerative joint disease	64.2%	63.3%	NS
Gastroesophageal reflux disease	40.3%	36.7%	NS
Stress incontinence	22.1%	15.2%	NS
Depression	43.8%	51.9%	NS
Asthma	13.4%	15.2%	NS
Hyperlipidemia	11.9%	3.8%	0.02
Venous insufficiency	2.4%	16.5%	<0.0001

NS = not significant.

DISCUSSION

This report is one of the largest reported single-institution gastric bypass series in superobese patients and the first to assess the outcome of RYGB in patients with a BMI of 70 kg/m^2 or greater. Based on our findings, superobese patients usually presented for evaluation at a younger age and the majority were men. Although the early and late morbidity was the same in morbidly obese and superobese patients, those with a BMI of 70 kg/m^2 or greater had a fivefold higher mortality rate, suggesting that patients with a BMI of less than 70 kg/m^2 better tolerate complications. RYGB was equally effective in morbidly obese and superobese patients in improving comorbid medical conditions and achieving adequate

Table 3. Short-term outcome of Roux-en-Y gastric hypass stratified by BMI of 70 kg/m^2

Body mass index (kg/m^2)	Length of stay (days)*	Early complications		Mortality
		Major	Minor	
<70	4.9 ± 4.6	54/779 (6.9%)	98/779 (12.6%)	4/779 (0.5%)
⩾70	6.2 ± 2.7	2/79 (2.5%)	16/79 (20.6%)	2/79 (2.5%)
P	0.0018	NS	NS	<0.05

*Values given as mean ± SD.
NS = not significant.

weight loss, but these effects took longer time to occur in the superobese group.

It is estimated that there are currently 5,324,123 people in the United States who are considered morbidly obese and are potential candidates for bariatric surgery.[9] Operative risk and weight loss vary significantly among individual morbidly obese patients.[2,10] Because body weight has been shown to influence the outcome of bariatric surgery,[11] subdivision of obesity into different groups according to BMI is important for risk stratification purposes and long-term patient expectations. The stratification of our patients according to a BMI of 70 kg/m^2 is arbitrary. In our practice, however, the mean BMI in 746 patients with a BMI of less than 70 kg/m^2 was 51.5 kg/m^2, which suggests that according to the "usual" definition of superobesity (>50 kg/m^2), the majority of our patients would be considered superobese. Based on this extensive experience with superobese patients, it is our observation that there are unique technical and perioperative factors related to "extremely" superobese patients that justify a separate analysis of the outcome of gastric bypass in patients with a BMI of greater than 70 kg/m^2. It is also important to emphasize that the inclusion of patients with BMI of 50–69 kg/m^2 to the "lower" BMI group did not affect our perioperative results, because further subdivision of our patients into three BMI groups (<50 kg/m^2, 50–69 kg/m^2, and >70 kg/m^2) had no effect on early complications and mortality.

According to our results, the demographic background of superobese patients with a BMI of 70 kg/m^2 or greater is somewhat different compared with morbidly obese patients with a BMI of less than 70 kg/m^2. Superobese patients who are being considered for RYGB are relatively younger and are more often of male gender and black race. Similar trends have been reported previously as well.[1] There was no significant difference in the number of preexisting comorbidities between the two groups. Similarly, a

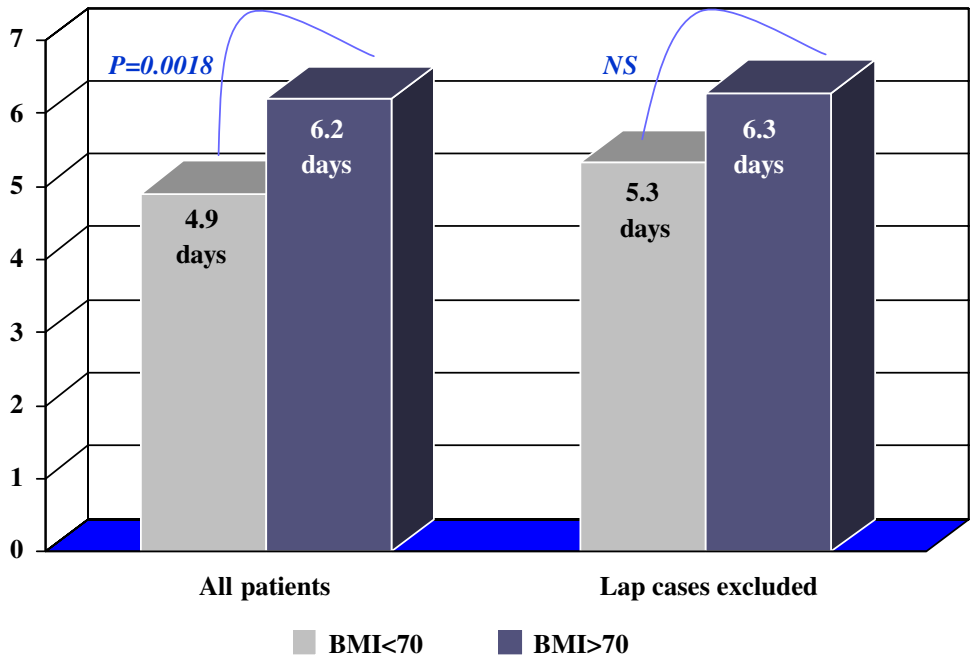

Fig. 3. Effect of access on length of stay. BMI = body mass index; Lap = laparoscopy.

Table 4. Early major complications

Complication	BMI <70 kg/m^2	BMI ⩾70 kg/m^2
Anastomotic leak	0.8%	0%
Pulmonary embolism	1.33%	1.36%
Small bowel obstruction	1.7%	0%
Pulmonary complications	0.8%	0%
Acute renal failure	0.4%	1.36%
Hemorrhage with return to the operating room	0.53%	0%
Hemorrhage without return to the operating room	0.53%	0%
Fascial dehiscence	0.67%	0%
Sepsis	0.13%	0%
Pancreatitis	0.13%	0%
Gastric remnant blowout	0.13%	0%
Splenic injury	0.13%	0%
Small bowel fistula	0.13%	0%

BMI = body mass index.

previous study reported no difference in the number of comorbidities per patient in morbidly obese and superobese patients (3 and 4.35 per patient, respectively).[10] In addition, this study,[10] like our study, showed that the distribution of comorbid conditions is similar in the two groups with the exception of sleep apnea and venous insufficiency, which are higher in superobese patients. An increased prevalence of sleep apnea and venous insufficiency in superobese patients has been demonstrated by others as well.[1] These findings suggest that the overall health risk appears to be similar in superobese and morbidly obese patients. Nevertheless, differences between superobese and morbidly obese patients may still exist as there is no standardized means of measuring severity of each coexisting medical condition.

Table 6. Late major complications

Complication	BMI <70 kg/m^2	BMI ⩾70 kg/m^2
Acute renal failure	0%	1.27%
Small bowel obstruction	1.2%	0%
Pneumonia	0.12%	0%
Gastrointestinal hemorrhage	0.12%	0%
Perforated duodenal ulcer	0.12%	0%
Severe vitamin deficiency	0.12%	0%
Fistula	0.12%	0%
Fascial dehiscence	0.12%	0%

BMI = body mass index.

In this study, laparoscopic access was more frequently used in the morbidly obese group. It has been shown that laparoscopic RYGB is safe and feasible in the superobese patients.[12,13] In most of these studies, however, a BMI of 50 kg/m^2 was used to define superobesity, and as a result mean BMI for the superobese group ranged between 57 and 58.4 kg/m^2. In contrast, a higher mean BMI of 51.5 kg/m^2 and 79.9 kg/m^2 was reported in this study in the morbidly obese and superobese group, respectively. In our practice, 48.4% of our patients have a BMI between 50 to 69 kg/m^2, and laparoscopic RYGB is routinely performed in these patients. Based on our experience, however, the use of laparoscopic RYGB in patients with a BMI of 70 kg/m^2 or greater is limited because of increasing technical difficulties related to patients' body habitus and capabilities of currently available laparoscopic instruments.

Our study indicates that mortality after RYGB is increased in superobese patients but remains within acceptable limits. A higher mortality rate in superobese patients has been shown by others as well. Oliak et al.[14] reported a 10-fold increase in mortality in patients with a BMI of 60 kg/m^2 or greater undergoing laparoscopic RYGB. Our study showed that

Table 5. Early minor complications

Complication	BMI <70 kg/m^2	BMI ⩾70 kg/m^2
Wound infection	8.6%	13.7%
Atelectasis	1.1%	2.7%
Re-admission	0.7%	2.7%
Arrhythmias	0.13%	2.7%
Deep vein thrombosis	0.53%	0%
Blood transfusion	0.7%	0%
Urinary tract infection	0.8%	0%
Uncontrolled hypertension	0.13%	0%
Ileus	0.13%	0%
Clostridium difficile colitis	0%	2.7%

BMI = body mass index.

Table 7. Late minor complications

Complication	BMI <70 kg/m^2	BMI ⩾70 kg/m^2
Incisional hernia	15.4%	15.1%
Anastomotic ulcer	3.7%	5.1%
Anastomotic stricture	4%	1.3%
Re-admission	1%	2.5%
Anemia	0.77%	1.3%
Wound infection	0.64%	1.3%
Deep vein thrombosis	0%	2.5%
Pneumonia	0.12%	0%
Clostridium difficile colitis	0.12%	0%
Vitamin deficiency	0%	1.3%

BMI = body mass index.

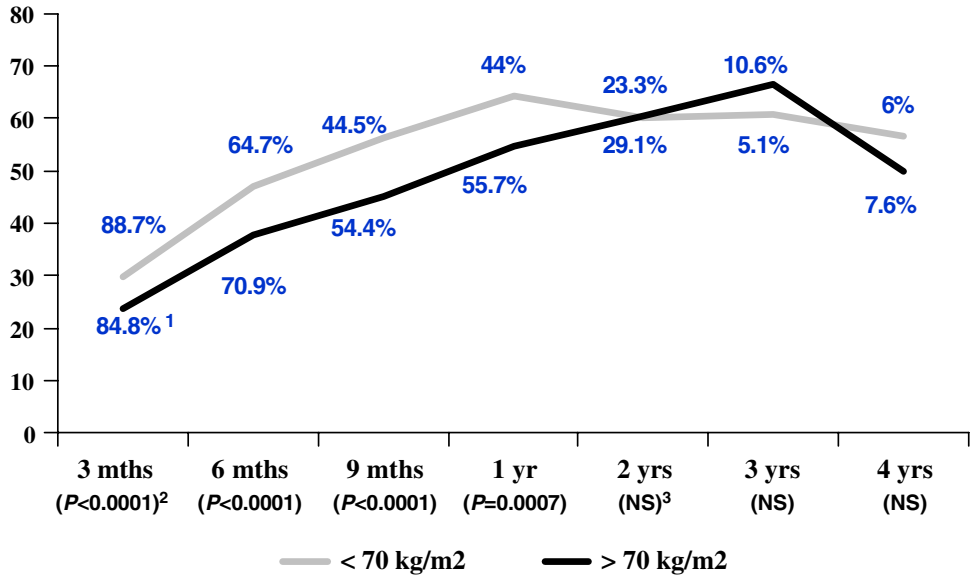

Fig. 4. Percent excess weight loss (EWL) during follow-up. [1]Percent of patients on follow-up for the specific time interval. [2]Statistically significant difference in percent EWL between the two groups for the specific time interval. [3]No significant difference in percent EWL.

the LOS was somewhat longer in the superobese group, but differences were not significant after adjustment for variations in the type of access. This is in contrast with a recent study by Shuhaiber and Vitello[15] that reported a longer LOS and intensive care unit stay in patients weighing greater than 500 pounds. The large discrepancy in the sample size of the superobese and morbidly obese group in our study may have influenced the results of our analysis. However, the mean hospital stay for both groups of our study is prolonged. Patients who had open gastric bypass before 2000 underwent routinely a UGI on postoperative day 4, which, as a result, has prolonged mean hospital stay. Currently in our practice, the minimum hospital stay for the laparoscopic and open gastric bypass patients is 3 and 4 days, respectively. In addition, because many of our patients live 2 or more hours away from our facility, we have a fairly low threshold for extending their hospital until they are 100% physically ready to be discharged and all home care issues are settled. It is our experience that patients who do not live in proximity with our facility often seek medical care for postoperative problems early on after surgery in outside facilities closer to their place of residence. This often leads to delays in diagnosis and may have serious consequences.

Early complication rates were similar in the two groups. As a result, we did not find any increase in the incidence of anastomotic leak and pulmonary embolism in the superobese group. In accordance

Table 8. Percentage of morbidly obese (BMI <70 kg/m^2) and superobese (BMI ≥ 70 kg/m^2) patients who remain at a BMI >40 kg/m^2 during follow-up

Year of follow-up	BMI <70 kg/m^2	BMI ≥ 70 kg/m^2	*P*
1 Year	20.1%	90.7%	<0.05
2 Years	25.4%	77.2%	<0.01
3 Years	32%	75%	<0.01

BMI = body mass index.

Table 9. Percentage of improvement of comorbidities during follow-up

Comorbidity	BMI <70 kg/m^2	BMI ≥ 70 kg/m^2	*P*
Sleep apnea	88.3%	81.25%	NS
Hypertension	78.1%	83.3%	NS
Diabetes mellitus	93.3%	87.5%	NS
Degenerative joint disease	72.8%	78.9%	NS
Gastroesophageal reflux disease	84.9%	91.7%	NS
Stress incontinence	81.4%	85.7%	NS
Depression	73.6%	62.5%	NS
Asthma	71.1%	100%	NS
Hyperlipidemia	84.2%	50%	NS
Venous insufficiency	80%	33.3%	0.013

BMI = body mass index; NS = not significant.

with our observations, a recent study has shown that anastomotic leaks, deep vein thrombosis, and pulmonary embolism did not occur more frequently in patients weighing more than 500 pounds.[15] A higher frequency, in our series, of small bowel obstruction in the morbidly obese group mostly reflects our early learning curve with the laparoscopic technique. Although the incidence of early minor complications was similar in both groups, wound infection was more common in the superobese group most likely due to differences in body habitus and type of access used. Late morbidity was also comparable between the two groups. Interestingly, incisional hernias did not occur more frequently in the superobese group. In accordance with our results, Bloomston et al.[1] found a similar incidence of incisional hernia in the morbidly obese and superobese of 10% and 13%, respectively.

One significant weakness of this retrospective study is the limited long-term follow-up available. Despite the fact that our study spans an 8-year period, our mean follow-up was only 18.25 months in the morbidly obese and 17.7 months in the superobese group. Only 50% of our patients remained at follow-up at the end of the first postoperative year, falling to a quarter after the second year, to 10% after the third year, and even less thereafter. More than 50% of the patients in this study, however, traveled from distant geographic locations, which limited their compliance with scheduled, follow-up visits. It is possible that our results with regard to weight loss and improvement of comorbidities may not accurately represent our patient population, because the status of a significant proportion of our patients is not known. On the other hand, although our follow-up is limited, the large sample size of our study allows for some valid conclusions with regard to our results for weight loss and improvement of comorbid conditions.

Based on our results, there was no significant difference in the % EWL between the two groups at the time of most recent follow-up. In addition, we confirmed previous observations that maximum weight loss in the superobese patients is not usually achieved within the first year from surgery, as in the morbidly obese group, but it continues until the third postoperative year.[1] Defining, however, a "successful" outcome after RYGB in superobese patients is a complex issue. Although % EWL was comparable between the two groups, 75% of superobese patients remained with a BMI of greater than 40 kg/m^2 at the end of the third year after surgery compared with only 32% of morbidly obese patients. In accordance with our results, Brolin et al.[5] reported that only 17% of their 298 patients with a BMI of 50 kg/m^2 or greater stabilized at a BMI of 30 kg/m^2 or less. Similar observations have been reported by others as well.[1,10] On the other hand, we noted that over time the number of patients of the less-than-70 kg/m^2 BMI group who had a BMI of greater than 40 kg/m^2 increased. The increasing proportion of patients who have a BMI of greater than 40 kg/m^2 in the "lower" BMI group may have been influenced by the limited follow-up of the study. It is our observation that in our practice, patients who are not satisfied with their weight loss, as well as patients who have gained weight, have remained on closer follow-up than patients with optimal outcome. Therefore, it is imperative that all patients who are considered for RYGB be appropriately educated regarding their expectations from surgery. Superobese patients should be informed that although weight loss in absolute numbers may be greater, it may take as many as 3 years until maximum weight loss is accomplished. On the other hand, morbidly obese patients should be encouraged to continue follow-up after the first year, as this is when weight stabilization occurs and risk for weight gain begins.

This study also showed that there were some differences in the preoperative incidence of comorbidities between the two groups. In accordance with previous reports,[1] the incidence of sleep apnea is significantly higher in the superobese group. Routine preoperative screening for sleep apnea with appropriate questionnaires such as the Epworth Sleepiness Scale and full polysomnographic evaluation when indicated is particularly important for the superobese population. In addition, the incidence of hypertension (50.9% versus 39.2%) and diabetes (24.4% versus 19%) preoperatively was lower in the superobese group but it did not reach statistical significance. The preoperative incidences of hypertension (38%) and diabetes (22%) are similar to those reported by Bloomston et al.[1] in patients with a BMI of greater than 50 kg/m^2. Interestingly, we noted a significantly lower incidence of hyperlipidemia in the superobese group, which has not been reported previously. Further studies are required to validate this finding. Although some of the preoperative risk factors for coronary artery disease reported in our study (diabetes, hypertension, hyperlipidemia) were less frequent in the superobese population, the preoperative incidence of coronary artery disease was similar in both groups. As expected, the incidence of venous insufficiency was more commonly observed in the superobese group. Nevertheless, improvement in comorbid medical conditions was equally dramatic in both groups. The percentage of preexisting medical conditions that improved or resolved after surgery ranged between 66% and 100% in both groups. Venous insufficiency, which improved more frequently in the morbidly obese group, was the only exception.

In conclusion, RYGB is safe and effective in the superobese population, with outcomes similar to those in morbidly obese patients. Complications in superobese patients undergoing RYGB are not increased, but they are more often fatal. Weight loss and improvement of health status in superobese patients are as dramatic as in the morbidly obese. It is probably unrealistic to expect that most patients with a BMI of 70 kg/m^2 or greater will reach a BMI of less than 40 kg/m^2 after weight stabilization.

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Discussion

Dr. B. Schirmer (Charlottesville, VA): Congratulations. I think it is important that the data be published about the fact that the mortality rate definitely is higher in patients with these higher BMIs. I do not think there is any question about it, even though, as you have shown, the PE rate and the leak rate may not be higher, but they die when they get those problems.

I do have a couple of problems with your paper. One is your title. I really think you cannot include in your title "long-term follow-up." I do not think, based on your data, that applies at all. Second is, I really would recommend that with your open technique the stomach be divided, because otherwise you will see staple line breakdowns. That has been the experience of everyone who has not divided the stomach. And finally, two other things. Hyperventilation syndrome of obesity—I did not see that in premorbid conditions, and I would expect that is significantly higher in this >70 BMI group. Finally, I disagree with your conclusion about long-term complication rates being no different, because you give a rate of only 1% or 2% and you do not include incisional hernias, which clearly, in my experience, represented the highest number of complications that resulted from long-term follow-up of open gastric bypass patients.

Dr. Raftopoulos: Thank you for your comments. As far as the title, I do agree, as I said in my presentation, that the overall long-term follow-up was not adequate. The reasons I think that we did not achieve a better follow-up are two, actually. The first is that our referral base spans a very large geographic area, including western Pennsylvania, West Virginia, and the eastern Ohio area, and many of our patients drive 3 and 4 hours to come to us, and I think that is part of the reason that they did not follow up with us as close as we would like. And the second reason is that the majority of patients we see are of low socioeconomic status and with very frequent changes in their

insurance, which also makes long-term follow-up difficult. What we have done for that recently is we have tried to revise our database in a way that we set alarms for patients who will miss the follow-ups, and hopefully more telephone calls and letters mailed will bring some of those patients back for follow-up.

As to your question about incisional hernias, actually this was included. I skipped those slides for the sake of time. The 1% and 2% rates you quoted refer to the late major morbidity rate. Incisional hernias were included at the late minor morbidity rate, which were significantly higher, 25.6% for the lower BMI group and 27.8% for the superobese group. Actually the incisional hernia was not higher in the superobese group. Their percentages were 15% and 16% for the superobese and lower BMI group, respectively.

As far as the hyperventilation syndrome that is included in the sleep apnea rates, and it is more common in the superobese group.

Although there is no definitive evidence, I do agree that division of stomach rather than partitioning may decrease the incidence of gastrogastric fistulas. Partitioning of the stomach, however, allows for a better exposure at the time of gastrojejunostomy and gastroenterotomy closure, because the pouch is attached to the stomach and can be retracted down easier. I think this is important for superobese patients with BMI >70, especially if the linear stapler technique is used for the gastrojejunostomy.

Dr. M. Cahan (Chapel Hill, NC): I noticed that you did not note significant differences in venous thromboembolism between your two groups. I was wondering if you did anything differently in terms of using low molecular weight heparins in the larger group or did any of these patients get filters or did you note any of the larger patients to have an increased incidence of hypercoaguable status?

Dr. Raftopoulos: No. The prophylactic measures we used were usually the same, which consisted of the SCD boots and subcutaneous heparin preoperatively and postoperatively. What, again, is important is that, as I mentioned in my preoperative workup, we are very aggressive in addressing any potential comorbidities. Patients who had previous questionable DVTs or a history of clotting problems, they were worked up with Doppler studies preoperatively, and we did find a certain amount of patients who had problems preoperatively and addressed them. Also, hematology consultation was obtained, in case we had any suspicion for any of these patients. But other than that, the prophylactic measures we used were the same.

Positron Emission Tomography With F-18-Fluorodeoxyglucose in a Combined Staging Strategy of Esophageal Cancer Prevents Unnecessary Surgical Explorations

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Distant metastases or local invasion are frequently found during the explorative phase of surgery for esophageal cancer. This study was performed to determine the rate of patients with incurable disease encountered during exploration and to examine the impact of preoperative staging, including positron emission tomography (PET), on the number of unnecessary explorations. The records of 203 patients with esophageal cancer who were eligible for curative resection were retrospectively reviewed. The surgical reports were analyzed to obtain the reasons for abandoning resection. Furthermore, the different staging modalities according to the related time interval were reviewed for each patient to analyze the influence of them on the number of explorations. After exploratory surgery, resection was abandoned in 78 of the 203 patients (38%) because of distant metastases (n = 59; 29%), metastatic spread and local irresectability (n = 5; 2%), and local irresectability (n = 14; 7%). In a logistic regression model with all preoperative staging modalities and the year of examination as independent variables, F-18-fluorodeoxyglucose (FDG)-PET) was the only modality that predicts intended curative resection in these patients ($P < 0.001$). In patients with esophageal cancer who are suitable for potentially curative surgery, resection was abandoned mainly because of distant metastases encountered during exploration. The addition of FDG-PET may have reduced the rate of unnecessary surgery in this group of patients.
(J GASTROINTEST SURG 2005;9:54–61)

KEY WORDS: Positron emission tomography (PET), esophageal cancer

Curative treatment of patients with esophageal cancer mainly depends on the stage of disease. Until now, surgical resection has been the only curative option in patients with locoregional stage of the disease, but it is accompanied by substantial morbidity and even mortality.[1] Patients with distant metastases (M1) or local invasion of adjacent vital structures by the primary tumor (T4) are beyond cure. These patients may benefit from less invasive methods, including stenting, external radiation, and/or brachytherapy for palliation.[2]

The primary aim in staging of esophageal cancer is to assess the prognosis, to select those patients who may benefit from surgery. Current preoperative staging is not completely reliable in determining curative resectability. As a result, distant metastases or local invasion are still found during the explorative phase of surgical treatment, rendering resection meaningless in these patients. Data on the number of unnecessary surgery in esophageal cancer are scarce. In the limited number of studies, unnecessary explorative surgery, including laparoscopy, is performed in 10%–60% of patients.[3–9]

During the past decade, preoperative noninvasive staging modalities have improved. Computed tomography (CT) of thorax and abdomen has been the

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first-line method to determine local resectability and metastatic spread for many years.[10] Later, endoscopic ultrasonography (EUS) was introduced and has become the most reliable method of identifying the depth of primary tumor invasion and to assess regional and distant lymph node involvement, particularly in combination with fine-needle aspiration (FNA).[11–13]

Recently, F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) has been gaining acceptance in the detection of distant metastatic disease.[14,15] Invasive and more expensive staging methods such as laparoscopy and thoracoscopy are generally not implemented in the preoperative work-up.[16]

In this study, we analyzed the patients with esophageal cancer who were suitable for potentially curative surgery after preoperative staging. The number of missed metastases or irresectable T4 tumors, which were encountered during surgery, was determined. Furthermore, we documented the combination of different staging modalities of the time interval for each patient to estimate the impact of them on the number of unnecessary explorations in these patients. In addition, the influence of the different combinations of staging on survival was estimated.

Table 1. Characteristics of 203 patients

Characteristic	No. of patients (%) (except for age)
Gender	
Male	168 (82.8)
Female	35 (17.2)
Age (yr)	
Median	62.0
Range	22–82
Histology	
Adenocarcinoma	171 (84.2)
Squamous cell carcinoma	32 (15.8)
Localization	
Mid esophagus	9 (4.4)
Distal esophagus	102 (50.2)
Gastroesophageal junction	92 (45.3)
Surgical procedure	
Transthoracic esophagectomy	119 (58.6)
Transhiatal esophagectomy	6 (3.0)
Explorative laparotomy	65 (32.0)
Explorative laparothoracotomy	13 (6.4)
Surgical staging	
T1-3 N0-1 M0	125 (61.6)
T4 N0-1 Mx	14 (6.9)
T4 N0-1 M1	5 (2.5)
Tx N0-1 M1	59 (24.6)

MATERIAL AND METHODS

A retrospective analysis was performed on medical records of 203 patients eligible for potentially curative surgery after an initial diagnosis of cancer of the esophagus or gastroesophageal junction (GEJ) between 1992 and 2002. All patients had biopsy-proved malignancy of the esophagus or GEJ. Patients with high-grade dysplasia, preoperative chemotherapy, or radiotherapy and patients who were unfit for surgery were excluded. Patient demographic and tumor characteristics are summarized in Table 1.

Resection with curative intention was considered on the basis of preoperative staging results, including tumors staged as T1-3 N0-1 M0 according to the Union Internationale contre le Cancer 2002 system.[17] All patients were staged with the available staging modalities (CT, EUS, PET) at the time of presentation. Patients were excluded from surgery if hematogenous (M1b) or distant lymph node metastases (M1a/1b) were present or if local invasion of adjacent vital structures by the primary tumor (T4) was established preoperatively. Therefore, all patients included in this analysis had resectable and curable disease at their preoperative staging. Esophagectomy as a palliative treatment was not performed. Surgery was carried out by or under the direct supervision of a surgeon with experience in esophageal surgery.

The surgical procedures started with laparotomy to exclude distant metastases to the liver, peritoneum, rectovesical or rectouterine pouch (M1b), and lymph nodes at the celiac axis. Lymph nodes localized at the origin of the celiac trunk, including para-aortic, splenic, and hepatic artery lymph nodes, were defined as distant lymph node metastases (M1a/b). Nodal involvement of celiac axis was considered as incurable due to the worse survival in these patients.[18,19] Ingrowth into vital structures like aorta, inferior vena cava, pancreas, or liver and/or extensive involvement of the diaphragm was considered to be irresectable (T4).

Subsequently, an extended resection by right or left thoracotomy was usually performed, but in the case of delicate cardiopulmonary condition, a transhiatal resection was preferred. During thoracic exploration, resectability of the tumor was assessed and the mediastinum was inspected for the existence of lymphangitis. Pleural metastases were considered to be incurable, as was tumor in-growth in pulmonary vessels, trachea, aorta, and pericardium (T4). After assessment of curability, the tumor and its adjacent lymph nodes were resected en bloc, the so-called two-field lymphadenectomy. A gastric tube restored gastrointestinal continuity, and cervical or intrathoracic anastomosis was performed.

Computed Tomography

CT scanning from the neck to the upper abdomen including the liver was performed with a single-slice spiral CT (Tomoscan SR 7000; Philips Medical Systems, Best, the Netherlands) with 10-mm collimation. The reconstruction interval was 5 mm and 10 mm for the thorax and abdomen, respectively. Scans were performed with intravenous and oral contrast media.

Endoscopic Ultrasound

A radial scanner (GF-UM 20, 7.5–12 MHz; Olympus, Tokyo, Japan) has been used for the performance of EUS since January 1997. Since 1999, EUS-guided FNA of suspected lymph node metastases was performed. The FNA was obtained via a separate linear-array echoendoscope (FGUX-36, 5–7.5 MHz; Pentax Benelux, Breda, the Netherlands). FNA was performed with a 22-gauge, 8-cm needle (Wilson-Cook Medical Inc., Bloomington, IN). If a stenotic tumor was not traversable with the GF-UM 20 scope, a small-caliber probe (MH-908, 7.5 MHz; Olympus) was used. One well-trained endoscopist performed all EUS procedures.

Positron Emission Tomography

Since 1998, PET was performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN). The ECAT 951/31 acquires 31 planes over 10.9 cm, and the HR+ camera acquires 63 planes over a 15.8-cm axial field of view. All patients fasted for at least 4 hours before 400–580 MBq FDG was administered intravenously. Data acquisition started 90 minutes after injection in whole body mode, for 5 minutes per bed position from the skull to the knees. Transmission imaging was obtained during 3 minutes per bed position for attenuation correction. Images were reconstructed using an iterative reconstruction technique and were read from computer monitors.

Data Analysis

To estimate the impact of different staging modalities on the occurrence of unnecessary surgery in patients eligible for potentially curative surgery, the preoperative work-up was documented. Comparison of proportions was performed using the χ^2 test. For each patient, it was recorded whether CT, EUS, and/or FDG-PET was performed. All staging procedures were performed within a median interval of 2 weeks (range, 1–4 weeks) to the time of surgery. These data and the year of examination were entered as independent variables in a logistic regression model to find a factor predicting the possibility to perform a curative resection. A binary logistic method with forward stepwise regression was used. Survival data were analyzed using the Kaplan-Meier method, and differences in the cumulative survival rate between subgroups were compared with the log-rank test. A value of $P < 0.05$ was considered significant. Statistical analyses were executed with the statistical software package SPSS, Version 10 (SPSS Inc., Chicago, IL).

RESULTS

Surgical Outcome

Resection was performed in 125 patients but was abandoned in 78 patients (38%). Resection was contraindicated because of M1 disease in 59 patients (29%), locally irresectable tumors (T4) in 14 patients (7%), and metastatic spread and local irresectability in 5 patients (2%) (Table 1).

Nineteen patients had a tumor that invaded adjacent structures (T4). The tumor invaded the aorta in seven patients, the pancreas in five patients, the pulmonary vein in four patients, the diaphragm in one patient, the inferior vena cava in one patient, and the bronchus in one patient. Of the 19 T4 tumors, 6 were considered to be irresectable at laparothoracotomy, and 13, during laparotomy.

In 64 patients, 68 metastases were encountered during surgical exploration, with resection abandoned in these patients. The localization of these 68 metastases is summarized in Table 2. Metastases were found at the celiac axis in 45 patients (45 of 64, 70%), including lymph nodes along the hepatic and splenic artery. Two patients had celiac lymph node metastases and liver metastases. Metastases in the omentum or parietal peritoneum were present in 10 patients, of whom 2 patients had both peritoneal spread and liver metastases. Liver metastases alone were determined in one patient. Extensive nodal metastases with lymphangitis in the mediastinum and involvement of the aortopulmonary window were found in five patients and judged as pleuritis carcinomatosis. Therefore, the tumors in these patients were considered not to be curatively resectable. In one patient, a metastatic lymph node was determined at the distal part of the left pulmonary hilus and classified as a distant metastasis (M1b).

Preoperative Staging

Patients were staged by different preoperative staging techniques and were retrospectively allocated in three groups according to the comprehensiveness of preoperative staging. The first group was staged with CT, the second group was staged with CT

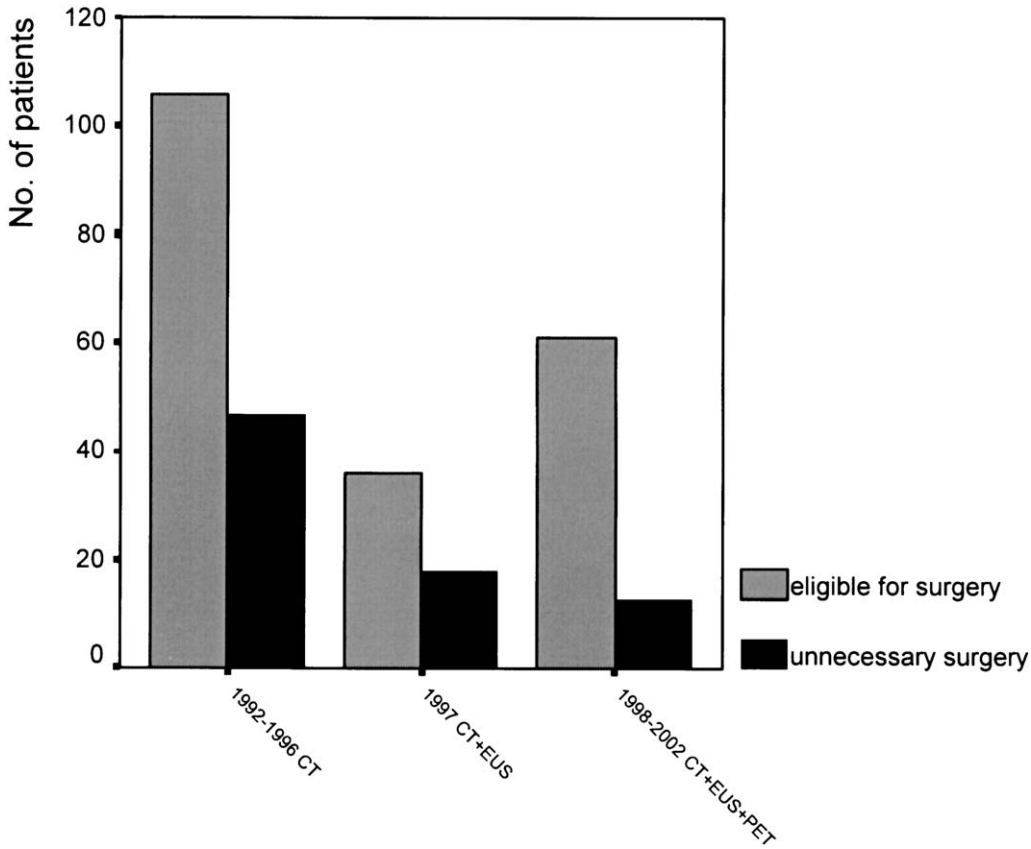

Fig. 1. Bar chart representing the number of patients of each group and the number of patients who underwent unnecessary surgery regarding the available staging methods for each time interval. CT = computed tomography; EUS = endoscopic ultrasonography; PET = positron emission tomography.

and EUS, and the remaining group was staged with CT, EUS, and FDG-PET. The number of unnecessary surgeries and the underlying reason to abandon resection regarding the three groups are represented in Figure 1 and Table 2.

The presence of celiac axis metastases during surgical exploration was significantly reduced in patients staged with EUS (13 of 97; 13%; $P = 0.013$) and with FDG-PET (4 of 61; 7%; $P < 0.001$) compared with the patients staged with CT alone (32%). The addition of FDG-PET reduces the rate of unnecessary surgery from approximately 44% and 50% to 21% (Table 2). The logistic regression model reveals preoperative FDG-PET without distant metastases as the only significant factor to predict curative resection in patients eligible for potentially curative resection ($P < 0.001$; 95% confidence interval, 1.55–6.25).

Survival

The median survival of 78 patients who underwent surgical exploration was 8.8 months compared with 36.4 months in 125 patients who had a curative esophagectomy ($P < 0.001$) (Fig. 2, *A*). Regarding the combination of preoperative staging, the median survival of the 125 patients who underwent a resection was 28.0 months for patients staged with CT, 25.6 months for patients staged with CT and EUS, and 48.2 months in patients staged with CT, EUS, and FDG-PET ($P = 0.34$) (Fig. 2, *B*).

DISCUSSION

The results from this study show that the resection rate in patients with esophageal cancer selected for potentially curative surgery depends on preoperative staging. The overall rate of unnecessary exploratory surgery in this study was 38% and is in the same range as that reported in the literature.[3–8] Irresectability because of local invasion (T4) was found in 36% of the patients who underwent exploration. However, resection was abandoned mostly because of distant metastases (M1), which were found in 82% of these patients.

Table 2. Reasons why surgical explorations were found to be unnecessary in patients with different preoperative staging modalities and the localization of undetected metastases by these methods

	Preoperative staging		
	CT	CT + EUS	CT + EUS + PET
No. of patients	106	36	61
Unnecessary exploration (n)	47 (44)*	18 (50)	13 (21)
Reason (n)			
T4	7	1	6
M1	35	17	7
T4 + M1	5	—	—
Localization of 68 metastases detected during exploration (n)			
Celiac trunk	34	9	4
Omentum/peritoneum	5	4	1
Pleural carcinomatosis	1	3	1
Liver	3	2	—
Bronchial lymph nodes	—	—	1

*Values in parentheses are percentages.

Most of the distant metastases in this study were located at the celiac axis. The optimal treatment in patients with celiac lymph node involvement is still a matter of debate.[20] In our opinion, resection should be omitted in these patients based on the worse survival rather than technical irresectability. As shown in this study and described in the literature, the poor median survival ranges from 3 to 9 months.[18,19,21] Currently applied neoadjuvant treatment might be of considerable value in this group of patients.[22,23]

Analysis of different staging modalities revealed a reduction of the number of unnecessary explorative surgery when the preoperative work-up was more advanced. The addition of FDG-PET reduced exploratory surgery in patients suitable for esophagectomy to a rate of approximately 20%. The impact of FDG-PET is confirmed by the logistic regression model, which shows that FDG-PET without the presence of metastases is the only significant variable in the prediction of resection in patients eligible for potentially curative surgery. Furthermore, the patients who were staged with CT, EUS, and FDG-PET seem to have a better survival (Fig. 2, *B*). This might be related to a higher accuracy of FDG-PET for the detection of distant metastases, which precludes surgery in such patients.

The exact impact of all staging modalities cannot be assessed in this study because the number of patients in whom surgery was abandoned after each preoperative staging method is not known. For years, CT was the initial staging test to detect distant metastases, and CT is currently widely available in most developed countries.[24,25] CT has poor accuracy for both the identification of metastatic spread to the celiac lymph nodes and the overall assessment of invasion into adjacent vital structures.[26,27]

EUS is the first-choice technique to assess local tumor invasion, with an accuracy about 89% for T4 tumors.[28] Still, there are a substantial number of understaged patients and they are incorrectly enrolled for surgical treatment, as seen in this study. Some possible reasons for understaging T4 tumors might be reservations of the endoscopist concerning undertreatment and the lower accuracy, especially for tumors located at the GEJ.[29] Our data show a substantial number of involved celiac lymph nodes in 47 patients (23%) encountered during exploration. This number was significantly reduced in the group of patients staged with EUS (13%) and FDG-PET (7%) compared with patients staged with CT (32%) in their preoperative staging (Table 2).

Upstaging with FDG-PET has been reported to range from 15% to 17% in patients who were staged with CT due to higher accuracy in detection of distant metastases.[14,30] Due to a high specificity and positive predictive value, FDG-PET is more reliable in the assessment of curability compared with CT.[15] The introduction of FDG-PET in the preoperative staging of our patients seems to reduce unnecessary surgery to 20%. However, FDG-PET and CT are still complementary in the detection of metastases.[31] The reduction in unnecessary surgery in the group of patients staged with FDG-PET is not only attributable to FDG-PET. Simultaneously, the experience with EUS-FNA and CT has increased. Furthermore, currently applied multidetector CT and imaging fusion

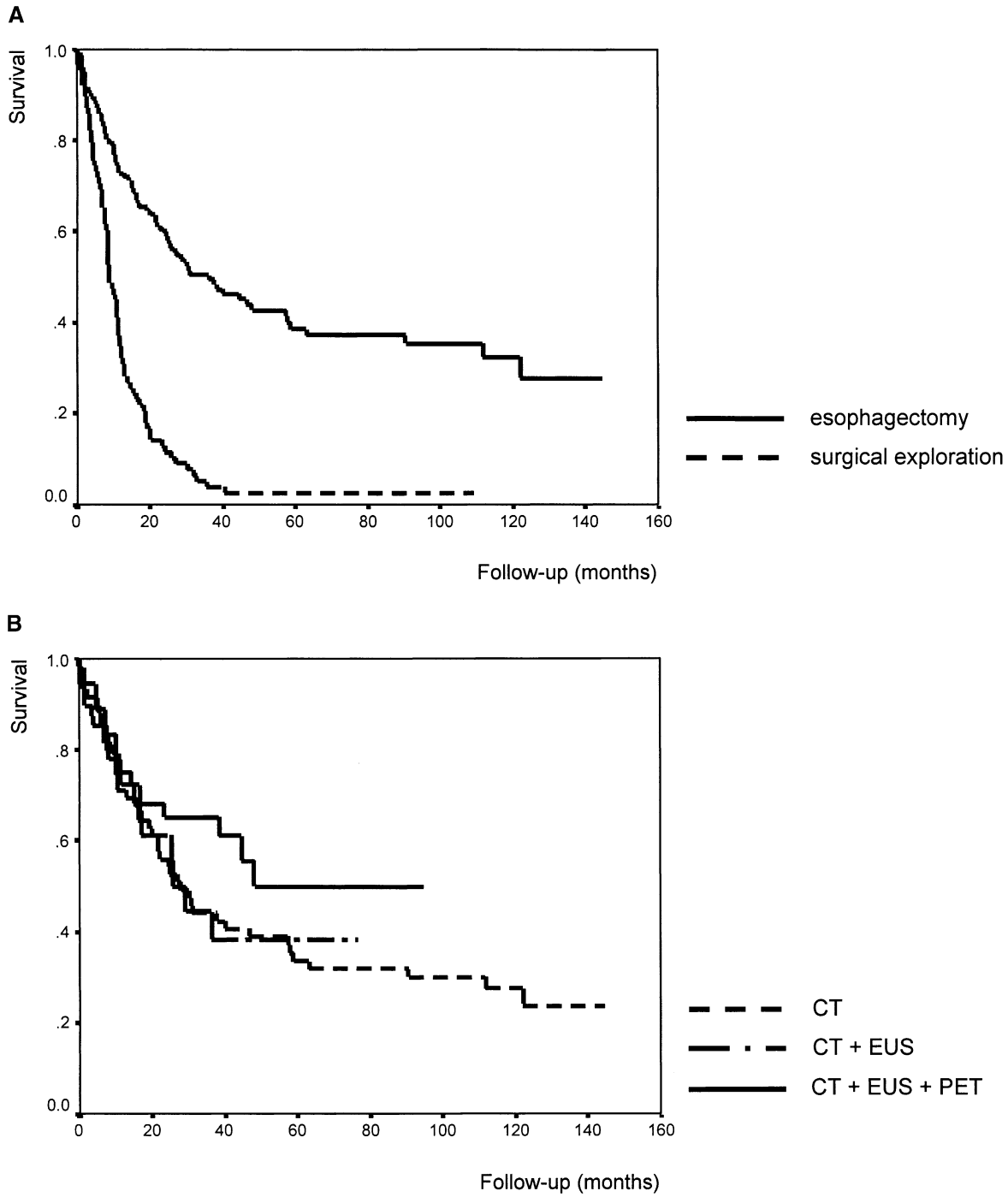

Fig. 2. (**A**) Kaplan-Meier cumulative survival plot of 203 patients. (**B**) Kaplan-Meier cumulative survival plot of 125 patients who underwent esophagectomy. Groups are based on preoperative tests. CT = computed tomography; EUS = endoscopic ultrasonography; PET = positron emission tomography.

of CT with PET are promising in the selection of these patients.

The rate of unnecessary surgery in the patients who were not staged with FDG-PET was high (about 50%) compared with the rate of 20% in patients who were staged with FDG-PET. Percentages deduced from the literature are around 20%.[3–5,8,9] A possible reason for the overall percentage of 38% found in

our study might be the presence of celiac trunk metastases defined as incurable in contrast to others. Furthermore, the percentage of unnecessary surgery in relation to the type of preoperative staging is not well described in the literature. Therefore, the comparison of our results with those at other centers is hampered, and other centers should report on this topic because of the paucity of the literature.

Recently, FDG-PET followed by EUS-FNA was proposed to be the most cost-effective strategy for preoperative staging and management of patients with carcinoma of the esophagus.[32,33] However, the exact role of FDG-PET remains unknown. A prospective multicenter study to investigate the impact of FDG-PET in patients eligible for curative resection after conventional staging with ultrasound of the neck, EUS-FNA, and multidetector CT is currently ongoing at our center.

In conclusion, this study shows a substantial rate of unnecessary surgery in patients suitable for curative treatment mainly because of distant metastases. Improvement of preoperative staging, especially by implementation of FDG-PET, may have reduced the rate of unnecessary surgery to approximately 20% in our center.

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Survival and Recurrences After Hepatic Resection or Radiofrequency for Hepatocellular Carcinoma in Cirrhotic Patients: A Multivariate Analysis

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Hepatic resection is still considered the treatment of choice for hepatocellular carcinoma in patients with liver cirrhosis. Radiofrequency ablation is a new emerging modality. The aim of this study was to compare two homogeneous groups of patients who underwent either surgical resection or laparoscopic radiofrequency, analyzing the factors predicting survival and intrahepatic recurrences with use of a multivariate analysis. From February 1997 to April 2003, 98 patients were enrolled in this prospective study. Inclusion criteria were a single nodule of less than 5 cm, Child A-B class of liver function, and no previous treatment: 40 patients were in the surgical group and 58 patients were in the radiofrequency group. The two groups were homogeneous as far as preoperative characteristics were concerned. Operative mortality was zero, and the rates of operative morbidity were similar. Actuarial survival at 4 years was not significantly different (61% after resection and 45% after radiofrequency). There was a significant higher incidence of intrahepatic recurrences after radiofrequency than after resection (53% versus 30%; $P = 0.018$). This was mainly due to local recurrences, whereas those appearing in other liver segments were similar in both groups. A multivariate analysis showed that the significant factors predictive of an intrahepatic recurrence were the level of α-fetoprotein, the etiology of cirrhosis, and the type of the treatment. On the other hand, multivariate analysis of the survival showed that only the level of α-fetoprotein was an independent predictor of survival. The results of our study showed a significant lower incidence of intrahepatic recurrences after resection compared with after radiofrequency. This seems not to significantly influence the overall survival, probably because of a prompt and effective treatment of the recurrences themselves. (J GASTROINTEST SURG 2005;9:62–68)

KEY WORDS: Hepatocellular carcinoma, hepatic cirrhosis, hepatic resection, hepatic tumor ablation, laparoscopic radiofrequency

Survival and intrahepatic recurrences represent the primary end points of the therapies performed for patients with hepatocellular carcinoma and liver cirrhosis. Surgical resection and interstitial therapies achieve a relatively high rate of complete response in properly selected candidates with liver cirrhosis and hepatocellular carcinoma (HCC).[1] However, postoperative recurrence rates after either liver surgery or interstitial therapies are high,[2] and there are no randomized clinical trials that compare these treatment options; the selection of a given approach should currently be individualized and based on analysis of prospective cohort studies.[2,3] The aim of our prospective study was to evaluate the efficacy (long-term survival and intrahepatic recurrences) of hepatic resection and radiofrequency under laparoscopy in two groups of patients with a single, small HCC on liver cirrhosis.

METHODS

From February 1997 until April 2003, 209 patients with HCC underwent an evaluation in our unit with

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the aim of a radical treatment. Patients included in this prospective analysis were selected on the basis of the following criteria: (1) single lesion, (2) tumor size less than 5 cm, (3) Child A-B class, (4) segmental or subsegmental resection (less than two segments) possible, and (5) no previous treatment of HCC.

Patients were assigned to either one or other of the two groups, surgical resection (SR) or laparoscopic radiofrequency (LRF), according to the chosen treatment.

The ultrasound scanner that was used was an Aloka SSD 1700 power color Doppler system (Aloka Co. Ltd., Tokyo, Japan). We used either an intraoperative or a laparoscopic probe with a multifrequency linear-array transducer. All examinations were performed by a surgeon trained in ultrasound techniques (R.S.). The development of laparoscopic ultrasound (LUS) scanning techniques of the liver was based on the standard intraoperative ultrasound examination performed during laparotomy.[4,5]

A 100-W, 500-KHz monopolar RITA generator (CC-1; Radionics, Burlington, MA) was used as the energy source. The technique of LRF was previously described.[6] Repeated needle placement into the lesion or the use of clustered electrodes (radiofrequency is applied simultaneously with three internally cooled electrodes spaced 5 mm apart) was performed when necessary.

The practical steps of the surgical technique used in this study are described here according to a standardized technique.[7] Briefly, after laparotomy has been carried out, an intraoperative ultrasound examination is performed, and the relative position of the main lesion and the vessels are determined. The porta hepatis is dissected; the lobe with the lesion is mobilized. Under ultrasound guidance, tattooing of the liver surface is obtained by injecting dye into the feeding portal branches of the nodule. An intermittent portal triad clamping is applied, with 15-minute clamping and 5-minute release periods. The liver parenchyma is dissected using a Kelly clamp (tissue fracture technique).

Sonography and dynamic computed tomography (CT) scanning was performed within 1 month after the treatment to assess the completeness of tumor destruction and cancer evolution. A *complete response* was defined as no enhancement or a thin peripheral rim of enhancement caused by an inflammatory response within 1 month of LRF. An *incomplete response* was defined as persistent nodular enhancement within 1 month of LRF. The post-treatment results were further evaluated by spiral CT after 3 months and then every 6 months thereafter. Recurrence was defined as *local* when a new lesion was found within 2 cm of the ablated nodule or resected area or *at distance* when the new nodule arose more than 2 cm from the original lesion.

Initial evaluation and subsequent follow-up data of both groups were collected in a dedicated database (FileMaker Pro; FileMaker Inc., Santa Clara, CA) for personal computer input (Macintosh G4; Apple Computer Inc., Cupertino, CA) and subsequent analysis (Statistica-Mac; Statsoft, Tulsa, OK). Cumulative actuarial curves were analyzed by the Kaplan-Meier method and were compared by use of the log-rank test. Comparison of means between and within groups was done by using the Mann-Whitney *U* test and the Wilcoxon matched pairs test. Data are expressed as mean ± SD. Comparison of proportions was done with the Fisher exact probability test. In all patients, a total of 19 preoperative and 10 intraoperative variables were recorded, and their influence on the survival and HCC recurrence in each treatment group was assessed by means of univariate analysis and either the logistic regression or the Cox's proportional hazards regression model.[8] The association of each parameter with the HCC recurrence rate was univariately estimated with the Spearman *R* test. The association of each parameter with the survival was univariately estimated by comparing actuarial curves (Kaplan-Meier product-limit method and log-rank test) after the categorization of the continuous variables in a multivariate setting.[9] Only those parameters showing a statistical value of $P < 0.1$ were included in the multivariate analysis. The results of the univariate analysis helped to substantially reduce the number of prognostic factors. For each parameter analyzed in the multivariate analysis, the regression coefficient (β), the t values (hazard ratio), and the 95% confidence intervals (CIs) are given.

RESULTS

Fifty-eight patients who underwent LRF and 40 who underwent SR were included in the analysis. The characteristics of both SR and LRF groups are shown in Table 1. No differences were found with regard to age, gender, or liver function (Child class). All the patients had cirrhosis. Impairment of some parameters of liver disease (prothrombin activity and AST) was more pronounced in LRF-treated cases. At the time of analysis (August 2003), no difference was evident with regard to the mean follow-up of patients submitted to SR (22.4 ± 16.7 months) or LRF (25.7 ± 17.5 months; $P = 0.346$).

The resection group included 37 segmentectomies or subsegmentectomies and 3 bisegmentectomies. The length of operation was significantly longer in the SR group (210 ± 43 minutes; median, 210 minutes; range, 150–406 minutes) than in the LRF

Table 1. Baseline characteristics of 98 patients

Preoperative findings	40 Resections	*P* value	58 LPS RF ablations
Gender (M/F)	33/7	0.329	43/15
Age (yr)	67 ± 9	0.799	67 ± 6
Hepatitis C virus etiology (%)	72	0.212	72
Child A class (%)	80	0.415	69
Bilirubin (mg/dl)	0.93 ± 0.41	0.081	1.2 ± 0.78
Albumin (gl)	3.65 ± 0.45	0.937	3.64 ± 0.60
Prothrombin time (INR)	1.12 ± 0.12	0.047	1.18 ± 0.14
Platelets count ($\times 10^2$/L)	119.3 ± 61.2	0.055	97.4 ± 49.6
Alanine aminotransferase (10/L)	79.8 ± 56.5	0.083	107.4 ± 86.8
Aspartate aminotransferase (10/L)	68.8 ± 38.2	0.020	104.0 ± 71.1
α-Fetoprotein (ng/ml)	361.3 ± 1026.2	0.472	377.7 ± 1051.8

(75 ± 17 minutes; median, 70 minutes; range, 35–120 minutes) ($P < 0.01$). The intermittent clamping method was used in 31 patients with a mean clamping time of 45 minutes (range, 15–85 minutes). The mean time for the radiofrequency ablation was 16.4 ± 5.6 minutes (median, 13.5; range, 8–32 minutes).

Four (10%) of the 40 patients who underwent HCC resection were found to have additional tumor nodules at the time of surgery; in the LRF group, LUS identified 10 cases (18%) with new malignant nodules: no statistically significant difference was found between the two groups ($P = 0.241$). All new nodules were treated in the same session.

At 1 month, a complete necrosis was obtained in 55 of 58 patients (95%): in the remaining three patients, a complete response was obtained with an additional transarterial chemoembolization in two, whereas one patient required a subsequent surgical resection. At the time of analysis, 12 (30%) patients of the SR group and 31 (53%) of the LRF group had tumor recurrence ($P = 0.018$). The recurrences in the SR group occurred at distance from the surgical resection in all patients, whereas in the LRF group, they occurred near the ablated area in 11 cases (35% of the recurrences; $P = 0.017$). Also, the actuarial recurrence rate calculated by the Kaplan-Meier product-limit method in patients subjected to LRF was higher than in those treated with SR ($P = 0.024$) (Fig. 1). By multivariate analysis (Table 2), only the level of α-fetoprotein, the etiology of cirrhosis, and the type of treatment were independent predictors of recurrence among patients with HCC.

There were no operative deaths in either group. At the end of follow-up, 10 (25%) patients in the SR group and 20 (34%) of the LRF group died ($P = 0.219$). The main cause of death was liver failure with or without diffuse HCC and was similar in both groups of patients (SR group, 20%; LRF group, 22%; $P = 0.207$).

As shown in Figure 2, the 1-, 2-, 3-, and 4-year actuarial survival rates were 84%, 79%, 73%, and 61% in the SR group and 85%, 75%, 61%, and 45% in the LRF group, respectively ($P = 0.139$). By multivariate analysis (Table 3), the level of α-fetoprotein was the only independent predictor of survival rate.

DISCUSSION

Although the hyperthermic ablative therapies are mainly performed percutaneously, these techniques can also be performed via a laparoscopic or an open approach.[10] Laparoscopy is useful for deeply located lesions not accessible to percutaneous puncture or superficial nodules adjacent to diaphragm or bowel.[11,12] Apart from these specific indications, a laparoscopic approach allows the use of the intraoperative ultrasound; it allows the detection of small tumor nodules not identified by preoperative imaging with the chance of performing a single-step treatment.

Even if this study is not randomized, we believe that the results may be of interest for some reasons. First, all of the included patients were matched for tumor characteristics and liver function known to influence the prognosis. In the present series, the SR group had a slight prognostic advantage over the LRF group with regard to liver function (INR and AST) and a disadvantage with regard to histologic differentiation. It is possible that the sampling error of US-guided needle biopsy due to the minute and thin biopsy specimen and the heterogeneity of the tumor nodule, which can consist of components with various degrees of histologic differentiation, might underestimate the actual pathology.[13] Other variables known to influence the postoperative recurrence,

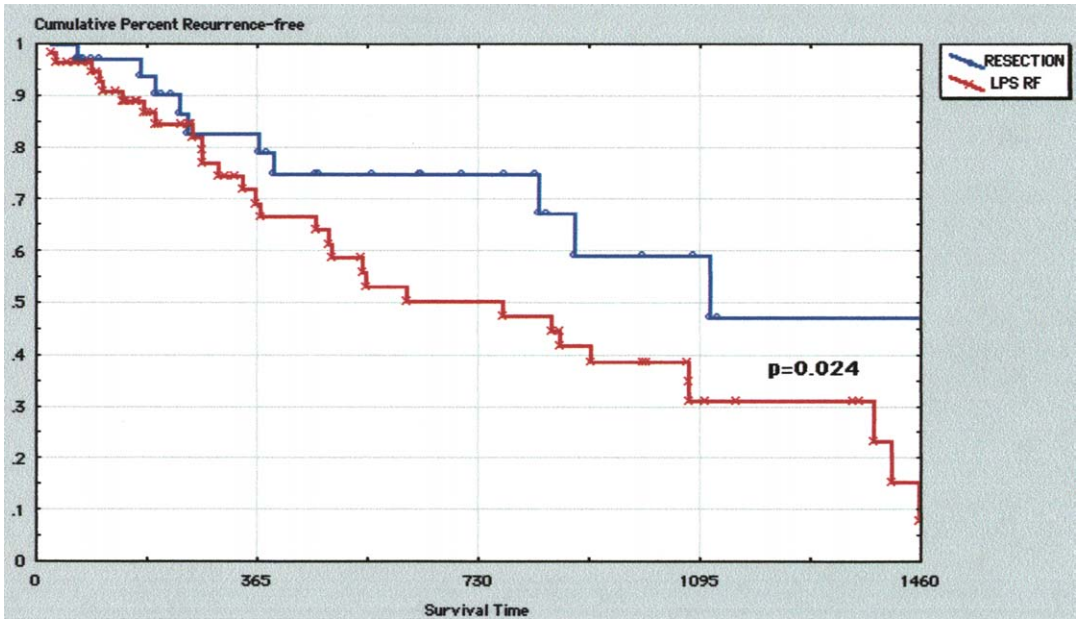

Fig. 1. Recurrence-free actuarial curves comparing surgical resection (*upper curve*) and laparoscopic radiofrequency (LRF) (*lower curve*) ($P = 0.024$).

such as gender, age, preoperative α-fetoprotein, LUS tumor patterns, and oncologic staging, were also similar in both selected groups. Moreover, in this study, intraoperative or laparoscopic ultrasonography using a high-frequency transducer placed directly over the liver surface allowed the detection of small tumor nodules not identified on preoperative imaging. In this way, both the surgical resection and the LRF group had the best available staging: the ablation of the newly detected tumor nodules may be important if the goal of the treatment is potential cure.

The different recurrence rate between the two treatments was mainly related to the new HCC nodules arising close to the treated area (0 cases in SR group versus 11 cases in LRF group). These results seem to be in accordance with the concept of anatomic segmentectomy.[7,14] The removal of the tumor and its portal venous territory may reduce the risk of HCC recurrence arising near the lesion.[15]

This hypothesis has not been confirmed in a previous study comparing surgery and percutaneous ethanol injection: the long-term tumor-free survival rate was not different in both groups.[13] The cumulative 1-, 3-, and 5-year tumor-free survival rates in the PEI and surgery group were 64%, 30.3%, and 9.7% and 75%, 44.7%, and 25.7%, respectively. Even if the result was not statistically significant, surgery tended to give a higher recurrence-free rate. Moreover, the surgical group has more large (72% versus 43%) and multinodular (40% versus 15%) tumors as opposed to the PEI group.

More recently, other authors showed that percutaneous radiofrequency had a higher recurrence rate

Table 2. Multivariate analysis of prognostic factors of hepatocellular carcinoma recurrence using a logistic regression

	Coefficient β	Hazard risk	95% Confidence interval
α-Fetoprotein (<40 or >40 ng/mL)	0.472	2.444	2.06–2.82
Etiology of cirrhosis (hepatitis virus C or not)	0.924	2.368	1.61–3.13
Type of treatment (resection or LPS RF)	0.602	2.011	1.32–2.70
US HCC visualization	0.360	0.967	—
Spleen volume	−0.286	−0.824	—
IOUS vascular infiltration	0.319	0.793	—
IOUS mosaic pattern	0.127	0.328	—

LPS RF = laparoscopic radiofrequency ablation; US HCC = ultrasound hepatocellular carcinoma; IOUS = intraoperative ultrasound.

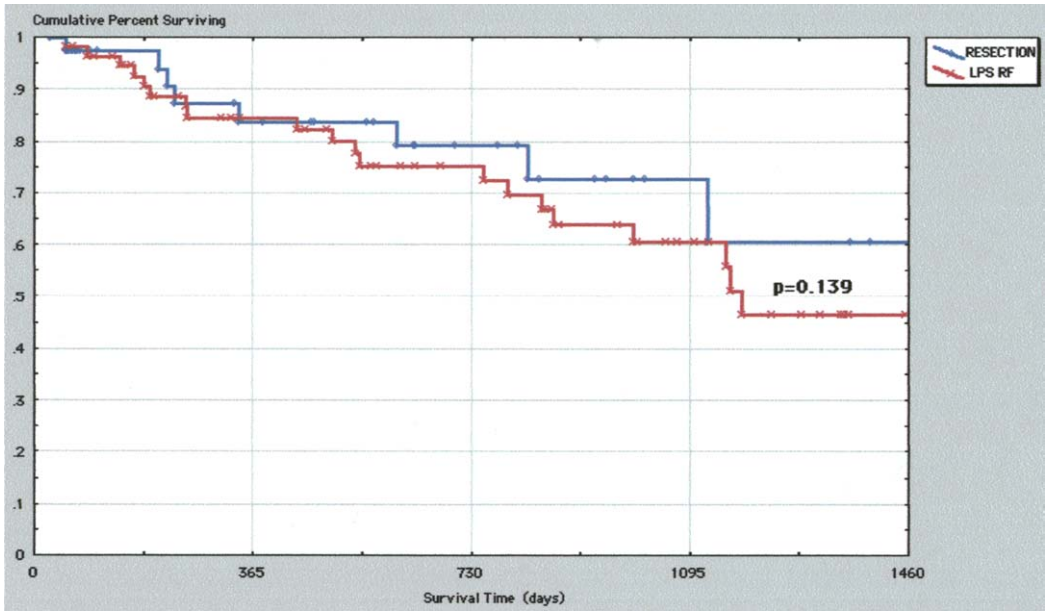

Fig. 2. Actuarial survival curves comparing surgical resection (*upper curve*) and laparoscopic radiofrequency (LRF) (*lower curve*) ($P = 0.139$).

than liver resection and a high number of recurrence developed at the site of the treated tumor (12 of 38 recurrences).[16] Nevertheless, in our study, other factors could contribute to the HCC recurrences (level of α-fetoprotein and the etiology of cirrhosis) and they could influence the overall outcome.

In fact, no statistical difference in long-term survival was found between SR and LRF groups even if surgery had a clear tendency toward a better survival. It is otherwise possible that prompt and aggressive treatment of the recurrences may play a significant role and can increase patient survival, decreasing the differences between the two groups.[17] Furthermore, other causes could influence the survival of the patient with the hepatic tumor and a concomitant liver cirrhosis, which the HCC treatment can not modify.

Table 3. Multivariate analysis of prognostic factors of overall survival using a Cox model

	Coefficient β	Hazard risk	95% Confidence interval
α-Fetoprotein (<40 or >40 ng/mL)	0.612	2.947	2.54–3.36
Gender	0.799	1.883	—
Bilirubin	0.824	1.857	—
Time to recurrence	0.831	1.465	—
Grading	0.684	1.412	—
Platelets	−0.581	−1.287	—
Child classification	0.026	0.052	—

In fact, the deaths due to liver failure were similar in both groups: it is probable that in more severe cirrhotic patients, a less-invasive procedure as well as radiofrequency can induce long-term deterioration of liver parenchymal function.[18]

However, in our study, only serum α-fetoprotein greater than 40 ng/ml was an independent significant factor of poor overall survival. The importance of α-fetoprotein as a prognostic factor for patients with HCC has been shown in several reports[14,19,20] and, in the future, inhibition of α-fetoprotein promoter/enhancer could contribute to an improvement of the long-term results of HCC treatment.[21] Serum α-fetoprotein probably reflects the degree of cellular differentiation and thus the spreading of the tumor.[22–25]

However, a previous multicenter retrospective analysis showed that ethanol injection had similar survival rates as surgical resection, also in patients with a deteriorated liver function.[26]

In conclusion, intrahepatic recurrences were statistically higher after LRF than after resection: the difference was mainly due to local recurrence rate. The multivariate analysis found that α-fetoprotein, etiology of liver cirrhosis (hepatitis B virus infection), and the type of treatment (LRF) were the independent prognostic factors for recurrences. Anyway, the improved care of cirrhotic patients and an early detection and effective treatment of these recurrences did allow a survival curve at 4 years not statistically different from that of the surgical group. However, a

further increase in patient recruitment and a longer follow-up can show a more evident difference in the survival rates above all in those patients with good liver function: LRF could represent a good option in those patients at high risk in whom surgical resection is not indicated.

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Discussion

Dr. David Mahvi (Madison, WI): This is a very interesting study. To summarize it, ablation seems to have a higher incidence of local recurrence but does not really affect survival. The study does have the limitation, as mentioned, of it being a prospective but nonrandomized study, with the problem of selection bias. The local recurrence rate of this study is significantly less than that in the literature. The reported

local recurrence rate after RF is probably in the 40% range, in some series 60%, and this is 18%. I suspect that is due to the open nature of this and the inflow occlusion, which is similar to the work of Curley from M. D. Anderson. I have a global question and then some specific questions.

One is the conclusion that local recurrence does not matter. As you know, local recurrence in breast cancer does not affect survival, whereas in pancreatic cancer local recurrence is a lethal event. Is liver cancer more like breast cancer, or is it more like pancreatic cancer? So the specific questions.

I guess I am still a little bit concerned about the authors' conclusions based on a nonrandomized study. It seemed like you had more well-differentiated cancers in the RF group as opposed to the resection group and the resection group still did better. So I would question your second conclusion that these two therapies are equivalent. I suggest that there is a tradeoff here, that radiofrequency is well tolerated and effective, but it has a higher local recurrence rate. Resection seems to have a better outcome in the long term. Do you feel that for a patient with resectable disease, should they have radiofrequency or resection?

Second, I would like you to comment a little bit on the role of transplantation in these patients. For a lot of the patients we see with small hepatocellular cancers (certainly those with Child's class C cirrhosis), we would lean toward transplantation and not resection. These are the patients who are going to do the best with transplantation with the lowest recurrence rate. I enjoyed the presentation.

Dr. Lygia Stewart (San Francisco, CA): I have two very short questions. The first question is, what was the incidence of portal hypertension in your two groups? The second question is, you commented that in some of your radiofrequency ablation groups you also gave ethanol injection. That might account for your lower local recurrence rate. I was wondering if you could tell us what percentage of those in the radiofrequency ablation group also got ethanol injection?

Dr. Montorsi: Thank you for your comments. I will begin with the liver transplantation. As you see, most of these patients have a mean age approaching 70 years, and so they are clearly away from the time limit of liver transplantation. Even in our center, liver transplantation is the first option for young patients up to 60 years with small single nodules and with good liver function, but this is not the case for most of the hepatocellular carcinomas we usually observe in Italy. When they came to observation, their age is roughly between 65 and 70 years.

I understand your concern about the nonrandomized nature of our study. The two groups were well balanced for most of the pre- and intraoperative prognostic factors. As far as the difference in differentiation of the tumors, we discussed this issue with our pathologists. It is possible that the sampling limitation of the ultrasound-guided needle biopsy due to the minute and thin liver specimen and the heterogeneity of the tumor nodule, which can consist of components with various degrees of differentiation, may underestimate the actual pathology of the tumor. When a large specimen is available for the pathologic examination—as after resection—they usually classified the tumor with the worst degree of differentiation. There are other papers in the literature that stress this point.

I do think that the conclusions of our study are sound. Surgery seems to offer a better chance of long-term survival; probably if we'd have many more patients and a longer follow-up, we can find a difference.

And as far as the question about ethanol, we used the ethanol injection for some very small nodules, mainly the new ones we found with the intraoperative ultrasound. Sometimes we used ethanol to obtain a necrosis of the small arterial vessels at the periphery of the tumor to reduce the vascular inflow and then perform radiofrequency. It is a sort of combination treatment.

And the other question was portal hypertension. No patient had severe portal hypertension. We measured the hepatic venous pressure gradient in most of these patients, as suggested in the paper of the Barcelona group, but no patient had HVPG exceeding 10.

Interleukin-3 Induces Hepatocyte-Specific Metabolic Activity in Bone Marrow–Derived Liver Stem Cells

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Bone marrow–derived adult liver stem cells (BALSC) are a promising target for the development of future cell-based therapies for a variety of liver disorders. However, the ability of stem cells to fully function, as hepatocytes, is limited and differentiation is time dependent. Therefore, it will be conducive to find a growth factor that is able to enhance liver-specific metabolic activity in freshly isolated liver stem cells. Recently, a subpopulation of BALSC was isolated and characterized (β2-microglobulin–negative/ Thy-1–positive cells). We hypothesized that using interleukin-3 (IL-3), a hematopoietic differentiation growth factor, we may be able to enhance liver-specific metabolic activity in freshly isolated BALSC. Rat BALSC from normal and injured livers (bile duct ligated) were isolated and stimulated with IL-3 in culture. Cells were co-cultured with or without hepatocytes, separated by a semipermeable membrane. We measured the effect of IL-3 on BALSC to metabolize ammonia into urea (a liver-specific metabolic activity). IL-3 increased the ability of BALSC, purified from normal animals, to metabolize ammonia into urea by several folds. Interestingly, no such effect was found in cell cultures from bile duct–ligated animals. Additionally, co-cultures of BALSC with hepatocytes induced higher rate of ammonia metabolism, which was further enhanced by IL-3. Our study indicates that IL-3 may be used as an agent to enhance differentiation of BALSC, both qualitatively and quantitatively. It is conceivable that stem cells may undergo IL-3 priming before their clinical application in cell transplantation or bioartificial liver systems. (J GASTROINTEST SURG 2005;9:69–74)

KEY WORDS: Hepatic stem cells, cytokine, metabolism, in vitro study, rodent

Ever since the first reports that a liver-specific stem cell can be isolated from the bone marrow of adult animals and humans, the clinical community has been enthralled by the potential promise of stem cell–based therapies for the treatment of the failing liver.[1–9]

Recently, we purified a heterogeneous population of progenitor cells that differentiated both in vivo and in vitro into hepatocytes.[7,8] We sorted bone marrow cells by means of MHC surface proteins and found that various subpopulations expressed several stem cell markers.[7] Consequently, using magnetic beads, we developed a two-step immunoisolation procedure, further purifying cells expressing hepatocyte-specific markers. These β2-microglobulin–negative/ Thy-1–positive cells or bone marrow–derived adult liver stem cells (BALSC) were capable of multilineage differentiation, metabolizing ammonia into urea, and producing albumin and α-fetoprotein (AFP).[7] Furthermore, BALSC were able to repopulate and repair injured livers.[8]

However, one caveat is the need of these cells to be co-cultured with injured hepatocytes, separated by a semipermeable membrane, to maximally function, possibly due to yet unknown growth factor secreted by the hepatocytes in an attempt to recruit stem cells from the bone marrow.[7]

Interleukin-3 (IL-3) has a unique ability to stimulate the growth and differentiation of hematopoietic stem cells.[10–13] However, its effect on BALSC is not known.[14–19] Therefore, this study was undertaken to systematically evaluate the effect of IL-3 on BALSC.

We report here on the effects of IL-3 on liver stem cells in culture, with and without co-culture

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with normal or injured hepatocytes (isolated from common bile duct–ligated animals). This study demonstrates that IL-3 might be used to stimulate more efficient function in freshly isolated BALSC, to render them competent to be used in cell transplantation therapies or bioartificial systems.

MATERIAL AND METHODS

All animal experiments were approved by the local committee for animal welfare in accordance with the European Convention on Animal Care. Male Sprague-Dawley rats (220–250 g; RCC Ltd., Füllinsdorf, Switzerland) were used in all experiments. There were eight experimental groups. In the first four (A–D), we isolated BALSC from the bone marrow of normal animals, and in the remaining four (E–H), the BALSC were derived from the bone marrow of rats after 7 days of bile duct ligation. We further divided groups A–D and E–H into cultures with (C, D, G, and H) and without (A, B, E, and F) IL-3 and/or co-culture (A, C, E, and G) with syngeneic hepatocytes (Table 1).

Culture Media

Small hepatocyte culture media were prepared as described previously[7,20] and supplemented with 5% heat-inactivated fetal calf serum (FCS; Invitrogen, Basel, Switzerland). The following growth factors were added to the cultures: hepatocyte growth factor (25 ng/ml; R&D Systems, Minneapolis, MN), epidermal growth factor (10 ng/ml; Biosource, Camarillo, CA), and IL-3 (groups C, D, G, and H; IL-3, 10 ng/ml; R&D Systems).

Serum Harvest

Whole rat blood was spun for 10 minutes at 1000*g*, and 1 ml of sterile filtered serum (5%, v/v) was added to 19 ml of culture media.

Hepatocyte Isolation

Hepatocytes from normal animals were isolated by a two-step portal collagenase perfusion of the liver as described previously by Berry and Friend.[21] In 7-day bile duct–ligated animals, a retrograde perfusion was performed through the inferior vena cava.

For co-culture experiments, freshly isolated hepatocytes were seeded at a density of 150,000 cells/cm^2 onto a collagen-coated 0.4-μm, 6.5-mm Transwell-COL-Inlay (Corning Costar Corporation, Bodenheim, Germany), and the hepatocyte culture transferred to an incubator with 5% (v/v) of CO_2 atmosphere at 37°C.

Harvesting of Bone Marrow Cells, Isolation and Culture of β2-Microglobulin–Negative, Thy-1–Positive Cells

We isolated BALSC from bone marrow as described recently by Avital and Inderbitzin.[7] Freshly isolated β2-microglobulin–negative/Thy-1–positive cells were then seeded at a density of 50,000 cells/cm^2 onto Matrigel-coated (25 μg/cm^2; Becton Dickinson, Bedford, MA), 24-well cell culture plates (Corning Costar Corporation, Bodenheim, Germany). In the co-culture groups, the COL-Inlay with attached hepatocytes was inserted after 30 minutes, allowing the BALSC to achieve full attachment to the Matrigel layer. Single cultures and co-cultures were maintained in 500 μl of media, changed every 3 days.

Immunohistochemistry

Freshly isolated BALSC (β2-microglobulin–negative/Thy-1–positive cells) were cyto-spun on glass slides, and the Universal Elite ABC Kit (PK-7200; Vector Lab Inc., Burlingame, CA) was used to stain for IL-3 receptor-α according to the manufacturer's guidelines (sc-681; Santa Cruz Biotechnology, Santa Cruz, CA).

Determination of Urea Synthesis

At 3, 6, 9, and 12 days of culture, the hepatocyte inlay was removed from the co-culture groups and

Table 1. Experimental groups

Normal rat			Bile duct–ligated rat		
Group	**Coculture with hepatocyes**	**Interleukin-3**	**Group**	**Coculture with hepatocyes**	**Interleukin-3**
A	Yes	No	E	Yes	No
B	No	No	F	No	No
C	Yes	Yes	G	Yes	Yes
D	No	Yes	H	No	Yes

β2-Microglobulin–negative, Thy-1–positive bone marrow cells from normal (A–D) and bile duct–ligated rats (E–H) were cultured alone (B, D, F, and H) or in coculture with isogeneic hepatocytes (A, C, E, and G), with (C, D, G, and H) or without interleukin-3 (A, B, E, and F).

the culture media aspirated carefully. Then, 500 µl of ammonia in Dulbecco's modified Eagle's medium (Sigma A 4514, 2.5 mmol/L, pH 7.40; Sigma Chemical, St. Louis, MO) was added to the BALSC cell cultures. After 5 hours, 400 µl of media were removed, and ammonia and urea contents were determined using an enzymatic colorimetric test kit (Kit 542 946; Roche Diagnostics, Rotkreuz, Switzerland).

Real-time Polymerase Chain Reaction

Total RNA Extraction and Reverse Transcription. BALSC were harvested from culture using 500 µl of TRIzol after complete removal of the media and immediately after determination of urea formation (Invitrogen AG). Total RNA was extracted using the Promega Reverse Transcription System (Promega Corporation, Madison, WI).

Expression of Albumin mRNA and 18S rRNA Content

The content of 18S rRNA in each individual culture dish was quantified by TaqMan real-time polymerase chain reaction (PCR) (AB Applied Biosystems, Rotkreuz, Switzerland). Average threshold cycle values (cycle of threshold values) from triplicate real-time PCRs were obtained. Standardization of the metabolic signal for total cell number was achieved with the following formula: (Urea formation/h)/(35 – CT value of 18S rRNA).[22]

Albumin mRNA expression by BALSC was quantified by real-time PCR using the following primers and probe: forward primer: 5′-TTG GTG CAG GAA GTA ACA GAC TTT-3′; reverse primer: 5′-GTG TGA ATG GAC TTG TCA CAG TTT T-3′; and TaqMan probe: 5′-FAM-CAA AAT CAT GTG TCG CTG ATG AGA ATG CC-TAMRA-3′. Albumin ΔCT values were related to 18S rRNA content in the following manner (ΔCT albumin = CT albumin – CT 18S rRNA).

Interleukin-3 Determination in Serum

IL-3 was measured using a colorimetric ELISA kit (900-K48; PeproTech EC Ltd., London, UK).

Statistical Analysis

Results are expressed as mean ± SD. We compared parallel cultures from the same animal using a paired *t* test. Intergroup comparisons were made using the Student *t* test for normally distributed data. For correction of pairwise multiple comparisons, Student-Newman-Keuls method was applied (Jandel Scientific 1.0; Jandel Scientific, San Rafael, CA). The significance level was set at $P < 0.05$.

RESULTS

Interleukin-3 Receptor-α Surface Expression

Immunohistochemistry staining for IL-3 receptor-α on BALSC from normal (n = 3) and bile duct–ligated (n = 3) animals revealed that BALSC highly express IL-3 receptor-α: 95 ± 5.0% in normal animals and 98 ± 2.5% in bile duct–ligated animals ($P = 0.70$).

Isolation of BALSC (β2-Microglobulin–Negative, Thy-1–Positive Cells) from Normal and Bile Duct–ligated Rats

All rats survived 7 days of bile duct ligation. Body weight remained stable, and no signs of biliary or abdominal infection were observed. The subpopulation of β2-microglobulin–negative cells was increased (400%) in bile duct–ligated animals (9.1 ± 6.8% of all nucleated cells of the bone marrow in normal [n = 28] versus 37.1 ± 6.1% in bile duct–ligated animals [n = 12], $P < 0.0001$). To obtain a pure fraction of albumin-positive cells, a Thy-1–positive selection was performed.[7] Interestingly, no significant difference in the total cell number obtained after the second immunoisolation step was detected between cells isolated from normal and bile duct–ligated animals (2.7 ± 2.0% of all nucleated bone marrow cells in normal versus 3.4 ± 1.0% in bile duct–ligated animals, $P = 0.25$).

Real-time PCR for Albumin

Albumin mRNA expression was assessed systematically in all BALSC used for culture experiments. ΔCT values for albumin mRNA in β2-microglobulin–negative/Thy-1–positive cells from normal (19.9 ± 2.4) and bile duct–ligated animals (21.4 ± 4.1) were not different.

Real-time PCR Analysis of 18S rRNA Content

The determination of 18S rRNA content in every single culture dish by real-time PCR showed stable CT values on culture days 3, 6, 9, and 12 (Table 2). Although the average standard deviation of the CT 18S rRNA content in the groups E, F, G, and H (cells from bile duct–ligated animals) was higher than that in groups A, B, C, and D (cells from normal animals), the statistical analysis revealed no significant differences among the eight experimental groups (Table 2).

Ureagenesis

Urea synthesis from ammonia was determined in BALSC on days 3, 6, 9, and 12 after removal of the hepatocyte inlay from the co-culture (Table 3).

Table 2. 18S rRNA content of experimental groups

Experimental group	Average 18S rRNA content (CT values ± SD)
A	24.5 ± 1.2
B	25.0 ± 0.8
C	26.6 ± 1.4
D	25.8 ± 1.3
E	26.0 ± 4.0
F	21.3 ± 2.6
G	21.4 ± 3.9
H	21.4 ± 2.0

Total 18S rRNA content of the bone marrow–derived adult liver stem cells was determined at 3, 6, 9, and 12 days in culture and did not differ significantly over time under the various culture conditions examined, indicating constant cell number in all eight experimental groups.

Addition of IL-3 to the culture media increased the capacity of β2-microglobulin–negative/Thy-1–positive cells for urea formation in cell cultures from normal (A versus C, B versus D; $P < 0.05$) but not from bile duct–ligated animals (E versus G, F versus H; P = NS) (Fig. 1).

As BALSC in single culture (B, D, F, and H) and co-culture (A, C, E, and G) were strictly isolated from the same animal and kept in parallel cultures, a paired statistical analysis was performed (A versus B, C versus D, E versus F, G versus H). All co-culture groups showed superior urea formation ($P < 0.05$).

When comparing urea formation capacity of BALSC from normal and bile duct–ligated donor animals under the same culture conditions (groups A versus E, B versus F, C versus G, D versus H), no significant differences were detected between the groups.

Table 3. Metabolism of ammonia into urea in bone marrow–derived adult liver stem cells (BALSC)

Experimental group	Urea synthesis (average ± SD) in BALSC cultures			
	3 Days	6 Days	9 Days	12 Days
A	1.3 ± 0.2	1.0 ± 0.3	1.9 ± 0.1	1.4 ± 0.4
B	1.3 ± 0.4	0.5 ± 0.1	1.4 ± 0.2	0.8 ± 0.1
C	2.2 ± 1.2	2.1 ± 0.9	3.0 ± 0.7	3.4 ± 1.5
D	1.4 ± 0.6	1.8 ± 1.3	1.6 ± 0.2	2.0 ± 0.3
E	1.2 ± 0.8	2.0 ± 0.4	3.3 ± 2.7	3.1 ± 0.1
F	1.1 ± 1.0	1.1 ± 0.4	2.7 ± 2.2	1.5 ± 1.1
G	2.3 ± 0.7	2.9 ± 0.6	3.9 ± 0.6	3.7 ± 0.2
H	2.0 ± 0.1	2.0 ± 0.1	2.9 ± 0.1	2.9 ± 0.2

Urea synthesis was significantly increased ($P < 0.05$) in BALSC from normal animals after addition of interleukin-3 (groups C and D) but unaltered in BALSC from bile duct–ligated animals (groups G and H). All coculture groups (groups A, C, E, and G) showed superior ureagenesis compared with single BALSC cultures ($P < 0.05$). No significant differences were detected when comparing cell cultures from normal animals with parallel cultures from bile duct–ligated rats (groups A versus E; B versus F; C versus G; D versus H).

Interleukin-3 Levels in Serum

IL-3 levels in serum were determined in normal (n = 3, day 0), sham-operated (n = 3, day 7), and bile duct–ligated animals (n = 3, day 7). Values were below the detection limit of the ELISA Kit used (<0 ng/ml).

DISCUSSION

The effect of IL-3 on proliferation and differentiation in early hematopoietic progenitor populations is well recognized.[10–13] However, its effect on other progenitor cell populations like liver stem cells is not known. Using immunohistochemistry on freshly isolated BALSC revealed IL-3 receptor-α surface expression on virtually all β2-microglobulin–negative/Thy-1–positive cells isolated from rat bone marrow. This directed us toward the hypothesis that IL-3 may have a differentiation effect on BALSC. To test this hypothesis, we added IL-3 to cell cultures from normal animals (group D), which resulted in significantly stronger urea formation. This effect elicited a certain degree of excitement because it may provide a way to circumvent one of the most crucial problems in stem cell use for cell therapies. There are two cardinal problems for clinical application of stem cells: to obtain sufficient quantities ready for cell transplantation and to render these cells functional as soon as possible. Our study demonstrated that inducing hepatocyte-specific metabolic activity in BALSC within days of culture is feasible.

Previously, it has been established that to render BALSC functional in vitro, a co-culture with injured isogeneic hepatocytes separated by a semipermeable membrane is mandatory.[7] Therefore, we compared the effect of IL-3 (groups C and D) on ureagenesis in cultures and co-cultures of BALSC from normal animals (groups A and B) to the potentially additional inductive effect of co-culturing injured hepatocytes from bile duct–ligated animals with BALSC (groups E and G). Although ammonia metabolism into urea was impressively increased after stimulation with IL-3 in BALSC cultures from normal animals (groups A versus C, B versus D; $P < 0.05$), the metabolic signal was unaltered in BALSC co-cultures with hepatocytes from bile duct–ligated rats (groups A versus E, C versus G; P = NS). Furthermore, no IL-3 was found in the serum of normal, sham-operated, or bile duct–ligated animals, which indicates that the induction of metabolic activity is highly specific for IL-3.

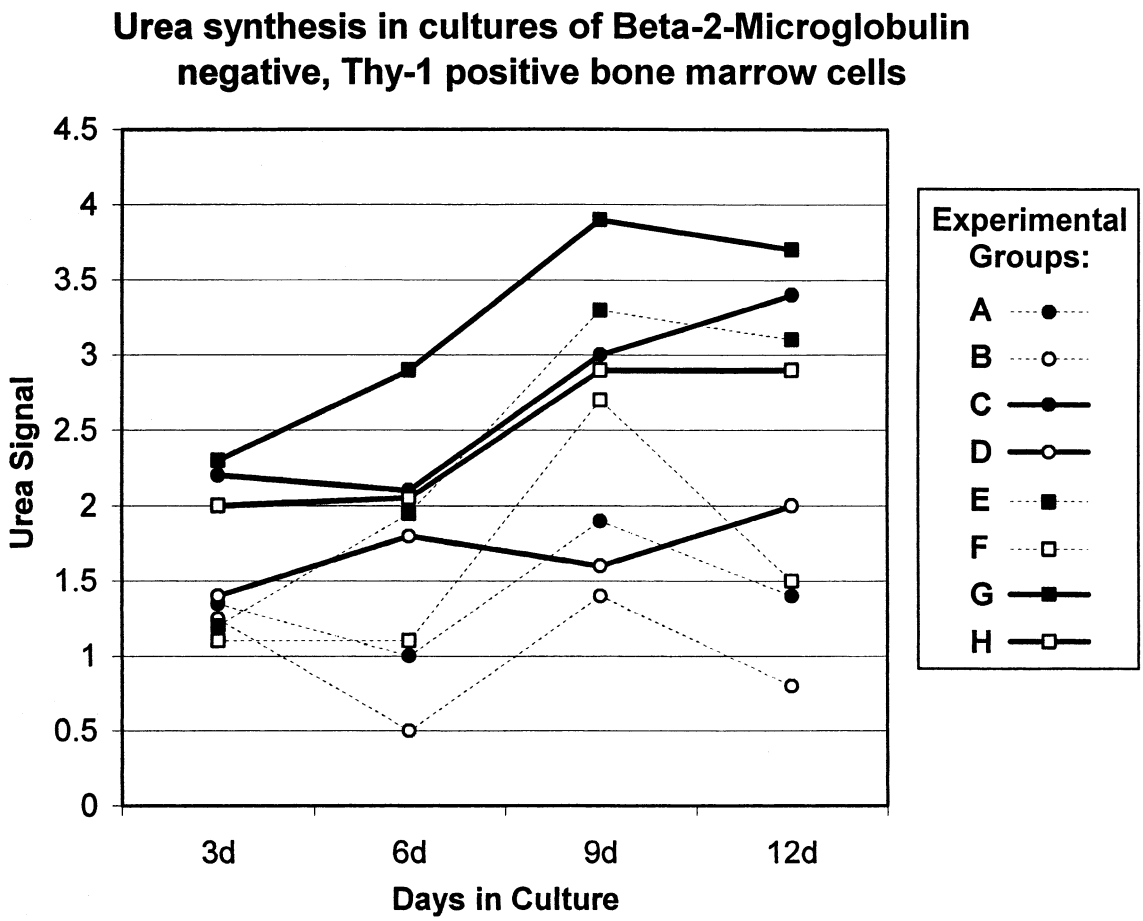

Fig. 1. β2-Microglobulin–negative/Thy-1–positive cells from normal (● = co-culture, ○ = single culture), and bile duct–ligated (■ = co-culture, □ = single culture) male rats were cultured in the presence (▬) or absence (…) of interleukin-3 (IL-3). Urea synthesis from ammonia was determined on days 3, 6, 9, and 12 and standardized for cell number. Average urea formation is depicted and was strongest in group G. By addition of IL-3 to co-cultures of BALSC with hepatocytes from normal animals (group C), strong ureagenesis was inducible.

To further ascertain this phenomenon and to control for different cell numbers in the various cultures; we demonstrated that IL-3 did not promote cell expansion as 18S rRNA content was stable in all eight culture conditions examined. This indicates a broader biological spectrum for the multilineage hematopoietic growth factor IL-3 than previously recognized.[10–13]

In culture experiments without tissue (liver) integration, mRNA or protein expression alone is not considered a reliable marker for the identification of organ-specific stem cells.[6] We therefore determined the urea formation capacity of β2-microglobulin–negative/Thy-1–positive bone marrow cells under the culture conditions examined. The applied method of ammonia determination before and after urease addition to the sample allows internal control of total ammonia content. No background urea or ammonia was detected in the culture media sample alone. Standardization of urea formation was achieved by relation of the metabolic signal to individual 18S rRNA content of the respective culture dish. This sensitive method allows quantitative assessment of urea formation in low-density cell cultures.

From a clinical point of view, the constant cell number in culture and the sustained urea formation of group D are most important. Human adult progenitor cell populations are readily accessible from the bone marrow, the peripheral blood after granulocyte colony-stimulating factor activation, and the umbilical cord blood. However, it is a difficult task to develop a hormonally defined culture medium that propagates unlimited liver progenitor cell division and liver-specific differentiation on demand. Interesting reports from various groups[14–19] include different progenitor cell isolation procedures from the bone marrow and a variety of culture conditions used. Due to the different end points chosen (e.g., mRNA or protein expression of liver-specific genes like albumin), a comparison of the results obtained is not

feasible and the effect of single additives (e.g., hepatocyte growth factor, acetic fibroblast growth, leucocyte migration inhibition factor) to the culture media remains unclear at best. Therefore, the hepatocyte-specific metabolic capacity such as the urea production should be included in future in vitro studies of hepatic progenitor cell populations to obtain comparable results.

All co-cultures showed stronger ureagenesis than their corresponding parallel single cultures, and it is a formidable task to determine the factors responsible for this phenomenon. The BALSC cell pool, the serum added to the culture media, and the dynamic interplay between hepatocytes and BALSC during co-culture will have to be carefully elucidated in the future.

Based on the urea formation data obtained from co-cultures, we conclude that hepatocytes exert a direct inductive effect on β2-microglobulin–negative/Thy-1–positive cells in culture. In a comparable in vitro study, Okumoto et al.[16] showed a similar induction of albumin expression in co-cultures of a subpopulation of adult rat bone marrow cells with hepatocytes. As the bone marrow and liver cells in the described co-culture system are separated by a 0.4-μm membrane, direct cell-to-cell interaction is precluded and paracrine soluble factors must be responsible for the induction of hepatocyte-specific function. Cell fusion between hepatocytes and progenitor cells as described as a potentially important in vivo mechanism is physically excluded in the two-chamber co-culture experiments.[23,24]

CONCLUSIONS

Ethical and immunologic considerations indicate that adult bone marrow–derived liver stem cells may be superior to embryonic stem cells. The ability of IL-3 to induce strong liver-specific metabolic activity in bone marrow–derived liver progenitors may render these cells more suitable for use in future cell-based therapies.

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Intestinal Transplantation in Children: A Summary of Clinical Outcomes and Prognostic Factors in 108 Patients From a Single Center

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We performed 124 intestinal transplants on 108 children (median age, 1.5 years) since 1994. Initial graft types included isolated intestine (I) (n = 26), liver and intestine (LI) (n = 26), multivisceral (MV) (n = 50), and multivisceral without liver (MMV) (n = 6). Four groups were defined by type of induction therapy: none, OKT3, or cyclophosphamide (August 1994–December 1997, n = 25), early experience with daclizumab (January 1998–December 2000, n = 26), recent experience with daclizumab (January 2001–April 2004, n = 40), and Campath-1H (January 2001–April 2004, n = 17). Actuarial patient survival at 1 year for groups 1–4 was 44% ± 10%, 54% ± 10%, 83% ± 6%, and 41% ± 12%, respectively, with group 3 having the most favorable survival ($P = 0.0004$). Using Cox stepwise regression, the hazard rate of developing severe rejection was significantly higher in patients with transplant type I or LI ($P = 0.0002$), with no difference between these groups ($P = 0.24$) but a significantly higher rate for LI versus MV ($P = 0.005$). Three factors associated with improved patient survival were recipient of MV or MMV ($P = 0.008$), age at transplantation greater than 1 year ($P = 0.01$), and use of daclizumab ($P = 0.0006$). Cause-specific hazard analysis revealed a decreased rate of rejection-related mortality for recipients of MV or MMV ($P = 0.0007$), whereas age greater than 1 year indicated a lower rate of infection-related mortality ($P = 0.0009$). Pediatric intestinal transplantation provides an increasingly realistic chance of survival, particularly with the more recent use of daclizumab and multivisceral transplantation. A protective effect of multivisceral transplantation appears to exist with respect to the development of severe rejection.
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Key words: Intestinal transplantation, children, clinical outcomes, prognostic factors, single-center experience

Intestinal transplantation has been performed as a life-saving treatment for children with intestinal failure and associated complications.[1–6] Childhood diseases that cause intestinal failure include short gut syndrome due to congenital anomalies (e.g., gastroschisis, jejunal atresia), necrotizing enterocolitis (NEC), and midgut volvulus. Other diseases include functional abnormalities such as megacystis-microcolon syndrome,[7] Hirschsprung's disease, and microvillus inclusion disease.[8] Due to the early onset of these childhood causes of intestinal failure, patients often require intestinal transplantation early in their lives. Fortunately, with advances in surgical technique, immunosuppression, and the monitoring of rejection, the results of intestinal transplantation have improved dramatically in recent years.[9,10] We began performing intestinal transplantation in children at this center in 1994. Overall, we have now performed intestinal transplantation in more than 100 children. The current report is a review of our decade-long experience in pediatric intestinal transplantation, focusing on the overall clinical outcomes in this cohort of 108

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patients as well as to provide a comprehensive analysis of prognostic factors.

MATERIAL AND METHODS

We retrospectively reviewed the medical records of all children who underwent intestinal transplantation at the University of Miami/Jackson Memorial Hospital between August 1994 (the first case) and April 2004 (the most recent case). The date of last follow-up was May 15, 2004. Isolated intestinal transplants as well as combined intestine plus other abdominal organ transplants were included in this series. A total of 124 intestinal transplants were performed on 108 patients. Patients were categorized into four distinct groups based on the transplant year and immunosuppressive induction regimen. The first group (group 1) comprised 25 patients who were transplanted between August 1994 and December 1997. During this period, three different induction regimens were used (in chronologic order): OKT3 induction (n = 4), cyclophosphamide induction (n = 3), and no induction with triple maintenance immunosuppression (n = 18). Because the numbers of patients receiving the first two immunosuppression regimens were small, these patients were combined with those receiving no induction to form group 1. Patients who received either OKT3 or cyclophosphamide induction received maintenance therapy with tacrolimus (Prograf; Fujisawa Healthcare, Deerfield, IL) and corticosteroids, whereas the patients who received no induction therapy received mycophenolate mofetil (MMF) (Cell Cept; Roche Laboratories, Nutley, NJ) as maintenance therapy in addition to tacrolimus and corticosteroids. The second group (group 2) received daclizumab (Zenapax; Roche Laboratories, Nutley, NJ) induction therapy between January 1998 and December 2000 (early daclizumab experience). No other induction regimen was offered to patients during this time period, and a total of 26 patients comprised group 2. Daclizumab was administered at 2 mg/kg at days 0, 7, and 14 and every 2 weeks thereafter during the first 3 months. Daclizumab was continued with a reduced dose of 1 mg/kg every 2 weeks for the next 3 months and discontinued thereafter. Group 3 comprised 40 intestinal transplant patients who received the same daclizumab induction protocol as those in group 2 between January 2001 and April 2004 (recent daclizumab experience). Maintenance immunosuppression of tacrolimus and corticosteroids was the same for groups 2 and 3. However, during the latter time period an alternative induction regimen using Campath-1H was offered to the patients. Thus, group 4 comprised 17 intestinal transplant patients who received Campath-1H induction during the same time period as group 3 (between January 2001 and April 2004). It should be noted that Campath-1H was initially used at our center as an induction regimen in adults and then expanded to use in children.[11–13] However, because the initial results using Campath-1H induction in small children were not considered to be satisfactory, its use has been limited to patients older than 4 years since August 2002. The patients who received Campath-1H induction received tacrolimus with no steroids as maintenance therapy.

Corticosteroid boluses and OKT3 were used to treat rejections in all groups. Sirolimus (Rapamycin; Wyeth, Madison, NJ) has been used for treating patients with refractory rejection and tacrolimus toxicity since 1999. The pathologic diagnosis and grading of rejection have been described elsewhere.[14]

Finally, a patient's cause of death was categorized as a rejection-related death, an infection-related death, or a death due to other causes, according to the triggering event that led to death. For example, a patient who developed severe rejection requiring graft removal and who subsequently died of its consequences was categorized as a death due to rejection, regardless of the immediate cause of death. On the other hand, a patient who died of infectious complications with no ongoing or recently treated rejection was classified as a death due to infection.

Statistical Analysis

Cox stepwise regression analyses were performed to determine a most important set of prognostic factors for the hazard rate of developing severe acute rejection and the hazard rate of death (overall survival). In the first analysis, patients who had intestinal graft loss or died without having severe rejection were censored at the time of graft loss or death. Factors found to be associated with the overall rate of death were then considered for their associations with cause-specific hazard rates of death: death due to rejection, death due to infection, and death due to other causes. Each patient death was classified according to one of these three types. In the cause-specific hazard rate analysis, deaths due to the cause of interest were treated as failures and deaths due to the other causes were treated as censored observations.[15,16] For each of these analyses, the score χ^2 test criterion was used. To avoid the possibility of obtaining spurious results with relatively small sample sizes, only variables with univariable values of $P < 0.05$ were considered for entry into the cause-specific hazard Cox models. Kaplan-Meier curves were performed for visual display of the effects of the prognostic factors on the cause-specific hazards along with

log-rank tests of their differences. Actuarial estimates of the probabilities of overall survival at various post-transplantation times along with their standard errors were quoted from the appropriate Kaplan-Meier formulas. Tests of association among the important prognosticators were performed using Pearson (uncorrected) χ^2 tests.

It should be noted that all of the statistical analyses and reported number of failures were based on the complete follow-up of all individuals. However, because there were only 22 patients who were followed beyond 36 months, for the purpose of providing greater visual clarity, all of the Kaplan-Meier curves shown in this report were truncated at 36 months. Therefore, one observed severe acute rejection episode at 45 months and four observed deaths at 37, 38, 46, and 73 months, respectively, were not visually displayed.

Factors considered for their prognostic value included the underlying disease (e.g., short gut syndrome versus functional abnormality), date of transplantation, waiting time from date of listing to transplant, patient gender and race, patient age and body weight at transplantation, donor age and donor body weight, ratio of donor to patient body weight, type of graft and organs transplanted, whether a reduction in the donor's liver was required, type of venous drainage (portal or systemic) of the small bowel, immunosuppressive regimen, whether donor bone marrow was given, cytomegalovirus (CMV) serology, ABO match, cytotoxic cross-match, and whether there was primary abdominal closure.

RESULTS

A total of 108 children received 124 intestinal transplants at our institution during the study period; 14 patients received a total of 16 retransplants. Causes of intestinal failure were due to gastroschisis (n = 32), necrotizing enterocolitis (NEC) (n = 17), intestinal atresia (n = 15), chronic pseudo-obstruction/megacystis microcolon syndrome (n = 13), Hirschsprung's disease (n = 10), volvulus (n = 9), microvillus inclusion disease (n = 4), and others (n = 8). Initial graft types were isolated intestinal graft (n = 26), liver and intestinal graft (n = 23), noncomposite liver and intestine graft (n = 3), multivisceral graft (n = 50), and multivisceral graft without the liver (n = 6). Retransplant graft types were isolated intestinal graft (n = 5), liver intestine graft (n = 1), noncomposite liver and intestine graft (n = 1), multivisceral graft (n = 7), and multivisceral graft without the liver (n = 2). Pancreas was included in the initial grafts of 15 composite liver and intestine transplants and in 1 isolated intestinal transplant. Inclusion of pancreas (either the part [head] or the whole) has been performed due to technical reasons.[17–19] The technique to include the head of the pancreas was originally proposed by the University of Nebraska group (Omaha technique) and was modified by our group to include the entire pancreas.[17,18] This technique is now widely used at most centers. If the entire pancreas is included in the graft, then the distinctions between the liver-intestine-pancreas and multivisceral techniques are the addition of the graft stomach and removal of the native foregut in the multivisceral procedure. Beginning in 2001, we expanded the indication of multivisceral transplantation to perform it as an alternative to liver-intestine-pancreas transplantation in very small children. Detailed explanation of the expanded indication for multivisceral transplantation is described elsewhere.[20] Other organs were also included in some of the initial grafts. For example, a total of 23 patients received a spleen—20 with a multivisceral and 3 with a modified multivisceral (i.e., no liver) transplant. A total of nine patients received one or both kidneys—seven with a multivisceral, one with a modified multivisceral, and one with a liver-intestine transplant. Last, a total of 19 patients received a large bowel—13 with a multivisceral, 3 with a liver-intestine, and 3 with an isolated intestine transplant. One patient received a multivisceral transplant without a stomach in the graft. Median age at transplant for the 108 recipients was 1.5 years (range, 6 months to 17 years). Median body weight of the patients was 10.0 kg (range, 4.5–67 kg), and that of their donors was 12.0 kg (range, 2.7–67.0 kg). Distributions of patient demographics and graft types for each group are summarized in Table 1.

One hundred five patients (97%) received their initial grafts from a blood group ABO-identical donor, whereas three received grafts from ABO compatible donors: O into B (n = 1), O into A (n = 1), and B into AB (n = 1). Recipient and donor CMV serology were recipient negative–donor negative (n = 34, 32%), recipient positive–donor negative (n = 14, 13%), recipient negative–donor positive (n = 36, 33%), and recipient positive–donor positive (n = 24, 22%). Cytotoxic cross-match results were positive in 7 cases (6%) including T- and B-cell cross-match positive (n = 6) and T-cell cross-match negative–B-cell cross-match positive (n = 1); cross-match was negative in 101 cases (94%). Liver graft reduction was performed in 17 cases, including right lobe resection (n = 4), left lateral lobe resection (n = 8), and right trisegmentectomy (n = 5). Abdominal closure at the time of transplantation occurred in 49% of the patients, whereas staged abdominal closure

was required in 51%. Four patients received abdominal wall transplantation at the time of transplant to facilitate closure.[21]

A total of 76 patients (70%) received an initial graft that included the liver. The indication for liver inclusion was liver failure in all except two patients. One exception was a 17-year-old recipient who received a multivisceral graft; her native liver was given via domino transplantation[22] to another recipient who needed it urgently, having UNOS status 1. The other exception was a 7-month-old girl with megacystis-microcolon syndrome who received a liver containing multivisceral graft from a 7-month-old donor, because separation of the liver from the multivisceral graft might have caused injury to the small vascular structures. The patient's explanted liver was not used as there was no appropriate recipient at the time. The presence of accompanying liver failure at the time of transplantation was more common in younger patients, occurring in 87% (47 of 54) of those 1.5 years old or younger versus 54% (29 of 54) in those older than 1.5 years ($P = 0.0003$).

Twenty-one patients developed an episode of severe rejection with their first graft. The median time from transplantation to the onset of severe rejection was 1.5 months (range, 10 days to 45.4 months). Fourteen episodes of severe rejection occurred within 6 months post-transplantation, and the remaining seven episodes occurred after 6 months (late severe rejection). All of the late severe rejection episodes were related to a reduction in immunosuppression due to either infection (n = 1), post-transplant lymphoproliferative disease (PTLD) (n = 2), noncompliance (n = 1), or planned immunosuppression reduction (n = 3). One of these seven patients was successfully treated with OKT3, two died, and four underwent graft removal and subsequent retransplantation. In contrast to the late-onset cases, early onset of severe rejection did not appear to be related to a reduction in immunosuppression. Among the 14 patients with early onset of severe rejection, 2 patients (14%) were successfully treated. Five patients died, and five additional patients underwent graft removal and subsequent retransplantation. Two remaining patients underwent graft removal but died while waiting for a retransplant. Among the nine patients who underwent retransplantation, three are currently alive. As of the date of last follow-up, 16 of the 21

Table 1. Distributions of patient demographic characteristics and transplant type by group*

Characteristic	Percentage (No./total) with characteristic			
Race				
White	66% (71/108)			
African/American	16% (17/108)			
Hispanic	17% (19/108)			
Asian	1% (1/108)			
Gender				
Male	57% (62/108)			
Female	43% (46/108)			
Age (yr)				
<1.5	50% (54/108)			
⩾1.5	50% (54/108)			
	Percentage (No./total) with characteristic, by group			
Characteristic	**Group 1**	**Group 2**	**Group 3**	**Group 4**
Transplant type				
Isolated intestine	20% (5/25)	31% (8/26)	23% (9/40)	24% (4/17)
Liver-intestine	44% (11/25)	50% (13/26)	5% (2/40)	0% (0/17)
Modified multivisceral	0% (0/25)	4% (1/26)	2% (1/40)	23% (4/17)
Multivisceral	36% (9/25)	15% (4/26)	70% (28/40)	53% (9/17)
Age (yr)				
<1.5	28% (7/25)	54% (14/26)	65% (26/40)	41% (7/17)
⩾1.5	72% (18/25)	46% (12/26)	35% (14/40)	59% (10/17)

*Group 1: patients who were transplanted between August 1994 and December 1997 and received no induction or induction with OKT3 or cyclophosphamide. Group 2: patients who were transplanted between January 1998 and December 2000 and received induction with daclizumab. Group 3: patients who were transplanted between January 2001 and April 2004 and received induction with daclizumab. Group 4: patients who were transplanted between January 2001 and April 2004 and received induction with Campath-1H (alemtuzumab, ILEX Pharmaceuticals, San Antonio, TX).

patients have died—15 due to rejection and 1 due to subsequent development of PTLD. Actuarial survival after the date of severe rejection (n = 21) was 37%, 26%, and 18% at 3, 6, and 24 months, respectively.

The Cox stepwise regression analysis of the hazard rate of developing severe rejection found only one independent prognostic factor for this outcome. Specifically, patients who received a multivisceral (n = 50) or modified multivisceral (n = 6) transplant had a significantly lower rate of developing severe rejection ($P = 0.0002$) in comparison with patients who received either an isolated intestine (n = 26) or liver-intestine (n = 26). Once this factor was selected into the Cox model, no other factors contained additional prognostic information. Although the incidence of severe rejection appeared to be higher among patients who received no induction therapy (5 of 18 developed severe rejection versus 16 of 90 among patients who received induction therapy), the hazard rate comparison was not significant in either univariable ($P = 0.27$) or multivariable ($P = 0.17$) analysis. Kaplan-Meier curves showing the comparison of the hazard rate of developing severe rejection by the four transplant types are shown in Fig. 1, *A*, and the comparison of the multivisceral/modified multivisceral (n = 56) versus isolated intestine/liver-intestine (n = 52) groups is shown in Fig. 1, *B*. Only 3 of 56 patients in the combined multivisceral/modified multivisceral group were observed to develop severe rejection in comparison with 18 of 52 patients in the other two groups combined. Although inclusion of the liver (comparing the multivisceral and liver-intestine groups combined versus the modified multivisceral and isolated intestine groups combined) was significantly favorable for protecting the development of severe rejection ($P = 0.001$), the log-rank test comparing the rate of developing severe rejection between

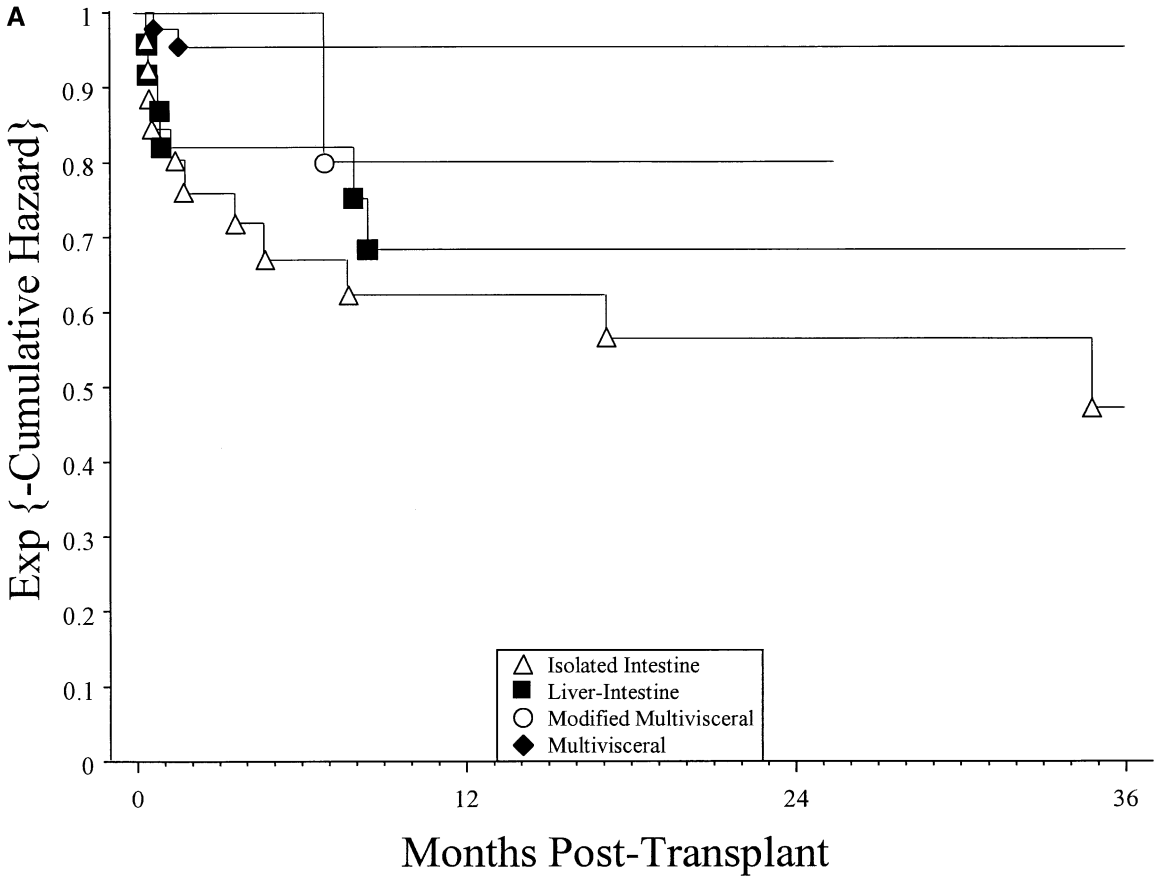


Fig. 1. (**A**) Kaplan-Meier comparison of the hazard rate of developing severe rejection by transplant type ($P = 0.0009$). Isolated intestine (n = 26, 12 failures); liver-intestine (n = 26, 6 failures); modified multivisceral (n = 6, 1 failure); multivisceral (n = 50, 2 failures). Patients followed beyond 36 months: 4, 7, 0, and 7, respectively. (**B**) Kaplan-Meier comparison of the hazard rate of developing severe rejection between patients who received an isolated intestine or liver-intestine transplant versus modified multivisceral or multivisceral transplant ($P = 0.0002$). Isolated intestine or liver-intestine (n = 52, 18 failures); modified multivisceral or multivisceral (n = 56, 3 failures). Patients followed beyond 36 months: 11 and 7, respectively.

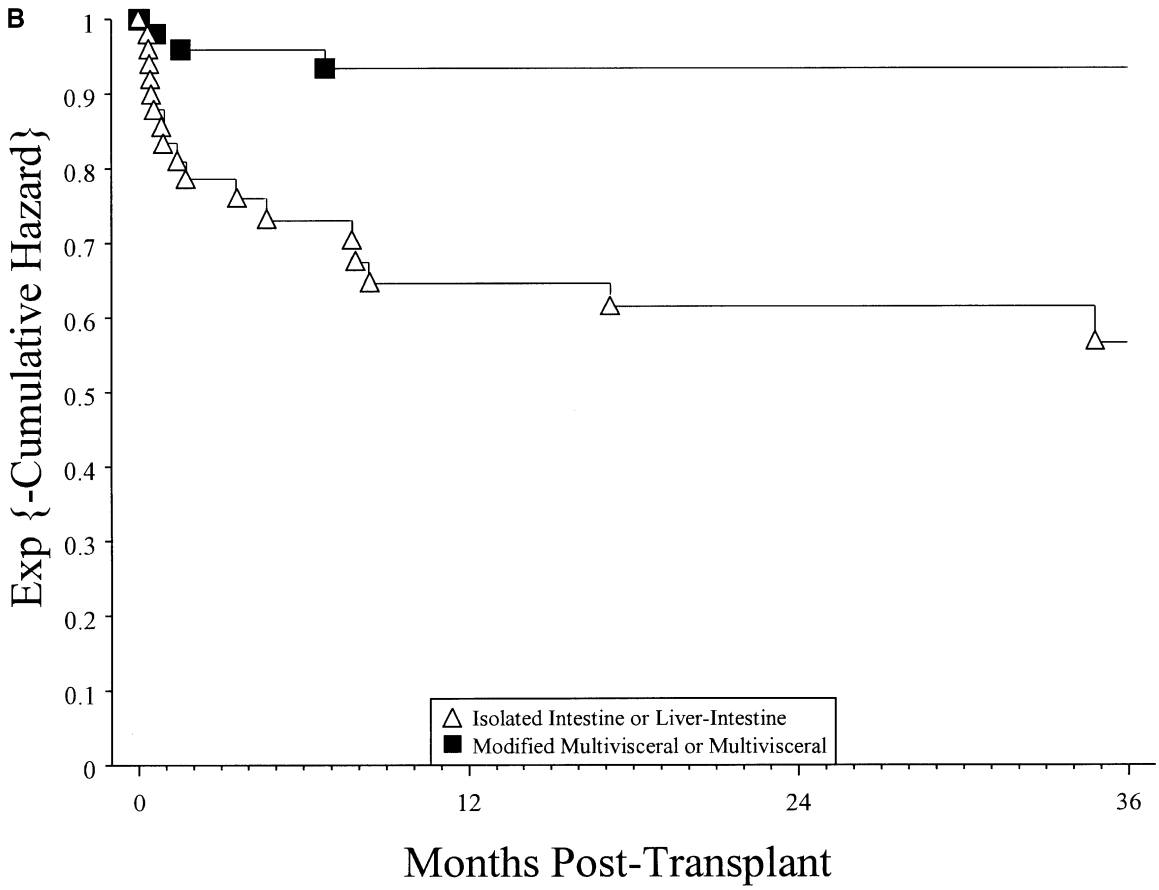


Fig. 1. Continued

the isolated intestine and liver-intestine groups was not significant ($P = 0.24$). In addition, among the patients who received a liver, the hazard rate of developing severe rejection was significantly higher among the patients who received a liver-intestine in comparison with a multivisceral transplant ($P = 0.005$). To simplify the comparison, the analysis was re-run excluding the 25 patients who were transplanted before 1998 (patients who received no induction or induction with OKT3 or cyclophosphamide were excluded). The results were the same. For example, 2 of the 47 patients who received a multivisceral or modified multivisceral transplant since 1998 developed severe rejection in comparison with 12 of 36 patients who received an isolated intestine or liver-intestine since 1998 ($P = 0.002$ by the log-rank test). In the same subpopulation (groups 2, 3, and 4), the hazard rate of developing severe rejection was not significantly different between the patients who received an isolated intestine (n = 21) in comparison with the patients who received a liver-intestine (n = 15) ($P = 0.46$). Conversely, the hazard rate of developing severe rejection was significantly higher among the patients who received a liver-intestine (n = 15) in comparison with the patients who received a multivisceral transplant (n = 41) ($P = 0.01$). In summary, these results suggest that the observed protective effect of a multivisceral transplant with respect to the incidence of severe rejection may not be due to the inclusion of a liver.

With respect to overall survival, 53 of 108 patients were still alive at last follow-up. Median follow-up among the 53 ongoing survivors was 29.3 months (range, 0.5–108.5 months) posttransplantation, and 10 patients have ongoing survival times of more than 5 years post-transplantation (the two longest survivors are alive at 9 years). All patients who are currently alive have been off TPN and have restored intestinal autonomy except for those who are still in the hospital postoperatively. For the whole cohort, actuarial patient survival at 1, 2, and 5 years post-transplantation was 59 ± 5%, 52 ± 5%, and 41 ± 6%, respectively (the number of patients still alive at 1, 2, and 5 years is 59, 38, and 11, respectively).

Figure 2, *A*, displays significant differences in survival among the four cohort groups ($P = 0.003$:

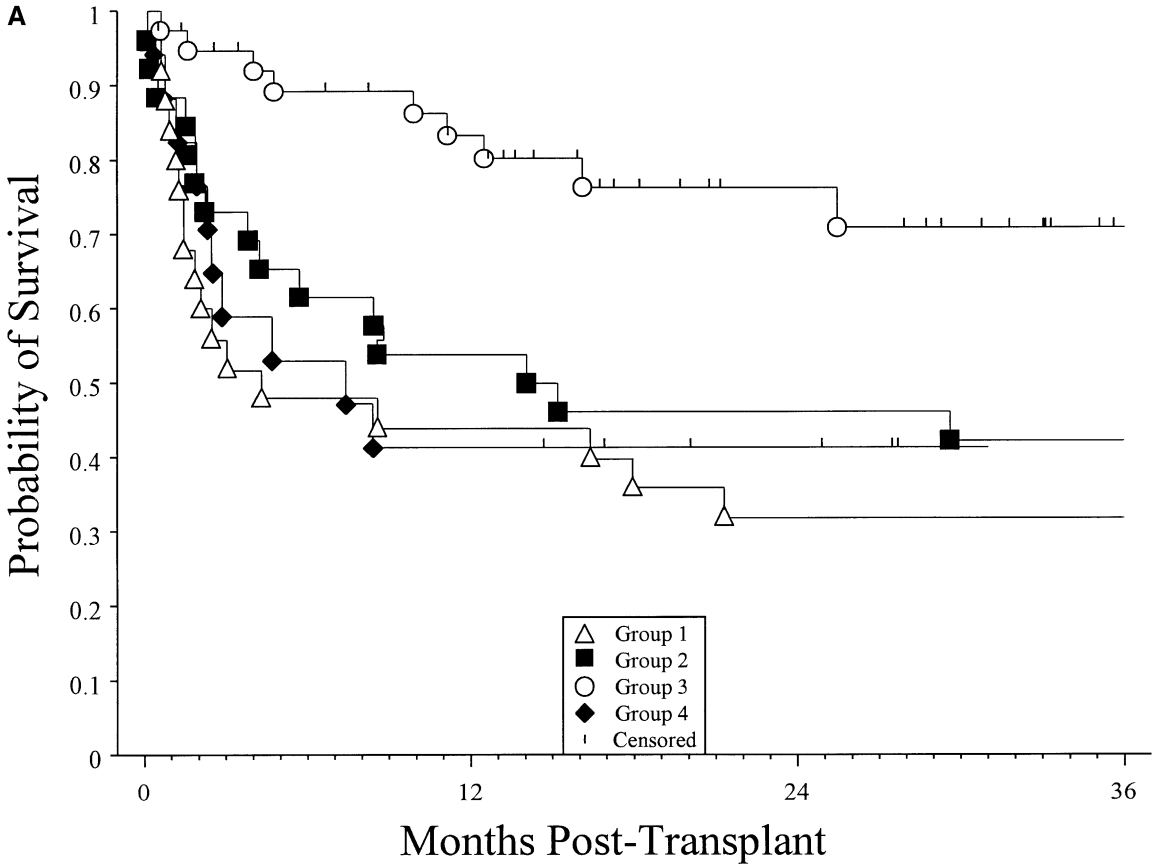


Fig. 2. (**A**) Kaplan-Meier comparison of overall survival by group ($P = 0.003$). Group 1 (n = 25, 20 failures); group 2 (n = 26, 16 failures); group 3 (n = 40, 9 failures); group 4 (n = 17, 10 failures). Patients followed beyond 36 months: 8, 11, 3, and 0, respectively. (**B**) Kaplan-Meier comparison of overall survival by group among patients who received a multivisceral transplant ($P < 0.0001$ for the comparison of groups 1, 2, and 4 combined versus group 3). Group 1 (n = 9, 6 failures); group 2 (n = 4, 2 failures); group 3 (n = 28, 2 failures); group 4 (n = 9, 7 failures). Patients followed beyond 36 months: 3, 2, 3, and 0, respectively.

actuarial patient survival at 1 year for groups 1–4, 44 ± 10%, 54 ± 10%, 83 ± 6%, and 41 ± 12%, respectively), with a distinct advantage for group 3 in comparison with the three other groups combined ($P = 0.0004$). Actuarial survival at 2 years post-transplantation was 71 ± 9% for group 3 in comparison with 37 ± 6% for the three other groups combined. Figure 2, *B*, shows that among the 50 patients who received a multivisceral transplant, overall survival was significantly more favorable for the 28 patients in group 3 in comparison with the 22 patients in the three other groups combined ($P < 0.0001$); actuarial survival at 2 years post-transplantation was 89 ± 7% for group 3 in comparison with 32 ± 10% for the three other groups combined.

The Cox stepwise regression analysis of the hazard rate of death found three variables containing independent prognostic value: more favorable outcomes were predicted by multivisceral or modified multivisceral transplants ($P = 0.008$), age at transplantation of greater than 1 year ($P = 0.01$), and induction with daclizumab ($P = 0.0006$). Once these three factors were selected, no other variables contained additional prognostic value ($P > 0.1$). The Cox model coefficients for these three variables were −0.78 ± 0.30, −0.77 ± 0.31, and −0.95 ± 0.28, respectively. Because these model coefficients were not significantly different from one another ($P = 0.60$), a simple count of the number of unfavorable patient characteristics provides a reasonable criterion for separating patients according to their prognosis. A strong separation of survival outcomes using this criterion is shown by the Kaplan-Meier survival curves in Fig. 3: the actuarial 2-year survival times for the 21, 45, 40, and 2 patients with no, one, two, and three unfavorable characteristics (isolated

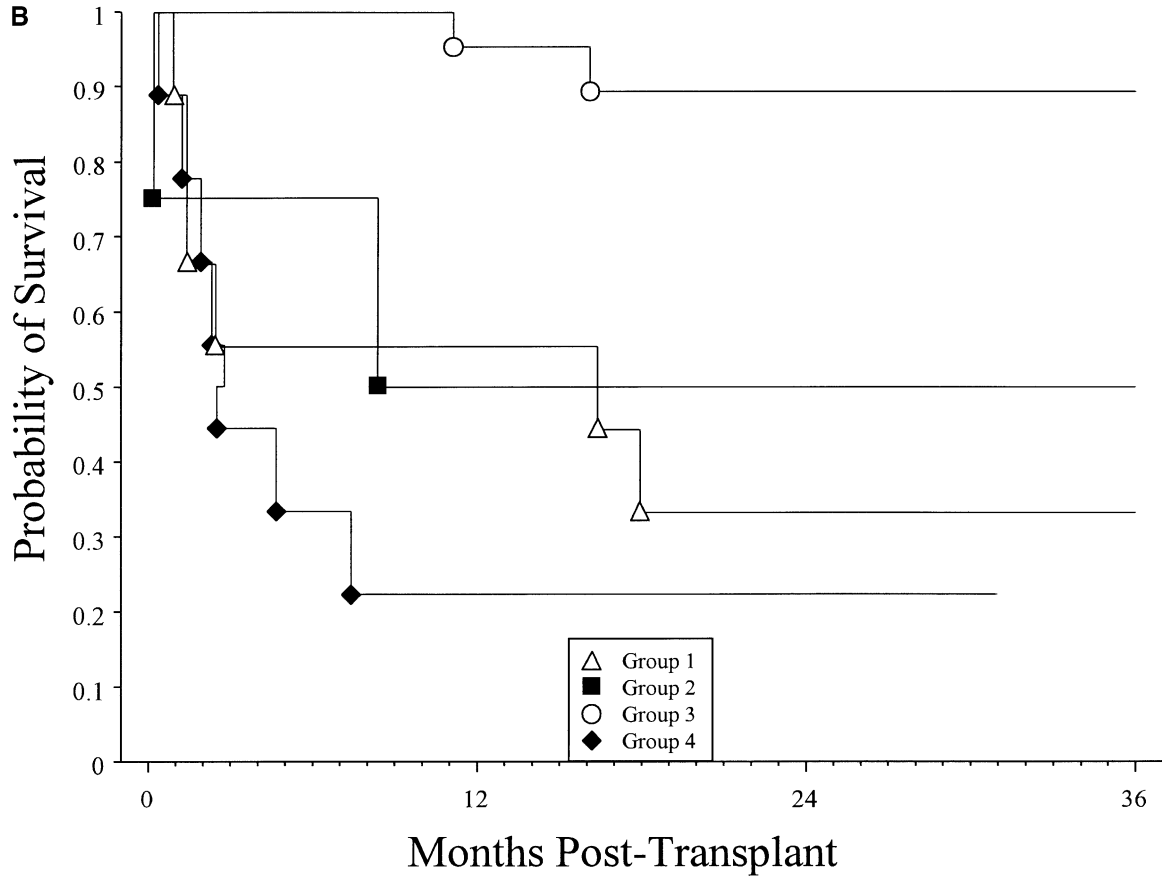


Fig. 2. Continued

intestine or liver-intestine transplant, age at transplantation of less than 1 year, and no use of daclizumab) were 73 ± 12%, 55 ± 8%, 33 ± 8%, and 0%, respectively. It should be noted that although a more recent date of transplantation was associated with a significantly more favorable survival in univariable analysis ($P = 0.007$), the date of transplantation was significantly associated with both the type of induction administered ($P < 0.0001$) and the type of transplant ($P < 0.0001$). For example, all of the patients who received no induction were transplanted before 1998, whereas all of the patients who received daclizumab induction were transplanted since 1998. Similarly, 27% (14 of 51) of the patients transplanted before 2001 received a multivisceral or modified multivisceral transplant, in comparison with 74% (42 of 57) of the patients transplanted since 2001 (Table 1).

Finally, among the 55 observed deaths, 19 were due to rejection, 19 were due to infection, and 17 were due to other complications. Among the 19 deaths due to rejection, 15 patients had a prior episode of severe rejection. Causes of death due to infection included sepsis (n = 10), viral pneumonia (n = 5), necrotizing fasciitis (n = 2), and PTLD (n = 2). Causes of death due to other complications included primary nonfunction (n = 2), intestinal leak (n = 2), enterocutaneous fistula (n = 2), aortoenteric fistula (n = 1), poor clinical status at transplantation (n = 1), pancreatitis (n = 1), anoxic brain injury (n = 2), intracranial bleeding (n = 1), respiratory arrest (n = 1), graft-versus-host disease (n = 2), aplastic anemia (n = 1), and severe hemolytic anemia (n = 1).

A Cox stepwise regression analysis of the hazard rate of death due to rejection found two factors to be independently associated with a significantly higher hazard rate: those who did not receive a multivisceral/modified multivisceral transplant ($P = 0.0007$) and those who did not receive any induction therapy ($P = 0.003$). The Cox model coefficients for the two factors were 1.87 ± 0.63 and 1.34 ± 0.48, respectively. Age at transplant of less than 1 year had no association with the hazard rate of death due to rejection ($P = 0.58$), nor did the type of induction received ($P = 0.43$). The Kaplan-Meier curves for death due to rejection (Fig. 4, *A*) show the significantly favorable impact of both a multivisceral/modified multivisceral

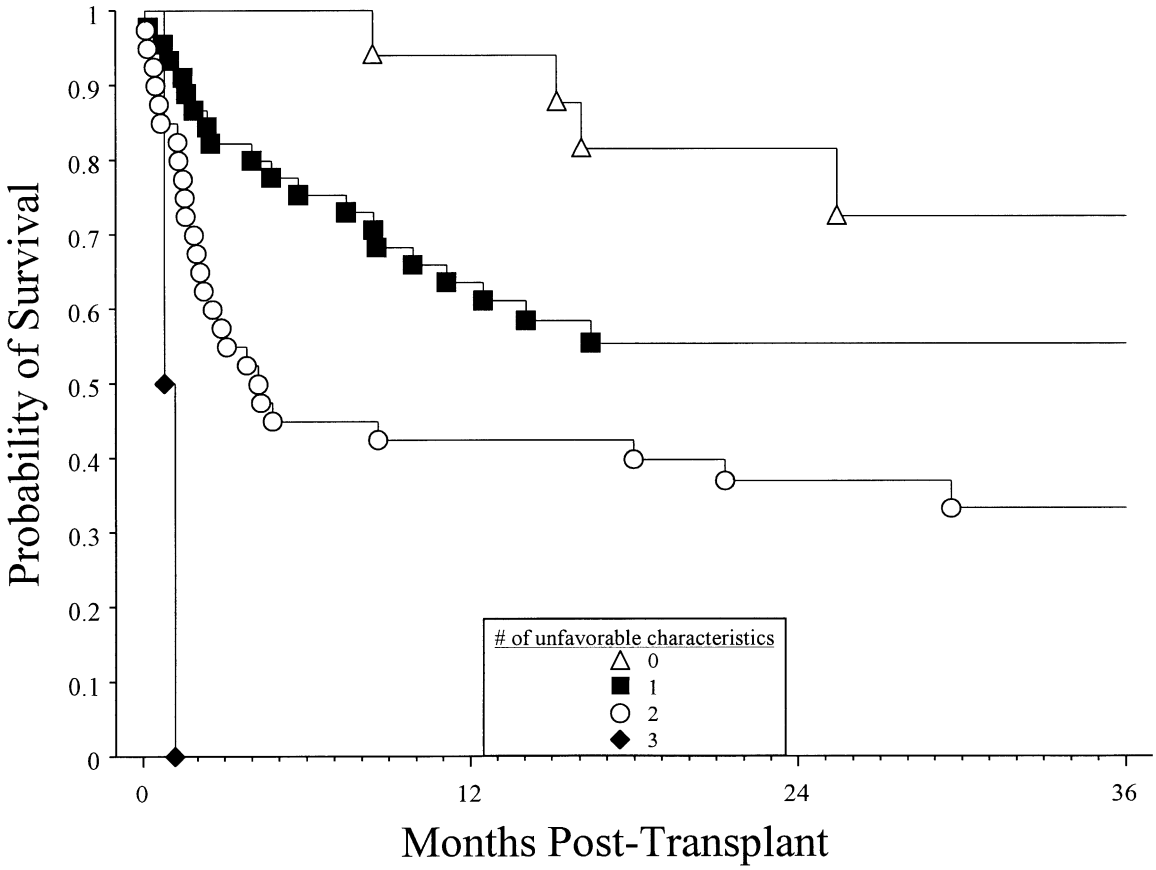


Fig. 3. Kaplan-Meier comparison of overall survival based on the number of unfavorable patient characteristics established by the Cox model: none, one, two, or three ($P < .0001$). 0 Unfavorable characteristics (n = 21, 4 failures); 1 unfavorable characteristic (n = 45, 20 failures); 2 unfavorable characteristics (n = 40, 29 failures); 3 unfavorable characteristics (n = 2, 2 failures). Patients followed beyond 36 months: 2, 13, 7, and 0, respectively.

transplant and induction therapy. Among the 90 patients who received induction therapy, 2 of 48 patients receiving a multivisceral or modified multivisceral transplant died of rejection in comparison with 10 of 42 patients who received an isolated intestine or liver-intestine transplant. Similarly, among the 18 patients who received no induction therapy, 1 of 8 patients receiving a multivisceral or modified multivisceral transplant died of rejection in comparison with 6 of 10 patients who received an isolated intestine or liver-intestine transplant. Kaplan-Meier curves for death due to rejection for the four transplant types are shown (Fig. 4, *B*). Similar to the results for the hazard rate of developing severe rejection, this figure shows no difference in the hazard rate of death due to rejection between those who received an isolated intestine versus a liver-intestine transplant ($P = 0.94$); this comparison remained nonsignificant among the patients who received induction therapy ($P = 0.96$). Conversely, among patients who received a liver, the hazard rate of death due to rejection was significantly more favorable among those who received a multivisceral versus liver-intestine transplant ($P = 0.002$); this comparison remained significant among the patients who received induction therapy ($P = 0.008$).

Analysis of the hazard rate of death due to infection found only two factors that significantly influenced this outcome: patients who were younger than 1 year age at transplantation had a significantly higher hazard rate ($P = 0.0001$), as did patients who were transplanted before 2001 ($P = 0.01$). The Cox model coefficients for the effects of age of less than 1 year and transplantation year before 2001 were 1.70 ± 0.49 and 1.20 ± 0.51, respectively. The Kaplan-Meier curves for death due to infection (Fig. 4, *C*) show the significantly less favorable prognosis for the younger patients: 12 of 37 patients younger than 1 year died of infection in comparison with only 7

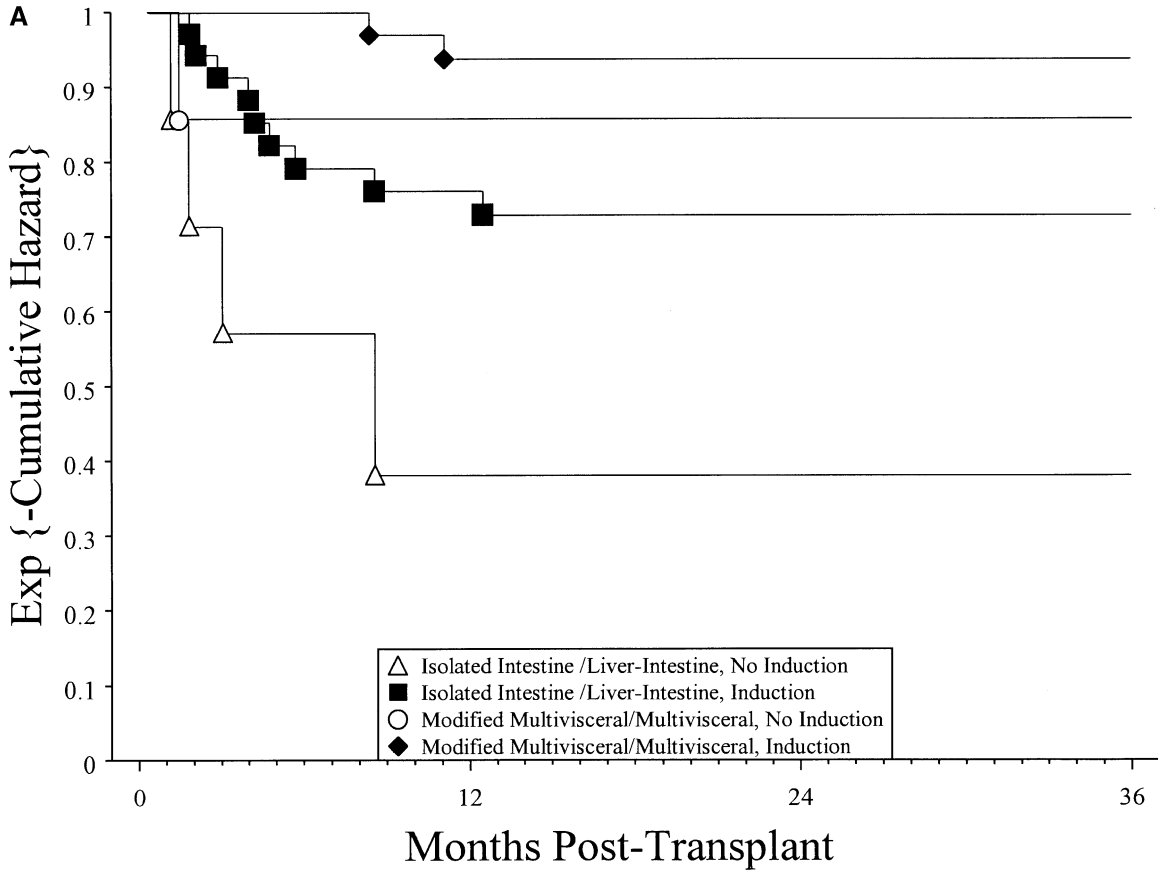
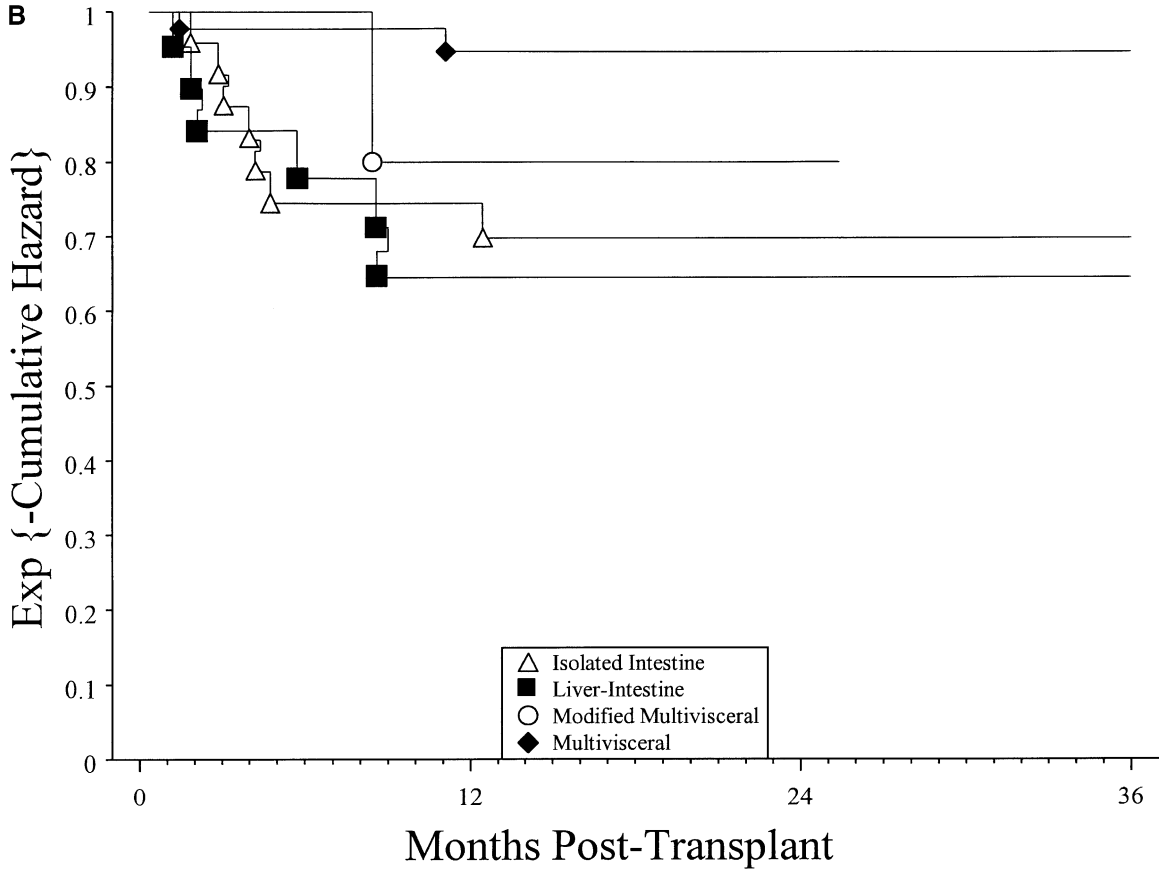
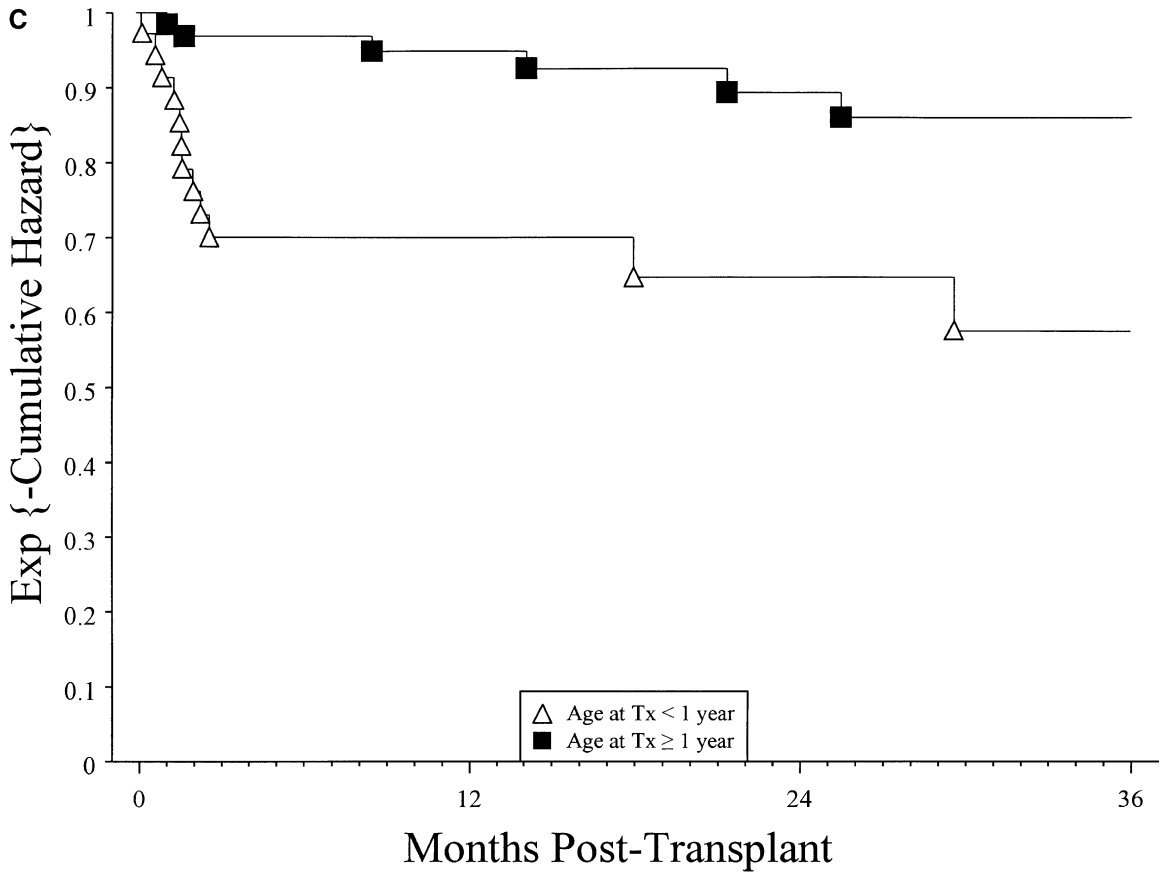


Fig. 4. (**A**) Kaplan-Meier comparison of the hazard rate of death due to rejection by transplant type (isolated intestine or liver-intestine versus modified multivisceral or multivisceral) and induction therapy (no versus yes) ($P < 0.0001$). Isolated intestine/liver-intestine, no induction (n = 10, 6 failures); isolated intestine/liver-intestine, induction (n = 42, 10 failures); modified multivisceral/multivisceral, no induction (n = 8, 1 failure); modified multivisceral/multivisceral, induction (n = 48, 2 failures). Patients followed beyond 36 months: 12, 2, 5, and 3, respectively. (**B**) Kaplan-Meier comparison of the hazard rate of death due to rejection by transplant type ($P = 0.002$ for the comparison of the isolated intestine and liver-intestine groups combined versus the modified multivisceral and multivisceral groups combined). Isolated intestine (n = 26, 9 failures); liver-intestine (n = 26, 7 failures); modified multivisceral (n = 6, 1 failure); multivisceral (n = 50, 2 failures). Patients followed beyond 36 months: 7, 7, 0, and 8, respectively. (**C**) Kaplan-Meier comparison of the hazard rate of death due to infection for patients younger than 1 year versus 1 year of age or older at transplantation ($P = 0.0009$). Age at transplantation less than 1 year (n = 37, 12 failures); age at transplantation of 1 year or older (n = 71, 7 failures). Patients followed beyond 36 months: 5 and 17, respectively. (**D**) Kaplan-Meier comparison of the hazard rate of death due to other causes by type of induction therapy ($P = 0.009$ for the comparison of daclizumab versus the other four groups combined). OKT3 (n = 4, 1 failure); cytoxan (n = 3, 0 failures); no induction (n = 18, 5 failures); daclizumab (n = 66, 6 failures); Campath-1H (n = 17, 5 failures). Patients followed beyond 36 months: 1, 2, 5, 14, and 0, respectively.

of 71 older patients ($P = 0.0009$ by the log-rank test). There was no significant difference in the hazard rate of death due to infection between those receiving a multivisceral/modified multivisceral transplant in comparison with those receiving an isolated intestine/liver-intestine ($P = 0.44$). In addition, type of induction had no significant influence on the hazard rate of death due to infection (infection deaths: 3 of 18 with no induction, 2 of 4 who received OKT3, 1 of 3 who received cytoxan, 10 of 66 who received daclizumab, and 3 of 17 who received Campath).

Last, the hazard rate of death due to other causes was not influenced by the type of transplant ($P = 0.70$) or patient age ($P = 0.58$). However, this





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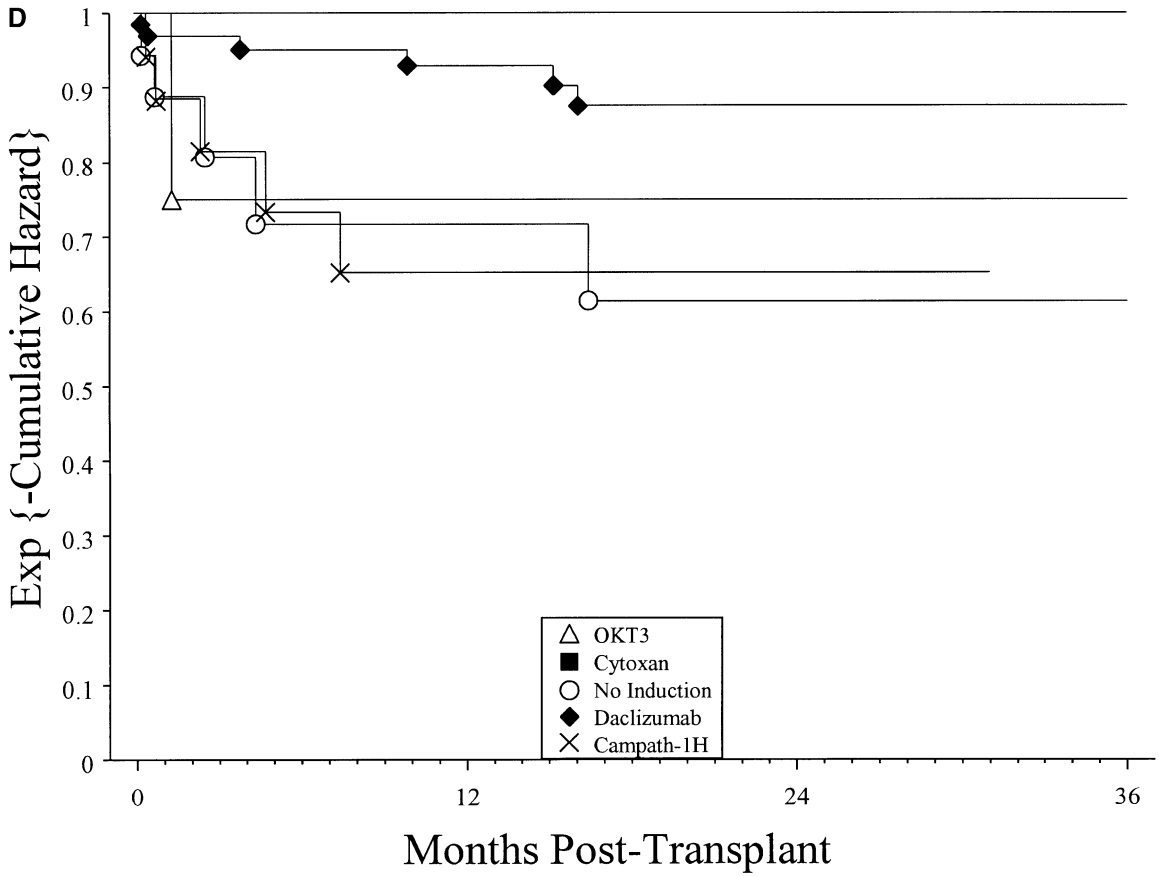

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hazard rate was significantly higher among the 42 patients who did not receive daclizumab as induction therapy ($P = 0.009$) (Fig. 4, *D*). The Cox model coefficient for the effect of not receiving daclizumab was 1.24 ± 0.51. Other deaths occurred in 5 of 18 with no induction, 1 of 4 who received OKT3, 0 of 3 who received cytoxan, 6 of 66 who received daclizumab, and 5 of 17 who received Campath-1H.

DISCUSSION

Small bowel was one of the first organs transplanted in an animal model; however, its application to humans was difficult in the early era.[23–26] Clinical intestinal transplantation became successful for the first time in the late 1980s to the early 1990s.[9,10] At our institution, we started an intestinal transplantation program in 1994. Since then, we have been performing a larger number of cases every year with improving clinical outcomes. Patients receiving intestinal transplants with or without the liver, and with or without other gastrointestinal organs, have been included in the general category of intestinal transplantation, because (1) the indication for such a procedure originates mainly from the underlying bowel disease and (2) the small bowel requires the closest follow-up in comparison with the other concomitantly transplanted organs.

The indications for performing intestinal transplants in children with intestinal failure are life-threatening complications of parenteral nutrition (PN). The most common life-threatening complication of PN is the development of liver failure. The children who develop liver failure seem to develop it early. The age of transplantation among those with accompanying liver failure at the time of transplantation was significantly younger in comparison with those without liver failure. The precise pathogenesis of PN-induced cholestatic liver disease in children is unclear, but there appears to be a subset of children (infants) who do not tolerate PN and who develop liver failure within the first 1 to 2 years of age.

The development of severe rejection is known to carry a dismal prognosis,[27,28] and our data support this view with roughly a 20% probability of patient survival beyond 2 years from the development of severe

rejection. Once the rejection progresses to the level where the mucosal surface is sloughed, it becomes very difficult to reverse. The occurrence of an early severe rejection (within 6 months) did not appear to be related to any reduction in the levels of immunosuppression; thus, it may be more strongly related to the recipient's immune reactivity to the donor. One clear message is the extreme importance in diagnosing any rejection as soon as possible to prevent further worsening as well as to be able to successfully treat the rejection.

Our statistical analysis found multivisceral or modified multivisceral transplant to be associated with significantly reduced risk of developing severe rejection. Interestingly, there appeared to be no significant difference in the rate of developing severe rejection between those who received an isolated intestine versus a liver-intestine transplant. Conversely, among the patients who received a liver, the rate of developing severe rejection was significantly higher among those who received a liver-intestine versus multivisceral transplant. In addition, these same results were found in the analysis of the hazard rate of death due to rejection. Thus, although we are not able to identify precisely which aspect of a multivisceral transplant is playing a protective role with respect to the incidence of severe rejection, our data suggest that it may not be due to liver inclusion.

The results of our overall patient survival analysis showed three factors to be significantly associated with a more favorable outcome: multivisceral or modified multivisceral transplant, age at transplantation of greater than 1 year, and use of daclizumab induction. The cause-specific hazard rate analyses were then used to more precisely identify the exact nature of these associations. Specifically, transplant type was associated with the hazard rate of death due to rejection but had no impact on the hazard rates of death due to infection and other causes. Patients who received no induction therapy also had a significantly higher rate of death due to rejection. Conversely, age at transplant had no impact on the rates of death due to rejection and other causes but was highly predictive of the hazard rate of death due to infection. Although less strong in comparison with the effect of age, patients who were transplanted before 2001 also had a significantly higher rate of death due to infection. One possible explanation is that with greater experience over time, our transplant team has become more able to provide an accurate and timely diagnosis of rejection, thereby achieving greater avoidance of overimmunosuppression.[29] Finally, patients who did not receive daclizumab had a significantly higher hazard rate of death due to other causes. This result appears to be explained by the fact that a larger proportion of deaths due to other causes were observed in patients who received Campath-1H as well as in patients who were transplanted before 1998.

In univariable analysis, a more recent transplant year had a positive effect on patient survival. A similar observation was made using the International Registry data.[30] In fact, the results show that among patients who received exactly the same immunosuppressive regimen with daclizumab induction, a more favorable survival was found for those transplanted since 2001 versus during 1998–2000 (Fig. 2, *A*). Two particular associations appear to explain this finding: (1) the significantly higher mortality rate due to infection that was seen among patients transplanted before 2001 and (2) a significantly greater use of multivisceral and modified multivisceral transplantation at our center since 2001 (see Table 1). In addition to the more recent use of multivisceral transplants and the ongoing use of induction therapy at our center, other reasons for the recent improvement in survival outcome are likely to be multifactorial. Factors that were not evaluated in the statistical analysis, such as improved surgical skills, improvements in overall postoperative management, and the team's growing familiarity with patient and donor selection issues, may have each contributed to the improvement.

Although prevention of rejection is one of the most important issues in intestinal transplantation, just escalating the use of immunosuppression would obviously increase the risk of infection. In an attempt to induce tolerance, or near tolerance (prope tolerance),[31] we began using Campath-1H in intestinal transplantation since 2001. Preliminary results of its use in adult liver, intestinal, and multivisceral transplants were encouraging.[11–13] However, despite the intention to improve outcome, the use of Campath-1H in young children has, to date, not improved survival. Survival of the Campath-1H group (group 4) was not significantly different ($P = 0.46$) from the precedent periods (groups 1 and 2) and was significantly worse ($P = 0.004$; see Fig. 2, *A*) than the group of patients who received daclizumab induction during the same time period (group 3). It is certainly possible that some type of selection bias existed in that sicker patients may have been more likely to be given Campath-1H. However, the percentage of patients younger than 1 year of age was not different between groups 3 and 4 ($P = 0.74$). There was no significant difference in the hazard rate of death due to rejection between groups 3 and 4 ($P = 0.48$), with 4 of 40 and 2 of 17 deaths due to rejection in the two groups. However, there was a significantly higher hazard rate of death due to nonrejection causes (infection or other causes) for group 4 in comparison with group 3 ($P = 0.003$), with 8 of 17 and 5 of 40 such deaths

observed in the two groups. Thus, although it must be emphasized that these results are not based on a randomized clinical trial, in children Campath-1H appears to be tolerated less well than daclizumab.

CONCLUSION

Children who underwent intestinal transplantation at our center during the past 10 years due to intestinal failure and TPN-related complications had favorable overall rates of success and survival. The outcomes have significantly improved in recent years with the greater use of multivisceral transplantation, induction with daclizumab, and a lower mortality rate due to infection. Severe rejection in the intestinal allograft continues to be a major problem for these patients. The exact reason for a protective effect of multivisceral transplantation has not been established; however, our results indicate that it is most likely not explained by the inclusion of the liver. Specifically, among the patients who received a liver, the incidence rate of severe rejection and the mortality rate due to rejection were significantly higher for those who received a liver-intestine transplant in comparison with those who received a multivisceral transplant. In addition, these two failure rates were similar for those who received an isolated intestine versus a liver-intestine transplant. Last, the exact role that Campath-1H induction would optimally play in pediatric intestinal transplantation has yet to be established.

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Discussion

Dr. M. Callery (Boston, MA): Could you say something about the quality of life for these children who survive after the transplant? Do they go on to develop, get off to school, etc.?

Dr. Kato: Perhaps I should have included some of the pictures of the children in my presentation to show how they do. Usually, once children survived 2 years post-transplant, they have gone back to school, achieved an excellent quality of life. Of course, there are some developmental delays in most children, particularly for the ones who were sick most of the time. Remember, many of these children have remained in the hospital since birth, have never been home prior to transplant. There are some delays in the cognitive skills and/or motor skills in these children. Although they look pretty normal to the hospital workers, these delays can be significant in the formal psychological evaluation.

Dr. N. Ameen (Pittsburgh, PA): Tom, can you comment on the problem of secretory diarrhea in the patients post-transplantation? In the isolated small bowels, we have a problem with profound secretory diarrhea in the absence of rejection or infection. Can you comment on your observations of multivisceral transplantation and that particular problem, whether it is better or not, in your mind?

Dr. Kato: Secretory diarrhea has not been a major problem; however, actually we are facing one very bad secretory diarrhea case in a multivisceral transplant recipient. We have often seen diarrhea that were attributed to hypermotility, but not pure secretory diarrhea. So I cannot really comment on the difference between multivisceral versus isolated intestine. I guess it could happen in both multivisceral and isolated intestinal transplant if you have seen cases in Pittsburgh with isolated graft.

Dr. J. Thompson (Omaha, NB): Dr. Kato and his colleagues are to be congratulated for continuing to seek innovative approaches in this challenging group of patients. You analyzed the outcome based on the type of transplantation that was performed, but, of course, that is determined in part by etiology. Have you looked at the different groups like gastroschisis or pseudo-obstruction to see how their outcome was influenced by transplantation? Second, have you used the strategy of isolated liver transplant in some of these individuals with intestinal failure, anticipating that they would be able to adapt with time? Thank you.

Dr. Kato: With regard to your first question, we have not looked at differences between each cause of intestinal failure. No significant differences were found. Clearly this is something we should continue to evaluate as the number of transplants increases and meaningful comparisons are performed.

And to your second question, so far we have performed an isolated liver transplant in one patient with short gut syndrome in Miami. We believe that it is a procedure that is rarely indicated. I know that Nebraska has used this strategy on multiple occasions. We have found that patients who develop liver failure and who have already achieved adaptation of the bowel tend to recover without the transplant. We have seen several children who managed to adapt the bowel improved the liver function to the point that no transplant was needed. So once adaptation happens early on, it seems to have a reversible effect even on relatively advanced liver problem.

On the other hand, if the patient has not achieved bowel adaptation, we feel uncomfortable performing isolated liver transplant without being able to reliably predict the likelihood of adaptation. As a matter of fact, in our only case of isolated liver transplant, the patient still has not adapted after 3 years from the transplantation and suffering from the side effect of TPN, which seems to be a very big penalty to the patient. The key word here is "patient selection." We need more experience with the various options available in our menus.

Dr. J. Howard (Toledo, OH): Have you isolated the reason that the patients on long-term hyperalimentation may have hepatic failure?

Dr. Kato: No, we have not. As you know, there have been studies looking at that subject in intestinal failure management, but we have not looked at it here.

Dr. Howard: Pretransplant?

Dr. Kato: Yes, I understand what you mean. We have seen many patients who already have liver failure at the time of referral because, as I mentioned, the liver failure is the most common indication for intestinal transplantation. I think, in the future, it would be useful to analyze from these patients going backward in time.

Long-term Results of Preoperative Chemoradiation for Distal Rectal Cancer Correlation Between Final Stage and Survival

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Neoadjuvant chemoradiation treatment (CRT) has resulted in significant tumor downstaging and improved local disease control for distal rectal cancer. The purpose of the present study was to determine the correlation between final stage and survival in these patients regardless of initial disease stage. Two hundred sixty patients with distal (0–7 cm from anal verge) rectal adenocarcinoma considered resectable were treated by neoadjuvant CRT with 5-FU and leucovorin plus 5040 cGy. Patients with incomplete clinical response 8 weeks after CRT completion were treated by radical surgical resection. Patients with complete clinical response were managed by observation alone. Overall survival and disease-free survival were compared according to Kaplan-Meier curves and log-rank tests according to final stage. Seventy-one patients (28%) showed complete clinical response (clinical stage 0). One hundred sixty-nine patients showed incomplete clinical response and were treated with surgery. In 22 of these patients (9%), pathologic examination revealed pT0 N0 M0 (stage p0), 59 patients (22%) had stage I, 68 patients (26%) had stage II, and 40 patients (15%) had stage III disease. Overall survival rates were significantly higher in stage c0 ($P = 0.01$) compared with stage p0. Disease-free survival rate showed better results in stage c0, but the results were not significant. Five-year overall and disease-free survival rates were 97.7% and 84% (stage 0); 94% and 74% (stage I); 83% and 50% (stage II); and 56% and 28% (stage III), respectively. Cancer-related overall and disease-free survival may be correlated to final pathologic staging following neoadjuvant CRT for distal rectal cancer. Also, stage 0 is significantly associated with improved outcome. (J GASTROINTEST SURG 2005;9:90–101)

KEY WORDS: Rectal cancer, treatment, survival

Treatment of distal rectal cancer remains a challenge for colorectal surgeons worldwide. Surgery is still the mainstay of all treatment strategies and may be associated with significant stoma creation, morbidity, and mortality rates.[1] Introduction of total mesorectal excision (TME) to surgical treatment led to significant reduction in local recurrence rates.[2] However, extremely low recurrence rates may be achieved only in highly selected cases with TME alone.[3] For this reason, adjuvant and neoadjuvant chemoradiation therapy (CRT) have been used to determine the treatment strategy associated with improved local control and overall survival.[4]

Preoperative CRT may have the advantage of significant tumor shrinkage, allowing higher rates of sphincter-saving procedures.[5,6] In this situation, higher grades of tumor regression may also be associated with improved survival rates.[7] Moreover, CRT delivered preoperatively may be associated with less toxicity rates.[5,6]

Ultimately, these effects observed after preoperative CRT may lead to significant changes between preoperative and postoperative staging.[8,9] Therefore, correlation between final staging and survival may offer additional information on the patient's prognosis regardless of preoperative (initial) staging.

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More often, preoperative CRT results in incomplete tumor regression. This situation may be immediately diagnosed after CRT completion. However, sometimes significant tumor regression may lead to difficulties in residual primary tumor identification. In both situations of patients with incomplete pathologic response, survival may be correlated to final pathologic staging (TNM).

Preoperative CRT may ultimately result in complete tumor regression after complete pathologic examination of the resected specimen in 10–30% of patients, termed *complete pathologic response* or *stage p0*.[10–15] Observation of this complete tumor regression in some patients during our initial experience led us to manage this subset of patients without immediate surgery and with a close follow-up program.

To determine the correlation between final stage and survival, we report long-term results of patients with distal rectal cancer after CRT regardless of pretreatment staging.

PATIENTS AND METHODS

Two hundred sixty patients with distal rectal adenocarcinoma (0–7 cm from anal verge) were treated by preoperative CRT with 5-FU, leucovorin, and 50.4 cGy as described elsewhere.[10] Patients with evidence of synchronous metastatic disease were excluded from this study. Initial staging included complete physical examination, digital rectal examination, rigid proctoscopy, chest radiography, abdominal and pelvic standard computed tomography (CT) scans, and serum CEA level. Full colonoscopic examination was performed before CRT when feasible or after CRT completion.

At 8 weeks after CRT completion, patients were reevaluated using the same clinical, endoscopic, and radiologic studies performed at initial staging, performed by the same experienced colorectal surgeon. During proctoscopy, biopsy samples were obtained for pathologic examination. Tumor regression assessment after CRT was identical for all patients. The presence of any significant residual ulcer suspicious for residual tumor or positive biopsy sample was considered to be an incomplete clinical response. Patients without any abnormality during this assessment after CRT were considered as complete clinical response.

Patients with incomplete tumor regression, at 8 weeks after CRT completion, were referred to surgery. Operations included abdominal perineal resection (APR) and low anterior resection (LAR). In the latter situation, colorectal, coloanal anastomosis (CAA) or end-colostomy (Hartmann's operation) was performed. Patients with CAA also had diverting loop ileostomies performed. Patients were staged according to final pathologic report and UICC/AJCC recommendations (stage p0, T0 N0 M0; stage I, pT1-2 N0 M0; stage II, pT3-4 N0 M0; and stage III, pTx N1-3 M0). Patients treated by surgery were followed by the same colorectal surgeon every 3 months in the first 2 years and every 6 months thereafter.

Patients with complete clinical response were not immediately operated on. They were enrolled in a close follow-up program and were fully informed that detection of residual tumor at any time during follow-up would require immediate surgery. Patients with sustained complete tumor regression for at least 12 months were considered as having complete clinical response and were managed by observation alone (stage c0). Follow-up visits were performed monthly for the first year, every 2 months for the second year, and every 6 months for the remaining years. Radiologic studies (chest radiographs and CT scans) were performed every 6 months in patients even with no clinical suspicion of recurrence during the first year. CEA serum levels and full clinical examination, including rigid proctoscopy, were obtained at all follow-up visits.

Patients with complete clinical response (stage c0) and patients with stage p0-II did not systematically receive any adjuvant therapy. Patients with stage pIII were referred to systemic adjuvant chemotherapy with 5-FU and folinic acid.

Recurrence was classified into endorectal, pelvic, and systemic. Patients with recurrence were referred to a specialist surgeon according to recurrence site (liver surgeon, thoracic surgeon, colorectal surgeon, or urologist). In patients with systemic recurrence or stage pIII, follow-up visits were also performed by an oncologist.

Patients with stage p0 were compared with patients with stage c0 in terms of disease recurrence, cancer-related overall and disease-free survival, stoma creation, and morbidity and mortality rates. Also, cancer-related overall and disease-free survival rates were compared according to final staging (0–III).

Statistical analysis was performed using Chi-squared and Student *t* tests. Survival analysis was performed using Kaplan-Meier curves and log-rank tests.

RESULTS

Incomplete Clinical Response—Stage p0-III

One hundred eighty-nine patients (72%) had incomplete clinical response and were treated by radical

surgery at 8 weeks to 14 months from CRT completion (Table 1). Twenty-two of these patients (9%) showed pT0 N0 M0 after full pathologic examination of the resected specimens (stage p0). Fifty-nine patients (22%) had pT1-2 N0 M0 tumors (stage pI), 68 (26%) had pT3-4 N0 M0 tumors (stage pII), and 40 patients (15%) had Tx N1-3 M0 tumors (stage pIII) (Table 2).

Stage pIII

Forty patients treated by CRT followed by radical surgery had stage pIII disease (pTx N1-3 M0). Mean age was 57 years (range, 30–79 years), and the male-to-female ratio was 0.8. Mean initial tumor size was 3.9 cm (range, 2–5 cm), and distance from anal verge was 4.4 cm (range, 2-7cm). Final tumor size on the pathology report was 3.6 cm (mean) (range, 1.6–8 cm). According to pretreatment clinical and radiologic staging, 4 patients had T2 lesions (10%), 35 patients had T3 lesions (87.5%), and 1 had a T4 lesion (2.5%). Twelve patients had radiologic evidence of N+ lesions (30%). Mean follow-up period was 20.6 months (range, 12–56 months) (Table 3).

Twenty-eight patients (70%) were treated by APR of the rectum, and 13 were treated with anterior resection of the rectum (42.5%) (Table 4). All patients received postoperative systemic chemotherapy. Thirteen patients (32.5%) developed systemic recurrence at 6–42 months (mean, 8 months) of follow-up. Nine of these patients died of the disease at 18–72 months of follow-up. Two patients developed isolated hepatic metastases amenable to surgical resection, performed at 8 and 15 months of follow-up. These patients are currently alive and receiving systemic chemotherapy. Six patients developed unresectable isolated pelvic recurrence at 6–24 months of follow-up (mean, 13.3 months). One of these patients died of the disease at 90 months of follow-up after recurrence at 24 months. Five patients developed endorectal recurrence after sphincter-saving operations at 8–20 months of follow-up (Table 5). Three were treated by APR, one by anterior resection, and the other by Hartmann's operation. All of these patients are alive with no signs of disease recurrence after 18–26 months of follow-up. Cancer-related 5-year overall and disease-free survival was 50% and 28%, respectively (Fig. 1, *A* and *B*).

Table 1. Clinical response

Tumor regression	No. of patients (%)
Complete (stage c0)	71 (28)
Incomplete	189 (72)
Total	260 (100)

Table 2. Incomplete clinical response

Stage (pathologic)	No. of patients (%)
p Stage 0 (T0 N0 M0)	22 (9)
p Stage I (pT1-2 N0 M0)	59 (22)
p Stage II (pT3-4 N0 M0)	68 (26)
p Stage III (pTx N1-N3 M0)	40 (15)
Total	189 (72)

Stage pII

Sixty-eight patients treated by CRT followed by radical surgery had stage pII disease (pT3-4 N0 M0). Mean age was 60.2 years (range, 27–88 years), and male-to-female ratio was 2.2. Mean initial tumor size was 3.7 cm (range, 1.4–6 cm), and distance from anal verge was 4.3 cm (range, 0–8 cm). Final tumor size at pathology report was 3.5 cm (mean) (range, 1.5–7.4 cm). According to pretreatment clinical and radiologic staging, 8 patients had T2 lesions (12%), 56 patients had T3 lesions (82%), and 4 had T4 lesions (6%). Twenty-two patients had radiologic evidence of N+ lesions (32%). Mean follow-up period was 36 months (range, 12–132 months) (see Table 3).

Thirty-eight patients (56%) were treated by APR of the rectum, 29 by anterior resection of the rectum (42.5%), and 1 by Hartmann's operation (1.5%) (see Table 4). Eleven patients (16%) developed systemic recurrence at 12–49 months (mean, 19.8 months) of follow-up. Three of these patients died of the disease at 17, 22, and 23 months of follow-up. Another patient had isolated pulmonary metastases amenable to surgical resection, performed at 12 months of follow-up. The patient is now undergoing systemic chemotherapy. Six patients developed unresectable isolated pelvic recurrence (8.8%) at 19–48 months of follow-up (mean, 28 months). One of these patients died of the disease at 90 months of follow-up after recurrence at 48 months. Two other patients developed endorectal recurrence after sphincter-saving operations before 12 months of follow-up (Table 5). Both were treated by APR, and are alive with no signs of disease recurrence after 16 and 18 months of follow-up. Cancer-related 5-year overall and disease-free survival was 83% and 50%, respectively (Fig. 1, *A* and *B*)

Stage pI

Fifty-nine patients treated by CRT followed by radical surgery had stage pI disease (pT1-2 N0 M0). The mean age was 59.7 years (range, 21–82 years), and the male-to-female ratio was 1.45. Mean initial tumor

Table 3. Pretreatment characteristics

Characteristic	Stage c0	Stage p0	Stage pI	Stage pII	Stage pIII	*P*
Gender (M/F)	1.05	1.2	1.45	2.2	0.8	NS
Mean age (yr) (range)	58.1 (35–92)	53.6 (25–73)	59.7 (21–82)	60.2 (27–88)	57 (30–79)	NS
Prechemoradiation tumor size (mean cm) (range)	3.6 (1–7)	4.2 (2.5–7)	4.1 (1–7)	3.7 (1.4–6)	3.9 (2–5)	NS
Distance from anal verge (cm) (range)	3.6 (0–7)	3.8 (2–7)	3.7 (0–7)	4.3 (0–7)	4.4 (2–7)	NS
T2	14 (19.7%)	1 (4.5%)	2 (3%)	8 (12%)	4 (10%)	NS
T3	49 (69%)	19 (86.5%)	56 (95%)	56 (82%)	35 (87.5%)	NS
T4	8 (11.3%)	2 (9%)	1 (2%)	4 (6%)	1 (2.5%)	NS
N+	16 (22.5%)	6 (27.2%)	16 (25%)	22 (32%)	12 (30%)	NS
Total	71	22	59	68	40	

NS = not significant.

size was 4.1 cm (range, 2–7 cm), and distance from the anal verge was 3.7 cm (range, 0–7 cm). Final tumor size at the pathology report was (mean) 3.2 cm (range, 1–7.6 cm). According to pretreatment clinical and radiologic staging, two patients had T2 lesions (3%), 56 patients had T3 lesions (95%), and 1 patient had a T4 lesion (2%). Fifteen patients had radiologic evidence of N+ lesions (25%). Mean follow-up period was 64 months (range, 12–148 months) (see Table 3).

Twenty-six patients (44%) were treated by APR of the rectum, 31 by anterior resection of the rectum (53%), and 2 by Hartmann's operation (3%) (see Table 4). Four patients (6.7%) developed systemic recurrence at 12, 25, 48, and 52 months of follow-up not amenable to surgical resection and were treated with chemotherapy. The patient with systemic recurrence at 25 months died at 32 months of follow-up with central nervous system and pulmonary metastasis. There were three cases (5%) of pelvic unresectable recurrences at 19, 25, and 50 months of follow-up. The patient with pelvic recurrence at 25 months died of the disease. There were 4 (6.7%) endorectal recurrences following sphincter-saving operations at 12 (two cases), 21, and 22 months of follow-up (see Table 5). All of them were treated with APR and are alive after 47, 90, 94, and 106 months of follow-up. Cancer-related 5-year overall and disease-free survival was 94% and 74%, respectively (Fig. 1, *A* and *B*).

Stage p0

Twenty-two patients had stage p0 disease. Mean age was 53.6 years (range, 25–73 years), and male-to-female ratio was 1.2. Mean distance from anal verge of the primary tumor was 3.8 cm (range, 2–7 cm), and mean tumor size was 4.2 cm (range, 2.5–7 cm). According to pretreatment clinical and radiologic staging, one patient had a T2 lesion (4.5%), 19 patients had T3 lesions (86.5%), and 2 patients had T4 lesions (9%). Six patients had radiologic evidence of N+ lesions (27.2%). Mean follow-up period was 48 months (range, 18–83 months), and 18 patients (82%) had a minimum of 24 months of follow-up (Table 6).

Nine patients were treated with APR (41%), and the remaining 13 patients were treated with sphincter-saving procedures. Of these latter patients, 7 had protective loop ileostomies for coloanal anastomosis. Overall, 16 patients had a stoma, either temporary or definitive (72.7%). There was no perioperative mortality or significant morbidity requiring either reoperation or transfer to the intensive care unit. However, two patients developed parastomal hernias requiring reoperation at 12 and 18 months from initial treatment (see Table 6). Mean residual scar size at the pathology report was 2.4 cm (range, 1–6 cm), reflecting a significant lesion size reduction ($P < 0.001$). One patient developed unresectable central nervous system metastases at 19 months of follow-up and died at 21 months from APR. Another patient

Table 4. Operations performed

	Stage c0	Stage p0	Stage pI	Stage pII	Stage pIII	*P*
APR	—	9 (41%)	26 (44%)	38 (56%)	28 (70%)	NS
SSO	—	13 (59%)	33 (56%)	30 (44%)	12 (30%)	NS
Total	0	22 (100%)	59 (100%)	68 (100%)	40 (100%)	

SSO = sphincter-saving operation; APR = abdominal perineal resection; NS = not significant.

Table 5. Recurrences

	Stage c0	Stage p0	Stage pI	Stage pII	Stage pIII
Endorectal	2 (2.8%)	0	4 (6.7%)	2 (3%)	5 (12.5%)
Pelvic	0	0	3 (5%)	6 (8.8%)	6 (15%)
Systemic	3 (4.2%)	3 (13.6%)	4 (6.7%)	11 (16%)	13 (32.5%)
Total	5 (7%)	3 (13.6%)	11 (18.4%)	19 (27.8%)	24 (60%)

developed unresectable liver metastases at 21 months of follow-up and died at 24 months after a low anterior resection. One last patient developed multiorgan metastatic disease at 24 months of follow-up after a low anterior resection and is still alive, receiving systemic chemotherapy. None of the patients developed pelvic recurrence (see Table 5). Five-year overall and disease-free survival rates were 88% and 83%, respectively (Fig. 1, *A* and *B*). Overall recurrence rate and cancer-related mortality rate were 13.6% and 9%, respectively.

Complete Clinical Response–Stage c0

Seventy-one patients (28%) presented with sustained complete tumor regression following CRT and were managed by observation alone (stage c0) (see Table 1). Mean age was 58.1 years (range, 35–92 years), and male-to-female ratio was 1.05. Mean distance from anal verge of the primary tumor was 3.6 cm (range, 0–7 cm), and mean tumor size was 3.7 cm (range, 1–7 cm). According to pretreatment clinical and radiologic staging, 14 patients had a T2 lesion (19.7%), 49 patients had T3 lesions (69%), and 8 patients had T4 lesions (11.3%). Sixteen patients had radiologic evidence of N+ lesions (22.5%) (see Table 2).

Mean follow-up period was 57.3 months (range, 18–156 months), and 60 patients (84.5%) had at least 24 months of follow-up. Two patients developed endorectal recurrence (2.8%) after 56 and 64 months of CRT completion. The former patient was treated with transanal full-thickness excision. Pathology report revealed a pT1 and the patient is alive without recurrence, with 72 months of follow-up. The latter patient refused surgery and was managed with salvage brachytherapy. He is alive without recurrence after 132 months of follow-up (more than 5 years after brachytherapy). Three patients developed systemic unresectable metastases (4.2%) at 18, 48, and 90 months of follow-up. All three patients are alive and being treated with systemic chemotherapy. None of the patients developed pelvic recurrence. Overall recurrence rate was 7% (see Table 5). There were no cancer-related deaths in stage c0. Five-year cancer-related overall and disease-free survival rates were 100% and 92%, respectively. Ten-year cancer-related overall and disease-free survival rates were 100% and 86%, respectively (Fig. 2, *A* and *B*).

Comparison of Final Stage and Survival

There were no statistical differences between stages 0 through III in terms of patient's age, gender distribution, initial tumor size, distance from anal verge, and final tumor size at pathology report ($P > 0.1$). Initial (clinical, radiologic, and endoscopic) staging showed no significant differences between stages as well ($P = 0.8$). Although APR was more frequently performed over sphincter-saving operations in stage III, this difference was not statistically significant ($P = 0.7$)

Recurrence and cancer-related mortality rates showed no statistical difference between stage p0 and stage c0 ($P = 0.2$). Because there were no cancer-related deaths in patients with stage c0, this group showed slightly but significantly higher 5-year survival rates ($P = 0.01$) according to Kaplan-Meier curves (see Fig. 2, *A*). Disease-free survival, however showed no significant difference between Kaplan-Meier curves in the same period ($P = 0.09$) (Fig. 2, *B*).

Altogether, 93 patients were considered to have stage 0 (stage c0 plus stage p0) disease (35%) after CRT. Six patients developed systemic recurrence not amenable to curative resection (6.4%), and two of them died from disease progression (2.2%). Endorectal recurrence occurred in two patients (2.8%) treated by nonoperative approach and were successfully managed by salvage local transanal surgical resection and brachytherapy. Ten-year overall and disease-free survival rates were 97% and 84%, respectively (Fig. 2, *A* and *B*). Operative treatment was performed in 22 patients with stage 0 disease (23.6%), and definite or temporary stomas in 16 patients (17.2%). There were four non–cancer-related deaths at 14, 48, 54, and 86 months of follow-up. Overall, local endorectal recurrences occurred in 13 patients (5%), and all of them were successfully managed by salvage surgery. Also, 15 patients (5.7%) had pelvic recurrences during follow-up. Finally, systemic recurrence occurred in 34 patients (13%).

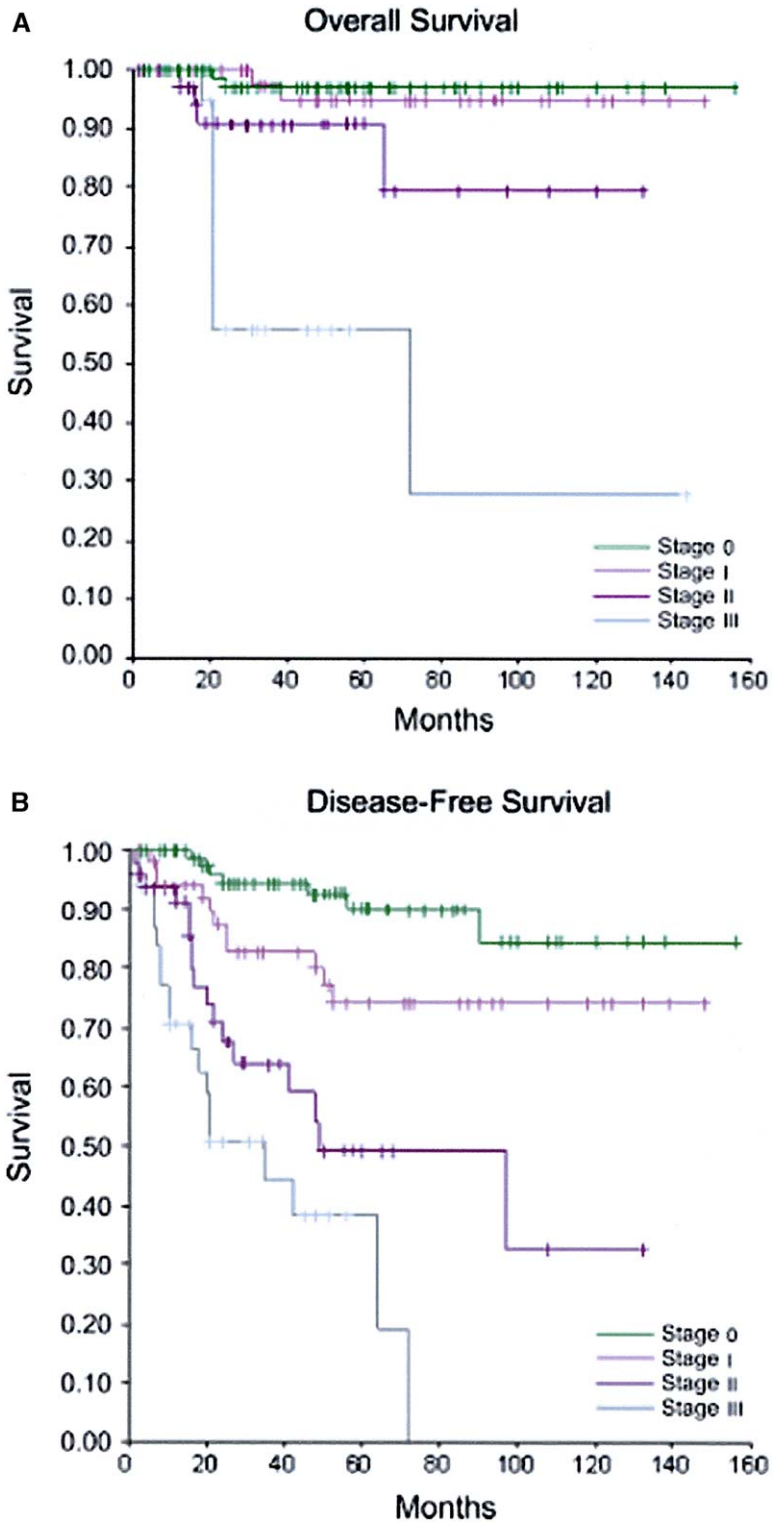

Fig. 1. (**A**) Overall survival according to final stage. Stage 0 versus stage I ($P = 0.6$); stage I versus stage II ($P = 0.08$); and stage II versus stage III ($P = 0.02$). (**B**) Disease-free survival according to final stage. Stage 0 versus stage I ($P = 0.04$); stage I versus Stage II ($P = 0.009$); and stage II versus stage III ($P = 0.04$).

Table 6. Stage p0—Operations performed

Operation performed	No. of patients (%)
APR	9 (41)
LAR + CAA (loop ileostomy)	7 (31.8)
LAR (without ileostomy)	6 (27.2)
Total	22 (100)

APR = abdominal perineal resection; LAR = low anterior resection; CAA = coloanal anastomosis.

There was a significant correlation between final stage and overall and disease-free survival. Stage 0 disease (stage c0 plus stage p0) had significant better disease-free survival rates compared with stage I determined by Kaplan-Meier curves ($P = 0.04$), even though these differences were not observed in cancer-related overall survival ($P = 0.6$). Stage I had significant better disease-free survival rates compared with stage II according to Kaplan-Meier curves ($P = 0.009$). Stage I was associated with higher overall survival rates compared with stage II, but this difference was not statistically significant ($P = 0.08$). There was significant statistical differences between stages II and III in both overall and disease-free survival rates ($P < 0.05$) (Fig. 1, *A* and *B*).

DISCUSSION

Total mesorectal excision is considered to be one the most important principles in rectal cancer surgery.[2] Initial reports suggested that TME alone could be sufficient to local disease control, minimizing the benefits.[2] However, reported rates of local recurrence after operation may vary significantly, ranging from 3% to 45%, and surgery with TME alone failed to reproduce lower rates of local recurrence in controlled randomized trials.[2–4,16–18] TME alone may ultimately result in lower recurrence rates in highly selected cases of small and superficial distal rectal tumors.[4,19]

Therefore, multimodality approach, including surgery, radiation, and chemotherapy, has been considered the preferred treatment strategy for distal rectal cancer.[4] The use of chemoradiation either preoperatively or postoperatively may lead to better local disease control. For this reason, adjuvant CRT is currently considered the standard of treatment for T3-4 or N1-2 rectal cancer.[5,7,8,14,20,21]

Preoperative chemoradiation has the advantage in tumor downstaging leading to significant primary tumor size reduction, depth of penetration, and possibly lymph node sterilization.[7,10,20] This effect may ultimately result in higher frequency of sphincter-saving operations performed and limit the need for definitive colostomies in the treatment of distal rectal cancer, once considered standard of care for this condition. Furthermore, the extent of tumor downstaging determined by the final stage may be correlated with overall and disease-free survival.[4]

The use of preoperative CRT may lead to a high number of patients exposed to radiation, exceeding by far those who will actually benefit from this treatment strategy in terms of lower recurrence rates.[8,9] However, the observation of significant tumor regression and increased rates of sphincter-saving procedures may justify the use of CRT in selected patients without T3-4 or N1-2 tumors. In our study, inclusion of patients with preoperative T2 tumors at initial staging was considered whenever an APR was considered, with the expectation that CRT could potentially make possible a sphincter-saving operation, avoiding definitive stoma creation.

Tumor downstaging may occur in the primary rectal tumor (pT) and in metastatic lymph nodes. In the latter situation, CRT may lead to decreases in size and number or sterilization of lymph nodes during surgery. Therefore, there are possible detrimental effects of preoperative CRT on exact pathologic staging. As a result, there is a significant decrease in the number of patients with positive lymph node–bearing tumors after preoperative CRT.[10–15] In our study, no more than 15% of patients had positive lymph nodes during pathologic examination. Still, this group of patients had significantly worse cancer-related overall and disease-free survival rates than did patients with stage II, stage I, and stage 0 disease. These results suggest that, even after CRT and possible related downstaging effects, lymph node metastases remain as one of the most important prognostic factors in resectable rectal cancer. Also, these results suggest that final staging, determined by either pathologic staging in patients with incomplete tumor regression or clinical staging in patients with complete tumor regression following CRT, may represent an important prognostic factor. This information may have special interest in terms of disease recurrence, because disease-free survival was significantly different between each of the final stages.

To determine tumor downstaging following CRT, accurate pretreatment staging is required. This may be obtained with endorectal ultrasonography, magnetic resonance imaging, or spiral CT scanning. In the present study, however, we searched for a correlation between final stage and survival, regardless of initial staging (pre-and post-CRT). Therefore, there was no intent to accurately determine the extent and rate of tumor downstaging.

Moreover, CRT may lead to complete tumor regression resulting in the absence of viable tumor cells

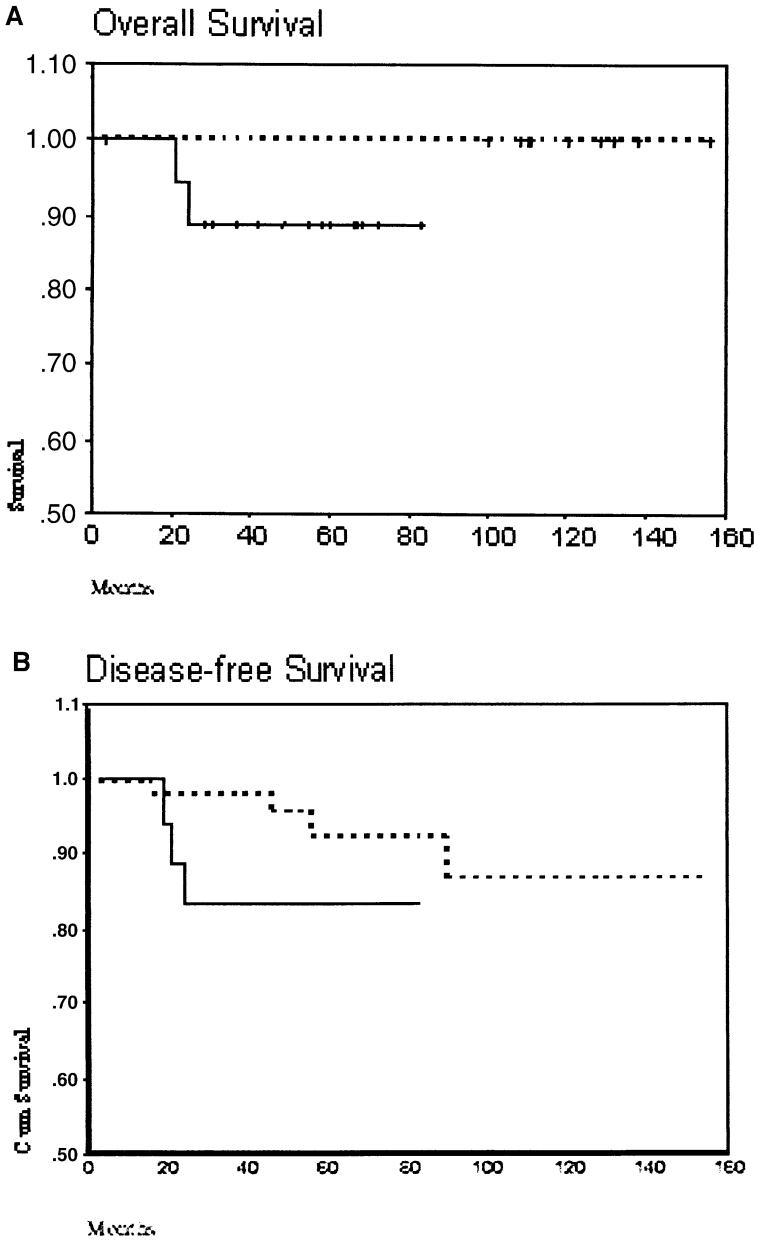

Fig. 2. (**A**) Overall survival in patients with complete clinical response (stage c0, dotted line) and complete pathologic response (stage p0, straight line) ($P = 0.01$). (**B**) Disease-free survival in patients with complete clinical response (stage c0, dotted line) and complete pathologic response (stage p0, straight line ($P = .09$).

during pathologic examination of the resected specimen. This situation (complete pathologic response—stage p0) occurs in 10–30% of the cases and may be associated with better overall prognosis.[10,11] This wide range of complete tumor regression may be the result of different CRT regimens and, more important, different intervals between CRT completion and tumor assessment.[22] Possibly, longer periods between CRT and surgery may result in higher rates of complete pathologic response.[11]

Complete pathologic response may occur even in the presence of a clinically significant residual rectal ulcer after CRT classified as incomplete clinical response. In this situation, diagnosis of complete tumor

regression can be safely determined only by thorough pathologic examination of the resected specimen.[10,11] In our study, 22 patients (9%) with incomplete clinical response treated by surgery resulted in pT0 N0 M0 after pathologic examination.

Identification of complete pathologic response in these patients following CRT led us to consider close observation in patients without clinically detectable residual rectal tumor. If there is no tumor tissue removal, the importance of surgery in this situation may be questionable. A significant proportion of patients may present complete tumor regression without any clinically detectable residual ulcer (determined by clinical, endoscopic, and radiologic studies).[10,23] In this situation, the only advantage of surgical resection may be pathologic confirmation of stage 0 disease. Moreover, nonoperative treatment in these patients may avoid significant morbidity, mortality, and stoma creation. In our study, 71 patients were considered to have complete clinical response (stage c0) and were managed by observation alone.

Identification of these patients with complete tumor regression by clinical, endoscopic, and radiologic studies may not be straightforward. In fact, it may be extremely difficult to distinguish between transmural fibrosis or actinic ulcers and residual tumor following CRT.[11] For this reason, these patients should be carefully followed and aware that initial tumor regression may be temporary. In our study, 14 patients had inconclusive tumor response at initial assessment following CRT. However, a strict follow-up program led to identification of residual tumor at 3–14 weeks of follow-up and patients were referred to immediate surgery. Recently, others have reported a poor correlation between clinical and pathologic response, even when the examination is performed by an experienced specialist.[11] Hiotis et al.[11] reported surprisingly high rates of missed T2-3 and N+ lesions in patients initially considered to have complete clinical response. Histologically, these tumors presented small microscopic foci, frequently seen as deep nests of tumor cells. However, the majority of the patients of this series were operated on within only 6 weeks from CRT, possibly interrupting ongoing tumor necrosis, since longer periods may be associated with higher rates of complete pathologic response. Also, approximately 15% of patients with pT0 tumors had lymph node metastases, an occurrence not observed by us in any of the 22 patients or by others.[15] Accordingly, even in patients with distant metastases at operation, pT0 N1 tumors were not a frequent observation.[24–26] In parallel with micrometastases in lymph nodes of rectal cancer, the clinical significance, if any, of small microscopic tumor cell nests or clusters is not yet determined.[27–29]

Local or pelvic recurrence is a major concern in rectal cancer and is associated with decreased survival and quality of life.[24] These local recurrence rates may be associated with tumor response rate to CRT. For this reason, in patients with complete tumor regression, local recurrence is expected to be minimal. In fact, in our study, none of the patients with stage c0 or stage p0 developed pelvic recurrences. However, control of distant or systemic recurrence may not be ensured by CRT. Patients may develop systemic metastases during CRT or shortly after, usually reflecting the presence of microscopic metastases undetectable by standard radiologic studies. In our study, three patients with stage p0 developed systemic recurrence before 24 months of follow-up, which may represent such initial staging underestimation. In this setting, improvements in radiology studies such as preoperative PET SCAN may have a role in identifying these patients earlier. Considering all stages, endorectal recurrences occurred in 5% of patients and all were successfully managed by salvage surgery in our study. However, 70% of these patients required APR as salvage procedure. Furthermore, 5.7% of the patients developed unresectable pelvic recurrences. Even though these two types of recurrence can be considered separately, altogether locoregional recurrence occurred in 10.7% of the patients.

Interestingly, patients with complete pathologic response treated by surgery did not have any survival advantage over patients with complete clinical response managed by observation alone. Overall, stage 0 had better survival rates compared with stages pI–III, including significantly better disease-free survival compared with stage I disease. Also, final stage 0–III correlated well with survival, even though there were no statistical differences between overall survival rates between stages 0 versus I and I versus II. However, longer follow-up periods may further increase these differences, because there already are significant differences in disease-free survival rates in both situations.

In conclusion, final pathologic stage is an important prognostic factor in distal rectal cancer following preoperative CRT and correlates with overall and disease-free survival, regardless of initial clinical and radiologic staging. Even though preoperative CRT may result in significant tumor regression, leading to discrepancies between pretreatment and post-treatment staging, final pathologic staging (in patients with incomplete tumor regression) or final clinical staging (in patients with complete tumor regression) may represent a useful and objective prognostic factor for the colorectal surgeon and oncologist.

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Discussion

Dr. R. Beart (Los Angeles, CA): I appreciate, Dr. Perez, the opportunity to review the paper prior to the meeting. This is a very important paper. Although it is not a randomized prospective study, it addresses issues that cannot be addressed in a randomized prospective study. By following patients very carefully, you and Dr. Habr-Gama have made important observations and are to be congratulated on initiating this a number of years ago and following through.

I think there are two messages that I took away. The first is that you manage the cancer based on the tumor stage after neoadjuvant therapy and not on the pre–neoadjuvant therapy stage.

The other lesson is that we do not need to operate on everybody with rectal cancer. Now, this is something we have finally learned in the management of anal cancer, and I suspect we will be learning this in rectal cancer as well. In your series, about 25% of the patients did not need surgery after neoadjuvant therapy. I might say, I believe this. In my practice we have about eight patients we are following based on your previous report, and I have not had any problems with those patients, although my series is small.

I do have just a couple of questions. The first is, tumors continue to regress after radiation therapy for some number of weeks. We don't know how long. So my question is, how long is your group willing to follow a patient before they say that the biological effects of the radiation therapy are no longer continuing?

Second, based on your work, a group in Philadelphia reported last week that they are taking patients who have had a vigorous clinical response and can now excise those locally, and so they, based on the post–neoadjuvant therapy, will offer local treatment of rectal cancer. Will your group do that?

The final question I have is that the most recent work from Memorial and other places suggests that even after a complete endoscopic response, 10–15% of patients will have histologically positive lymph nodes at the time of resection. How do you reconcile that with your results?

Thank you.

Dr. Perez: Thank you, Dr. Beart, for those excellent questions. I will try to address all of them. The first one, I think this is the most important one, which is, what is the message of this? We strongly believe that there is a subset of patients who may not benefit from surgical treatment following preoperative chemoradiation therapy. In fact, these patients may do worse in terms of morbidity, mortality. If we could increase the number of patients with complete regression and operated on, you might get some mortality and you certainly will get some significant morbidity other than the parastomal hernias we have just presented. So the first message is we do believe there is a subset of patients who may not benefit from surgical resection. I would say that if you agree with that, we can conclude that the final status following chemoradiation therapy is also important rather than just the initial staging.

Are we willing to do local excisions? Well, that is a very good question, and we strongly agree with you, especially for those small lesions for which you are not sure if there is residual tumor, mural fibrosis, or actinic ulcer. For those small lesions that you may have a complete tumor regression but still have a clinical ulcer or a clinical scar, we recommend that local excision would be best. After these initial results, we have been performing local excisions in selected patients since 2002. We already have 30 patients treated by local excision following chemoradiation therapy, and interestingly, almost a third of these patients have complete tumor regression seen on pathology. So that might add up to these patients we just reported on.

The third question is how long are we willing to wait to see if there is complete tumor regression? This is the toughest question. It is very difficult to distinguish between mural fibrosis or actinic ulcers. Sometimes you can wait a little longer to see if there is further regression or not or you can even perform a local excision. If the patient has a complete tumor regression without any clinical, radiologic, or endoscopic abnormality, we are convinced they have a complete response after 12 months. Before that, we are not really convinced. That is why we do follow up so closely these patients. We see them monthly, because we strongly believe that you must follow these patients very carefully before you say they have a complete clinical regression.

The last question is how do we address the risk of lymph node involvement in 5–7% of the patients with T0–T2 tumors? That brings us back to the question, what is the optimal interval between chemoradiation and tumor assessment? These studies you just mentioned waited between 4 and 6 weeks. We waited at least 8 weeks for our patients, and there are some data in the literature that says the longer you wait, the more you get for tumor regression. So this might be one difference. And the second point is, you don't know what these lymph nodes really mean from a clinical point of view. In a parallel to micrometastatic disease in lymph nodes for rectal cancer, these lymph nodes may represent ongoing necrosis, and we are not sure what those mean.

Dr. H. Freund (Jerusalem, Israel): Congratulations on an excellent and timely study. Sometimes following chemoradiotherapy, we find in the operative-pathologic specimen some small lakes of mucin, no tumor, just mucin. Was this considered as evidence of tumor, or was this disregarded by your pathologists?

Dr. Perez: That is a very good question. We also found that, and we considered that if there were no cells during pathology examination, we would perform immunohistochemistry. If there are still no cells, only mucin, we consider that there is no tumor. We found that as well. Especially we found those when we looked for micrometastatic disease in patients with stage 0 disease. We actually could not see cells on the lymph nodes but we could see some mucin, and

that could be an indirect evidence of tumor regression at the lymph node.

Dr. V. Fink (Chicago, IL): What tests are you doing at monthly intervals? Are you doing an endoscopy, are you doing deep biopsies, are you doing an ultrasound, or are you doing a CT scan? You have a 7% recurrence rate, and the question is whether some of these patients might be hurt by waiting the year or so. Do you think that you are losing any patients in waiting?

Dr. Perez: As to the first question, after we complete the chemoradiation therapy protocol, we wait 8 weeks and then we completely restage these patients. At this point, they have a complete workup with CT scans, abdominal and pelvic, endoscopic, either a proctoscopy or a colonoscopy in those in whom we could not do that at the initial staging, CEA levels, chest radiographs, and a complete digital and clinical examination. At all monthly follow-up visits, clinical examination, proctoscopy, and CEA level determinations are performed. However, there is no use in performing CT scans on a monthly basis, so that is up to the colorectal surgeon. Roughly, at least two CT scans are done after the completion of chemoradiation therapy during the first year.

Dr. Fink: And your rectal ultrasound?

Dr. Perez: We do not perform rectal ultrasounds after chemoradiation therapy. We do not have the equipment widely available to us, so we do not perform them after the chemoradiation therapy. In fact, we do not perform them in many patients preoperatively, but we do perform them in a subset of these patients. After chemoradiation, we usually do not perform rectal ultrasound.

Dr. Fink: And do you think anybody gets hurt?

Dr. Perez: Well, of the patients who were not operated on, two of them developed endorectal recurrences, and both of them could be salvaged, one by surgery and the other by brachytherapy. Chemoradiation therapy does not control systemic disease, and so the patients who developed systemic disease during follow-up probably could not be prevented by immediate surgery at chemoradiation completion. That is what we saw, similar rates of systemic recurrences in patients treated by surgery following chemoradiation therapy and by observation alone. So we think we are not losing patients by this follow-up program.

Dr. Fink: Chemoradiation in the colon has not been too effective. Why do you think that it is effective in the rectum?

Dr. Perez: A very interesting question. We feel that rectal cancer is a different disease from colon cancer, and especially when you get close to the anus, we might be looking at different diseases actually.

Thank you.

Absence of the Interstitial Cells of Cajal in Patients With Gastroparesis and Correlation With Clinical Findings

Jameson Forster, M.D., Ivan Damjanov, M.D., Zhiyue Lin, M.S., Irene Sarosiek, M.D., Paul Wetzel, M.D., Richard W. McCallum, M.D.

The interstitial cells of Cajal (ICCs) are fundamental in the generation of gastric slow waves. The role of these cells in gastroparesis has not been established. We studied 14 gastroparetic patients (9 diabetic, 4 idiopathic, and 1 postsurgical) for whom standard medical therapy had failed and who had been treated with a gastric electrical stimulator for at least 3 months. All patients had a full-thickness antral gastric wall biopsy at the time of surgery. The biopsy samples were stained with c-*kit* and scored for the presence of ICCs. Baseline electrogastrogram recordings were obtained for 30 minutes in the fasting state and for 2 hours after a test meal. The patients assessed their total symptom score at baseline and at 3 months. Five patients had almost no ICCs and were compared with nine patients with 20% to normal cell numbers. Both groups did respond symptomatically to gastric electrical stimulation. However, patients with depleted ICCs had significantly more tachygastria and had significantly greater total symptom scores at baseline and after 3 months of gastric electrical stimulation. ICCs are absent in some patients (up to a third) with diabetic or idiopathic gastroparesis, and the absence of these cells is associated with abnormalities of gastric slow waves, worse symptoms, and less improvement with gastric electrical stimulation. (J GASTROINTEST SURG 2005;9:102–108) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Electrogastrogram, gastric myoelectrical activity, gastric electrical stimulation, gastroparesis, interstitial cells of Cajal

The condition of gastroparesis predominately affects patients with longstanding diabetes but may occur after surgery or without a known etiology (idiopathically). Patients suffer from a variety of symptoms, including nausea, vomiting, epigastric pain, premature satiety, abdominal fullness, bloating, epigastric pain, and weight loss.[1] The major diagnostic abnormality is gastric dysmotility, which is commonly measured scinitigraphically. The presence of more than 10% of a standard meal remaining at 4 hours has been suggested to be the gold standard diagnostic test.[2]

Treatment has long focused on improving gastric motility with prokinetic medications, including metoclopramide, domperidone, and erythromycin, and on treating nausea with antiemetics.[3] If standard medical therapy fails, surgical options include placement of a feeding gastrostomy or jejunostomy or performing a vagotomy and pyloroplasty, partial gastrectomy, or a total gastrectomy.[4,5] Electrical pacing of the stomach to promote contractions has been introduced, but the treatment requires an external stimulator and transabdominal electrodes.[6] This technique additionally converts the abnormal gastric rhythm of

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tachygastria to a normal rhythm. Recently, an implantable device (Enterra Therapy, Medtronic, Minneapolis, MN), initially termed, incorrectly, a gastric pacemaker, has become available from Medtronic for treatment of gastroparesis. Our initial published report demonstrated a marked reduction in both nausea and vomiting and a mild effect on gastric emptying in 25 patients suffering from longstanding gastroparesis.[7] This device does not promote contractions or normalize tachygastric rhythms[17] and should be called a gastric electrical stimulator (GES).

Networks of the interstitial cells of Cajal (ICCs) pace gastrointestinal phasic motor activity necessary for the orderly propulsion of digested food, by producing slow waves. The ICCs were discovered by Dr. Cajal in 1893 and thought originally to be fibroblasts.[8–10] These slow waves are initiated by inward currents in the ICCs, which depolarize in the muscularis propria smooth muscle. The depolarizations activate ion channels, which initiate contractions ensuring coordinated motor responses to neural reflexes. In the stomach, the networks of ICCs in the myenteric plexus pace these slow waves. These cells occur throughout the gastrointestinal tract and are in close proximity to enteric nerves. They stain for CD117, and on electron microscopy have dense granules.[10,11] Their loss has been implicated in the gastroparesis of diabetes based on a strain of mice that spontaneously become both diabetic and gastroparetic as ICCs are lost.[12] There are no published data addressing ICCs in patients with diabetes or other types of gastroparesis.

We hypothesized that the ICCs may play a role in gastroparetic patients. We obtained full-thickness biopsies of the antrum of the stomach during the surgery to place the GES and specially stained these biopsy samples for the presence of ICC. The presence of ICCs was correlated with both gastric electrical recordings and the patient's self-assessed total symptom score (TSS). We learned that those patients with absent or deficient ICC populations had dysrhythmic gastric myoelectric activity and more severe symptoms of gastroparesis.

MATERIALS AND METHODS

Subjects

The gastric wall biopsy samples of 14 patients with refractory gastroparesis (9 diabetic, 4 idiopathic, and 1 postsurgical) undergoing laparotomy for GES placement were analyzed. The research protocol was approved by the Human Subjects Committee at The University of Kansas Medical Center, and written consent forms were obtained from all subjects.

Surgical Procedure

The GES system used consisted of three components: the implanted pulse generator, two leads, and the stimulator programmer (Medtronic). During the abdominal surgery, one pair of unipolar electrodes was placed into the muscularis propria of the stomach 9.5 and 10.5 cm proximal to the pylorus on the greater curvature. The electrodes were secured to the serosa of the stomach using 5-0 silk sutures. The other ends of the electrodes were connected to the pulse generator, which was placed in a subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus.[7] The GES was initiated within 48 hours of surgery. The stimulus parameters used in this study were low energy and high frequency parameters: pulse width, 330 μsec; pulse (current) amplitude, 5 mA; and frequency, 14 Hz, cycle ON time of 0.1 second and cycle OFF time of 5.0 seconds. During the implantation surgery, gastric wall biopsy samples were taken from the antrum and preserved in formalin. These biopsies were taken by cutting out 1 cm^2 of gastric wall and leaving the mucosa intact. The defect was closed with interrupted 3-0 silk sutures.

Immunohistochemistry

Immunohistochemical staining was performed using the Dako Autostainer (Dako, Carpenteria, CA). Monoclonal antibodies purchased from Dako were used according to the standard protocol. To this end, the paraffin-embedded tissue was deparaffinized in xylene and alcohol, rehydrated, and placed into 10 mmol/L citrated buffer, pH 6, antigen retrieval solution. The tissue covered with buffer was placed into the microwave for 10 minutes, followed by blockage of endogenous peroxidase in 0.3% hydrogen peroxide for 30 minutes. The primary antibodies to CD117, neurofilaments, and S-100 were applied for 30 minutes, washed, and incubated with the secondary horseradish peroxidase−labeled antibodies and streptavidin peroxidase. For color development, diaminobenzidine hydrogen peroxide was used creating a brown reaction. Ethyl green was used for counterstaining.

All slides were examined microscopically and scored by a pathologist (I.D.) blinded to the clinical status of the patient for the presence of ICCs. The findings were expressed as follows: normal number of ICCs, equivalent to normal controls; reduced number of ICCs equivalent to 20–40% of the control: almost complete loss of ICCs, to the point that not more than 5 cells were seen per 10 high-power fields (<10% of the control). The slides stained with antibodies to neurofilaments and S-100 were used for general orientation and to ascertain that nerve cells

and ganglia are present in the specimen and that they can be demonstrated by using a immunohistochemical approach.

Recording and Analysis of Gastric Myoelectrical Activity

Gastric myoelectrical activity was measured with surface electrogastrography (EGG) for 30 minutes in a supine position in the fasting state and for 2 hours after the ingestion of a meal as previously described.[13] Before the placement of electrodes, the epigastric skin was shaved, cleaned, and abraded with sandy skin-prep jelly (Omni Prep; Weaver & Co., Aurora, CO) to reduce the impedance. Two silver-silver chloride ECG electrodes (DNM, Dayton, OH) were placed: the first one at the midpoint between the xiphoid process and the umbilicus and the second on the subject's left side, just below the ribcage and above the level of the first electrode. A reference electrode was placed on the left costal margin, horizontal to the first active electrode. These electrodes were connected to a portable battery-operated recorder (Synectics Medical Inc., Irving, TX) with cutoff frequencies of 1 and 18 cpm. On-line digitization was done at a sampling frequency of 4 Hz, and digitized samples were stored on the recorder. All recordings were made in a quiet room, and the subject was asked not to talk and to remain as still as possible during the recording to avoid motion artifacts. These measurements were made before placement of the GES or activation of the GES.

At the end of the recording, the EGG data were downloaded to an IBM 586 personal computer for data analysis. After the EGG segments with motion artifacts were identified by visual analysis and removed by using a locally developed program, the following parameters were computed from the EGG data using spectral analysis methods: (1) EGG dominant frequency, the frequency at which the power spectrum of the EGG recording had peak power (range, 0.5–9 cpm); (2) EGG dominant power, the power at the dominant frequency in the power spectrum of the EGG recording; (3) the change of postprandial EGG dominant power (δP), the difference between the EGG dominant power before and after test meal consisting of a turkey sandwich or scrambled egg substitute and two slices of bread; (4) the percentage of normal slow waves (2–4 cpm), the percentage of tachygastria (4–9 cpm), and the percentage of bradygastria (0.5–2 cpm) present over the entire observation period.[14] To be called a dysrhythmia, the abnormal rhythm had to be recorded for at least 2 minutes, with the normal signal simultaneously absent.

Symptom Assessment and Total Symptom Scores

Each patient completed a self-assessment form at baseline and at 3 months. This form assessed the symptoms of gastroparesis occurring during the 2 weeks before the interview for severity and frequency of vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain, and epigastric burning. The severity of each symptom was graded by the patients as 0 = absent, 1 = mild (not influencing the usual activities), 2 = moderate (diverting from, but not urging modifications, of usual activities), 3 = severe (influencing usual activities, severely enough to urge modifications), and 4 = extremely severe (requiring bed rest) and frequency of each symptom as 0 = absent, 1 = rare (1/week), 2 = occasional (2–3/week), 3 = frequent (4–6/week), and extremely frequent (⩾7/week). The TSS is the sum of the grades of these seven symptoms for both severity and frequency.

Statistical Analysis

Results are reported as mean ± SEM. Student's *t* test was performed to investigate the difference of the EGG parameters between baseline and at 3 months (Microsoft Excel, Redmond, WA). Analysis of variance (ANOVA) was used to compare the TSS between the two groups at baseline and 3 months (SuperANOVA; Abacus Concepts, Inc., Berkeley, CA). $P < 0.05$ was considered to be significant.

RESULTS

Based on the analysis of the gastric wall biopsy samples, five patients had a normal number of ICCs, four patients had reduced numbers of ICCs, and five had almost none or depleted numbers of ICCs (Table 1). Representative microscopic images are presented in Fig. 1. Because we were interested in whether the ICC number was important for gastric myoelectric activity, we compared the group of nine patients with some or adequate number of ICCs (ICC+ group) with the group of five patients with depleted or no ICCs (ICC− group). The two groups were demographically similar in that the average age of the ICC+ group (35.9 ± 3.8 years) was no different than the age (37 ± 1.8 years) of the ICC− group; seven of the patients in the ICC+ group and all five patients in the ICC− group were female. In addition, the etiologies were similar; five of the patients in the ICC+ group were diabetic, three were idiopathic, and one was identified to have gastroparesis after a vagotomy and pyloroplasty. In the ICC− group, four patients were diabetic and the fifth was idiopathic.

Table 1. Patient information

Patient	Age (yr)	Gender	Etiology of gastroparesis	Years with diabetes	Years with gastroparesis	No. of interstitial cells of Cajal (ICC)
1	27	F	Diabetes	15	2	Normal (+)
2	32	M	Diabetes	8	6	Normal (+)
3	30	F	Diabetes	19	2.5	Normal (+)
4	31	F	Diabetes	11	5	Normal (+)
5	22	F	Idiopathic	—	2.5	Normal (+)
6	44	F	Idiopathic	—	6	Reduced (+/−)
7	36	M	Diabetes	20	19	Reduced (+/−)
8	60	F	Postsurgical	—	4	Reduced (+/−)
9	41	F	Idiopathic	—	6	Reduced (+/−)
10	39	F	Idiopathic	—	1.25	None (−)
11	38	F	Diabetes	26	2	None (−)
12	36	F	Diabetes	12	2	None (−)
13	31	F	Diabetes	24	6	None (−)
14	41	F	Diabetes	30	20	None (−)

Normal number of ICC equivalent to normal controls; reduced number of ICC equivalent to 20–40% of controls; none equivalent to less than 10% of control.

The EGG recordings of the two groups revealed marked differences (Table 2). In the fasting state, the ICC− group patients had significantly more tachygastria (slow wave frequency, >4 cpm) than the ICC+ group (54 ± 36% versus 11 ± 13%, $P < 0.05$) and hence less percentage of time in normal rhythm. Postprandially, the ICC− group continued to have significantly less normal rhythm (81 ± 4.9% versus 42 ± 17%, $P < 0.05$) and associated dominant tachygastria.

In terms of the TSS, the ICC+ group had a significantly lower TSS than the ICC− group at baseline and after 3 months of GES (Fig. 2). Both groups responded to the GES with a significant decrease in both the severity and frequency of gastrointestinal symptoms. However, as noted in Fig. 2, the ICC− group had

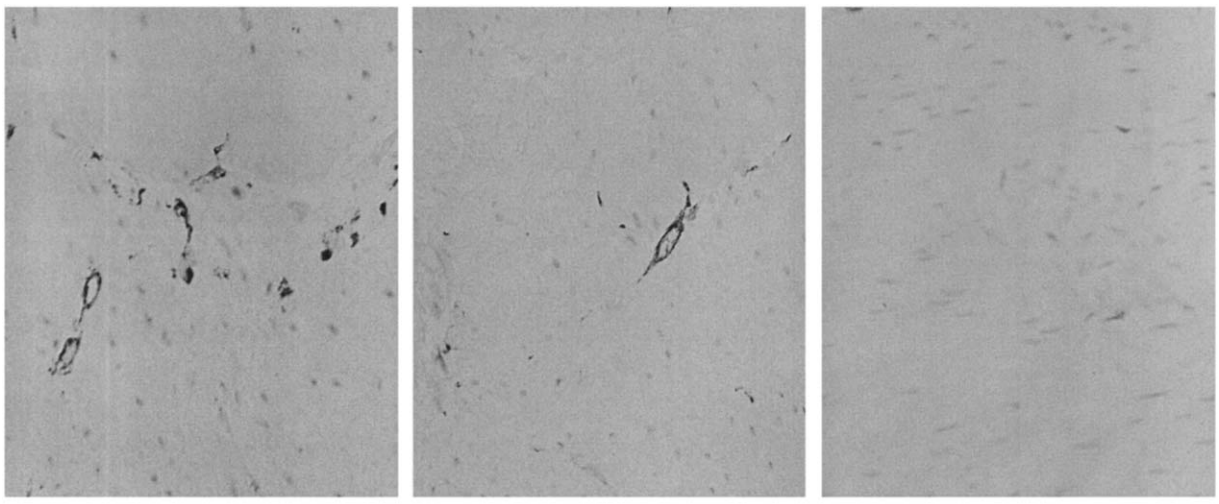

Fig. 1. Microscopic images of antral gastric wall biopsy samples. These images were taken at ×160 magnification of formalin-preserved full-thickness 1-cm^2 surgically obtained gastric antral biopsy samples, with staining of CD117. These images are representative of the three grades that were assigned for the numbers of interstitial cells of Cajal (ICCs) that could be stained. Specifically, a normal result is A, where normal numbers of ICCS would be approximately 10 cells per high-powered field; 20–40% of normal numbers of ICCS was graded as B, and depleted numbers of ICCS (<10% of normal) was graded as C.

Table 2. Results of electrocardiogram (ECG) analysis

	DF (cpm)	2–4 cpm (%)	T (%)	B (%)	δP (dB)
Preprandial EGG					
ICC−	4.0 ± 0.68	41 ± 16	54 ± 16	4.8 ± 3.0	—
ICC+	3.2 ± 0.24	73 ± 5.0	11 ± 5.3*	17 ± 4.9	—
Postprandial EGG					
ICC−	4.2 ± 0.73	42 ± 17	50 ± 21	8.4 ± 4.0	−1.0 ± 2.4
ICC+	3.2 ± 0.22	81 ± 4.9*	11 ± 5.2	8.5 ± 2.2	0.65 ± 1.9

Patients with depleted interstitial cells of Cajal (ICC) had significantly more tachygastria and a tendency to less bradygastria and less normal slow waves before a meal than did those with ICC. After a meal, the patients with no ICC had significantly less slow waves in the normal frequency range and tended to have more tachygastria.
DF = EGG dominant frequency; 2–4 cpm = percent normal slow waves; T = percent tachygastria; B = percent bradygastria; δP = EGG postprandial power change.
*$P < 0.05$ compared with ICC− group.

on average a 39% reduction in their symptoms, whereas the ICC+ group had a 66% reduction. By ANOVA, there was a significant effect of both time and ICC group but not in their interaction.

DISCUSSION

In this retrospective analysis of prospectively gathered data, the presence of the ICCs in the antral gastric wall was associated with less tachygastria by cutaneous EGG measurements and less symptoms in this group of medically recalcitrant gastroparetics requiring treatment with GES. The patients in this study are a highly selected group of gastroparetics requiring GES treatment because all standard medical therapies had failed and some of the patients required surgical placement of a gastrostomy tube or nutritional assistance with parenteral or enteral approaches. Five of the patients, or 30% of the group of 14, had depleted ICCs. This observation could be relevant to their clinical outcomes, which was only a 39% reduction in TSS. On the other hand, the ICC-intact patients had a 66% reduction in TSS, similar to the

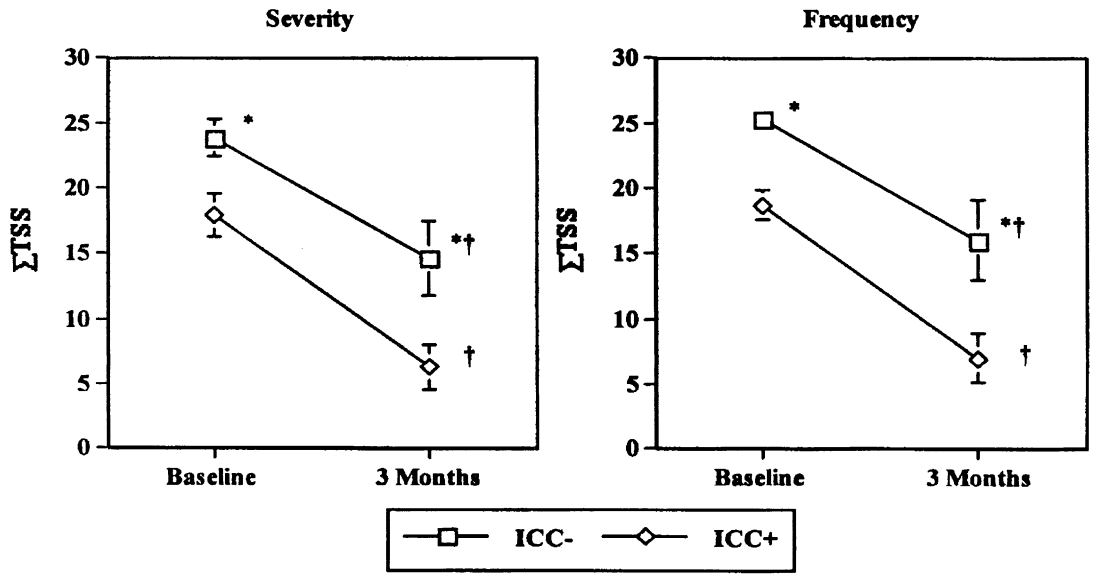

Fig. 2. Total symptom scores (TSSs) at baseline and after 3 months of gastric electrical stimulation (GES). TSS was calculated for each patient based on self-assessment of symptoms at baseline and at 3 months. Patients with depleted interstitial cells of Cajal (ICCs) had greater symptoms for both severity and frequency than those with normal or adequate ICCs at both time points; both groups experienced a reduction in symptoms after GES. *Significant difference between two groups at baseline and at 3 months by analysis of variance (ANOVA) ($P < 0.05$). †Significant difference in TSS at 3 months compared with baseline by ANOVA ($P < 0.05$).

expected levels that have been reported for GES therapy.[15,16] One could hypothesize that patients deemed to be less responsive or treatment failures may have depleted ICC populations, contributing to their refractoriness to both medical and GES approaches.

The importance of ICCs is to maintain normal gastric electrical activity. The cutaneous measurement of this electrical activity (EGG) demonstrated evidence of marked tachygastria in the ICC− group, whereas the ICC+ group remained in the normal range. It is interesting that about one third of the last 100 patients in whom we have evaluated and who underwent placement of the GES system had tachygastria on their EGG,[17] consistent with the percentage of patients in the current report who had ICC depletion. In the future, it may be better to stimulate this subset of patients with different parameters, specifically a higher energy (long pulse trains), to either induce smooth muscle contractions directly and/or convert dysrhythmia into a regular rhythm of 2–4 cycles per minute.

What pathophysiologic ramifications result from our observation of depleted ICCs in some patients with gastroparesis? Dysrhythmia represents an attempt at remodeling of the impaired myoelectrical network related to areas where ICCs are depleted. Tachygastria is the observed dysrhythmia and prevents electromechanical coupling, and hence contractions are diminished, and this results in gastroparesis. By our study, low numbers of ICCs may permit normal rhythms, but when ICCs are truly depleted or absent, an abnormal gastric rhythm results. We believe that our definition of *depletion* is defendable. Although the ICC distribution could be patchy, our large full-thickness surgically obtained sample of the antrum should adequately represent the status of the cells. We have recently had the opportunity to examine the distribution of ICCs in the body and antrum of total gastrectomy specimens from patients with severe diabetic gastroparesis. ICC depletion is selectively manifested in the antrum and not the body, and within the antrum, the depletion is relatively uniform.[18] Hence, our full-thickness surgical biopsy of the antrum is an adequate representative of the status of ICCs in these chronic gastroparetic patients.

Clearly, from the animal studies, diabetics have ongoing loss of ICCs.[12] Patients who suffer from idiopathic gastroparesis may have become gastroparetic due to a viral illness that damaged their gastric nerves and/or their ICCs. Patients who became gastroparetic after gastric surgery or vagotomy would be unlikely to have a loss of ICCs. Here we believe gastroparesis is related to preoperative gastric outlet obstruction and prolonged distention with food plus the postoperative effects of vagotomy. In fact, the one postgastric surgery patient in our group had normal numbers of ICCs, as did the completion gastrectomy specimens we recently studied from Billroth I and II patients.[18]

Patients with some or normal numbers of ICCs had clearly fewer symptoms before and after 3 months of GES. Thus, the ICC number was important in gastric function and as well in the response to GES. The manner by which the GES improves symptoms remains unclear. Although the majority of the patients had a marked reduction in symptoms, only a minority of patients had improved gastric emptying after GES.[7] On average, there was no improvement in gastric emptying at 3 months, suggesting that the GES may not improve gastric motility.

There are two identified regions of ICCs. The ICCs associated with the myenteric plexus initiate the slow wave or basal electrical rhythm and then conduct it to the smooth muscle layer by inducing depolarization. The other region of ICCs termed the intramuscular ICCs (IM) is deeper in the muscularis propria smooth muscle layer. The IM amplifies the gastric slow wave signal so that it may achieve an action potential level, which results in muscle contractions through activation of calcium channels. Hence, the ICCs in the myenteric plexus layer are fundamental for initiating the slow wave frequency in the smooth muscle, whereas the IM propagates the slow wave and permits peristalsis.

If there are no ICCs (IM), then short-pulse duration (low energy, in microseconds) electrical stimulation (Enterra Therapy) could not influence gastric slow wave frequency or motility. However, long train (high energy, in milliseconds) could entrain or pace the smooth muscle directly even if the IM is absent. In gastric biopsy samples from normal patients, the ICCs (IM) are preferably stained by the c-*kit* technique used in our study. In our gastroparetic patients, the ICC layer that is depleted represents this deeper layer (IM) because those ICCs (IM) are more vulnerable to initial damage or loss. The short-duration pulse stimulation utilized by the Enterra device does not require intact ICCs (IM), because short-pulse stimulation does not affect motility. However, this low-energy or neural stimulation could be conducted afferently to the central nervous system and influence central control of nausea and vomiting, leading to relief of symptoms via this pathway. Further studies to pursue the mechanisms of action of the Enterra device are in progress.

CONCLUSION

This work describes for the first time that ICC populations are impaired in gastroparetic patients.

ICCs were absent in about a third of the studied population of gastroparetic patients for whom standard medical therapy failed and who required a GES. The absence of ICCs was associated with increased abnormalities of gastric slow waves, more severe symptoms, and a poorer response to GES. The EGG could be a clinical marker for depleted ICCs and a possible predictor of treatment response to GES. In the future, a different stimulating device with high-energy and low-frequency parameters may be necessary to induce muscular contractions in the group with depleted ICCs, given the evolving knowledge regarding the role of ICC subgroups in controlling gut myoelectric function.

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Training, Practice, and Referral Patterns in Hepatobiliary and Pancreatic Surgery: Survey of General Surgeons

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Subspecialization has changed the way that general surgery is practiced. Hepatobiliary and pancreatic surgery (HPB) is maturing as a subspecialty. The objective of this study was to identify the current levels of practice, self-assessments of adequacy of training, referral patterns, and perceptions regarding regionalization of HPB care to high-volume centers. A total of 240 nonstratified general surgeons from across Canada were randomly selected to receive a survey developed by an expert work group. A reference group of 10 HPB specialists were also polled for a total of 250 respondents. The overall response rate was 73% (182 responders). Subspecialty training had been completed by 65% of respondents. This included surgical oncology (15%), HPB (15%), HPB and transplant (8%), laparoscopy (7%), liver transplantation (5%), and other (50%). This training was obtained in Canada (51%), the United States (35%), Europe (11%), and Australia (3%). Ninety-five percent of responders believed that some HPB services should be regionalized. Similarly, most responders thought that they were not adequately trained to perform these procedures. The following were especially considered subspecialty procedures: major hepatectomy (93%), pancreaticoduodenectomy (90%), and biliary reconstruction (79%). The majority of non-HPB surgeons do not consider themselves adequately trained to perform complex HPB procedures. Furthermore, most surgeons think that major hepatectomy, pancreaticoduodenectomy, and biliary reconstruction should be referred to HPB specialists at high-volume centers. (J GASTROINTEST SURG 2005;9:109–114)

KEY WORDS: Hepatobiliary, pancreas, survey, general surgeons, volume-outcome

The discipline of general surgery has been experiencing an evolution in practice patterns, and in some ways a crisis of identity. Subspecialization has changed the way general surgery is practiced, especially at large academic and multidisciplinary referral centers. Many large academic institutions now deal with many of the diseases historically dealt with by general surgeons in "organ-based" specialty units (e.g., colorectal, hepatobiliary, breast, upper gastrointestinal) or discipline-specific units (e.g., surgical oncology, vascular, trauma, and endocrine). The role of the "generalist" general surgeon in these settings is not well defined. This pattern of practice does not hold to the same degree in nonacademic and geographically remote areas. However, the move toward specialization is evident to a lesser degree in these settings as well. The impact that this paradigm shift has had in the field of general surgery with regard to residency and fellowship training is not well delineated and, in fact, likely varies depending on the institution.

Of all the disciplines under the purview of general surgery, hepatobiliary and pancreatic surgery (HPB) deals with some of the most complicated diseases and technically demanding operations. Indeed it has been well documented in this area that many HPB procedures have improved outcomes when performed at

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high case-volume centers.[1–8] For this reason, our objective was to identify the current levels of practice, self-assessments of training adequacy and referral patterns, and whether or not time and location of training had an impact on these other outcomes with regard to HPB surgery.

MATERIAL AND METHODS

An expert work group comprised of the authors generated a novel survey to evaluate hepatobiliary and pancreatic surgery in Canada. The domains of this construct include training, referral patterns, procedural volume, and self-assessments of adequacy of training to perform various procedures. The survey was piloted in a focus group of surgeons and trainee surgeons (5 total). This resulted in the removal of a number of items, and the modification of some items, to streamline the survey. Pilot assessments of the survey revealed it could be completed in 5 to 10 minutes.

Using the Royal College of Physicians and Surgeons of Canada website (Directory of Fellows), a list of 1871 general surgeons and their respective addresses was compiled. Of these 1871 surgeons, 977 had addresses listed. This list was compiled in November of 2002. From this list, 240 nonstratified surgeons were randomly selected to receive the survey. Ten other surgeons known to have primarily HPB practices were similarly selected to have the survey mailed to them. Therefore a total of 250 surveys were mailed out in November 2002. Surveys were mailed out with an introductory letter and a return self-addressed envelope with postage attached via first class mail. By December 31, 2002, a total of 160 surveys had been returned for an initial response rate of 64%. Two months elapsed before a second mailing was sent out in January 2003 to the 90 nonresponders of the first mailing. Twenty-two more surveys were returned, to bring the total to 182, for an overall response rate of 73%.

The survey consisted of 23 questions. Eleven were ordinal formatted dealing with various HPB surgical procedures and procedural volumes. As a corollary to each of these 11 questions, respondents were asked whether or not they felt adequately trained to perform the procedure in question (binary response–yes or no). The exact wording of the questions is included in the Results section, and in Tables 1 to 5. Data are presented as proportions unless otherwise stated.

RESULTS

Overall response rates for individual questions among responders averaged greater than 90%.

Table 1. Characteristics of survey population

Question	Responses (%)
Age (yr)	
20–30	1
31–40	32
41–50	36
51–60	21
>60	11
How many years have you been in practice since completion of most recent training?	
<1	4
1–5	23
5–10	19
10–20	29
>20	25
How would you describe your academic setting?	
Academic/university	49
Nonacademic	33
Academic affiliate	18
What is your practice setting?	
Large city (population > 250,000)	65
Suburban	8
Community (population < 100,000)	19
Rural/remote	7
Please indicate which of the colleges you hold fellowship in.	
FRCSC	57
FACS	1
Both	42

Table 1 describes the characteristics of the study population. The majority of respondents were 31 to 50 years of age, with 31% being greater than 50 years of age. Most responders (54%) had been in practice for more than 10 years, with 42% practicing between 1 and 10 years, and the rest less than 1 year. Residency training was obtained across the country of Canada, with all schools being represented. The "other" category for training most often translated into training in the United Kingdom. Forty-nine percent of responders described their practice as Academic/University in nature, with a full third of responders describing their practices as nonacademic. All respondents held fellowships in either the Royal College of Surgeons of Canada (RCPSC), the American College of Surgeons, or both.

Table 2 shows that 65% obtained further subspecialty training after general surgery residency training. Among this group, 67% obtained training in surgical oncology, HPB disease, liver transplantation, colorectal surgery, and trauma/critical care. Training was obtained to a lesser degree in vascular (4%), endocrine (2%), breast (2%), and laparoscopic (2%) surgery. The "other" group (16%) was mainly composed of persons who trained in upper gastrointestinal

Table 2. Subspecialty training

Do you have subspecialty/fellowship training?	
Yes	65%
No	35%
Where did you do your subspecialty/fellowship training?	
Canada	50%
United States	34%
United Kingdom	11%
Australia	3%
Other	1%
What is your training in?	
Colorectal	12%
Vascular	4%
Surgical oncology	16%
Breast	2%
Trauma/ICU	11%
Endocrine	2%
Transplantation	5%
HPB	16%
Laparoscopy	2%
Other	16%
HPB/transplant	7%

surgery, thoracic surgery, and combinations of the above-listed specialties. These programs were, for the most part, located in Canada and the United States.

When questioned regarding referral patterns (Table 3) when dealing with complicated HPB disease, 91% would refer the patient on to some form of HPB expert. Six percent would refer to either a senior surgical colleague or a surgical oncologist (some respondents marked more than one response). Ninety-five percent of responders thought that some HPB procedures should be regionalized to high-volume, expert centers (Table 4). The procedures that were most frequently considered best treated

Table 3. Referral patterns

Faced with a complicated hepatobiliary or pancreatic surgery clinical scenario that you wanted to refer on for a second opinion or further management, you would choose which of the following?	
Senior surgeon	6%
Liver transplant surgeon	1%
Hepatobiliary surgeon	86%
Surgical oncologist	4%
Laparoscopic surgeon	0%
Other-Answers below	
Senior/HPB surgeon	1%
Transplant/HPB surgeon	1%
Surgical oncologist/HPB	2%
Senior/transplant/HPB surgeon	1%

Table 4. Regionalization of services

Do you feel that some hepatobiliary and pancreatic surgical procedures should be done in regional referral centers?	
Yes	95%
No	5%
If Yes, which procedures should be regionalized?	% responding that they should be regionalized
Common bile duct exploration (open)	5
Pancreatic resection-tail	13
Pancreatic resection-head (Whipple)	90
Biliary reconstruction (bile duct injury)	79
Biliary bypass for obstruction	14
Wedge resection of liver (nonanatomic)	12
Minor hepatectomy (1 segment or left lateral segmentectomy)	44
Major hepatectomy (2 or more liver segments)	93

in specialized units were pancreaticoduodenectomy resection, biliary reconstruction following bile duct injury, and major hepatectomy (defined as 2 or more Couinaud segments, excluding left lateral segmentectomy).

Table 5 outlines the annual volume of procedures performed for a number of HPB procedures of variable complexity, stratified by surgical specialty. As well, self-assessments regarding whether or not responders feel adequately trained to perform the various procedures outlined are contained in this table. Only HPB and liver transplant surgeons (majority) feel adequately trained to perform major hepatectomies, and biliary reconstruction after bile duct injury; whereas only a few of surgeons from other specialties felt they had adequate expertise. Similarly, those groups in which the majority of individuals expressed sufficient confidence to perform minor hepatectomy, pancreaticoduodenectomy, and laparoscopic staging of upper gastrointestinal malignancies included HPB surgeons, surgical oncologists, and liver transplant surgeons, although nearly half (44%) of the surgical oncologists felt inadequately trained to perform pancreaticoduodenectomy. The majority of all surgeons felt they were trained properly to perform all of the remaining procedures except for laparoscopic common bile duct exploration, for which only a minority of any group of surgeons except those with subspecialty training in laparoscopic surgery felt sufficiently competent to perform.

Subgroup analysis was performed to assess whether age, academic setting of the practice, or years in practice had any effect on self-assessments of training

Table 5. Volume and adequacy of training for HPB procedures

Procedures	HPB surgeon's %	Surgical oncologist's %	Liver transplant surgeon's %	All other surgeon's %
Major hepatectomy				
No. performed = 0	13	89	8	93
1–2	0	11	0	5
3–5	0	0	17	2
6–10	33	0	17	0
11–20	20	0	33	0
>20	33	0	25	0
Do you feel adequately trained to perform this procedure?				
Yes	93	44	92	19
No	7	56	8	81
Minor hepatectomy				
0	7	61	0	80
1–2	7	28	18	14
3–5	20	11	9	4
6–10	20	0	36	1
11–20	26	0	36	1
>20	20	0	0	0
Adequately trained?				
Yes	93	83	100	46
No	7	17	0	54
Wedge resection liver				
0	7	39	18	50
1–2	20	39	9	36
3–5	33	17	36	10
6–10	33	0	36	4
11–20	7	6	0	1
>20	0	0	0	0
Adequately trained?				
Yes	100	94	100	86
No	0	6	0	14
Biliary bypass for obstruction				
0	0	67	0	54
1–2	7	17	0	30
3–5	33	11	42	13
6–10	33	6	33	2
11–20	20	0	8	0
>20	7	0	17	0
Adequately trained?				
Yes	100	89	100	86
No	0	11	0	14
Biliary reconstruction				
0	13	94	0	93
1–2	53	0	42	6
3–5	20	6	33	1
6–10	13	0	17	0
11–20	0	0	8	0
>20	0	0	0	0
Adequately trained?				
Yes	100	33	100	43
No	0	67	0	57
Whipple resection				
0	13	83	0	93
1–2	7	6	0	4
3–5	0	11	33	2
6–10	7	0	25	1
11–20	67	0	33	0
>20	7	0	8	1
Adequately trained?				
Yes	87	56	100	38
No	13	44	0	62
Distal pancreatectomy				
0	14	61	0	70
1–2	14	17	50	26
3–5	36	11	25	4
6–10	36	11	25	1
11–20	0	0	0	0
>20	0	0	0	0
Adequately trained?				
Yes	93	83	100	80
No	7	17	0	20
Common bile duct exploration				
0	7	56	25	39
1–2	53	22	25	40
3–5	27	17	50	13
6–10	13	0	0	7
11–20	0	6	0	0
>20	0	0	0	1
Adequately trained?				
Yes	100	89	100	94
No	0	11	0	6
Open cholecystectomy				
0	0	6	8	10
1–2	13	17	8	20
3–5	27	33	25	25
6–10	27	28	42	32
11–20	13	11	8	6
>20	20	6	8	7
Adequately trained?				
Yes	100	100	100	99
No	0	0	0	1
Laparoscopic common bile duct exploration				
0	73	94	83	88
1–2	13	0	8	5
3–5	7	0	8	4
6–10	7	0	0	1
11–20	0	6	0	0
>20	0	0	0	1

Table 5 Continued.

Table 5. *Continued*

Table 5 Continued.

Table 5. *Continued*

Procedures	HPB surgeon's %	Surgical oncologist's %	Liver transplant surgeon's %	All other surgeon's %
Adequately trained?				
Yes	40	11	25	22
No	60	89	75	78
Laparoscopic staging of upper gastrointestinal malignancy				
0	27	67	25	71
1–2	7	11	42	21
3–5	20	22	8	5
6–10	47	0	8	2
11–20	0	0	8	0
>20	0	0	8	1
Adequately trained?				
Yes	80	56	67	48
No	20	44	33	52

All volume estimates are total number for average 1-year period.

adequacy for all surgeons surveyed. In general, with increasing age, surgeons felt less adequately trained to perform complex HPB procedures. The percentages of surgeons who considered themselves adequately trained to perform a major hepatic resection and pancreaticoduodenectomy, respectively, are listed by age as follows: 31 to 40 years (39% and 50%), 41 to 50 years (39% and 52%), 51 to 60 years (26% and 47%), and greater than 60 years (21% and 36%). As well, academic surgeons felt better trained to perform major (54%, 13%, 21%) and minor (82%, 33%, 48%) hepatic resections compared to surgeons practicing in a nonacademic setting or academic affiliate, respectively.

DISCUSSION

The results from this survey generate a number of important points dealing with: regionalization of services, practice trends, referral patterns, and levels of training of both general surgeons and subspecialists falling under the umbrella of general surgery as they apply to HPB surgery.

Performance of certain complex surgical procedures at high-volume centers has been shown in prior studies in the United States[1–8] and in Canada[9] to lead to improved outcomes. Both pancreaticoduodenectomy and liver resection have been shown to be affected by the volume-to-outcome relationship.[3,4] These studies used large administrative databases. It is difficult, however, to know whether or not these findings translate themselves into changes in practice in both academic and non-academic surgical communities. This is the first report surveying these concepts across a broad spectrum of general surgical disciplines. Our results demonstrate that fully 95% of respondents do feel that some HPB surgical procedures should be performed at high-volume centers. The procedures for which more than 75% of those surveyed felt should be regionalized included pancreaticoduodenectomy, major hepatectomy, and biliary reconstruction following injury. This is congruous with the published volume-outcome relationships previously stated. It is encouraging to see that general surgeons appreciate this important concept in determining optimal outcomes. When asked who should manage these HPB cases, 91% responded that they would refer the patient to an HPB surgeon. This indicates that the "center" perhaps is not the most important factor, but rather the "expertise." The acceptance of the volume-outcome (or expert-outcome) relationship will likely lead to the avoidance of preventable morbidity and death in the future.

In terms of the absolute number of procedures that need to be performed to improve outcomes, it is difficult to know because there is no sharp cutoff point but rather a trend toward improved outcomes with increasing volume of procedures performed. For pancreaticoduodenectomy some series have found more than 20 cases per year,[10] whereas another large study found more than 16 cases per year translate into improved outcomes with low mortality.[11] In our analysis, only HPB surgeons (as a group) approached this level of yearly volume with 72% performing more than 10 per year, whereas only 7% of this group actually performed more than 20 per year. All other groups, including transplant/HPB and surgical oncologists, were far below this level of pancreaticoduodenectomies per year. High volumes of hepatic resections have been variably defined as more than 11cases/year[3] and >17cases/5 years[4] for hepatoma resections specifically. Our results show that only the HPB and liver transplant surgeons perform at this level, with just over 50% in both groups performing 10 or more liver resections per year. However, despite the broad understanding of the volume-outcome relationship, 11% of the surgical oncologists surveyed performed one to two liver resections per year, and 7% of the "other" general surgeons performed five or fewer liver resections per year. These are precisely the low-volume cases that theoretically may contribute to preventable morbidity and mortality.

It is clear that the group most comfortable with the majority of HPB procedures is HPB specialists. Liver transplant surgeons also feel adequately trained to perform most of these procedures, albeit at a slightly lower overall level than HPB surgeons. This

likely relates to the heterogeneity of HPB training in transplant fellowships in which some integrate HPB resection surgery and others do not. Surgical oncologists reveal in our survey that, in general, they do not feel adequately trained to perform the majority of complex HPB procedures. This may represent the move toward subspecialization in the field of surgical oncology, as well as the heterogeneity of training program strength in teaching these particular procedures. In our survey, 50% of the surgical oncologists received their training in the United States and the other 50% in Canada. An interesting corollary regarding this area is whether HPB and liver transplant programs that emphasize the technical/operative aspects of care actually provide adequate education and exposure to the multidisciplinary oncology paradigm that is the cornerstone of surgical oncology training.

The issue of laparoscopy as it applies to this field is intriguing. The results demonstrate that no group is very comfortable when it comes to performing laparoscopic exploration of the common bile duct and, to a lesser degree, laparoscopic staging of upper gastrointestinal malignancies. Clearly the present training obtained during surgical residency, HPB fellowships, liver transplant fellowships, and surgical oncology fellowships is inadequate for properly preparing surgeons to perform complex laparoscopic HPB procedures. This raises the question of whether these operations should be performed by laparoscopic experts who are not trained in HPB diseases or, alternatively, HPB/oncology surgeons trained in laparoscopy. The latter would require changes to the present training programs. More likely, collaboration between HPB experts and laparoscopic experts will lead to the best outcomes in the future.

This survey has a number of possible sources of bias. First, we randomly selected our mailing list from a compilation of those whose addresses were listed on the RCPSC website, excluding the nearly 50% of fellows without a listed address. This selection bias may affect the results. Second, we selected 10 surgeons known to have primarily HPB practices to receive our mailing. The majority of this group was trained in an "organ based" approach/program (University of Toronto–HPB fellowship) that addresses all aspects of HPB disease. However, the surgical oncologists who were surveyed were selected randomly and were not selected based on any particular focus. Thus the results with regard to surgical oncologists represent the group as a whole, but not necessarily those who have a special interest, or have undergone extra training in diseases of the HPB system.

CONCLUSION

The results of this survey demonstrate a number of important points. First, the majority of general surgeons appreciate that complex HPB procedures should be referred to regional centers of excellence. Second, based on surgeon self-assessment, most post-residency training programs do not adequately train surgeons to perform these complex procedures. It appears that adequate training to perform these procedures is obtained at: HPB, liver transplant, and surgical oncologist training programs that have a focus in HPB diseases. Finally, the procedures for which most surgeons feel expert training is required include major hepatectomy, pancreaticoduodenectomy, and biliary reconstruction following bile duct injury.

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Anal Manometric Parameters: Predictors of Outcome Following Anal Sphincter Repair?

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Controversy exists over the utility of manometry in the management of fecal incontinence. In light of newer methods for the management of fecal incontinence demonstrating favorable results, this study was designed to evaluate manometric parameters relative to functional outcome following overlapping sphincteroplasty. Twenty women, 29 to 84 years of age (mean age 50 years), with severe fecal incontinence and large (≥50%) sphincter defects on ultrasound were studied. All participants underwent anal manometry (mean resting pressure, mean squeeze pressure, anal canal length, compliance), pudendal nerve terminal motor latency (PNTML) testing, and completed the American Society of Colon and Rectal Surgeons fecal incontinence severity index (FISI) survey before and 6 weeks after sphincter repair. Statistical analysis for all data included the Wilcoxon rank-sum test, Mann-Whitney test, and Spearman's correlation. Significant perioperative improvement was seen in the absolute resting and squeeze pressures and anal canal length. Overlapping sphincteroplasty was also associated with significant improvement in fecal incontinence scores (FISI 36 vs. 16.4; $P = 0.0001$). Although no single preoperative manometric parameter was able to predict outcome following sphincteroplasty, preoperative mean resting and squeeze pressures as well as anal canal length inversely correlated with the relative changes in these parameters achieved postoperatively. These findings suggest that either the physiologic parameters studied are not predictive of functional outcome or the scoring system used is ineffective in determining function. The perioperative paradoxical changes in resting pressure, squeeze pressure, and anal canal length would support the use of overlapping sphincteroplasty in patients with significant sphincter defects and poor anal tone. (J GASTROINTEST SURG 2005;9:115–120)

KEY WORDS: Fecal incontinence, anal sphincter defect, overlapping sphincteroplasty, anal physiology, manometry

The estimated prevalence of fecal incontinence in the United States ranges from 0.5% to 11%.[1] Overlapping sphincteroplasty, when a sphincter defect exists, remains the procedure of choice for the surgical treatment of fecal incontinence in the United States. However, the success of this procedure is unpredictable, and long-term results following overlapping sphincteroplasty are associated with failure rates approaching 50% at 5 years.[2–5] This has led to the development of several new therapies including the artificial bowel sphincter, radiofrequency therapy, and sacral nerve root stimulation for the treatment of fecal incontinence.

Anal manometry is an objective test used by investigators to better understand and predict success with treatment for fecal incontinence. Conflicting data exist regarding the use of anal manometry including pudendal nerve conduction studies (pudendal nerve terminal motor latency [PNTML]) to predict outcome following sphincter reconstruction.[6–9] Therefore the goal of this study was to prospectively evaluate several manometric parameters in an attempt to correlate these parameters with successful outcome as indicated by a validated fecal incontinence survey.

PATIENTS AND METHODS

Twenty female patients were prospectively evaluated and surgically treated with an overlapping sphincter repair from 1999 to 2001 at the Cleveland Clinic Center for Pelvic Floor Disorders. All patients

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were gravid women between 29 and 84 years of age with a mean age of 50. The mean body mass index (BMI) at the time of sphincter repair was 28.74 kg/m^2 (range 21 to 50). The mean length of time of incontinence prior to surgery was 75 months with a range of 3 to 360 months. The median number of vaginal deliveries was two (range 1 to 6). Obstetric injury was the most common cause of fecal incontinence (85%) with other causes including trauma and iatrogenic injury.

Overlapping Sphincteroplasty

All patients underwent overlapping anterior sphincteroplasty for repair of their sphincter defects by one surgeon. Patients with urinary incontinence were evaluated by the urogynecology service and underwent a combined procedure at the time of sphincter repair. The procedure was performed with the patient in the prone jackknife position. A curvilinear incision was made, and the external and internal sphincter was mobilized, isolated, and repaired with interrupted Prolene and Polydioxanone (PDS) mattress sutures. No attempt was made to separately dissect the internal sphincter muscle. The perineal wound was closed with interrupted Vicryl sutures with the central portion of the wound left open for drainage. The patients remained on intravenous antibiotics with a Foley catheter in place for 2 days. Upon discharge, the patients remained on oral antibiotics for 5 days. One patient underwent formation of a diverting loop ileostomy because of the complexity of her repair.

Anal Manometry

Anal manometry was performed in all patients before and 6 weeks after overlapping sphincteroplasty by the same examiner. For this procedure the patient was placed in the left lateral position, and a rectal examination was performed prior to the procedure. A capillary perfusion system (Medtronics, Shoreview, MN) with four radial ports and a continuous flow rate of 0.5 ml/min per channel was inserted and then withdrawn through the anal canal by a 1 cm station pull-through technique. The catheter channel readings were averaged at all intervals to determine the mean resting pressure and mean squeeze pressure in millimeters of mercury (mm Hg). The interval with the highest pressure reading was reported as the mean resting and squeeze pressure for that patient. Anal canal length, in centimeters, was determined to be the distance in which the mean resting pressure was greater than 20 mm Hg. With the catheter inserted the full 5 cm into the rectum, a balloon located at the end of the catheter was inflated with water to determine the following parameters: the volume of first sensation, the volume of first urge, and the maximum tolerated volume. The compliance of the rectum was determined by measuring the intrarectal pressure at the point of maximum tolerated volume.

PNTML was determined using a disposable St. Marks electrode strapped to the investigator's hand and placed in the anal canal in the region of the pudendal nerve. A stimulus (Dantec Neuromatic 2000; Medtronics) was applied through the electrode, and the resulting motor unit potentials were recorded. The calibration of the equipment has been set such that a PNTML greater than 2.0 msec in our laboratory is considered abnormal.

Endoscopic Anal Ultrasound

With patients in the left lateral position, sphincter defects were detailed by endoanal ultrasound imaging (model 1846; Bruel & Kjaer, Marlboro, MA). A 10 MHz probe was inserted into the upper anal canal, and the probe was withdrawn through the anal canal. Serial images of the upper, middle, and lower anal canal were obtained. The percentages of both internal and external sphincter defects were determined.

Assessment of Fecal Incontinence

All patients evaluated for fecal incontinence at the Cleveland Clinic Center for Pelvic Floor Disorders were asked to complete the American Society of Colon and Rectal Surgeons (ASCRS) Fecal Incontinence Severity Index (FISI) questionnaire. Patients completed the questionnaire again at 6 weeks. One patient was asked to complete the questionnaire 6 weeks after loop ileostomy closure.

STATISTICS

Statistical analysis was performed using the Wilcoxon signed rank-sum and Mann-Whitney tests to compare nonparametric preoperative to postoperative data. Similarly, Spearman's correlation was used to compare relative changes in mean resting and squeeze pressures and the incontinence score (FISI).

RESULTS

Patient Characteristics

All patients had significant symptomatic fecal incontinence with a preoperative mean FISI score of 36 and large ($\geqslant$50%) sphincter defects. Five patients were noted to be obese as determined by a BMI

Table 1. Preoperative summary of manometric findings and FISI scores in patients with obesity (n = 5), postmenopausal patients (n = 12), and patients with other pelvic floor abnormalities (n = 14) compared to those without these characteristics

	ACL (cm)	MRP (mm Hg)	MSP (mm Hg)	Compliance	FISI (median)
Premenopausal	2.25	33.2	55.7	6.9	43.5
Postmenopausal	1.9	31.8	54.6	7.4	41.5
Urinary incontinence	1.86	36.6	54.4	7.5	42.5
No urinary Incontinence	2.5	32.8	56.4	6.5	28.5
BMI >30 kg/m^2	2.6	30.2	55.3	9.2	48
BMI <30 kg/m^2	2.1	33.2	57	6.9	40

ACL = Anal canal length; BMI = body mass index; MRP = mean resting pressure; MSP = mean squeeze pressure; FISI = fecal incontinence severity index.

greater than 30 kg/m^2. Twelve patients were postmenopausal. Overlapping sphincteroplasty was performed alone in six patients or in combination with the urogynecology service in 14 patients for the treatment of urinary incontinence. The average length of stay was 2.4 days (range 2 to 4 days). There were three patients with complications (15%); one had a urinary tract infection and two had wound infections requiring prolonged oral antibiotic therapy. Although not statistically significant, premenopausal women who had no associated pelvic floor abnormalities and were not overweight tended to have better outcomes (Tables 1 and 2).

Absolute Manometric Parameters and Outcome

Preoperative assessment of patients with fecal incontinence demonstrated that 15 patients (75%) had a low mean resting pressure (<40 mm Hg), and 19 patients (95%) had a low mean squeeze pressure (<100 mm Hg). Similarly, 12 patients were noted to have an anal canal length less than or equal to 2 cm. There was significant improvement in overall resting pressure ($P = 0.0005$), squeeze pressure ($P = 0.0005$), and anal canal length ($P = 0.02$); however, there was no change in compliance or PNTML (Table 3).

The mean FISI score in patients before they underwent sphincter repair was 36.5 ± 15.7. After sphincter repair, significant improvement was seen in patients' FISI scores ($P = 0.0001$, see Table 3). Furthermore, seven patients (35%) had perfect continence scores (FISI = 0). No absolute value for postoperative FISI scores could be correlated with preoperative manometric parameters to predict an improved outcome.

Relative Manometric Parameters and Outcome

To determine the relative change in mean resting pressure, squeeze pressure, and anal canal length, preoperative manometric values were correlated with the relative change in mean resting pressure (Fig. 1, *A*), mean squeeze pressure (Fig. 1, *B*), and anal canal length (Fig. 1, *C*) after surgery. Correlation of preoperative mean resting pressure and squeeze pressure with relative changes in mean resting and squeeze pressure after surgery demonstrated a significantly greater change in resting and squeeze pressure in patients with low initial anal canal pressures. Furthermore, the greatest change in anal canal length was

Table 2. Postoperative summary of manometric parameters and outcome in patients with obesity, postmenopausal patients, and patients with other pelvic floor abnormalities compared to those without these characteristics*

	ACL (cm)	MRP (mm Hg)	MSP (mm Hg)	Compliance	FISI (median)
Premenopausal	2.87	46.22	94.25	8	6
Postmenopausal	2.92	51.1	94.7	7.75	8
Urinary incontinence	2.86	48.3	84.3	7.8	8
No urinary incontinence	3	51.2	118.38	7.8	5.5
BMI >30 kg/m^2	2.8	44.3	88.9	8.4	23
BMI <30 kg/m^2	2.9	50.75	96.4	7.7	8

Abbreviations as in Table 1.
*None of the data between these groups of patients were statistically significant.

Table 3. Perioperative absolute change in manometric parameters and outcome in all patients

Parameter	Preoperative Mean ± SD	Postoperative Mean ± SD	Difference ± SD	*P* value
MRP (mm Hg)	32 ± 14	49 ± 17	17 ± 17	0.0005
MSP (mm Hg)	55 ± 23	95 ± 40	40 ± 47	0.0005
ACL (cm)	2.05 ± 1.3	2.9 ± 0.9	0.85 ± 1.6	0.02
Compliance	7.2 ± 2.1	7..85 ± 2.6	0.65 ± 2.7	0.22
FISI	36 ± 16	16.4 ± 16.5	−19.6 ± 18	0.0001

SD = standard deviation; other abbreviations as in Table 1.

found among individuals with the shortest anal canal. In other words, overlapping sphincteroplasty appeared to improve manometric findings more in patients with the lower anal canal pressure and shorter anal canal length (see Fig. 1, *A–C*). To determine if patients with a greater relative change in mean resting pressure, squeeze pressure, or anal canal length had more improvement in their FISI scores, these relative perioperative manometric findings were correlated with postoperative FISI scores and changes in FISI scores. No significance from this correlation could be demonstrated.

DISCUSSION

Anal sphincteroplasty for severe fecal incontinence was associated with early significant increases in mean resting pressure, squeeze pressure, and anal canal length. There was also a significant increase in the

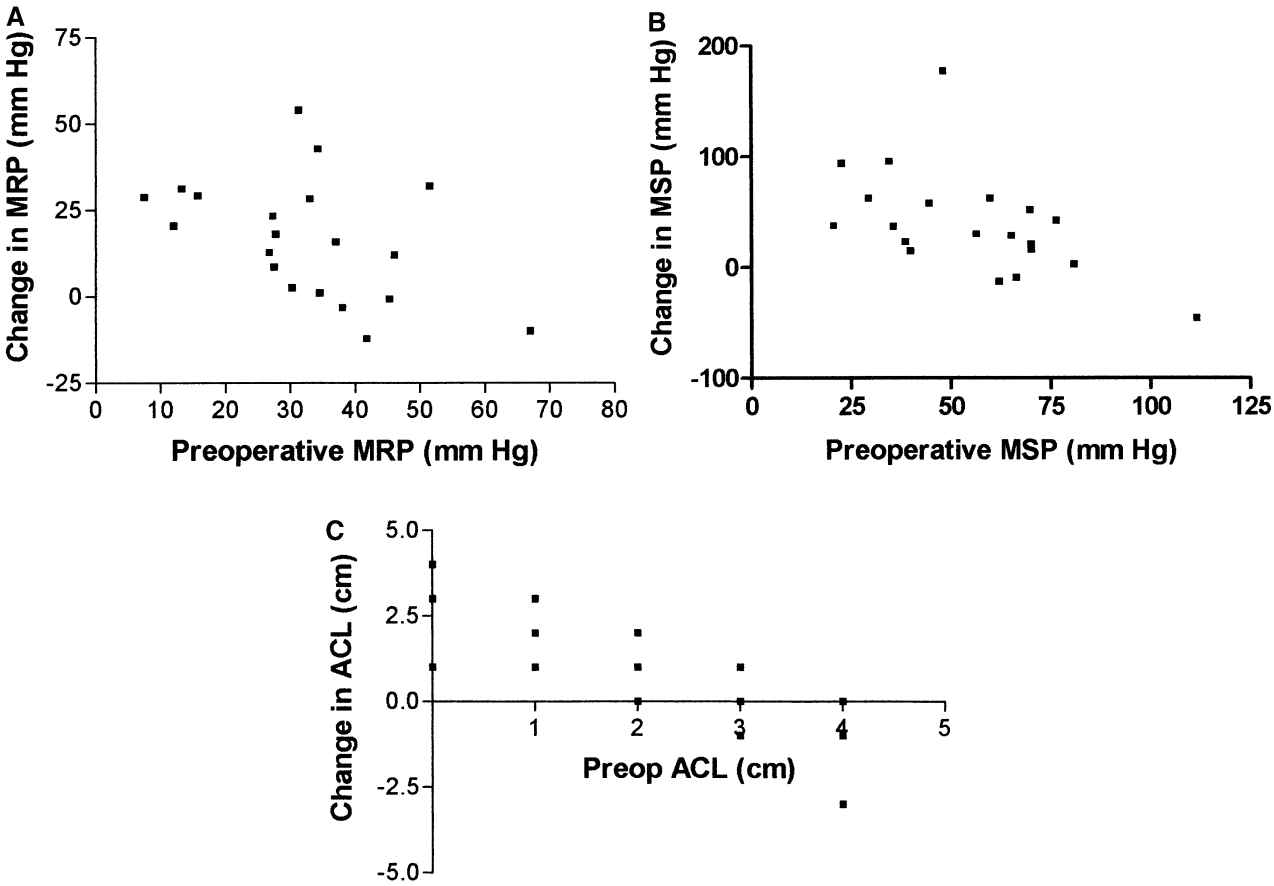

Fig. 1. Determination in all patients of perioperative relative changes in mean resting pressure (*MRP*) (*A*; −0.747 to 0.012 95% confidence interval, $r = -0.4435$, $P = 0.0501$), mean squeeze pressure (*MSP*) (*B*; −0.81 to 0.14 95% confidence interval, $r = -0.5636$, $P = 0.0097$), and anal canal length (*ACL*) (*C*; −0.9399 to −0.64-1, $r = -0.8477$, $P < 0.001$).

relative mean resting and squeeze pressures and in the anal canal length such that those patients who appeared to have worse sphincter function preoperatively had a more dramatic change in their postoperative manometric findings. Although the patient's perception of outcome, as determined by the FISI questionnaire, improved significantly at 6 weeks after sphincter repair, no single preoperative predictor of outcome could be found. Either the physiologic parameters studied are not predictive of postoperative outcome or the scoring system used is ineffective in determining function. One further explanation may be that the paradoxical manometric findings in this study prohibited finding a predictor of outcome following overlapping sphincteroplasty.

Several retrospective studies have evaluated the role of manometry in the management of fecal incontinence, and most report conflicting results. Some investigators believe that poor results are associated with a prolonged PNTML.[8,10,11] Determination of PNTML is observer and laboratory dependent such that many have stopped performing this test and are using EMG recordings instead.[12] The difficulty with EMG studies is that this is an uncomfortable test. All the patients in this study had normal results on PNTML testing, and EMG analysis was not performed. Obesity, increased age, and perineal descent have also been associated with a poor result following sphincter repair.[6] The patients in our study who were obese (body mass index >30 kg/m^2), postmenopausal, or had urinary incontinence also tended to have a worse outcome; however, the differences were not statistically significant. These findings support those in other studies from this institution.[4]

The manometric data that have been more convincingly associated with an improved outcome include an increase in mean squeeze pressure and anal canal length or high-pressure zone.[3,13] More recently Ha et al.[14] demonstrated that an increase in manometric squeeze pressure from a mean of 62 to a postoperative mean of 76 was associated with an improved outcome (Browning and Parks classification) at 6 months after sphincter repair. From this study, the investigators concluded that the most important factor in the return to normal sphincter function is an increase in squeeze pressure. Unfortunately there is a lack of prospective data evaluating the usefulness of manometry in predicting and monitoring of outcomes following sphincter repair.

In this study we prospectively evaluated 20 patients undergoing overlapping sphincteroplasty and followed them for 6 weeks in an initial attempt to evaluate outcome. Specifically, we chose to evaluate absolute and relative changes in resting and squeeze pressures as well as anal canal length at 6 weeks following sphincter repair. Church et al.[15] previously described relative changes in anal sphincter pressures following anal surgery. In their study, patients with initially low resting pressures had a smaller change in mean resting pressure following an anal anastomosis than those with initially a higher resting pressure. Conversely, our data demonstrated that those patients with low resting and squeeze pressures and shorter anal canal lengths had significant improvement in all of these parameters following sphincter repair. The relative change in mean resting and squeeze pressures and anal canal length appeared to be inversely correlated with the preoperative value. This suggests that the physiologic response from sphincter repair was dependent on initial function of the sphincter. Although we were unable to demonstrate a preoperative manometric predictor of postoperative outcome, it was demonstrated that in patients with an early postoperative increase in mean resting and squeeze pressures and anal canal length this was associated with a lower FISI score. Thus these data might suggest that early increases in postoperative mean resting and squeeze pressures and anal canal length may predict a better long-term outcome. Our failure to demonstrate this may be the result of a small sample size. Furthermore, these data suggest that patients with a low preoperative anal canal pressure and short anal canal length do achieve a significantly higher anal canal pressure and an increase in anal canal length following overlapping sphincteroplasty. Therefore our data strongly support the treatment of fecal incontinence with overlapping sphincteroplasty in all patients with significant sphincter defects. Further manometric studies in these patients or the accumulation of more patients may ultimately demonstrate a preoperative predictor of outcome. The prospective findings in this study serve as an initial attempt to determine predictive manometric parameters for the surgical management of fecal incontinence at a time when many new modalities are readily available.

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Results of Gastric Bypass Plus Resection of the Distal Excluded Gastric Segment in Patients With Morbid Obesity

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Surgical treatment is the procedure of choice for morbidly obese patients. Gastric bypass with a long limb Roux-en-Y anastomosis is the "gold standard" technique for these patients. We sought to determine the early and late results of open gastric bypass with resection of the distal excluded stomach in patients with morbid obesity. We included in this prospective study 400 patients who were seen from September 1999 through August 2003 (311 women and 89 men; mean age, 38.5 years). The mean body mass index of the patients was 46 kg/m^2. All underwent 95% distal gastrectomy, with resection of the bypassed stomach, leaving a small gastric pouch of 15 to 20 ml. An end-to-side gastrojejunostomy was performed with circular stapler No. 25. The length of the Roux-en-Y loop was 125 to 150 cm. In all patients, a biopsy was taken from the liver and routine cholecystectomy was performed. Follow-up was as long as 36 months. A barium study was performed in all patients at 5 days after surgery. Mortality and postoperative morbidity rates were 0.5% and 4.75%, respectively, mainly due to anastomotic leak in 10 patients (2.5%). Hospital length of stay was 7 days for 95% of the patients. Follow-up data for longer than 12 months were available in 184 patients. There was excess body weight loss of 70% at 24 and 36 months, and there was an inverse correlation among preoperative body mass index and the loss of weight. Anemia was present in 10%, and incisional hernia was present in 10.2%. At 1 year after surgery, the BAROS index demonstrated very good or excellent index in 96.6% of the patients. Gastric bypass with resection of the distal excluded segment has results very similar to those of gastric bypass alone but eliminates the potential risks of gastric bypass such as anastomotic ulcer, gastrogastric fistula, postoperative bleeding due to peptic ulcer and gastritis, and the eventual future development of gastric cancer. It is also possible to perform via laparoscopy, as we started to do recently. (J GASTROINTEST SURG 2005;9:121–131)

KEY WORDS: Morbid obesity, gastric bypass, gastrectomy

Surgical treatment is increasingly recognized as the procedure of choice for morbidly obese patients due to the severe metabolic, cardiovascular, and psychological comorbid conditions.[1–7] As the number of candidates for this type of therapy has increased in all developed countries, several surgical techniques have been designed, with different results.[4–7] Vertical banded gastroplasty (VBG) and gastric bypass via a Roux-en-Y loop have produced an impressive loss of weight, are well tolerated by the patients, and have become the most recommended procedures.[1–3, 7–9] Several prospective randomized trials and nonrandomized studies have shown that gastric bypass techniques are superior to VBG.[7–14] In recent years, laparoscopic procedures have also been used, mainly gastric banding techniques,[15–23] with results that are not as good as those for the gastric bypass operation.[24–27] We used the Griffen modification of the Mason-Aldin gastric bypass.[28–31] After some complications were seen postoperatively,[32,33] we changed to a new type of surgical procedure that eliminates some of the potential complications of the different gastric bypass procedures.

The purpose of the present prospective study was to report the surgical technique and the preliminary results of this operation.

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MATERIAL AND METHODS

Patients Studied

This prospective trial was begun on September 1999 and continued through August 2003. We included 400 patients, (89 men and 311 women; mean age, 38.5 years; range, 15–70 years). Of the 400 patients, 91 (22.7%) had a body mass index (BMI) between 35 and 39.9 kg/m^2; 228 patients (57%), 40 to 49.9 kg/m^2; and 81 patients (20.2%), greater than 50 kg/m^2. The mean BMI was 46 kg/m^2 (range, 36–64 kg/m^2). All patients had a complete preoperative medical evaluation, and 61% were found to have a comorbid state. All gave their consent to be included in this new protocol, and only three patients were excluded due to severe psychiatric disorders.

Surgical Technique

After general anesthesia and an upper middle laparotomy, a careful abdominal exploration was performed. The surgical technique (Fig. 1) consisted of the following sequential steps:

1. Skeletonization of the greater curvature is performed exactly as when performing gastrectomy for benign disease, with use of Ligasure equipment (Tyco Healthcare, USA, Mansfield, MA).
2. Dissection and section of all short vessels were performed to avoid splenic injury, using surgical clips or ligasure.
3. Section of the duodenum 1 to 2 cm distal to the pylorus was achieved by means of GIA-60 stapler (Tyco Healthcare, USA) (A).
4. The stomach is lifted from distal to proximal, leaving irrigation to the small remnant pouch via the left gastric artery.
5. A right clamp is placed on lesser curvature to determine the diameter of the anastomosis (B).
6. The stomach is sectioned by use of a GIA-80 stapler almost parallel to the lesser curvature, resecting all fundi and the greater curvature, leaving a small pouch of 15- to 20-ml capacity (C).
7. Reinforcement of the stapler line is achieved with a running suture of Biosyn 3-0.
8. Routine cholecystectomy is performed in all, as well as liver biopsy.
9. A Roux-en-Y limb of 125 to 150 cm in length is prepared and passed through a nonvascular area of the transverse mesocolon (retrocolic).
10. End-to-side gastrojejunostomy is achieved with the RS 25 circular stapler (Tyco Healthcare), which is set at an internal diameter of 15 mm (D).

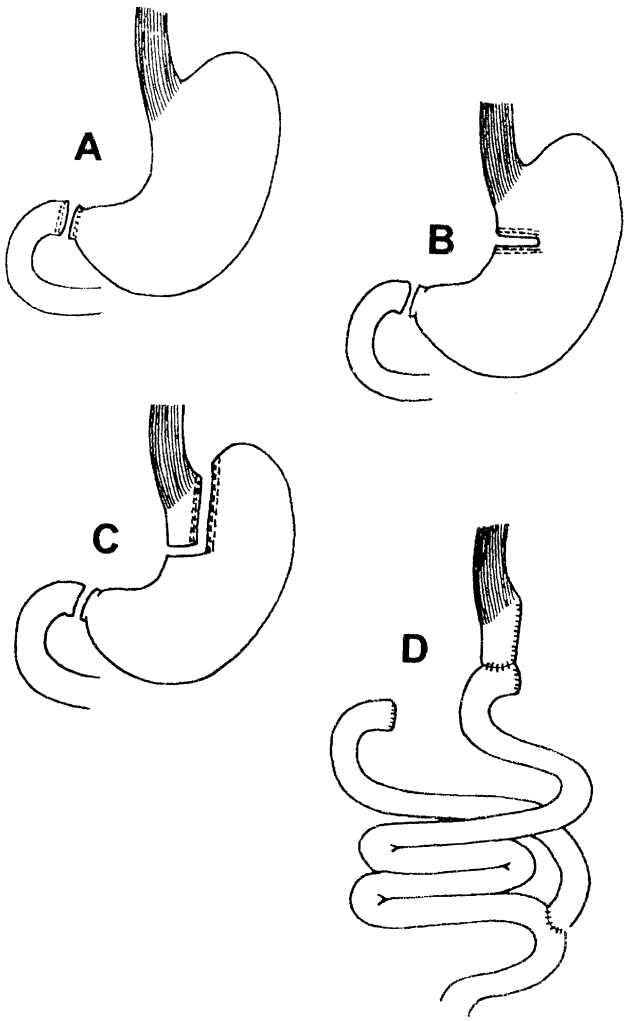

Fig. 1. Schematic representation of near-total gastrectomy, with section of the duodenum (A), section of the lesser curvature 3 cm below the cardia (B), resection of 95% of the stomach (C), and gastrojejunostomy with a Roux-en-Y limb of 125 to 150 cm (D).

11. End-to-side jejunojejunoanastomosis is made on a single layer with continuous suture using Biosyn 3-0.
12. Two soft drains are left next to the anastomosis and duodenal stump for 5 days.

Protocol of Postoperative Care

All patients were kept in the intensive care unit for 1 to 2 days, with use of special respiratory therapy. Oral feeding started on the fourth day after surgery, and intravenous solutions were ended on the fifth day after surgery. On the fifth day, radiologic control was performed with barium sulfate in all patients to check emptying through the anastomosis, size of the remnant stomach, and eventual leakage. Patients

were discharged 7 days after surgery. All patients received heparin for 6 days after surgery. In all, an ultrasound with color Doppler of the veins of both legs was performed 1 day before and 6 days after surgery.

Follow-up

After discharge, all patients were seen at the outpatient clinic on postoperative days 15 and 21 and at 3, 6, 12, 24, and 36 months after surgery. Postoperative weight and eventual complications were recorded. The impact on body weight loss was expressed as BMI before and late after the operation and as the mean percentage of excess body weight loss.

The final results of follow-up were expressed as four items, as follows:

1. Presence or loss of comorbidity at 12 months after surgery, evaluating the presence of diabetes (blood sugar >110 mg dl), dyslipidemia (total cholesterol >200 mg dl and tryglicerides >200 mg dl), arterial hypertension (blood pressure >140/90 mm Hg), and osteoarticular problems (osteoarthrytis, arthralgias, back pain, and so on). These conditions were defined at postoperative assessment as resolved (presence of normal values, without the need of any medication), improved (better values than before surgery or still the need of some medication to relieve disease), or unresolved.
2. The quality of life questionnaire 12 months after surgery:[34] this is a well-validated questionnaire that measures the following five health concepts:
   - Self-esteem (how patient feels or individual's perception of his or her overall health)
   - Work capacity (limitations in the performance during daily work)
   - Sociability (measures limitations in social functioning)
   - Physical capacity (limitations in performing various physical activities)
   - Sexual activity (interest in performing sexual activity and behavior)

   The total scores are expressed as follows, compared with before the operation, by each patient: worst, equal, better, or much better. All of these evaluations were performed by one of the authors who did not participate in any surgical procedures (K.P.).
3. The Bariatric Analysis and Reporting Outcome System (BAROS) was evaluated 12 months after surgery. The BAROS is a simple questionnaire that evaluates three main categories: percent of excess body weight loss, change in comorbidites, and the Moorehead-Ardelt Quality of Life Questionnaire.[34] A maximum of 3 points is given in each category. The Moorehead-Ardelt Quality of Life Questionnaire assesses the five parameters that were detailed previously. Points were added for positive changes and subtracted for negative changes. Points were also deducted for complications and eventual reoperation from the subtotal scores of the three categories. The BAROS outcome was classified based on total points as failure (<1 point), fair (1–3 points), good (4–5 points), very good (6–7 points), and excellent (8–9 points).
4. Late complications seen after surgery such as anemia (hemoglobin <12 g dl), incisional hernia, loss of hair, hypoglycemia, and so on.

RESULTS

The early postoperative results of all 400 patients who underwent near-total gastrectomy are shown in Table 1. The duration of the operation ranged between 2 and 3 hours. The mean estimated blood loss during surgery was 225 ml, and the blood hematocrit 12 hours after surgery changed from a mean of 41% to 38%. All patients were kept in the intensive care unit for 1 or 2 days, and postoperative ventilatory support was necessary in only 11 patients (2.75%) who required reoperation because of a complication.

Table 1. Early postoperative results in 400 morbidly obese patients who underwent 95% (near-total) gastrectomy with Roux-en-Y bypass

Complication	No.	%	Reoperation
Mortality	2	0.5	2
Morbidity			
Common to gastric bypass			
Anastomotic leakage	10	2.5	1
Postoperative bleeding of suture line	3	0.75	1
Necrosis of proximal segment jejunal loop	1	0.25	1
Partial dehiscence and necrosis of surgical wound	1	0.25	1
Intestinal obstruction	1	0.25	1
Due to gastrectomy			
Hemoperitoneum	1	0.25	1
Partial necrosis of greater omentum with abscess formation	1	0.25	1
Duodenal stump leakage	1	0.25	
Total	19	4.75	9 (2.25%)

Postoperative fluid requirements were used for 4 days after surgery, as established in our protocol. Prophylactic antibiotics (cephalosporine) were administered for 2 hours before and 24 hours after surgery. Fever was a frequent finding on days 1 and 2 after surgery and resolved spontaneously. Postoperative analgesia was easily managed with a high epidural analgesia placed 12 hours before surgery and was maintained for 3 days after surgery. Two patients died 23 and 32 days after surgery. One had a localized anastomotic leakage and massive pulmonary failure. The other patient presented with prolonged (16 days) severe hyperthermia (fever >41° C) and died from cardiovascular failure. Both deaths occurred in patients with hyperobesity and a BMI of greater than 50 kg/m^2. This corresponds to an operative mortality rate of 2.4% in these 81 patients and a mortality rate of 0% among 319 patients with a BMI of less than 50 kg/m^2. Surgical complications occurred in 19 patients (4.75%). These complications were divided into those common to any gastric bypass and those specifically related to gastrectomy. Among those complications common to any gastric bypass were 10 cases of anastomotic leakage. Nine of these patients received conservative treatment with parenteral nutrition and permanent suction through the drain left at surgery; and only one patient was reoperated. There were three patients with early postoperative intraluminal bleeding (1–5 days after surgery), and one underwent reoperation. There were other isolated rare complications in three patients, and all were reoperated. Three patients (0.75%) presented with a complication directly attributed to gastric resection, and two of them were reoperated. The postoperative hospital length of stay for 379 patients (94.75%) was 7 days. In all patients, radiologic studies with barium on the fifth postoperative day revealed a small gastric pouch of 15 to 20 ml and a good emptying through the gastrojejunal anastomosis. Only 21 patients (5.25%) remained in the hospital for longer than 7 days, and this was due to complications (Table 1).

There were 184 patients with a follow-up of longer than 12 months. The BMI values at different periods are shown in Table 2. The mean BMI was 33.5 at 6 months, 27.7 at 12 months, 27.6 at 24 months, and 27.7 kg/m^2 at 36 months. For surgical success, we established BMI of 30 kg/m^2 or less. At 12 months, 31% of the patients had a BMI above 30, value that decreased to 22% at 24 months after surgery and to 21% at 36 months. The body weight loss after surgery was closely related to the preoperative BMI. Forty-eight patients with BMI between 35 and 39.9 kg/m^2 are represented in Fig. 2. At 12 months, the mean BMI in this group was 25.4 kg/m^2, with only 1 patient (6%) who was over 30 kg/m^2. At 24 months, the mean BMI was 24.2 kg/m^2, which was maintained at 36 months. Figure 3 shows the same values in 93 patients with a BMI between 40 and 49.9 kg/m^2. At 12 months, the mean BMI was 29.7 kg/m^2, with 23% of patients above 30. At 24 months, the mean BMI decreased to 28.7 kg/m^2, which was similar at 36 months. Figure 4 shows the same findings in patients with a BMI equal to or above 50 kg/m^2. In these patients, at 12 months the mean BMI was 36.1, having 68% of them with a BMI over 30 kg/m^2. At 24 months, the mean BMI decreased to 33.1 kg/m^2, with 41% of the patients having a BMI above 30 kg/m^2; at 36 months, the values were similar.

Table 2. Body mass index (BMI) in patients with morbid obesity who underwent 95% (near-total) gastrectomy with Roux-en-Y bypass

Follow-up (mo)	No.	BMI at follow-up (kg/m^2)	% Patients with BMI kg/m^2 >30 (n)
6–9	198	33.5	52.0
12–15	115	27.7	31.0
24	55	27.6	22.2
36	14	27.7	21.0

Figure 5 shows a comparison of the percentage of excess body weight loss at 1 and 2 years after surgery. This loss was inversely proportional to preoperative BMI.

Table 3 shows the behavior of the main comorbidites evaluated in 142 patients. Among 27 patients with diabetes, all of them had normal blood sugar values at 1 year after surgery. In patients with hyperlipemia, 92.5% had complete resolution, with normal blood serum values. In patients with hypertension, only 63.6% had resolution of their disease. In patients with an osteoarticular problem, 73% had resolution of their disease. Evaluation of quality of life at 1 year after surgery (Table 4) demonstrated that some parameters, such as self-esteem and physical capacity, improved considerably. The worst response was seen concerning the return to sexual activity.

Table 5 shows the final BAROS index in these 184 patients; a very good or excellent index was obtained in almost 97% of the patients.

Table 6 illustrates the late complications seen at the late control period. Anemia, which was due to decreased absorption of iron, occurred in 20%. Incisional hernia occurred in 10%, whereas a partial loss of hair was a frequent finding. In 3%, severe depression was diagnosed and treated by a specialist.

DISCUSSION

There are many surgical procedures for the treatment of patients with morbid obesity. Three techniques

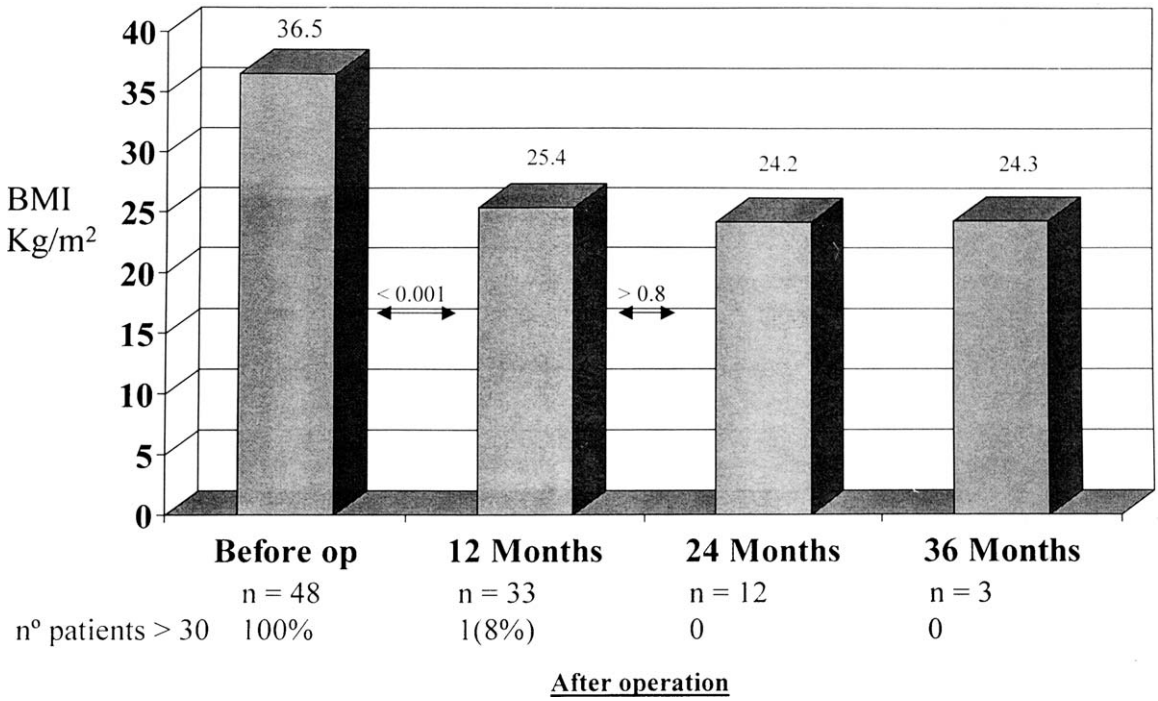

Fig. 2. Body mass index (BMI) (kg/m^2) in patients between 35 to 39.9 kg/m^2 before and 12, 24, and 36 months after surgery.

have had the best early and late results in terms of loss of weight and acceptance by the patients: 1) vertical banded gastroplasty, 2) gastric banding with a Silastic ring performed laparoscopically, and 3) gastric bypass procedures with a Roux-en-Y long limb.[1–4]

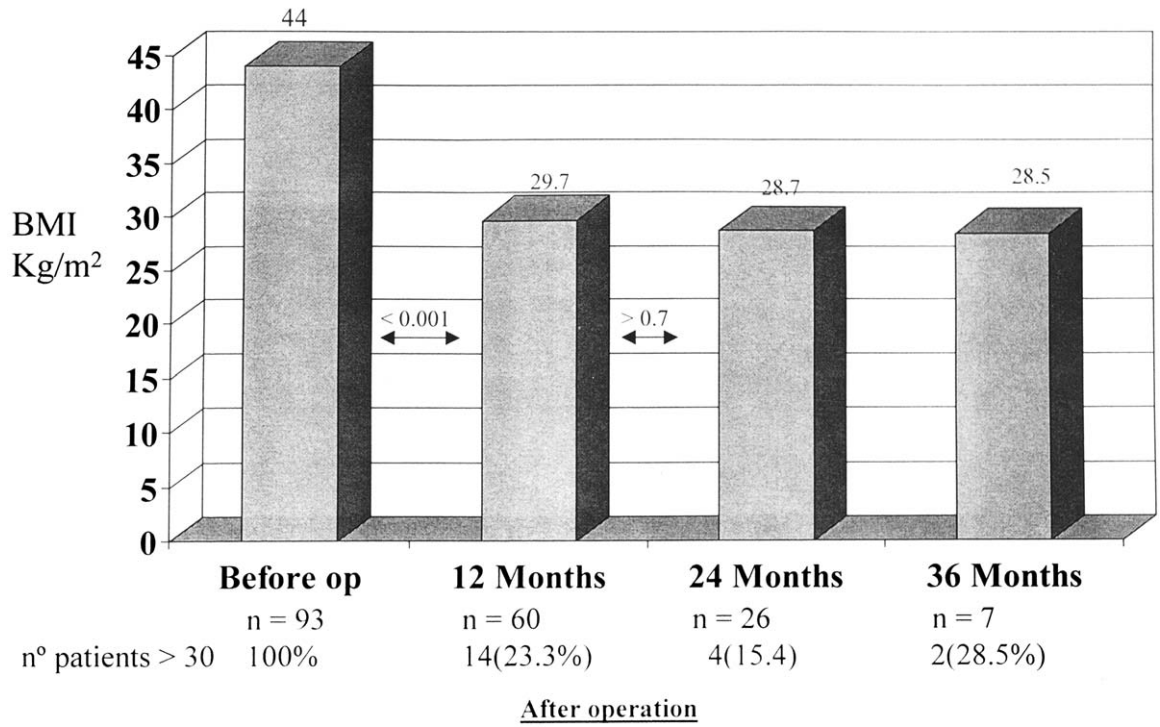

Fig. 3. Body mass index (BMI) (kg/m^2) in patients between 40 and 49.9 kg/m^2 before and 12, 24, and 36 months after surgery.

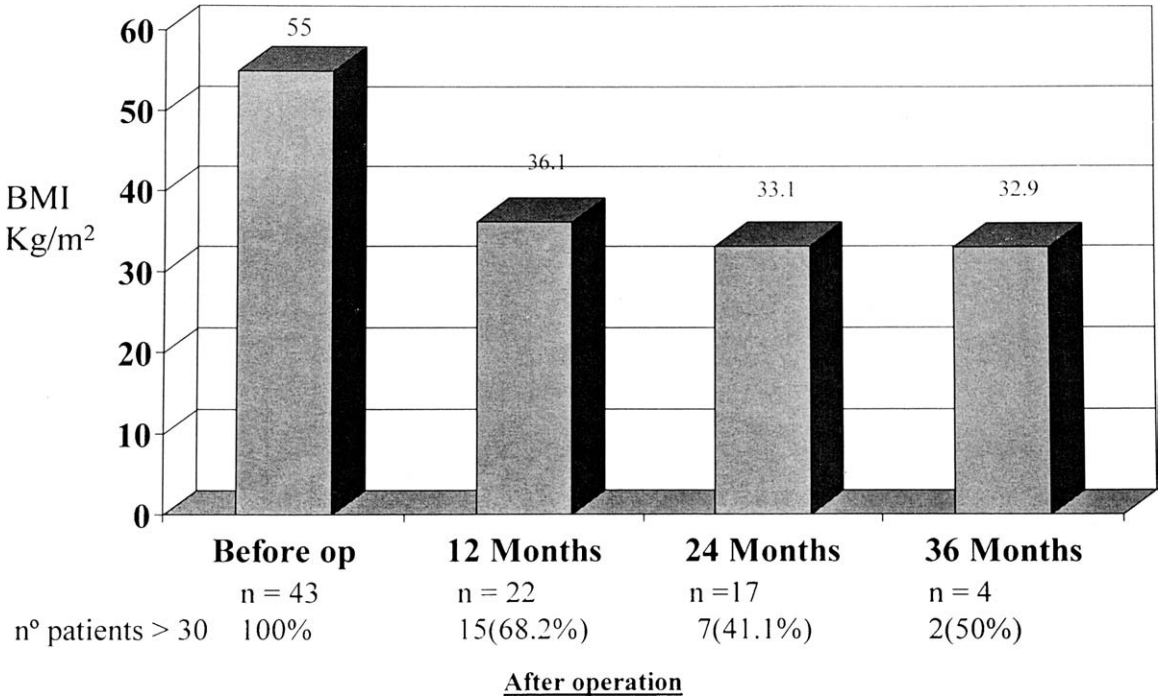

Fig. 4. Body mass index (BMI) (kg/m^2) in patients equal to or greater than 50 kg/m^2 before and 12, 24, and 36 months after surgery.

Vertical banded gastroplasty has been extensively used in the United States and Europe.[1,3,4,8,10,22] The late results, even in prospective randomized studies, have shown a worse outcome than the gastric bypass procedure.[3,8,10,14] There is a high incidence (17%) of vomiting, gastroesophageal reflux, and stenosis of the stoma with food impaction.[3,21,35] Several patients present with gastric dilatation due to this stricture, and revisional surgery is often performed.[3,21,35,36]

Gastric banding has also been used extensively, especially as a laparoscopic procedure due to its simplicity, noninvasiveness, ease of revision, and

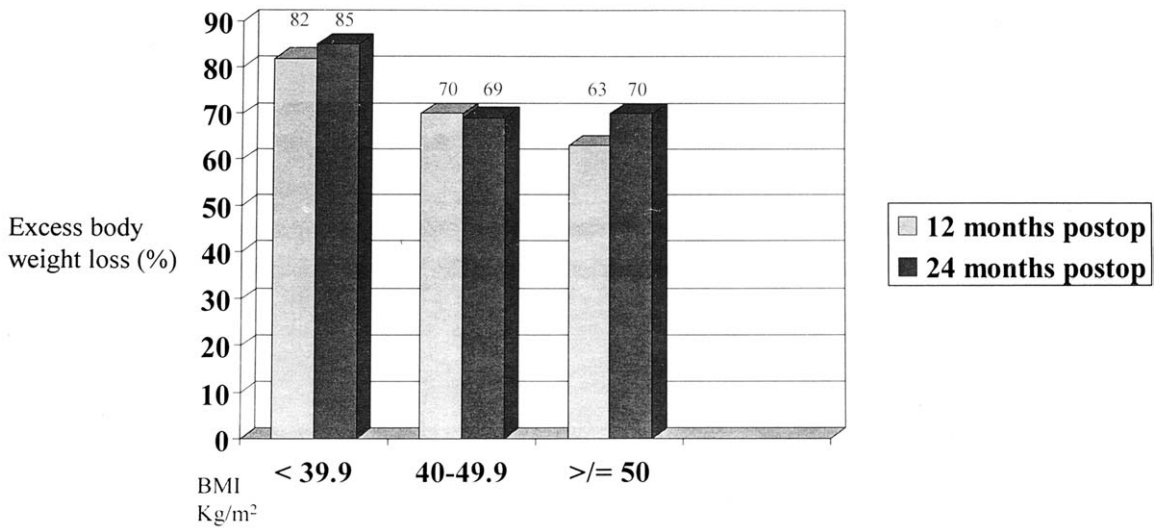

Fig. 5. Comparison of the percentage of excess body weight loss 1 and 2 years after gastrectomy with Roux-en-Y bypass according to preoperative body mass index.

Table 3. Evolution of comorbidities (N = 142)

Comorbidity	n	Improved (n)	Resolved (n)
Diabetes	27	0	27 (100%)
Dyslipidemia	67	5 (7.4%)	62 (92.5%)
Hypertension	33	12 (36.3%)	21 (63.6%)
Osteoarticular problems	15	4 (26.6%)	11 (73.3%)

Table 5. Final BAROS index in 184 patients with morbid obesity who underwent gastric bypass with 95% (near-total) gastrectomy

	Points	%
Failure	<1	0
Fair	1–3	0
Good	3–5	3.4
Very good	7–7	18.6
Excellent	7–9	78.0

complete reversibility.[15–23] It creates a small pouch that empties into the lower stomach through a narrow nonstretchable stoma, similar to the earlier gastrogastrostomy procedure. However, based on long-term follow-up, we believe that it is not an adequate procedure; several complications can occur: distention of the pouch, slippage of the band, entrapment of foreign material (bezoar) in the proximal stomach, prolapse of the stomach through the band (9% of the cases), high incidence of conversion due to difficult exposure of the hiatus, and frequent hypertrophy of the left liver lobe. In addition, a high incidence of severe gastroesophageal reflux is reported, as well as frequent deterioration of esophageal motility.[24–27] Also, several cases of band reposition or band removal have been reported. We disagree that a "less-invasive" procedure that the surgeons perform laparoscopically is therefore an "easier technique." These "easier procedures" (as were seen with some other laparoscopic techniques) performed via the laparoscopic route are as effective as other, "more complex operations." We are convinced that in very ill patients laparotomy and 3 or 4 additional days of hospital stay are of no importance when dealing with such a severe disease and an operation that should have life-long consequences. Our length of stay data indicate that our patients spend a considerably greater period of time in the hospital, with an average length of stay of 7 days, compared with most U.S. series that report a length of stay of 3 or 4 days for patients with open Roux-en-Y gastric bypass (GBP). This is due to the fact that we are not in a "hurry" to discharge our patients and we like to be sure that no complications will occur. We disagree with reported practices of discharging the patients 24 or 36 hours after surgery. Laparoscopic or even Roux-en-Y GBP corresponds to an operation with similar risks, and the only difference is a laparotomy.

Gastric bypass operation was first introduced by Mason and Ito and colleagues in 1969 with a horizontal transection of the stomach and a Billroth II type anastomosis.[5,7] Later, Alden proposed the use of mechanical stapler with an in-continuity division between the upper pouch and the distal stomach.[29] This change simplified the operation and made it technically less complex and safer. At the same time, Griffen and Young[28] used a Roux-en-Y gastrojejunostomy, which eliminated the problem of bile reflux. We have used this technique previously in 66 patients[32,33] and have seen only three main problems:

1. Dilatation of the pouch in 12 anxious patients, mainly at the fundus, that can easily dilate
2. Break down of the stapler line in five cases

Table 4. Quality of life after gastric bypass and gastrectomy (percent of patients) (N = 184)

Parameter	Worst	Equal	Better	Much better
Self-esteem	0	0	18.4	81.6
Work capacity	3.5	8	25.3	63.2
Sociability	2.4	16	28.7	52.9
Physical capacity	0	1.1	14.9	83.9
Sexual activity	1.2	42.5	32.2	24.1

Table 6. Late complications in 184 patients with morbid obesity who underwent gastric bypass with 95% (near total) gastrectomy

Complications	%
Anemia	20
Incisional hernia	10.2
Severe depression	3.1
Intestinal obstruction	2.0
Dumping	1.0
Hypoglycemia	1.0
Loss of hair	25.5

3. Anastomotic ulcer in two patients. These complications have been clearly seen and reported by other authors. Sugerman,[37] reporting on 672 patients who underwent gastric bypass, noted rates of 1.2% for anastomotic leakage, 1% for gastric staple line disruption (despite three superimposed applications of staples), 15% for stomal stenosis, 13% for marginal ulcer, and 10% for symptomatic gallbladder disease. MacLean and colleagues[9,12,38] reported staple line failure in 29% of patients after gastric bypass. Jordan et al.[39] and Sapala et al.[40] reported a high rate of marginal ulcer. When the bypassed stomach was separated from the distal stomach, a 6% rate of gastrogastric fistula was reported.[41]

We have noticed and agree completely with Fobi et al.[29] and Sugerman[37] that the maximal stomach capacity should be of 20 ml or less. If it is greater than 20 ml, the patient can eat more and the success rate is lower. In addition, the diameter of the anastomosis should be less than 15 mm to avoid a fast emptying and a dumping syndrome. However, we are concerned about what will happen to the distal stomach that is excluded from the gastrointestinal tract and becomes a real "blind loop." If any disease occurs that involves gastric mucosa (cancer, gastric ulcer, gastritis or bleeding, and duodenal ulcer), there is no way to reach it via endoscopic procedures and no therapeutic endoscopic techniques can be performed. Also, this excluded stomach will remain so for the rest of the patient's life, and because these patients are usually young and have a life expectancy of a normal subject after surgery, we are dealing with the fact of leaving as a "blind loop" this excluded stomach for 30 to 50 years. There are some important points to discuss in this aspect.

1. If a bleeding occurs within the postoperative period, it is very difficult to manage it, due to the fact that endoscopy cannot be used after a long Roux-en-Y loop. This bleeding can be severe in some cases and reoperation could be necessary, due to the presence of an unknown gastric or duodenal ulcer.
2. Gastrogastric fistula have been described after transection in up to 10% of cases,[41] even if a jejunal loop is interposed.
3. We believe that the high incidence of marginal ulcer described as between 3% and 16% after surgery[42] is due to an excessive production of gastric juice, which can be due to a greater amount of parietal cell mass (greater gastric pouch) or to a retained antrum effect. This is due to the presence of a denervated stomach that could release more gastrin. After gastrectomy, we have not seen any cases of anastomotic ulcer.
4. Up until now, no one has evaluated the eventual bacterial proliferation in the excluded stomach, except the study of Flickinger et al.,[43] who took bacteriologic samples in two patients with this excluded distal stomach and found enterobacteria in both.
5. What is the most important concern for us are the histologic changes that can occur in the excluded stomach many years after surgery. In a country such as the United States, gastric cancer is probably rare in this situation. There have been two cases of gastric cancer reported after gastric bypass, 5 and 13 years after surgery.[44,45] However, in countries with a higher prevalence of gastric cancer, such as Chile, this could represent an important late complication. The report of Flickinger et al.,[43] who performed endoscopy 4 to 48 months after gastric bypass through the Roux-en-Y loop, which was short, is very interesting. They found in the excluded stomach bile staining (53% of cases), chronic gastritis (21%), and intestinal metaplasia (9%). Gastric pH remained between 1.75 and 7.5 (mean, 3), documenting an acid environment, together with bile reflux. This gastritis did not disappear when endoscopy was repeated in some cases. The authors suggested the need for endoscopic surveillance every 5 years. We have studied the resected gastric segment in 423 patients and found chronic inactive superficial gastritis in 38% of the cases and atrophic gastritis with intestinal metaplasia in 6.5% of them at the time of operation, with one patient who had a carcinoid tumor. A more recent report by Sundbom et al.[46] demonstrated that in 22 patients who underwent gastric bypass with scintiscan evaluation 18 months after surgery, 36% showed an important duodenogastric reflux, which remained for a long time at the stomach. When this test was repeated, the results were similar.

We started to perform a resection of the distal stomach, thus avoiding all eventual problems at this level. We were not aware at the time we started using this operation of an excellent article by the surgical group of Tacoma,[47,48] who proposed the same operation in 1998. They performed 47 primary resectional operations, with excellent results. They had similar complications as seen in our patients, with no deaths. At the later follow-up, they noticed a high incidence rate of dumping. We have not seen dumping or

diarrhea in our patients, probably due to the fact that our end-to-side gastrojejunostomy is performed with circular stapler No. 25, with an internal diameter of 15 mm, while they constructed a hand-sewn widely patent anastomosis. In addition, the residual pouch that they construct has a capacity of 30 to 50 ml, which is in contrast to the 15- to 20-ml capacity of our patients. With our technique, emptying of the small pouch is slow.

We have also asked, "What are the reasons to leave the stomach in situ and not resect it, as is usual in other gastric procedures?" There could be several arguments against resecting the stomach and leaving it in situ.

1. There are fewer metabolic consequences. This is not true, because all late metabolic complications are related to the small remnant gastric pouch and to the long Roux-en-Y loop, and not to the presence or absence of distal gastric remnant.
2. In some patients, a revisional surgery could be necessary. This situation is highly improbable.
3. It is very difficult to resect the stomach, and morbidity and mortality rates could rise. This is not true, because the real morbidity attributed to gastric resection was only 0.75%, which is a very low figure. Our results have clearly shown that our patients are not sicker than patients who have Roux-en-Y GBP without gastric resection. The only difference is that we try to be more "prudent" and discharge our patients in 7 days instead of 3 or 4 days after surgery.
4. Gastric cancer will not develop in the residual stomach. As discussed earlier, we do not know about this peculiar point because there is no late follow-up.
5. Surgical team has no experience in gastric surgery and gastrectomy. We firmly believe that this is the main argument. The majority of surgeons performing laparoscopic procedures have no previous experience in open gastrectomies and they believe that it is very difficult. This clearly is not true, and if a surgeon has experience in gastric surgery, open gastric bypass with gastrectomy can be easily done in 2 hours. However, we accept this true argument in this discussion.

We recommend some surgical steps that seem to be essential to achieve optimal results: 1) initial division of all short vessels, ensuring there is no damage to the spleen; 2) it is not necessary to mobilize or dissect the abdominal portion of the esophagus or to perform bilateral vagotomy; and 3) gastric resection is greatly facilitated when it is performed from distal to proximal, elevating the stomach, which also facilitates its high section using Ligasure equipment. We section the stomach with the GIA stapler almost parallel to the lesser curvature, resecting all fundi to avoid later dilatation. The pouch is extensively irrigated by the left gastric artery, and we have not seen any case with gastric isquemic necrosis. The anastomosis is performed in an end-to-side manner in the most dependent part of the small stomach, measuring 15 mm. By performing the gastrectomy, we avoid Fobi's gastrostomy.[29] A radiologic control is performed in all patients 5 days after surgery, demonstrating a normal functioning anastomosis without leakage. After having 10 anastomotic leakages, we created an additional step, which consists of suturing the proximal end of the jejunal limb that is anastomosed to the stomach to the suture line like a jejunal patch, in this way covering the "death or sorrow angle," where the anterior and posterior layers of the stomach and the jejunum converge.

The results of this operation have been very encouraging. We will evaluate the late results, but we believe that it has the benefits of the gastric bypass procedure, avoiding the potential complications and problems that can appear late after surgery. We believe, as do Curry et al.,[47] that resection of this "blind loop," or excluded stomach, is a reasonable alternative. It is obviously a permanent effect, but it eliminates all complications seen with classic gastric bypass, such as staple line disruption, enlargement of residual stomach, anastomotic ulcer (gastrin-producing area is resected and the small residual capacity of 20 ml of the stomach practically eliminates acid production), the risk of future gastric disease, gastrogastric fistulas, etc. We have started to perform this operation with gastric resection via the laparoscopic route. We have operated on 71 patients with laparoscopy, but we still are in the learning curve. In the near future, we will probably change from the open to the laparoscopic approach. All of these patients are in a close follow-up by a multidisciplinary medical team. The optimal bariatric operation is still under debate and permanent evaluation. Also, the performance of a prospective randomized study is difficult to perform, because eventual differences and results will be seen very late after surgery, and therefore it could represent a great effort with very few short-term results. We postulate that this surgical procedure can be safely performed if an experienced surgical team in gastric surgery is dedicated to this problem. We are aware that Roux-en-Y GBP with resection of the distal gastric remnant is not performed by the great majority of U.S. surgeons dedicated to bariatric surgery. The purpose of our report is only to call

attention to the fact that we do not know the eventual pathophysiologic behavior of this excluded stomach 30 to 50 years after surgery, and therefore it deserves special attention and close late follow-up.

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Anatomic Study of Gastric Vascularization and Its Relationship to Cervical Gastroplasty

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The aim of this study was to perform an anatomic study of the stomach and its vascularization, evaluating the frequency of communication between the right gastroepiploic artery (RGEA) and the left gastroepiploic artery (LGEA), as well as their relationship to the length of the stomach without extramural (direct) vascularization in cervical gastroplasty. Forty-two fresh human cadaveric specimens were studied, and the presence of communication between the RGEA and the LGEA was observed in 26 of the dissected stomachs (61.9%). When communication was present (group 1), to a total length of 49.60 cm of greater curvature length, it was verified that approximately 16.48 cm of this curvature lacked direct extramural vascularization (33.20%). When there was non-communication (group 2), to a greater curvature length of approximately 45.41 cm, it was found that 18.96 cm of this curvature (gastric fundus) lacked direct extramural vascular perfusion (41.76%). Results obtained in both groups were tested for statistically significant differences by the Pearson correlation test ($P < 0.05$). A P value of 0.05 or less was considered statistically significant. It can be concluded that the presence of communication between the RGEA and the LGEA increases extramural vascularization in the great gastric curvature. (J GASTROINTEST SURG 2005;9:132–137)

KEY WORDS: Cadavers, cervical gastroplasty, anatomy

Several surgical procedures are employed for the treatment of benign and malignant esophageal diseases. Currently, esophagectomy still represents one of the greatest challenges in digestive tract surgery.[1]

Mobilization of the stomach through the mediastinum with cervical anastomosis is a common procedure following esophagectomy. This procedure requires ligation of the left gastric artery, the left gastroepiploic artery (LGEA), and the short vessels of the gastric fundus. The blood supply of the gastric fundus is maintained up to the level of resection of the lesser curvature, mainly by the right gastroepiploic artery (RGEA) and partially by the right gastric artery.[2] However, the gastric fundus, which is used for the anastomosis, might present reduced vascularization, representing a possible risk of late ischemia not detected during the operation.[3,4] Fistulas of the esophagogastric anastomosis occur in 3.5% to 21.5% of the cases and are currently responsible for 9% to 50% of operative deaths.[5–7] Therefore it is an important prognostic factor in postoperative recovery after esophagectomy.

According to some investigators,[8,9] communication between the RGEA and the LGEA occurs in approximately 35% of cases, and indirect communication of the two arteries through branches of the epiploic arteries in almost 5% of cases. Sixty percent of patients would thus lack communication between these arteries, increasing the possibility of ischemia and fistulas.

Because of the high postoperative mortality rate following esophagectomy with gastric pull-up, the identification of communication between the RGEA and the LGEA could identify those patients with better vascularization of the stomach and thus reduce the occurrence of fistulas. The aim of this study was to

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analyze the occurrence of communication between the RGEA and the LGEA in a random sample of fresh adult cadavers and its relation to the percentage of the length of the greater curvature of the stomach lacking extramural (direct) vascular perfusion.

MATERIAL AND METHODS

This study was approved by the Research and Ethics Committee of the University of São Paulo Medical School. Forty-two adult cadavers were studied 4 to 8 hours after death. Twenty-eight were male and 14 were female. The mean age of the cadavers was 55 years (range 42 to 80 years) and mean weight was 62.3 kg (range 51 to 82 kg). The cadavers did not have any gastrointestinal diseases or abdominal surgical procedures during life.

Through a midline laparotomy, the vessels of the greater gastric curvature (both the RGEA and LGEA) were identified and dissected from their origins in the gastroduodenal artery and the splenic artery, respectively. The presence or lack of communication between the two arteries was analyzed. Communication was considered to be present only in cases where the RGEA continued until the LGEA in the gastric fundus. We considered there to be a lack of communication when we observed the entrance of the RGEA in the stomach without any direct branch to the LGEA. Communications through arteries outside the arcade were not considered (Fig. 1).

The following measurements were taken:

1. Length of the greater curvature of the stomach (from the gastroesophageal junction to the pylorus)
2. When communication between the RGEA and the LGEA was identified (group 1), the length of the greater gastric curvature of the stomach from the first branch of the LGEA to the gastroesophageal junction was measured (see Fig. 1, *distance A*)
3. When communication between the RGEA and the LGEA was absent (group 2), the length of the greater gastric curvature of the stomach from the last branch of the RGEA to the gastroesophageal junction was measured (see Fig. 1, *distance B*)

Three different measurement techniques were adopted. First, the vessels of the greater curvature were identified without dissection, and measurements were taken using a thread and a simple ruler before the stomach was removed. Second, measurements were taken after the removal of the entire stomach, again using a thread and a ruler. The third and last measurements were taken using digital picture analysis software (University of Texas Health Science Center at San Antonio [UTHSCSA] Imaging Tools) after the removal of the stomach.

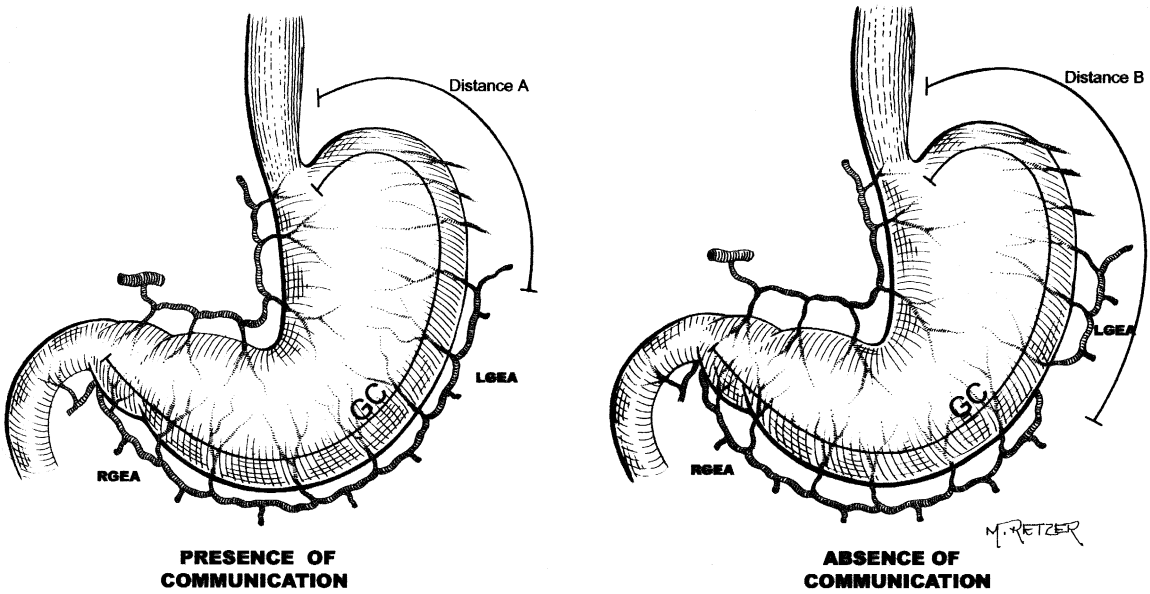

Fig. 1. Presence (**A**) and absence (**B**) of communication between the right gastroepiploic artery (*RGEA*) and the left gastroepiploic artery (*LGEA*). Distance A = measurement, in centimeters, from the first branch of the LGEA to the gastroesophageal junction in centimeters; distance B = measurement, in centimeters, from the last branch of the RGEA to the gastroesophageal junction in centimeters; GC = measurement of the greater curvature (extension of the pylorus to the gastroesophageal junction), in centimeters.

Because the gastric tube is considered to be a cylinder, the irrigated area was measured by multiplying the length of the gastric tube by 2 πR (R = the radius of the tube). As the radius is practically invariable in its cranial half, the proportion of the area lacking direct vascularization can be calculated by dividing the distance from the last directly irrigating vascular branch up to the gastroesophageal junction by the total length of the greater curvature (Fig. 2).

Statistical Analysis

Student's *t* test was used to analyze the three different measurement techniques (manual and electronic). To compare the groups of cadavers with and without communication between the RGEA and the LGEA, the Pearson correlation coefficient (SPSS for Windows, SPSS Inc., Chicago, IL) was employed. In both tests we considered $P = 0.05$ as the significance level.

RESULTS

Communication between the LGEA and the RGEA was found in 26 of the dissected stomachs (61.9%). The three measurements taken, their average, and the calculation of the area (proportion) with or without extramural vascularization in the greater curvature in each group are shown in Table 1.

In group 1 (see Table 1), for a mean greater curvature length of 49.60 cm, approximately 16.48 cm (see Fig. 1, *distance B* and Fig. 3) of the greater curvature lacked extramural vascularization (33.20%). However, in group 2, for a mean greater curvature length of 45.41 cm, 18.96 cm (see Fig. 1, *distance A* and Fig. 4) of the greater curvature (41.76%) did not possess extramural vascular perfusion through branches of the RGEA, which represents a significant statistical difference ($P = 0.044$).

When we compared the different measurement techniques (thread and ruler vs. UTHSCSA Imaging Tools), there was no statistically significant difference between the measurement techniques employed in each analysis ($P > 0.05$) following three comparisons (manual measurement before removal to manual measurement after removal, manual measurement before removal to electronic measurement, and manual measurement after removal to electronic measurement), which means that there was no statistically significant difference ($P > 0.05$) between the arcade

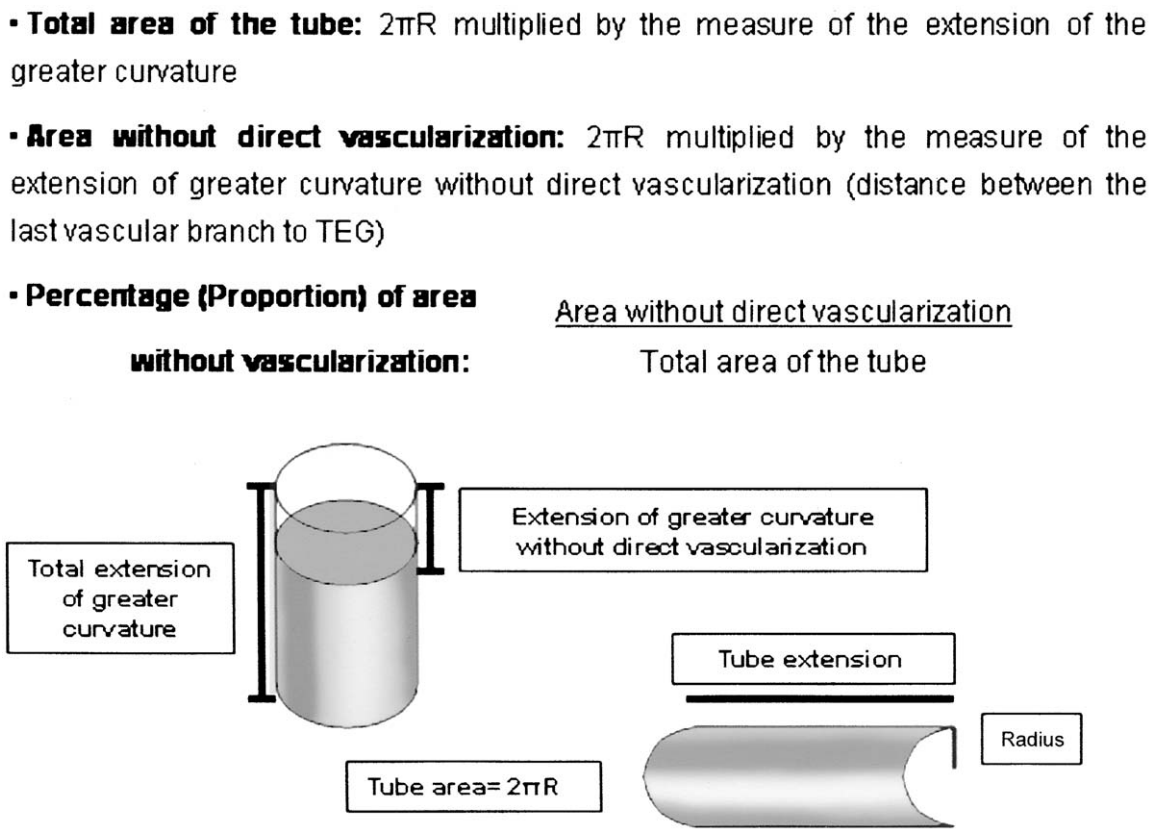

Fig. 2. Calculation of the proportion of the area lacking direct vascularization.

Table 1. Measurements of the greater curvature of the stomach

	Presence of communication (26 cadavers)	Absence of communication (16 cadavers)
Greater curvature (cm)		
Range	38.5–64.3	37.2–55.0
Median	49.0	45.5
SD	5.99	3.63
Average	49.6	45.4
Distance (cm)	Distance A	Distance B
Range	10.1–24.1	15.1–24.9
Median	16.2	18.9
SD	4.16	2.87
Average	16.5	18.9
% Area (average)	33.2	41.76
Pearson correlation	$P = 0.044$	

SD = standard deviation; distance A = measurement from the first branch of the LGEA to the gastroesophageal junction in centimeters; distance B = measurement from the last branch of the RGEA to the gastroesophageal junction in centimeters; %Area = percentage of area lacking direct irrigation Distance A (on average) or Distance B (on average) divided by the greater curvature length (on average).

measurements taken with the stomach "in situ" and those taken after its removal.

DISCUSSION

Reconstruction with gastric pull-up requires ligation of the left gastric artery, the LGEA, and the short vessels of the gastric fundus, and also part of the lesser curvature of the stomach. Perfusion of the transposed stomach through the mediastinum is thus performed mainly by the RGEA and the right gastric artery.[10] When the surgical details of this procedure are considered, several reasons for the occurrence of fistulas in the esophagogastric anastomosis become evident. The most important seems to be the result of ischemia due to the mobilization of the stomach being pulled up, or even the result of tension in the anastomosis.[1,10–14] Tension in the anastomosis is related to the level of esophageal resection and the length of the gastric tube mobilization. Previous investigators have already indicated that the gastric tube must reach the cervical region with a sufficient blood supply and without any tension in order to perform an adequate anastomosis.[11]

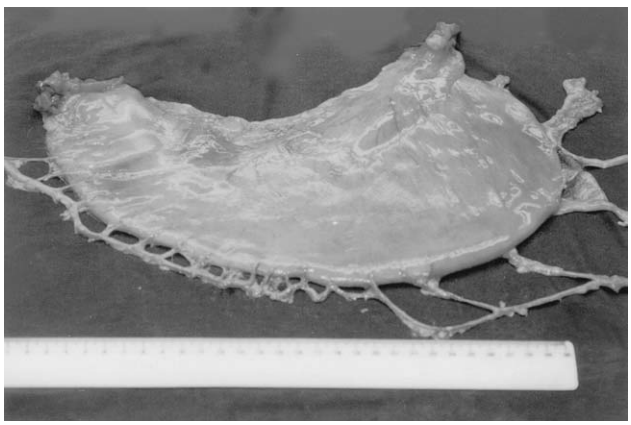

Fig. 3. Stomach dissected with communication between RGEA and LGEA.

Fig. 4. Stomach dissected without communication between RGEA and LGEA.

In this study, communication between the right and left gastroepiploic arteries was found in 61.9% of the cases studied, a larger percentage than that reported in the literature.[15] We consider our data to be an adequate sample of the general population because the 42 cadavers obtained from the Municipal Death Verification Service were studied in chronologic order and without any exclusions, thus reducing the possibility of bias in the study.

When we compared the extramural vascularization between the two groups, we found a statistically significant difference. Even taking perfusion through the submucous plexus into account,[16] this represents a considerable difference in the lack of perfusion area of the gastric fundus, precisely within the area of the anastomosis with the cervical esophagus, a fact that could explain the high incidence of postoperative ischemia following esophagectomy.

Another aspect to be discussed is the use of different measurement techniques. This variable tends to diminish even more when the average of the three measurements is obtained. The digital analysis technique, already widely used in other studies,[17] has the

additional advantage of removing the bias of manual measurements.

Liebermann-Meffert et al.,[15] analyzing the vascularization of the greater curvature, showed that the RGEA is the exclusive conduit of blood in the pedicles and communication between the right and left gastroepiploic arteries is minuscule. Furthermore, another study[16] of gastric vascularization showed that vascularization of the stomach is also widely derived from the vascular submucous plexus, full of anastomosis between its several branches. This occurs mainly in the greater gastric curvature, with the presence of the mucous arteries that communicate with each other at the level of the muscular mucous membrane. Therefore this submucous plexus should allow for sufficient perfusion of the mobilized gastric fundus, suggesting that other factors are related to ischemia and the development of fistulas following an esophagectomy.

Some investigators[18–20] propose performing an esophagogastric anastomosis in a second operation after mobilization of the stomach. This technique allows for subsequent evaluation of the vascularization of the gastric fundus in its new position and thus a better clinical condition of the patient and improved adaptation of the anastomosis. Another group of surgeons used to perform a preliminary laparoscopic surgery with a partial desvascularization of the stomach for the same purpose, with a concomitant staging of the disease, 2 to 3 weeks before the esophagectomy. This early desvascularization seeks to condition the gastric fundus to its new two-vessel irrigation.[9] Another experimental technique is the vascular anastomosis of vessels of the mobilized stomach to the pedicles of the left thoracic intern artery, thus improving its perfusion.[21] All of these reports, however, have presented only partial results with no proven benefits. Studies such as the one carried out by Khoury-Helou et al.[22] even go as far as to postulate that the most common cause of fistulas in esophageal surgery is diminution of vascularization, as confirmed through selective arteriographs of the mobilized stomach in the gastroplasty showing its vascular net. In that study the surgical technique employed did not interfere with the prognosis, but the patient's own vascularization was correlated to the emergence of fistulas.

As mentioned previously, the blood supply of the stomach is a significant factor in the occurrence of complications in the postoperative period following esophagectomy. The aim of this study was to evaluate the anatomy of the stomach, analyzing the area irrigated by the arcade of the RGEA and the eventual presence of communication with the LGEA. This communication probably increases this irrigated area. When there was no communication between the two arteries, only 58.24% of direct vascularization of the stomach was found. When communication was present, 66.8% of the directly irrigated area was observed. This fact represents an increase of 8.56% in the extension of the greater curvature that is directly irrigated, and these data could be an important factor in the incidence of fistulas and ischemia in esophagogastric anastomosis.

This anatomic study provides an important and new perspective with regard to this important risk factor in the development of esophagogastric fistulas after cervical gastroplasty. It should be continued and confirmed at the clinical level, however.

CONCLUSION

It may be concluded that communication between the RGEA and the LGEA increases the area of extramural vascularization of the greater gastric curvature. It is possible that this anatomic fact might decrease the risk of anastomosis-related ischemia and fistulas in the period following an esophagectomy.

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Pancreaticoduodenectomy

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KEY WORDS: Whipple operation, pancreaticoduodenectomy, pancreatic cancer, chronic pancreatitis

INTRODUCTION

Since Whipple's 1935 description of the two-stage operation that now bears his name,[1] pancreaticoduodenectomy has undergone a steady evolution. Formerly plagued by high perioperative morbidity and a mortality rate of approximately 30%, over the last several decades, improvements in technique and perioperative care have allowed this operation to be performed with mortality rates of less than 2% and major morbidity rates of 10%–15%.[2] A number of reports have documented superior immediate results in centers that perform pancreaticoduodenectomy with high frequency, although the precise contribution of surgical technique and surgeon experience to the observed volume-outcome relationship is not defined.[3] Numerous technical variations and options have been described for this complex operation. The following description outlines the preferred method at the University of Cincinnati.

PREOPERATIVE ASSESSMENT AND MANAGEMENT

Preoperative evaluation depends on the nature of the underlying pancreatic disorder. In patients with suspected neoplasia, a chest radiograph and a thin-section (5 mm) intravenous contrast-enhanced abdominal and pelvic computed tomograph (CT) are obtained. Acquisition of CT images is timed to sequentially maximize visualization of vascular structures and hepatic parenchyma (early hepatic arterial, portal venous, and delayed hepatic venous phases)[4] (Fig. 1). For patients with extrahepatic biliary obstruction without an evident mass on thin section CT, endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasonography (EUS) is performed. Routine tissue diagnosis is not necessary if the mass seems resectable and preoperative endoscopic or percutaneous transhepatic stenting is not endorsed. Preoperative laparoscopy is not routinely performed, because high-resolution spiral CT scans adequately predict resectability and the presence of distant metastases.[5] Surgical exploration with intent to resect is offered to patients without evidence of extra-pancreatic disease, local invasion into the celiac or the superior mesenteric artery, or circumferential involvement of the portal-superior mesenteric venous confluence.

For patients with chronic pancreatitis, a thin section contrast-enhanced CT scan is performed to exclude complications related to pancreatitis such as pseudocyst formation and portal vein thrombosis. Most patients undergo ERCP to delineate pancreatic ductal anatomy.

SURGICAL TECHNIQUE

Exposure and Initial Mobilization

Although a bilateral subcostal incision (Chevron type) is also popular, a midline incision provides adequate exposure of the porta hepatis, ligament of Treitz, and the periampullary region while avoiding bilateral division of the rectus abdominus, which is otherwise associated with wound complications, postoperative pain, and postoperative weakness of the

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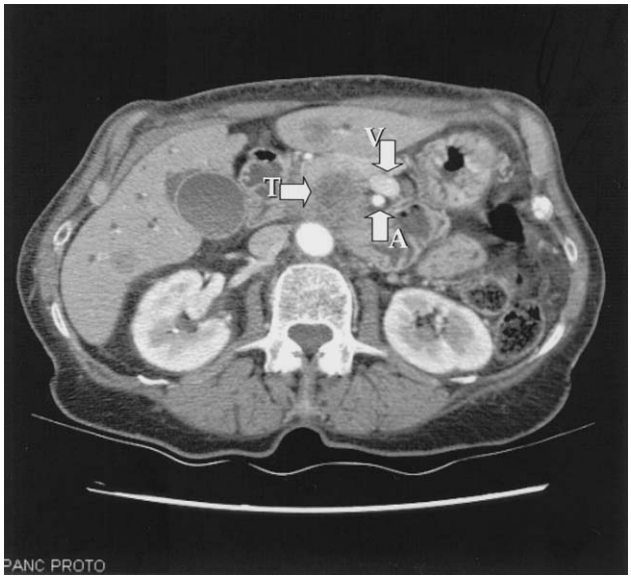

Fig. 1. A contrast-enhanced thin-section CT scan of the pancreas shows the relationship of the tumor (T) to the superior mesenteric artery (A) and vein (V).

abdominal wall. The liver and peritoneal surfaces are carefully examined for metastatic deposits to exclude stage IV disease. Placement of retractors is crucial for optimal exposure and safe dissection. We usually choose a self-retaining retractor system, which is affixed to the operating table just beneath the right armboard as far superiorly as possible, being certain to avoid hyperextension of the right arm. A large segmented circular ring is used. A bladder-blade retractor is used to retract the right costal margin superolaterally. We separate the umbilical/falciform ligament from the abdominal wall to create a vascularized pedicle that is later used to cover the gastroduodenal artery stump.[6] Next, we incise the posterior peritoneum along the C-sweep of the duodenum extending laterally to mobilize the hepatic flexure of the colon and to separate the duodenum from the base of the transverse mesocolon. A deep right-angled retractor blade is inserted over a laparotomy pad to retract the hepatic flexure inferolaterally. The duodenum and pancreatic head are then extensively mobilized (Kocher maneuver) from their retroperitoneal attachments to the level of the superior mesenteric vein (SMV) anteriorly and the left renal vein posteriolaterally (Fig. 2). The mobilization is sufficiently extensive that it becomes possible to incise the ligament of Trietz behind the superior mesenteric vessels from its supracolic aspect. This maneuver allows the distal duodenum and uncinate process of the pancreas to be delivered from the depths of the retroperitoneum and aids exposure. We do not routinely dissect the fibrofatty tissue overlying the kidney and retroperitoneum. The line of dissection of the posterior peritoneum is then extended into the porta-hepatis. A laparotomy pad is placed over the transverse colon, which is retracted under the abdominal wall using a medium-length right-angled retractor blade. This blade is positioned at the base of the transverse mesocolon over the inferior vena cava, being certain to avoid venous compression or excessive traction on the superior mesenteric vein. Careful placement of this retractor creates substantial working space around the duodenum and uncinate process and is useful later in the dissection. A fourth short-length right-angled blade over a laparotomy pad is used to retract the stomach to the left under the left costal margin.

Portal Dissection

Next, attention is turned to the portal dissection. The cystic duct and common bile duct (CBD) are identified and the cystic artery is clamped, divided, and doubly ligated. A cholecystectomy is performed. The CBD is then encircled with a silastic vessel loop. The common hepatic duct is then divided just above its junction with the cystic duct and the divided distal common duct is mobilized toward the pancreatic head. Early division of the CBD allows rapid and simple exposure of the anterior surface of the portal vein. A superior pancreaticoduodenal branch of the portal vein is usually identified at this level and care must be taken not to avulse this branch. Lateral to the portal vein, fibro-fatty and lymphatic tissue is usually present and care must be taken to assure that an aberrant right hepatic artery is not present within this area. Early division of the CBD and identification of the portal vein also helps to expose the proper hepatic artery and its gastroduodenal branch (GDA). A large lymph node is usually present in the hepatoduodenal ligament and the hepatic artery can usually be found just cephalad to this lymph node. The proper and common hepatic artery is then identified proximal and distal to the gastroduodenal artery (GDA). The GDA is then temporarily compressed to confirm its identity and to ensure that pulsatile arterial flow to the liver via the hepatic artery will be present after division of the GDA. Preservation of arterial flow to the liver is particularly critical in jaundiced patients who have reduced hepatic ischemic tolerance. The GDA is then clamped, divided, tied, and additionally suture ligated. The possibility of the rare but potentially catastrophic complication of postoperative hemorrhage from a GDA pseudoaneurysm should be recalled during this step. Gentle initial development of the supraduodenal avascular

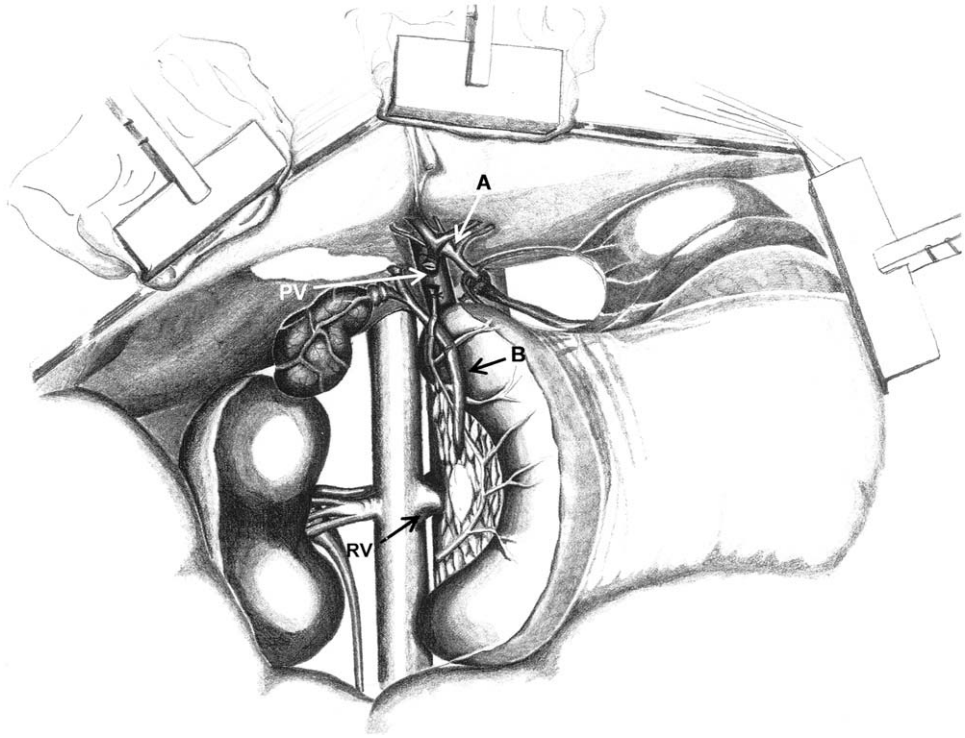

Fig. 2. The duodenum and the pancreatic head are extensively mobilized (Kocher maneuver) from their retroperitoneal attachments to the level of the superior mesenteric vein (SMV) anteriorly and the left renal vein posteriorly. RV = left renal vein, B = common bile duct, A = hepatic artery, PV = portal vein.

plane between the anterior border of the portal vein and posterior aspect of the pancreas is begun.

Identification of the Superior Mesenteric Vein

The retractors over the transverse colon and stomach are repositioned to allow delivery of the transverse colon and omentum into the wound. The greater omentum is then separated from the transverse mesocolon by electrocautery, allowing access to the lesser sac through this largely avascular plane. Once the transverse mesocolon is completely separated, the lower border of the pancreas is encountered. The middle colic vein is then followed distally and the infra-pancreatic portion of the superior mesenteric vein (SMV) is identified by incising the posterior peritoneum. It is important to identify and ligate the right gastroepiploic vein early after identification of the SMV, as it is otherwise easily avulsed. In some instances, it may also be wise to divide the middle colic vein to prevent undue traction on it. A plane of dissection is then created between the anterior surface of the SMV and the posterior aspect of the pancreas. This plane is connected to the supraduodenal portal vein dissection and a 1/4-inch Penrose drain is passed behind the neck of the gland. This step can be omitted if chronic inflammation makes dissection between the SMV and pancreas unsafe. This maneuver facilitates division of the pancreas, but does not confirm resectability; this is more typically determined by tumor involvement at the lateral and posterior aspect of the SMV/portal vein.

Division of the Stomach and Jejunum

We only infrequently perform pyloric-preservation with pancreaticoduodenectomy preferring a standard distal gastric resection. At this stage of the procedure, then, a transection point on the greater curvature is chosen at the junction of the left and right gastroepiploic arteries on the greater curvature and, on the lesser curvature, a point is chosen at the gastric incisura angularis. The Ligasure bipolar device (Valleylab, Boulder, CO) is useful for dividing the omentum between the gastroepiploic vessels. The descending branch of the left gastric artery is generally suture-ligated. The stomach is then transected with a linear cutting gastrointestinal anastomosis (GIA) stapler (Ethicon, Inc., Cincinnati, OH) using two firings of a blue (3.8 mm) cartridge, although a

green (4.8 mm) cartridge can be used if the gastric wall is thicker. The staple line at the lesser curvature is oversewn with 3-0 silk Lembert sutures. These sutures are left uncut so that they may be used for traction, which helps exposure for the later gastrojejunal anastomosis. The proximal stomach is then retracted under the left costal margin behind a laparotomy pad and a short right-angled retractor blade.

Next, the ligament of Treitz is exposed and fully incised. The jejunum is divided with a linear cutting GIA stapler approximately 8–10 cm distal to the ligament of Treitz, and the proximal mesojejunum and mesoduodenum are divided with a vascular load (white 2.5 mm load) GIA stapler. The Ligasure can also be used to divide the duodeno-jejunal mesentery. Once the distal duodenum and proximal jejunum are completely mobilized from their retroperitoneal attachments, the devascularized segment is reflected behind the superior mesenteric vessels into the supracolic compartment. The distal transected end of the proximal jejunum is oversewn with 3-0 silk Lembert sutures, which are left long for traction.

Division of the Pancreas

Figure-of-eight 2-0 silk stay sutures are placed on the superior and inferior borders of the pancreas both along the medial and lateral borders of the SMV and portal vein. Upward tension on the previously placed Penrose drain prevents iatrogenic injury to the SMV during transection of the pancreas, which is performed with electrocautery. The pancreatic duct is usually identified two-thirds of the way up from the inferior border and two-thirds of the way down from the surface of the pancreas. Bleeding from the pancreatic parenchyma is controlled with electrocautery. The left pancreas is mobilized approximately 3–4 cm off of the splenic vein to facilitate suture placement during the later pancreatico-jejunal anastomosis. The next step of the operation is perhaps the most difficult and most important in terms of oncologic principles and involves separating the pancreatic head from the SMV and the superior mesenteric artery (SMA). The transected pancreatic head is separated from the SMV by individual ligation of the small venous branches to the pancreatic head and uncinate process. These venous tributaries are very fragile and care must be taken not to accidentally avulse these branches. At the inferior aspect, the first jejunal tributary is identified. This vessel courses behind the SMA approximately 80% of the time. All venous tributaries from this branch to the uncinate process are controlled and divided so as to carefully preserve this first jejunal tributary. Once the SMV is completely separated from the pancreatic head and uncinate process, the SMV and portal vein are retracted medially, exposing the retroperitoneal attachment of the uncinate to the SMA.

The SMA is completely exposed and mobilized to its aortic origin. For oncologic operations, the uncinate process is separated from the right lateral wall of the SMA via serial ligation and division of the soft tissue attaching the uncinate to the SMA. This technique assures the best chance of obtaining a cancer-free retroperitoneal margin (the soft tissue along the proximal 3–4 cm of the SMA). A positive retroperitoneal margin is associated with decreased survival and every effort to achieve full tumor clearance must be made.[7] Once the entire specimen is separated from the SMA and removed, the retroperitoneal margin is identified for the pathologist with a marking suture. When the operation is performed for chronic pancreatitis or when retroperitoneal clearance is less critical, the soft tissue connecting the uncinate to the right lateral wall of the SMA can be divided en masse with the use of a vascular load GIA linear cutter (Fig. 3), provided the tissue is not overly thickened from chronic inflammation and

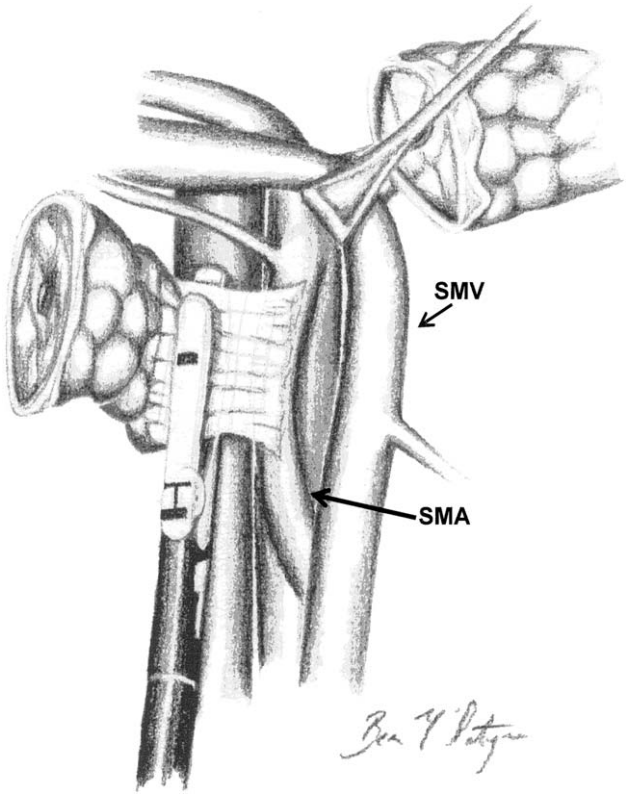

Fig. 3. When the operation is performed for chronic pancreatitis, the soft tissue connecting the uncinate process of the pancreas to the right lateral wall of the superior mesenteric artery (SMA) is divided en masse with the use of a vascular load GIA linear cutter.

scarring. Once the specimen has been removed, frozen section analysis of the transected pancreas margin and common bile duct margin is performed to ensure an R0 resection. If these margins are positive, additional mobilization and retransection is performed.

Reconstruction

A retrocolic pancreatico-jejunal anastomosis is the first step of reconstruction. The proximal jejunum is advanced through a mesenteric defect created to the left of the middle colic vessels and a two-layer end-to-side duct-to-mucosa anastomosis is constructed starting approximately 6–8 cm distal to the jejunal staple line. The posterior wall is created by a modified mattress technique using a 3-0 Vicryl suture that is passed full-thickness through the pancreatic parenchyma from anterior to posterior, horizontally through the seromuscular layers of the jejunum, and then back full-thickness through the pancreas from posterior to anterior. Three to four such sutures are placed, being careful to avoid the main pancreatic duct, and each suture is tagged with a hemostat (Fig. 4). This technique allows secure placement of the posterior row sutures, which are not tied until the inner duct-to-mucosa anastomosis is completed. Near the proximal stapled end of jejunum, a 3-0 chromic catgut pursestring suture is placed through which a 5 French pediatric feeding tube is introduced into the jejunal lumen. This tube is brought out opposite the main pancreatic duct via a small enterotomy approximately the size of the duct. The tube is advanced well into the pancreatic duct and the chromic pursestring suture is tied down. A duct-to-mucosa anastomosis is fashioned using 6-0 double-armed polydioxanone surgical suture (PDS) placed in a horizontal mattress fashion. This stent can be grasped with fine DeBakey forceps (Aesculap, Center Valley, PA) to expose the duct for accurate suture placement. At least one suture is placed in each quadrant of the duct. The sutures are placed so that knots will be on the outside for the anterior row and inside for the posterior row, which facilitates tying these knots securely. As these sutures are tied, the posterior-wall Vicryl sutures are held up to ensure lack of tension. These posterior wall mattress sutures are then tied to secure the back wall. The pancreatic stent is secured at the site of its exit from the jejunum with interrupted 3-0 silk sutures using the Witzel technique and later exteriorized through the abdominal wall through a separate stab wound and secured to the skin (Fig. 5). The anastomosis is completed with an anterior row of simple 3-0 Vicryl sutures.

Next, approximately 10–20 cm distal to the pancreatic anastomosis, an end-to-side single layer hepaticojejunostomy is performed. This is created using interrupted 4-0 polydioxanone (PDS) sutures implementing the technique described by Blumgart and

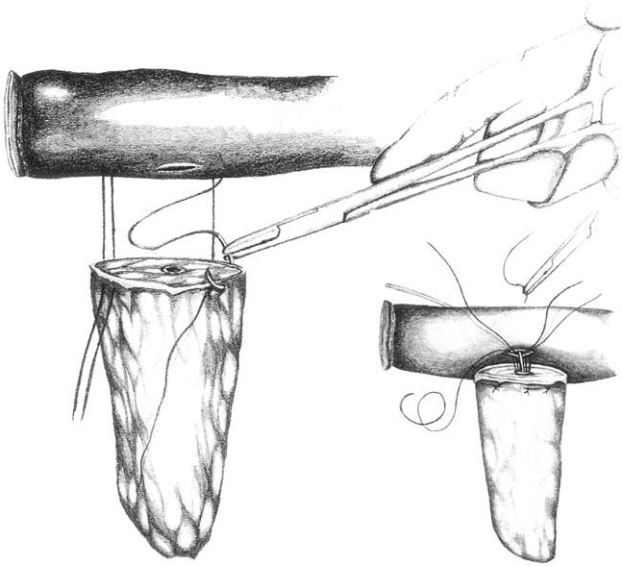

Fig. 4. The posterior layer of the pancreatico-jejunal anastomosis is created by a modified mattress technique using 3-0 Vicryl sutures that are passed full-thickness through the pancreatic parenchyma from anterior to posterior, horizontally through the seromuscular layer of the jejunum, and then back full-thickness through the pancreas from posterior to anterior (inset). A duct-to-mucosa anastomosis is fashioned using a 6-0 double-armed polydioxanone (PDS) suture placed in horizontal mattress fashion.

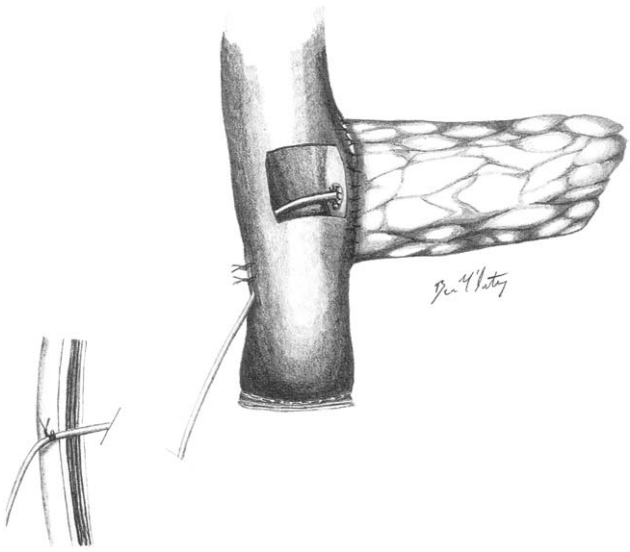

Fig. 5. The pancreatic stent is secured to the proximal jejunal wall with interrupted 3-0 silk sutures using the Witzel technique and later exteriorized through the abdominal wall through a separate stab wound and secured to the skin (inset).

Kelley.[8] If the bile duct has a diameter greater than approximately 1.5 cm, a running single-layer technique is used. Finally, a two-layer antecolic gastrojejunostomy is performed. The previously placed lesser curvature silk sutures are used for traction and we use interrupted 3-0 silk Lembert sutures for the posterior wall. The greater curvature staple line is cut off and a 3–4 cm enterotomy is made. An inner running 3-0 polyglyconate monofilament (Maxon) or chromic catgut is used (simple running posteriorally, Connell-style anteriorly). The anterior wall is completed with 3-0 silk Lembert sutures. A 3-0 silk suture secures the corner of the anastomosis near the angularis ["jammerecke" (angle-of-sorrow)]. This stitch incorporates a seromuscular bite of anterior wall stomach, then jejunum, and then posterior wall stomach.

We routinely place a 14 French feeding jejunostomy tube in the mid-jejunum using the Stamm technique. A gastrostomy tube is not used and closed-suction intraabdominal drains are not routinely placed. The vascularized umbilical ligament pedicle is positioned between the gastroduodenal artery stump and the proximal jejunum. The abdomen is then copiously irrigated with 4 gm/l cefazolin solution and the fascia of the abdominal wall is closed using #1 looped PDS continuous sutures. The subcutaneous tissue is irrigated with cefazolin solution and the skin is closed with staples.

POSTOPERATIVE MANAGEMENT

Our patients are monitored postoperatively in a surgical intensive care or step-down unit for the first 24–48 hours. Prophylactic antibiotics are redosed intraoperatively after 4 hours and then continued for the first 24 hours. Subcutaneous heparin is continued throughout the postoperative stay for prophylaxis against deep venous thrombosis. The nasogastric tube is removed on the first postoperative day and jejunostomy tube feeds are initiated on postoperative day 3. Patients are discharged with their pancreatic stent in place. The stent is clamped before they are sent home and typically removed 3 weeks postoperatively.

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Review Article

Current Surgical Management of Chronic Pancreatitis

Richard H. Bell, Jr., M.D.

Chronic pancreatitis is a challenging condition for surgeons to treat. The indications for surgery, although generally defined, are not clearly established by evidence and are open to interpretation.[1,2] In general, patients are referred for surgery late in the course of disease, which means that the pathologic process can at most be halted or stabilized but not reversed. Many patients are addicted to alcohol, opiates, or both at the time of surgery, and surgery does not address the underlying psychological or addiction issues attendant to the disease. The usual technical complexities of pancreatic surgery are made even more imposing by the presence of inflammation in the pancreas and peripancreatic areas, which can significantly obscure anatomic landmarks and planes. Nevertheless, the surgical procedures available for chronic pancreatitis have gradually been refined over several decades and clearly benefit patients if applied for the appropriate indications and performed in a technically competent fashion.

Performing surgery for chronic pancreatitis is a relatively uncommon event for most surgeons. The incidence of chronic pancreatitis is approximately 10 cases per 100,000 population, about the same as pancreatic cancer. The majority of cases of chronic pancreatitis are caused by alcohol abuse, although interestingly, chronic pancreatitis is about 30 times less common than alcoholic cirrhosis. In alcoholics, the disease typically manifests in middle age, although this is variable and sometimes the initial problems begin in patients of advanced age. It is important for surgeons to be aware of the fact that there are now well-defined inherited germline mutations that can cause chronic pancreatitis in families. Clinically, the familial form of the disease is similar to alcoholic chronic pancreatitis, with the exception that the onset of symptoms is typically earlier in life, often in teenagers. The two genetic causes of chronic pancreatitis that have been best characterized are mutations in the cationic trypsinogen gene and in the cystic fibrosis transmembrane regulator gene, and excellent reviews are available on the genetics of these conditions.[3] Finally, some cases of chronic pancreatitis are idiopathic (of unknown cause).

The diagnosis of chronic pancreatitis is generally made by detecting calcifications in the pancreas, either on plain film of the abdomen or on a computed tomography (CT) scan. Pancreatic calcifications, which are stones in the ducts of the pancreas, are pathognomonic of the disease, although their presence means the disease is advanced. The diagnosis of chronic pancreatitis can also be made by endoscopic retrograde cholangiopancreatography—the changes in the pancreatic duct system associated with chronic pancreatitis and the criteria for making the diagnosis by endoscopic retrograde cholangiopancreatography have been clearly delineated.[4] Recently, endoscopic ultrasonography has been used to diagnose chronic pancreatitis by detecting textural abnormalities in the pancreatic parenchyma.[5] The traditional pancreatic juice collection techniques used to diagnose chronic pancreatitis by demonstrating reduced secretion are rarely used anymore. Unfortunately, the pancreas is not generally biopsied, so it is extremely difficult to validate the sensitivity of any test for chronic pancreatitis. In fact, autopsy studies[6] suggest that chronic pancreatitis is substantially underdiagnosed during life.

INDICATIONS FOR SURGERY

The indications for surgery in chronic pancreatitis are shown in Table 1 and are worthy of some detailed

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Table 1. Indications for surgery in chronic pancreatitis

Pain
Chronic pain that is inadequately responsive to nonsurgical therapies
Frequent hospitalizations for acute flare-ups of pain
Effects of progressive fibrosis on neighboring structures
Symptomatic duodenal obstruction
Symptomatic colonic obstruction
Persistent common bile duct obstruction
Splenic vein occlusion with sinistral portal hypertension
Effects of ductal rupture
Persistent or symptomatic pseudocyst(s)
Pancreatic fistula unresponsive to nonsurgical management
Pancreatic ascites unresponsive to nonsurgical management
Suspected pancreatic cancer

consideration. The first and most common indication is pain. This usually takes the form of chronic pain that is inadequately responsive to nonsurgical therapies. In general, daily pain associated with chronic pancreatitis is managed initially by non–enteric-coated pancreatic enzymes via mouth and by non-narcotic analgesics, although the impact of these measures is modest.[7] Many patients are started on opiate analgesics as a result. Endoscopic stenting of the pancreatic duct results in "improvement" in pain in about two-thirds of patients followed over a period of 3 years but is not really a good permanent solution for most patients because of the need for multiple stent changes.[8] Extracorporeal shock wave lithotripsy is appropriate in some patients with a large dominant stone causing obstruction of the main pancreatic duct.[9] Celiac plexus block can be performed either percutaneously or under endoscopic ultrasonographic guidance, but it is generally not useful in chronic pancreatitis because the effect tends to be unpredictable and temporary.[10]

Another appropriate indication for surgical intervention is the need for frequent hospitalization for acute pain flare-ups, even if the background chronic pain can be adequately managed. Surgical intervention appears to significantly decrease the need for hospitalization in patients with acute-on-chronic pancreatitis.[11]

The next category of indications for surgery in chronic pancreatitis is fibrosis affecting structures adjacent to the pancreas. Most commonly involved is the common bile duct (Fig. 1), which is entrapped by chronic inflammation in the head of the gland, leading to obstruction, duct dilation, abnormal liver chemistries, and ultimately frank jaundice, sometimes with cholangitis. It is probably not appropriate to intervene surgically for isolated asymptomatic alkaline

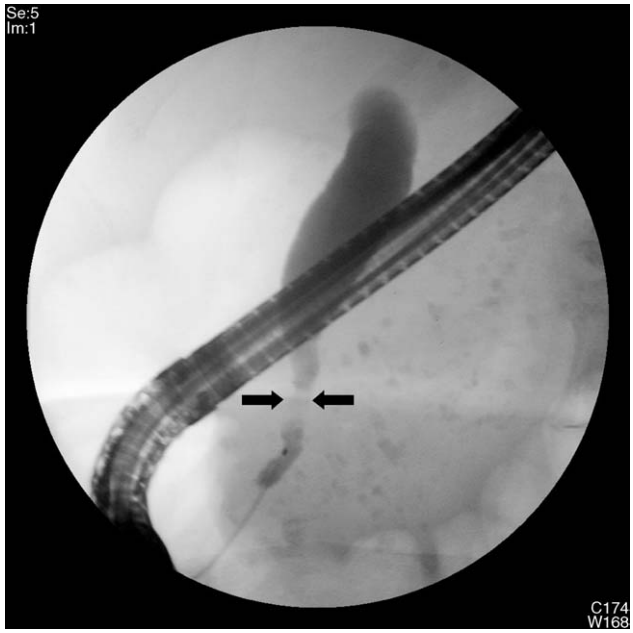

Fig. 1. Endoscopic retrograde cholangiopancreatography demonstrating obstruction of the common bile duct in a case of chronic pancreatitis. There is a long, smooth distal stricture of the bile duct (*arrows*) with dilation of the common bile duct proximal to the narrowing.

phosphatase elevation, but a liver biopsy is indicated to detect occult hepatic fibrosis, which is an indication for decompression if found. Surgery is indicated if patients develop frank jaundice or have an episode of cholangitis.[12,13] Some patients with preexisting chronic pancreatitis will develop jaundice with an acute pancreatitis episode, which resolves spontaneously as the acute episode improves. Such a situation is not an indication for surgery. Surgery is appropriate, however, when jaundice seems to be due to progressive chronic disease and fibrosis. If the jaundice is an isolated symptom and the patient does not have pain or other indications for surgery, a biliary bypass procedure, such as a side-to-side choledochoduodenostomy, is appropriate treatment. But if the patient has significant pain or other problems such as a pseudocyst, I prefer to deal with the bile duct obstruction and the other problems by performing a duodenum-preserving pancreatic head resection such as the Frey procedure (see later).

Duodenal obstruction is sometimes associated with bile duct obstruction but can present as an isolated complication of chronic pancreatitis. It is usually found in patients with "head-predominant" version of chronic pancreatitis, in which the head is significantly enlarged ($\geq$7 cm in diameter). Although isolated duodenal obstruction can be treated with a gastrojejunostomy, duodenal obstruction is often associated with

other indications for surgery and is generally best treated by a duodenum-preserving head resection. A pancreaticoduodenectomy may be appropriate in severe cases.

Occlusion of the splenic vein or the superior mesenteric vein is surprisingly common in patients with chronic pancreatitis and is detectable on a triphasic CT scan of the pancreas. Visceral arteriography is ordinarily not necessary to make the diagnosis of major venous occlusion but may be indicated if the CT scan is equivocal and the answer would be important in surgical planning. Patients with splenic vein occlusion develop gastric varices and may have significant upper gastrointestinal hemorrhage. They also develop varices in the omentum and in the retroperitoneal tissues around the distal pancreas (Fig. 2). The condition can be cured by splenectomy. When a patient with chronic pancreatitis requires surgery for pain and has splenic vein occlusion, I perform a splenectomy routinely whether the patient has experienced gastric bleeding or not. When a patient has bled from varices, splenectomy is indicated. If the patient has no other indications for surgery, splenectomy is sufficient. If the patient has other indications for surgery, splenectomy should be included with the proposed pancreatic operation. A more difficult problem arises when a patient is found to have chronic pancreatitis with splenic vein occlusion and varices but has no symptomatic indications for surgery and has not bled. The risk of bleeding in such patients is unknown. My practice is to inform such patients of the risk but not perform surgery in asymptomatic patients.

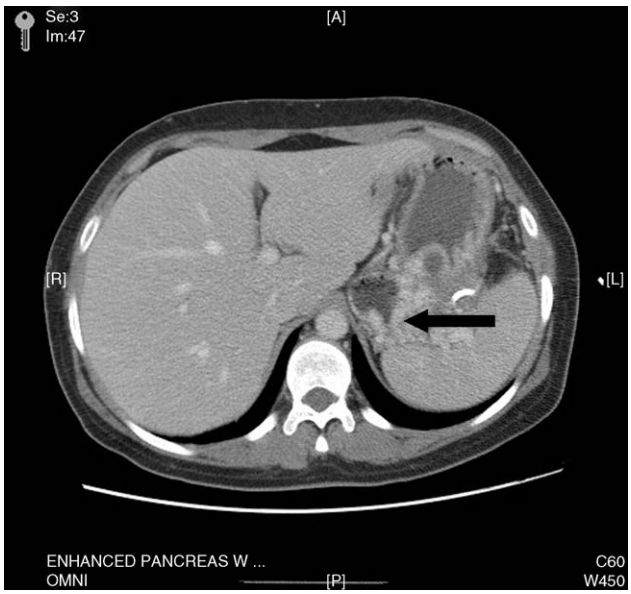

Fig. 2. Computed tomography scan demonstrating a large cluster of gastric and perigastric varices (*arrow*) secondary to splenic vein thrombosis in a patient with chronic pancreatitis.

Occlusion of the superior mesenteric/portal vein as it passes under the neck of the pancreas is also a complication of chronic pancreatitis (Fig. 3). Although it seems that intestinal variceal bleeding rarely, if ever, occurs in such patients, the varices can present a dangerous problem if surgery is attempted on the pancreatic head for some other reason. Difficulty arises when a patient with chronic pancreatitis requires surgery for a compelling indication like bile duct obstruction but is found to have portal vein thrombosis and peripancreatic varices. Although it is possible to perform a pancreatic head resection safely in such circumstances,[14] it is undoubtedly more challenging. A Frey procedure is preferred to either a pancreaticoduodenectomy or a Beger procedure in such a setting, in my opinion, because the dissection of the tunnel beneath the neck of the gland, required in the latter two operations but not in the Frey, is likely to be both extremely difficult and dangerous.

A third group of indications for surgery in chronic pancreatitis relate to complications of rupture of the pancreatic duct. These include pseudocyst, pancreatic fistula, and pancreatic ascites. Pseudocysts (Fig. 4) are the most common manifestation of a duct leak in chronic pancreatitis, and, unlike the pseudocysts that follow attacks of acute pancreatitis, they usually do not resolve spontaneously.[15] Pancreatic fistulas may occur after external drainage of pseudocysts in patients with chronic pancreatitis, a practice that is ill advised, in my opinion. Unlike pseudocysts that occur in patients with acute pancreatitis, where the main pancreatic duct may be normal, the pancreatic duct is often diseased and dilated in patients with chronic pancreatitis (Fig. 5) and the underlying degree of ductal obstruction/hypertension inhibits closure of the fistula when a pseudocyst is drained externally. For this reason, I recommend external drainage of pseudocysts in patients with chronic pancreatitis only when the pseudocyst is grossly clinically infected or in combination with planned surgery (see later). Pancreatic ascites is a variant of ductal rupture that often responds to prolonged total parenteral nutrition but may require surgical intervention.

In the past few years, my approach to pseudocysts in patients with chronic pancreatitis has changed completely (Fig. 6). I no longer perform internal drainage of pseudocysts in patients with chronic pancreatitis but instead focus on the underlying pathology in the pancreatic duct. My approach has been strongly influenced by the very insightful studies by Nealon and Walser[16] and by my operative experiences with the Frey procedure. I have found that the extensive opening of the pancreatic duct during that

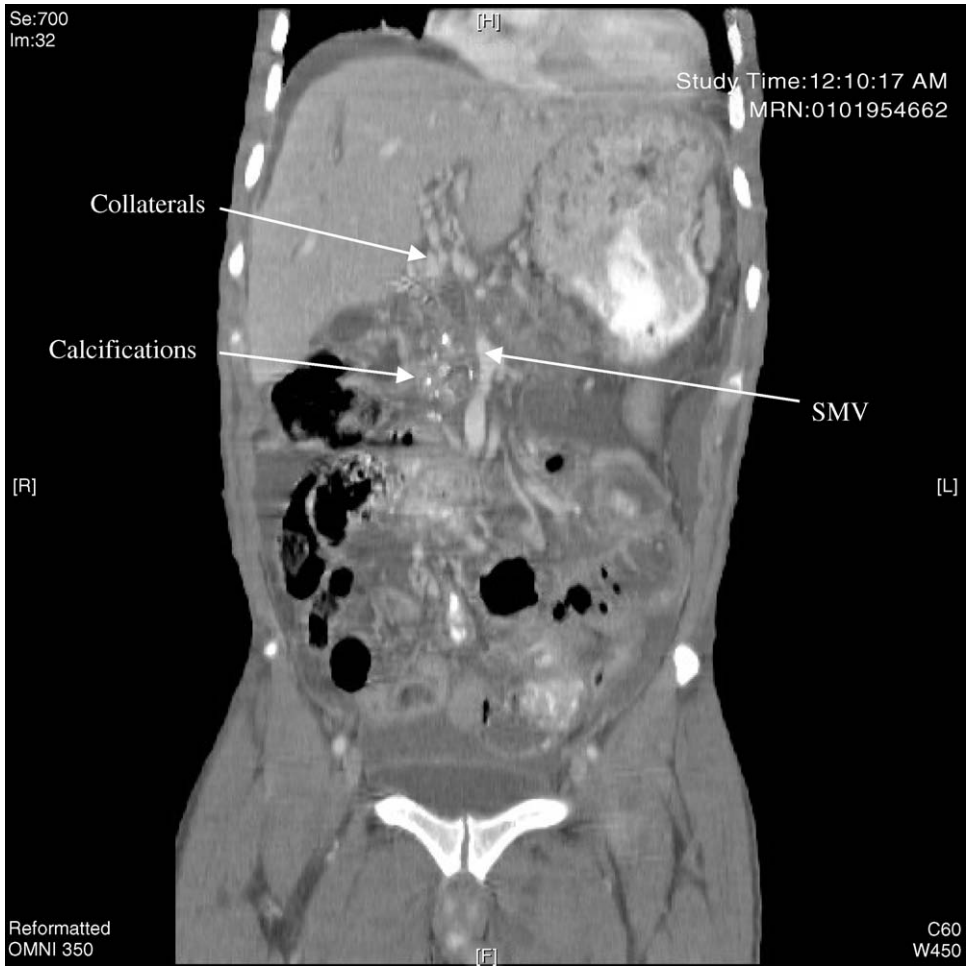

Fig. 3. Thrombosis of the superior mesenteric and main portal vein in a patient with chronic pancreatitis. Note cutoff in superior mesenteric vein (SMV) and collaterals in porta hepatis. Calcifications are visible in the head of the pancreas.

operation sometimes reveals the defect in the duct that is the source of a chronic pseudocyst and actually allows one to slightly enlarge the opening and "drain" the cyst back into the pancreatic duct. Because ductal hypertension is relieved by the pancreaticojejunostomy, it is no longer necessary to drain the pseudocyst itself in any other way. Nealon and Walser's[17] study, in which they compared pancreaticojejunostomy alone with pancreaticojejunostomy plus cystjejunostomy, demonstrates definitively that an anastomosis to the pseudocyst is unnecessary. A corollary conclusion on my part is that a pseudocyst that occurs on the background of chronic pancreatitis should never be treated with traditional internal drainage to the stomach or intestine as an isolated procedure, no matter how tempting and apparently easy the procedure will be. The pseudocyst is much more likely to recur if there is no direct anastomosis of bowel to the opened pancreatic duct. I emphasize once again that these principles apply to patients with *chronic* pancreatitis. The management algorithm of pseudocysts that follow *acute* pancreatitis is very different.

The final indication for surgery in chronic pancreatitis is the suspicion that the patient has developed a pancreatic carcinoma. This is a real concern, because patients with chronic pancreatitis of any kind are at much greater risk of the development of pancreatic cancer than are age-matched control subjects. The relative risk of developing pancreatic cancer in patients with chronic pancreatitis ranges from a 15- to 20-fold risk in patients with alcoholic pancreatitis to a 50-fold increase in patients with hereditary pancreatitis.[18,19] Patients with chronic pancreatitis develop cancer at a cumulative rate of about 0.2% per year. The distinction between chronic pancreatitis and cancer superimposed on chronic pancreatitis can be difficult. The imaging characteristics of cancer, which is primarily made up of fibrous stroma, are quite

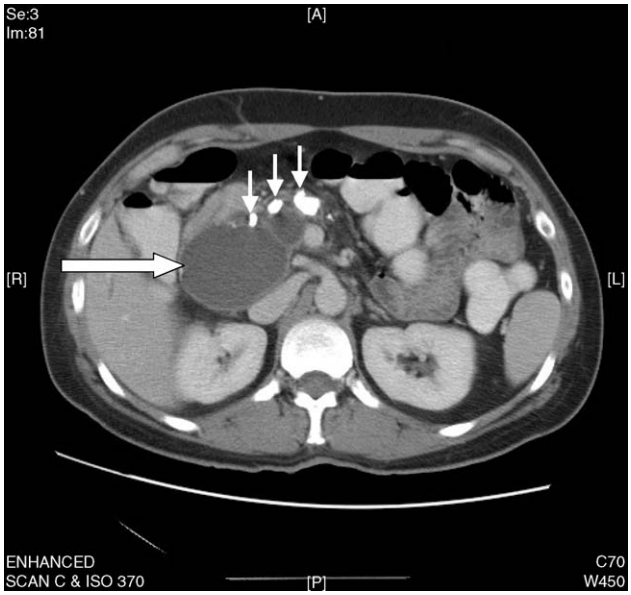

Fig. 4. Computed tomography scan of a pseudocyst (*large arrow*) in a patient with chronic pancreatitis. Note multiple pancreatic duct stones (*small arrows*).

similar to fibrosis from chronic pancreatitis alone. Patients with chronic pancreatitis can develop anorexia, weight loss, and jaundice as a complication of chronic inflammation alone. It is impossible to be dogmatic about when one should intervene surgically in a patient with chronic pancreatitis who is suspected of harboring a pancreatic cancer, but it is appropriate to be liberal about performing pancreaticoduodenectomy when either radiologic imaging or symptoms

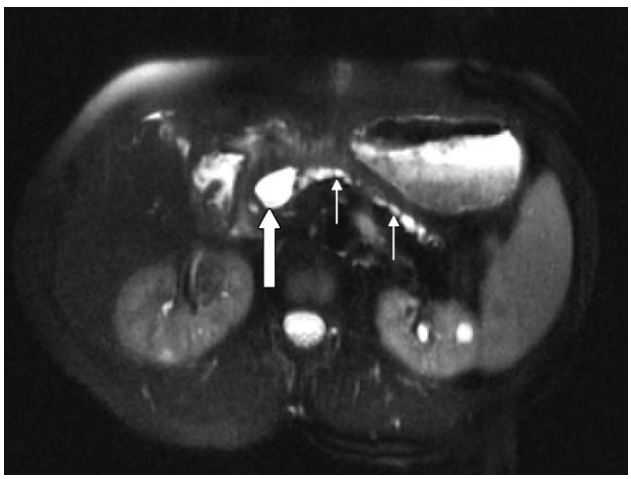

Fig. 5. Magnetic resonance cholangiopancreatography demonstrating a pseudocyst (*large arrow*) of the head of the pancreas in a patient with chronic pancreatitis. The main pancreatic duct (*small arrows*) is dilated and tortuous. (Image courtesy of Dr. Frank Miller.)

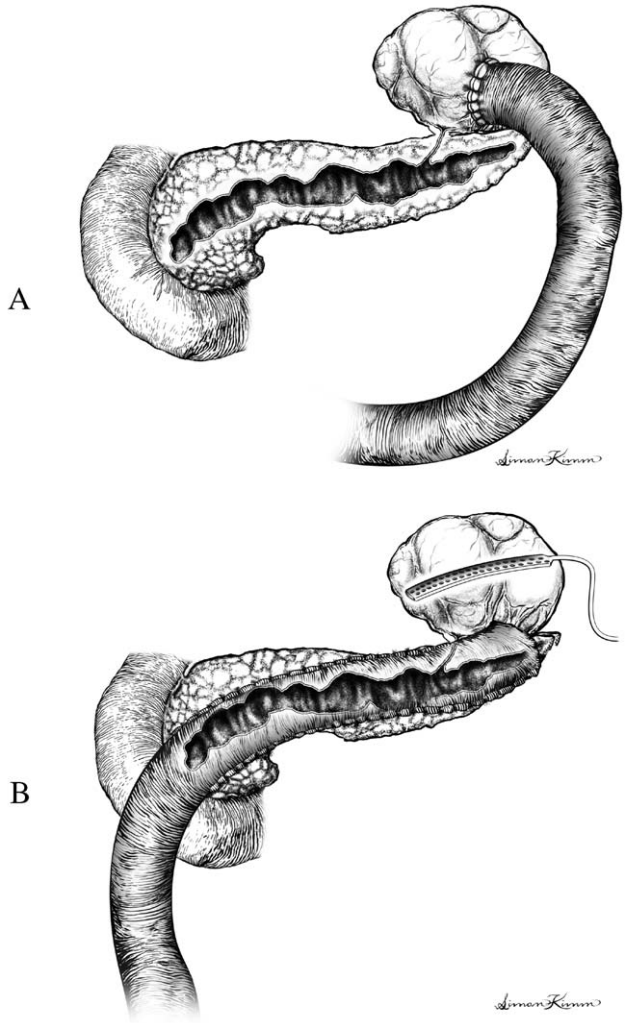

Fig. 6. Traditional internal drainage method for surgical management of pancreatic pseudocyst in patient with chronic pancreatitis (**A**) versus preferred method of pancreaticojejunostomy and pseudocyst drainage (**B**).

are concerning for cancer. This risk of death from pancreaticoduodenectomy in patients with chronic pancreatitis is low (about 1%), and many patients with pain will benefit from resection of the pancreatic head and duodenum even when the pathology reveals only benign disease.[20,21]

CHOICE OF OPERATION

Table 2 lists the operations that are currently performed for chronic pancreatitis.

The lengthy list is unfortunately a testimony to the fact that there is no ideal surgical solution for the

Table 2. Operations for chronic pancreatitis

Duct drainage procedures
Longitudinal pancreaticojejunostomy (Partington-Rochelle or Puestow procedure)
Combined duct drainage-resection procedures
Pancreaticoduodenectomy (classic or pylorus-preserving)
Longitudinal pancreaticojejunostomy with subtotal head resection (Frey procedure)
Duodenum-preserving subtotal resection of head of the pancreas (Beger procedure)
Pure resection procedures
Total pancreatectomy with islet autotransplantation
Neuroablative procedures
Thoracic splanchnicectomy

disease. Dissatisfaction with duct drainage procedures alone led for a time to the use of extensive resections of the pancreas, but the morbidity associated with those procedures was excessive, and we now find ourselves in an era where the operations that generally achieve the best results combine features of resection and duct drainage.

Pancreaticoduodenectomy is the correct operation when carcinoma of the head of the pancreas is suspected. Whether an antrectomy is performed or the pylorus is preserved is not particularly important. It is not fruitful to spend time doing biopsies, unless the suspicious area is outside the bounds of resection (celiac node, liver). Biopsies of the head of the pancreas are time consuming and may be misleading. Local nodes that would be removed in the course of the resection should not undergo biopsy. The operation should be performed as an oncologic procedure, assuming that cancer may be present, paying particular attention to the uncinate process margin, taking the uncinate process right on the superior mesenteric artery.

When suspected cancer is not an issue, I have found over the past few years that the Frey procedure[22,23] is a very versatile procedure for chronic pancreatitis. This procedure combines a longitudinal decompression of the pancreatic duct in the body and tail of the gland with a subtotal resection of the pancreatic head that preserves the duodenum. The operation was originally described for patients who have "head-predominant" disease on the assumption that the enlarged complex head, full of fibrosis and obstructed ducts, was not adequately addressed by simply decompressing the main pancreatic duct according to the method of Puestow. I have found that the procedure, while certainly appropriate for that type of patient, is actually applicable to a wide variety of patients with chronic pancreatitis and to a variety of complications of the disease. The Frey operation allows the surgeon to decompress an obstructed bile duct from within the head of the pancreas, an approach that results in maintenance of bile duct continuity and avoids the necessity for a biliary bypass. The Frey procedure is also applicable in patients with pseudocysts, fistulas, or pancreatic ascites. It is a particularly nice approach for patients with pseudocysts on the posterior surface of the head of the gland, an area very difficult to approach by traditional internal drainage methods. As I have gained experience in managing pseudocysts in patients with chronic pancreatitis, as I indicated earlier, I use the Frey procedure for most of them.

The Frey procedure has been slow to be adopted in the United States, as has its European cousin, the Beger procedure, a variant of the duodenum-preserving head resection. Both operations are unlike any other previous pancreatic operation in that they involve "coring out" the majority of the head of the pancreas while leaving a thin rim of remaining pancreas around the circumference. The dissection leaves nothing but fibrous tissue on the back side of the defect in the head of the gland. In the process of removing the head of the pancreas, the bile duct, which is closely adherent to the back of the head of the pancreas, is identified and freed up from the surrounding scar tissue. This is an approach that is fundamentally different than any other operation in the repertoire of most general surgeons, and it is difficult to learn. Because few surgeons perform the procedure, there are few teachers available. This has been an unfortunate barrier to more widespread use of the procedure, which has been shown in some studies to be superior to other traditional approaches such as pancreaticoduodenectomy (see later).

I perform the Frey procedure through either a midline or bilateral subcostal incision, depending on the angle of the patient's costal margin. The operation should begin with a thorough exploration of the peritoneal cavity, particularly looking at the liver and peritoneal surfaces for any evidence of unsuspected pancreatic cancer. Assuming that exploration is negative, I begin the operation by incising the retroperitoneal tissues above the hepatic flexure of the colon and gently sweeping the hepatic flexure inferiorly. The base of the right portion of the transverse mesocolon inserts on a line crossing the head of the pancreas, and it is critical to incise the upper peritoneal investment of the transverse mesocolon at its junction with the head of the pancreas and sweep the fat and vessels of transverse mesocolon inferiorly so that the anterior surface of the head of the pancreas is fully exposed. Failure to perform this critical step will make the subsequent resection of the head of the pancreas

impossible. Once the head of the pancreas and the anterior surface of the duodenum have been fully exposed, a Kocher maneuver is performed. The Kocher maneuver should be carried proximally as far as the hepatoduodenal ligament and distally as far the superior mesenteric vessels. If there is not too much inflammation or fat, this is a good time to make a preliminary identification of the main trunk of the superior mesenteric vein below the neck of the pancreas.

I then enter the lesser omental sac to fully expose the body and tail of the pancreas. I usually enter the lesser sac by taking the omentum completely off the transverse colon and retracting it superiorly with the stomach. It is also possible to leave the omentum attached to the colon and enter the lesser sac through the omentum. The exposure is equivalent, but the latter method seems to result in greater devascularization of the omentum and the need to sacrifice portions of the omentum at the end of the case. Once the body of the pancreas has been identified in the base of the lesser sac, its anterior surface must be completely exposed by a combination of sharp and blunt dissection. This is usually not difficult, but sometimes the stomach can be very adherent to the gland and make the dissection tedious. Once the body and tail have been exposed, I usually make an incision in the retroperitoneal tissues along the inferior edge of the pancreas. Careful dissection will then allow one to enter an avascular plane behind the body and tail of the pancreas. This maneuver elevates the inferior edge of the pancreas and makes the subsequent anastomosis easier, but is not essential if the dissection is difficult due to inflammation.

The next step in the operation is critical to providing satisfactory exposure. The middle colic vein on the upper surface of the transverse mesocolon is followed down to the point where it meets the right gastroepiploic vein, forming the so-called gastrocolic trunk. This short trunk then empties into the superior mesenteric vein *below* the neck of the pancreas. For this reason, the right gastroepiploic vein and its surrounding fat obscure the view of the neck of the pancreas. Therefore, the right gastroepiploic vein has to be ligated and divided close to its entrance into the gastrocolic trunk and then the anterior surface of the neck of the pancreas exposed by gently peeling the gastric side of the divided vein superiorly and away from the pancreatic surface.

At this point, I turn my attention to the upper portion of the neck of the pancreas and identify the gastroduodenal artery as it emerges from the common hepatic artery. In this case, one looks for the artery with the stomach and duodenum retracted upward

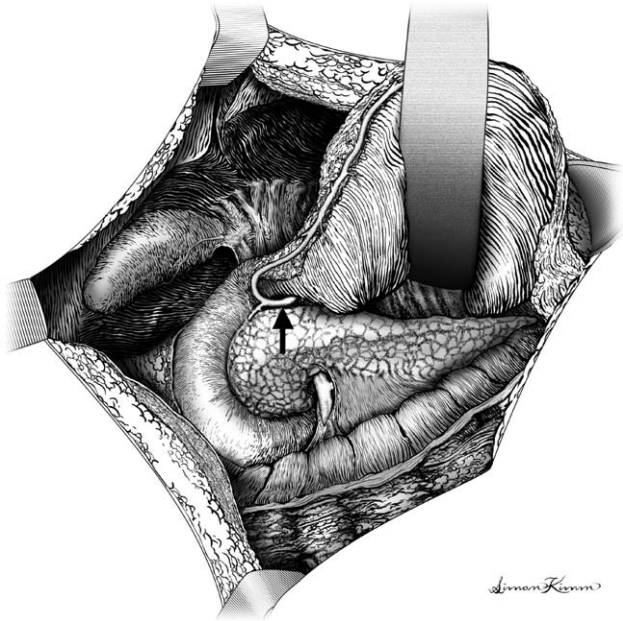

Fig. 7. Depiction of the gastroduodenal artery emerging from behind the duodenum at the pancreatic neck, where it gives off the right gastroepiploic and anterior superior pancreaticoduodenal arteries.

(Fig. 7). This is a completely different approach than the dissection of the gastroduodenal artery during a pancreaticoduodenectomy, when the artery is isolated above the duodenum. The dissection of the artery during a Frey procedure is done along the upper surface of the pancreas at the point where the postpyloric area meets the head of pancreas and becomes inseparable from it. The gastroduodenal artery emerges from above the upper edge of the pancreas and first gives off the right gastroepiploic artery, which I sometimes ligate at its origin from the gastroduodenal to further improve the exposure of the neck of the pancreas. The gastroduodenal artery then continues as the anterior superior pancreaticoduodenal artery. To perform a Frey procedure well, it is desirable to identify and expose the anterior pancreaticoduodenal artery on the surface of the upper portion of the head of the pancreas. Once the artery has been identified, I attempt to mobilize it and retract it superiorly to free up more of the anterior surface of the head of the gland. This may involve dividing tiny branches of the artery. It is usually possible to gain only a few additional millimeters of exposure of the head of the gland by doing so, but the extra exposure helps when doing the superior portion of the anastomosis between the pancreas and jejunum later.

Once satisfied that the exposure of the entire surface of the head, neck, body, and tail of the pancreas

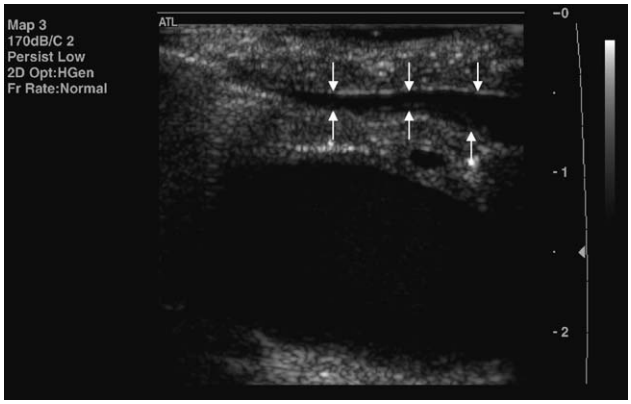

Fig. 8. Intraoperative ultrasound image of the pancreatic duct (*small arrows*). Pancreatic parenchyma is hyperechoic, consistent with chronic pancreatitis.

is as complete as possible, I use intraoperative ultrasound to locate the pancreatic duct (Fig. 8). Holding a needle perpendicular to the anterior surface of the neck or proximal body of the pancreas and puncturing the pancreas at approximately the mid-point between its upper and lower borders, I pass a needle under ultrasound guidance into the pancreatic duct and then make an incision in the pancreas, following the needle down until the duct is reached. Once the pancreatic duct is entered, a clamp is placed in the duct for guidance and the tissue over the clamp progressively divided in both directions. The head of the gland should be opened to within a centimeter of the duodenum. The duct should be opened to within 2–3 cm from the left end of the gland.

Before "coring out" of the head of the pancreas, I place a series of 3-0 polypropylene sutures for hemostasis around the circumference of the head of the gland, just outside the palpable edge of pancreatic tissue where possible. The tails of the sutures are left long and clamped. Using the cautery, I then mark the extent of the planned resection of the head of the gland just inside the sutures and inside the palpable edge of the head of the pancreas so that there is about a 4- to 5-mm cuff of pancreatic tissue, which will remain after the resection (Fig. 9). Starting at any convenient point, the dissection is then carried straight downward through the pancreatic tissue until a plane of dense areolar tissue is reached that invests the back of the head of the pancreas and envelops the bile duct. Once this plane is reached, the remaining attachments of the core of pancreatic head are dissected free. It is important to be aware that in this dissection the entire main pancreatic duct is completely excised as it courses through the head of the pancreas. The common bile duct will be visible or palpable to varying degrees after the head of the pancreas has been cored out, crossing the posterior aspect of the cavity (Fig. 10). If the operation is being done for bile duct obstruction, it is critical to be sure that any pancreatic tissue that might be restricting the bile duct is cautiously excised. For this

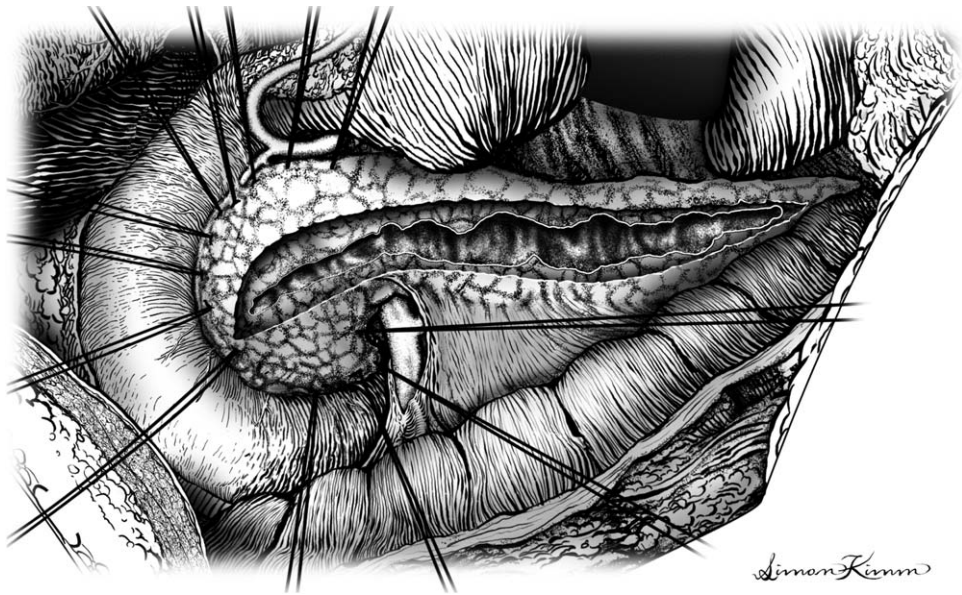

Fig. 9. Depiction of hemostatic sutures in place before resection of the core of the pancreatic head. The line of resection is circular and lies just within the sutures.

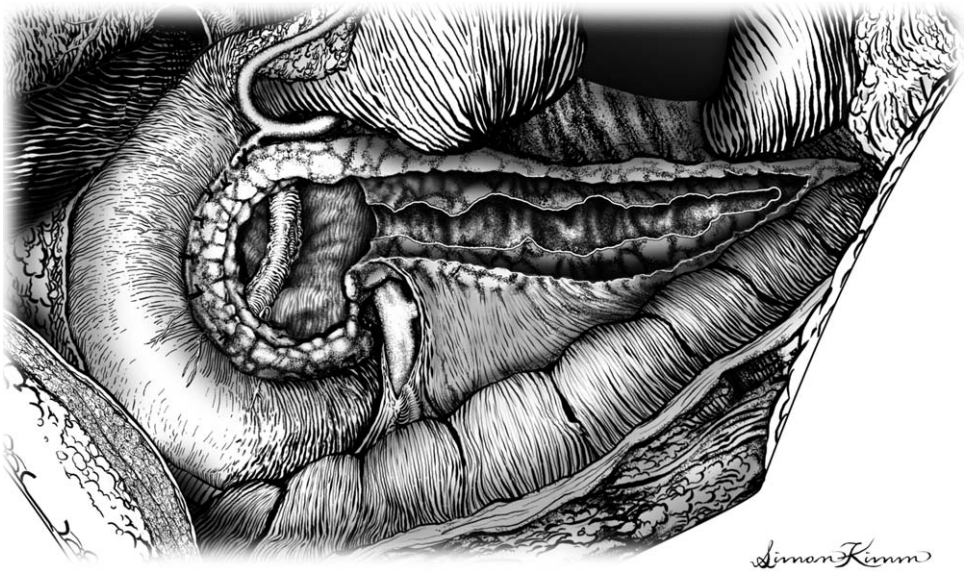

Fig. 10. Completed subtotal resection of the pancreatic head. The common bile duct crosses the bottom of the resection field.

part of the operation, I use scissors rather than cautery so that the plane along the bile duct is not obscured by charred tissue. If it is difficult to be sure where the bile duct is located, one can remove the gallbladder and pass a Bakes dilator through the cystic duct down the common bile duct to act as a guide to dissection. If the bile duct is inadvertently entered, it is opened widely and the edges tacked back to the surrounding fibrous tissue, thus allowing bile and pancreatic juice to drain together into the Roux-en-Y jejunal limb used to cover the defect in the pancreas.

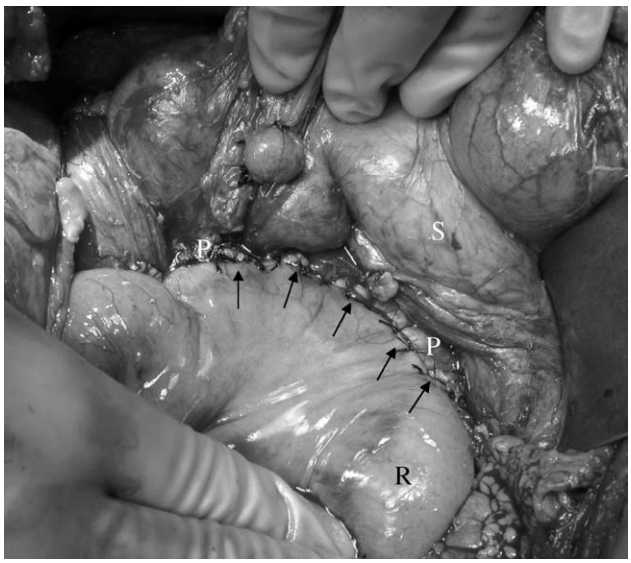

Fig. 11. Completed pancreaticojejunal anastomosis (*arrows*) in Frey procedure. P = pancreatic parenchyma; S = stomach; R = closed end of the Roux-en-Y limb of jejunum.

Once the dissection is complete, the tails of the hemostatic sutures are cut. A Roux-en-Y limb is prepared in the usual fashion and brought through the base of the right transverse mesocolon. The stapled or oversewn end of the limb generally lies best to the left toward the tail of the gland. I then perform a two-layer anastomosis between the pancreas and the jejunum (Fig. 11). The outer layer is done with interrupted 3-0 silk and the inner layer with a continuous suture of 3-0 polypropylene, which I use because I believe it is more resistant to digestion than other forms of suture material. When performing the pancreaticojejunostomy, it is important to be conservative about the size of the opening in the jejunum. It stretches and it is easy to make it too big. It is best to start small and enlarge as necessary. The operation is completed by performing a jejunojejunostomy 40 cm below the pancreatic anastomosis.

Pain control is often an issue in the immediate postoperative period. I always place an epidural catheter preoperatively in these cases, but this is sometimes inadequate and patients need to be changed to intravenous opiates. Particularly in patients who were narcotic dependent preoperatively, the amount of opiate that must be given for postoperative pain control can be prodigious. Otherwise, the postoperative care is similar to that for other major abdominal operations. The pancreatic leak rate is low—less than 5% overall—compared with that after resections for cancer.

The results of the Frey procedure are quite good and appear to surpass those of previous operations for chronic pancreatitis. There has been no direct

randomized trial of the Frey procedure against the traditional Puestow procedure, but it seems likely that the Frey procedure would be more effective in patients with a large pancreatic head and multiple obstructed side branches. Nevertheless, its superiority to standard pancreaticojejunostomy has not been proved in a rigorous way.

The Frey procedure was compared with pylorus-preserving pancreaticoduodenectomy in a prospective randomized trial at the University of Hamburg.[24] Sixty-one patients were randomly allocated to either the Frey procedure (n = 31) or pancreaticoduodenectomy (n = 30). The morbidity rate was 19.4% in the Frey group and 53.3% in the pancreaticoduodenectomy group. Both operations were effective in relieving pain; the pain score decreased after surgery by 94% in the Frey group and by 95% after pancreaticoduodenectomy. However, with median follow-up of 2 years, the global quality of life improved by 71% in the Frey group but by only 43% in the pancreaticoduodenectomy group ($P < 0.01$), suggesting that there was ongoing morbidity from the pancreaticoduodenectomy that had a negative affect on the long-term surgical outcome. Similar results were recently reported in a prospective but nonrandomized study of the two procedures by a different group of surgeons.[25]

In an extensive single-institution experience with the Beger variant of the duodenum-preserving pancreatic head resection, pain was relieved in 91% of patients who could undergo long-term evaluation.[11] Hospital admission for acute exacerbations of chronic pancreatitis fell from 69% before surgery to 9%.

Since 2000, I have performed the Frey procedure in 19 patients with chronic pancreatitis. Sixteen of the patients had chronic pain as the primary indication for surgery; two were operated with a primary indication of recurrent pseudocyst, and one with a primary indication of common duct obstruction. Two patients had concomitant splenectomy for sinistral portal hypertension. The approach through the head of the pancreas is not a familiar one to most surgeons, and I prepared for this procedure both by observing cases with Dr. Frey in California and by observing Beger procedures in Bern, Switzerland, and Stockholm, as well as performing some cadaver dissections. Despite this, it still takes some time to be comfortable with an aggressive subtotal head resection.

In follow-up of the 19 patients, 3 have continued to have pain. In two patients, both of whom were dependent on opiates preoperatively, the operation did not significantly help them. One patient experienced mild pain after 2 years of being symptom free and may require a left extension of his pancreaticojejunostomy to fully decompress the tail of the gland. All pseudocysts have resolved.

In summary, the duodenum-preserving pancreatic head resections described by Beger and Frey appear to represent an advance in the surgical management of chronic pancreatitis. They are useful in the management of most operative indications for surgery in patients with chronic pancreatitis, with the exception of the situation in which a superimposed carcinoma of the pancreas is suspected, in which case a traditional pancreaticoduodenectomy or distal pancreatectomy/splenectomy is required.

The author would like to thank Professors Charles Frey, Markus Buchler, and Johan Permert for the opportunity to observe and participate in duodenum-preserving head resection procedures in their operating rooms. Their teaching was much appreciated. I would also like to thank Simon Kimm for his excellent artwork created for this manuscript.

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Spontaneous Intramural Esophageal Hematoma

Sarah C. Thomasset, M.B.Ch.B., David P. Berry, M.D.

We report the case of an 80-year-old woman who developed a spontaneous intramural esophageal hematoma and review the available literature. Spontaneous intramural esophageal hematoma (SIOH) is a rare but important condition. Because the cardinal symptom is severe chest pain, the condition is often initially misdiagnosed as an acute cardiac event or aortic dissection. Increased awareness of SIOH may prevent misdiagnosis on the basis of endoscopic and radiological appearances. (J GASTROINTEST SURG 2005;9:155–156)

KEY WORDS: Esophagus, hematoma, spontaneous

CASE REPORT

An 80-year-old woman was admitted with severe, sudden-onset chest pain radiating to her back. There[1] was no history of breathlessness, nausea, or vomiting. Before admission, she was taking omeprazole, propranolol, and mebeverine for gastroesophageal reflux disease, anxiety, and diverticular disease, respectively. Omeprazole had been commenced 10 years previously when the patient presented to her general practitioner with heartburn. Esophagogastroduodenoscopy (EGD) performed at the time was unremarkable. On examination, the patient was alert and hemodynamically stable. Further examination was unremarkable. An electrocardiogram (ECG) showed T-wave inversion in leads V_5 and V_6, and a non–ST-elevation myocardial infarction was considered the most likely diagnosis. Initial treatment consisted of oxygen, diamorphine, metoclopramide, glyceryl trinitrate (GTN) spray, aspirin, and enoxaparin. However, severe chest pain persisted throughout days 1 and 2. Further doses of diamorphine were given and a GTN infusion commenced. The patient remained hemodynamically stable. On day 2 the patient experienced odynophagia and refused to eat. Serial cardiac enzyme results were negative, and results of all other blood tests, including amylase, were within normal limits. A chest radiograph was normal. On day 2, a thoracic computed tomography scan was obtained to rule out aortic dissection. There was no evidence of aortic dissection; however, a distended esophagus was seen in the upper mediastinum along with a filling defect just below the carina compressing the esophageal lumen (Fig. 1). An esophageal contrast swallow demonstrated a slightly delayed transit time, and an esophageal tumor was considered the most likely diagnosis. On day 3, the patient underwent an EGD where a submucosal esophageal hematoma was seen extending from 17 to 30 cm (Fig. 2). There was no evidence of an esophageal tumor. Echocardiography revealed a hypertrophied left ventricle, thought to be secondary to hypertension, which would account for the ECG finding of inverted T waves in leads V_5 and V_6. Following the diagnosis of an esophageal hematoma, a conservative approach was adopted; GTN, aspirin, and enoxaparin were stopped; and omeprazole was begun. Hemoglobin and clotting were monitored daily, and all results were within normal limits. On day 6, oral fluids were recommenced, and diet was introduced thereafter. After 14 days, the patient was discharged home and was asymptomatic at outpatient follow-up 6 weeks later.

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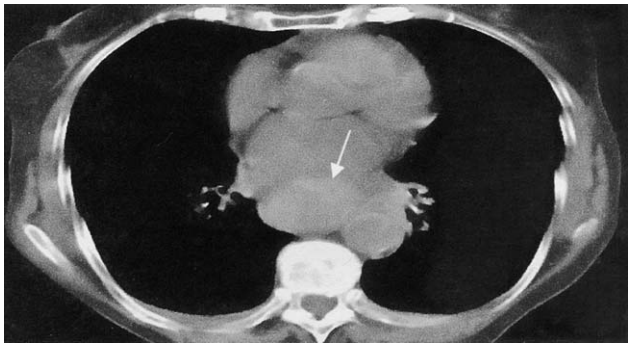

Fig. 1. Computed tomographic appearance of a spontaneous esophageal hematoma (white arrow).

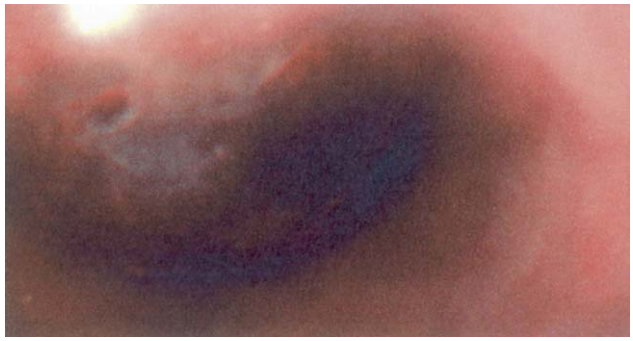

Fig. 2. Endoscopic appearance of a spontaneous esophageal hematoma. A bulging, purple lesion is seen projecting from the posterior esophageal wall.

DISCUSSION

Esophageal hematomas are uncommon but occur within the submucosal plane of the esophagus, causing dissection of mucosa from its underlying muscle. Esophageal hematomas can occur spontaneously, may be precipitated by direct trauma, or may be iatrogenic complicating procedures such as esophageal dilatation and sclerotherapy for varices. SIOH is most frequently described in elderly women, although the etiology and pathogenesis remain unclear.

Symptoms associated with an esophageal hematoma include chest pain (83%), hematemesis (71%), odynophagia (41%), and dysphagia (32%).[1] Chest pain is typically retrosternal and severe with radiation to the back, neck, or throat and is the cardinal symptom of SIOH, leading to frequent misdiagnoses of aortic dissection or an acute cardiac event. Distinguishing an esophageal hematoma from cardiac ischemia is important because SIOH can be worsened by thrombolysis and anticoagulation.

The diagnosis of SIOH is made on endoscopy. Initially, a bulging, purple lesion that is usually situated in the posterior esophagus is characteristic and may be confused with an esophageal carcinoma or a large varix.[2] The hematoma can also be demonstrated on computed tomography (CT), where it appears as an eccentric, well-defined intramural esophageal mass.[3] CT is helpful in excluding conditions that may mimic SIOH, for example, other mediastinal mass lesions and aortic dissection. An esophageal contrast swallow usually reveals a filling defect in the mid and lower esophagus; however, if contrast enters the intramural dissection space, a "double-barreled" esophagus is seen.[4]

Despite a dramatic presentation, most patients with SIOH have an excellent outcome when managed conservatively. The patient should be kept nil by mouth to prevent food impaction and further mucosal dissection.[4] Intravenous fluids should be commenced and blood transfusions given if required. Administration of a proton pump inhibitor seems sensible, although there is no trial evidence to justify this. Oral intake should be reintroduced gradually. The role of surgery is limited in patients with SIOH, and fatal outcomes have been reported following thoracotomy for the condition.[5] Recurrence is extremely rare.

SIOH, although rare, is an important differential diagnosis of retrosternal chest pain in elderly women, especially when the pain does not respond to cardiac medication.

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