"How I Do It" Session: Intraductal Papillary Mucinous Neoplasms of the Pancreas—The Year 2002

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This "How I Do It" session represents a continuing yearly series, focusing on current, timely, and hot topics in the field of pancreatic disease. Immediate past topics have included: imaging of benign and malignant pancreatic diseases, the role of adjuvant therapy in pancreatic adenocarcinoma, and the role of extended lymphadenectomy in patients with pancreatic adenocarcinoma.

This "How I Do It" session brought together three experts to discuss the topic of intraductal papillary mucinous neoplasms of the pancreas (IPMN). The audience was prompted to focus on six specific issues relevant to IPMN:

- What is new in the field of IPMN?
- Is the apparent epidemic of increasing numbers of patients with IPMNs real?
- What is the appropriate preoperative work-up in a patient suspected of harboring an IPMN?
- What is the appropriate extent of pancreatic resection?
- What should be done specifically, when in the operating room, when a surgeon is confronted with an IPMN?
- What are the specific strategies for postoperative surveillance in patients with a resected IPMN?

The invited speakers/participants for this session included N. Volkan Adsay, M.D., an expert pancreatic pathologist whose topic was "Pathology and Molecular Genetics." Next, Carlos Fernandez-del Castillo, M.D., discussed "Surgical Resection: The Conservative Approach." And last, L. William Traverso, M.D., discussed "Surgical Resection: The Aggressive Approach." A brief synopsis of these three topics follows.

Presented as part of the "How I Do It" Symposium of the Pancreas Club, May 19, 2002, San Francisco, California.

1091-255X/02/$—see front matter
PII: S1091-255X(02)00056-2

Intraductal Papillary Mucinous Neoplasms of the Pancreas: Pathology and Molecular Genetics

N. Volkan Adsay, M.D.

Intraductal papillary mucinous neoplasms (IPMN) form an increasingly well recognized category of neoplasms of the pancreas.[1–3] These neoplasms are characterized by intraductal proliferation of neoplastic mucinous cells, which often form papillae, and lead to cystic dilation of the pancreatic ducts, resulting in clinically and macroscopically detectable masses (Fig. 1). Originally recognized by Ohhashi et al. in 1982,[4] these tumors have been reported under a plethora of names, including villous adenoma, papillary neoplasia, mucin-producing tumors, and mucinous duct ectasia, each reflecting a different facet of these neoplasms. The nomenclature was unified under the heading of IPMN in 1994, a term also endorsed by the World Health Organization (WHO).[5]

As a category, IPMN has been differentiated from mucinous cystic neoplasms that are also cystic, papillary, and mucinous tumors. However, the latter are seen in perimenopausal females, form well-demarcated, thick-walled multilocular cysts with no connection to the native ducts, and occur almost exclusively in the tail of the pancreas.[6] Present in almost all cases of mucinous cystic tumors, including the rare male patient, is the pathognomonic and entity-defining ovarian-like stroma (positive for estrogen/progesterone receptors), which help distinguish them from IPMN (Fig. 2).

As a type of intraductal neoplasia, IPMN is also somewhat similar to pancreatic intraepithelial neoplasia (PanIN), the microscopic form of intraductal

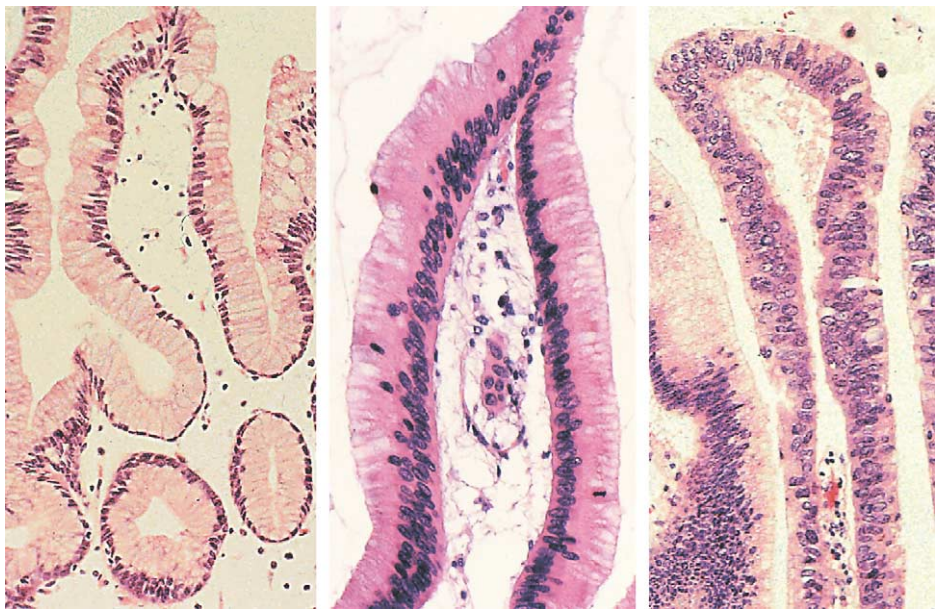

Fig. 1. Neoplastic spectrum in IPMN. Intraductal papillary mucinous neoplasms exhibit a spectrum of cytoarchitectural atypia from those with simple cysts and papilla (*left*) lined by cytologically bland, uniform, well-polarized, tall columnar cells (classified as adenoma), to those with significant atypia (*right*), displaying nuclear enlargement, overlapping of nuclei, hyperchromatism, and loss of polarity (classified as carcinoma in situ). In many patients, there is a mixture of different grades of this spectrum represented within a single tumor.

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00057-4

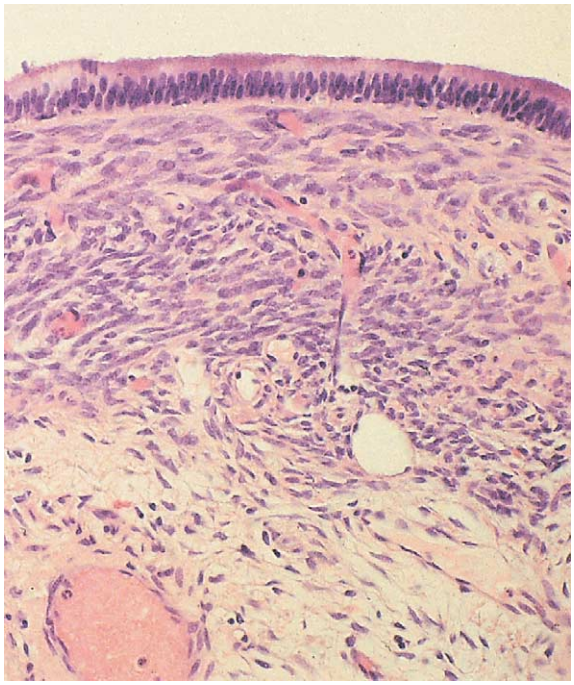

Fig. 2. Mucinous cystic neoplasm. Mucinous cystic neoplasm is a tumor seen almost exclusively in females (>90%) of perimenopausal age group (mean 50 years). Mucinous cystic neoplasms typically form a thick-walled multilocular cystic mass in the tail of the organ with no demonstrable communication with native ducts. Ovarian-like stroma depicted here is pathognomonic for mucinous cystic neoplasms. This stroma has striking histologic resemblance to ovarian stroma and commonly expresses estrogen and progesterone receptors. It is present in the vast majority (if not all) of mucinous cystic neoplasms, is specific to this tumor, and has arguably become a requirement for the histopathologic diagnosis of this tumor type.

dysplasia.[7] PanIN is often detected incidentally in pancreatectomy specimens, in contrast with IPMN which manifest clinically, radiologically, and macroscopically. Therefore, IPMN can be regarded as a mass-forming type of dysplasia, similar to villous adenomas of the colon. Preliminary data indicate that the molecular mechanisms involved in the pathogenesis of these microscopic (PanIN) versus mass-forming type of dysplasia (IPMN) appear to be different.[8] Another example of mass-forming dysplasia in the

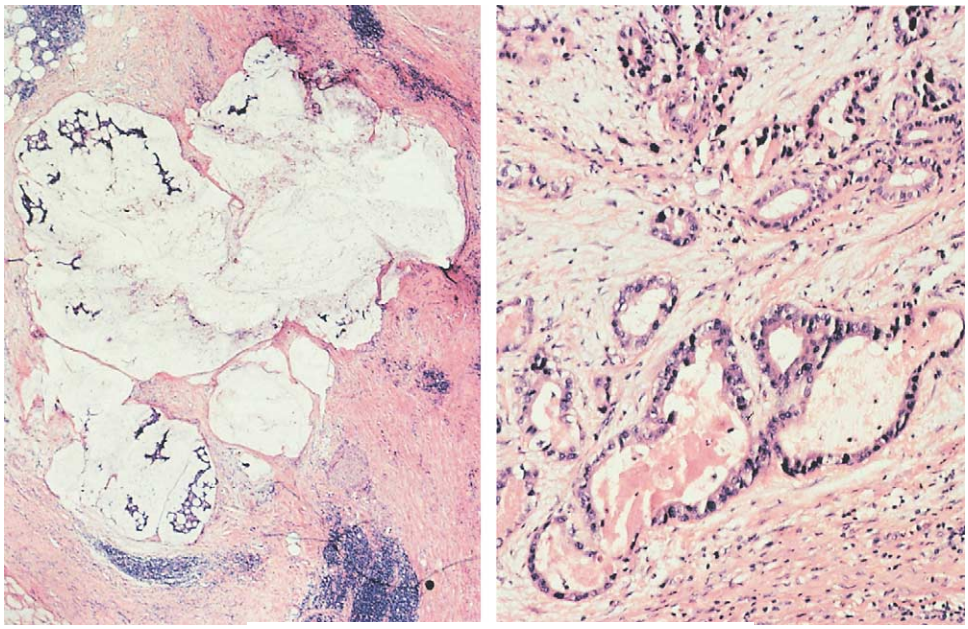

Fig. 3. Invasive carcinoma associated with IPMN: colloid (*left*) and tubular (*right*) types. In one-third of IPMN patients, there is an invasive carcinoma associated with IPMN at the time of resection. Colloid carcinoma (*left*), also referred to as mucinous non-cystic or muconodular; it is characterized by stromal lakes of mucin that contain scanty carcinoma cells floating within the mucin. Tubular-type invasive carcinoma (*right*) is morphologically indistinguishable from the conventional (ordinary) ductal adenocarcinoma of the pancreas, characterized by infiltrating tubular elements embedded in a desmoplastic stroma.

pancreas, recently recognized, is intraductal oncocytic papillary neoplasm which appears to be a close relative of IPMN.[9]

Whereas the general characteristics of IPMN as a group and its delineation from other pancreatic neoplasms have been well established, several issues remain unresolved. Foremost is how to define prognostic and therapeutic subgroups of this entity that encompasses such a wide range of lesions from nonproliferative to highly proliferative to invasive.[2] It is largely accepted that IPMNs have a spectrum of neoplastic transformation ranging from adenoma to borderline to carcinoma in situ. Further, in approximately one-third of the cases IPMNs are associated with invasive carcinoma of either tubular or mucinous non-cystic (colloid) types (Fig. 3).[10] The issue that causes the most concern in the grading/classification of IPMNs, are those cases that have behaved in an aggressive manner (i.e., metastasized) despite the lack of any identifiable histologic evidence of carcinoma in situ or invasive carcinoma.[2] Although these cases raise the possibility that IPMN is a tumor of undeterminable malignant potential, there are other, perhaps more credible explanations for the unexpected course of these cases. Some IPMNs appear to be multifocal. In addition, areas of carcinoma are often distributed randomly in the tumor, and may be missed both clinically and during incomplete pathologic sampling. Moreover, it appears that IPMNs may not only progress to invasive carcinoma, but also serve as a marker of invasion elsewhere in the pancreas; there are cases in which an IPMN in the head of the pancreas was associated with a seemingly independent invasive carcinoma in the tail of the gland.

On one hand, this grading scheme has occasionally failed to identify the tumors that subsequently behaved aggressively. On the other hand, the clinical course of those with invasive carcinoma (even those with tubular type invasion) have, at times, been unexpectedly protracted.[2] This raises the possibility that the invasive carcinomas that develop from IPMNs may be biologically different from those that develop de novo or from other types of precursor lesions.

Despite the occasional discrepancy, in my opinion, the grading/classification of IPMN as adenoma, borderline, and carcinoma in situ, and the identification and typing of invasive carcinoma, is still the best predictor of potential outcome in IPMNs. Further, in addition to the grade and size (extent) of the tumor, and presence or absence of invasion, some authors have also found that "main-duct" tumors may have a different biology than the "branch-duct" tumors.[11]

The type of epithelium is also a potential indicator of the differences in the biology of IPMN.[2,8,12] Some IPMNs have long papillae identical to those of villous adenomas, and in others, there are more complex papillae lined by cuboidal cells, similar to those of the biliary tree. These have been designated by various terms by different authors. Some have employed the terms villous dark cell, papillary clear cell, and compact cell type, while others have classified them into gastrointestinal and pancreatobiliary types, respectively. While some authors regard these patterns as a mere reflection of grades in the progression, others consider them to be morphologically distinct subtypes of IPMNs. Preliminary data suggest that the pancreatobiliary type papilla is more prone to be associated with tubular type invasion, while the intestinal type with colloid type invasion.

The molecular events involved in the pathogenesis of IPMN are under intense scrutiny by many researchers.[13–17] The incidence of mutations in the k-ras and p53 genes appear to be lower (almost half) in IPMN than in ordinary ductal adenocarcinoma.[18] This is largely expected, considering that most IPMNs are preinvasive but nonmalignant neoplasms. Interestingly, IPMNs appear to lack p16 mutations, which are found in 90% of conventional ductal adenocarcinoma. Similarly, the loss of DPC4 gene, noted in 50% of ductal adenocarcinomas, does not seem to occur in IPMNs.[19] Recently, STK11/LKB1 Peutz-Jeghers gene inactivation was detected in 30% of IPMNs studied.[20] Cox2 expression in IPMNs is not uncommon, rendering it, at least hypothetically, a candidate for chemoprevention with anti-cox2 agents.[21] Some molecular alterations may have potential application in prognostication of IPMNs.[22] For instance, in some studies MUC1 was found to be associated with pancreatobiliary type papillae and tubular type invasion, while MUC2 was associated with intestinal type papilla and colloid type invasion.[8,12]

Although there have been major advances in our definition and classification of IPMNs, there is still much to be learned about the natural course and biologic behavior of these tumors. Such advances will allow for more accurate prediction of prognosis and for the placement of patients into appropriate treatment categories.

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Surgical Treatment of Intraductal Papillary Mucinous Neoplasms of the Pancreas: The Conservative Approach

Carlos Fernandez-del Castillo, M.D.

In the 20 years that have elapsed since the initial description of intraductal papillary mucinous neoplasm (IPMN),[1] this entity has become one of the most common diagnoses in the field of pancreatology. Its epidemiology, natural history, and proper management remain in a state of flux, and therefore, surgical treatment is not standardized.

In its classic form, IPMN presents as a dilated main pancreatic duct, full of mucus that extrudes through a bulging ampulla. Patients may have recurrent episodes of pancreatitis-like pain, with or without hyperamylasemia, and not infrequently have steatorrhea, diabetes, and weight loss. In this form of IPMN, the neoplasm originates in the main pancreatic duct, more commonly in the cephalic portion (right side), and from there, spreads to the rest of the duct.

It is now well-recognized that IPMN can also originate in the side branches of the pancreatic ductal system. These occur mostly in the uncinate process of the pancreas. A large proportion of these patients are asymptomatic, and the tumors are detected by CT or ultrasound done for other reasons. A minority of patients present with abdominal pain or pancreatitis. It is unclear if this variant represents an entity that remains localized or one that can also spread into the main ductal system, but studies do show that the side-branch variety of IPMN is associated with smaller tumors and a lesser likelihood of malignancy.[2–5]

The surgical management of IPMN is different than that of serous cystadenomas and mucinous cystic neoplasms. Whereas, in the latter two, the preoperative studies allow the surgeon to accurately locate the tumor and accordingly plan a segmental pancreatic resection (either a Whipple, a distal, or a middle pancreatectomy), that is not always the case in IPMN. In IPMN, preoperative studies may show a dilated pancreatic duct in the main duct variety, but not necessarily the intraductal mass, which is often small. Because of the overproduction of mucus, dilation can occur both proximally and distal to the tumor, making location problematic. This difficulty is compounded by the propensity of the tumor to spread microscopically along the pancreatic duct.

At the Massachusetts General Hospital it is our policy to obtain a spiral CT and an ERCP or MRCP in all patients with suspected IPMN. Furthermore, we often obtain endoscopic ultrasound to better define an intraductal mass, and to sample both the fluid and solid components. With this information, we plan the surgical intervention (be it a Whipple procedure, or a distal, a total, or a middle pancreatectomy), but are prepared to change this plan depending on the intraoperative findings. We have not found that intraoperative ultrasound adds to the preoperative imaging, but rely heavily on the frozen section diagnosis at the transection margin of the pancreas. Since IPMN extends along the pancreatic duct and can do so without obvious macroscopic tumor, it is important to rule out presence of tumor at the margin, so as not to leave tumor behind. A denuded epithelium within the duct is not uncommon in this entity, and de-epithelization should not be erroneously interpreted as a "negative" margin, since recurrence has occurred in this setting.[6] We are also utilizing intraoperative pancreatoscopy to inspect the ductal system of the remaining pancreas. This can potentially identify "skip" lesions if they are macroscopic. The presence of skip lesions has been proposed as the cause of recurrence of IPMN in the remaining pancreas, in the setting of a truly negative transection margin.[7,8]

A conservative approach to the surgical management of IPMN theoretically opposes the unproven concept that these patients have a widespread neoplastic field defect in the pancreatic ductal epithelium. While it is true that a proportion of patients with main duct IPMN have disease extending throughout the pancreas, and therefore require a total pancreatectomy (15% in our experience), most patients with main duct IPMN, as well as those with side branch variety, have a circumscribed tumor, and long-term follow up at other institutions indicating

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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00058-6

that the risk of recurrence in the remaining pancreas is less than 10% in patients with non-invasive tumors and negative margins.[6,7] In patients with IPMN and invasive cancer the risk of recurrence is higher, but in these cases it is not always possible to ascertain that the recurrence is due to the presence of other foci of IPMN in the remnant pancreas, as opposed to lymphatic and perineural spread from the original primary cancer. In our own experience with 80 resected patients since 1990, there have been no instances of recurrence in the remnant pancreas in the absence of invasive cancer. We are aware of one patient at the MGH who had a distal pancreatectomy in 1973 for a presumed mucinous cystadenoma, and who had an IPMN found in the remnant 20 years later. He then underwent resection of the neck and body of the pancreas with a positive margin, and 7 years later required a Whipple procedure for adenocarcinoma in the head of the gland. Thus, the phenomenon of synchronous "skip" lesions that eventually grow or metachronous tumors seems to be extremely uncommon. Furthermore, series in which there have been recurrences of IPMN show that reresection is possible in most of the cases.

An even more conservative approach would argue expectant management for some patients with IPMN. Since the risk of malignancy is lower in side-branch tumors, especially when smaller than 3 cm and in the absence of solid component, some authors have proposed non-operative management for elderly patients,[3,5] arguing that most of them are asymptomatic and that the time required to develop invasive malignancy may be greater than their life expectancy.

Thus, treatment of patients with IPMN needs to be individualized carefully. Because of the potential to modify or extend the surgical resection plans at the time of surgery, it is important that the surgeon discuss and evaluate preoperatively the risks and consequences of a total pancreatectomy with the patient. Whereas a total pancreatectomy may be appropriate in a young, fit patient who has an IPMN with invasive carcinoma in the head of the pancreas that is extending into the body and tail, it may not be the right operation for an elderly or frail patient with an IPMN that is only an adenoma or borderline tumor, even if present at the transection margin.

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Surgical Treatment of Intraductal Papillary Mucinous Neoplasms of the Pancreas: The Aggressive Approach

L. William Traverso, M.D.

Intraductal papillary mucinous tumors (IPMT) of the pancreas are being seen more frequently in my practice, so that I usually see one case per week and perform a resection at least once per month. These resections are usually pancreaticoduodenectomy.

My definition for IPMT combines two criteria—histology and location. First, the histology is that this tumor is associated with specific intraductal histologic changes within the main pancreatic ductal system. These changes are mainly a transition from cuboidal epithelium to a mucinous columnar epithelium and then a whole host of progressive dysplastic disorders until finally carcinoma in situ may be reached. Occasionally, there is not a mucinous preponderance, but rather a micropapillary change so that these tumors have been called intraductal papillary and/or mucinous epithelium. One or the other predominates, usually mucinous epithelium, therefore, the use of the combination term. IPMT is a confusing term because usually the preponderance of changes is the "M" rather than the "P."

Second, the location of the neoplastic change has to be intraductal to qualify as an IPMT. Since these lesions involve a proliferation of epithelial cells, the result is usually a cystic dilatation, not from obstruction, but from the increasing number of neoplastic cells. These cystic dilatations must be proven to connect to the pancreatic ductal system to qualify for an IPMT. Therefore, these ducts are the main pancreatic duct (MPD) with or without its primary side branch ducts. If the tumor only resides within the primary side branch ducts, then they are termed side branch type (SBT). If the neoplastic changes also are in the main pancreatic duct, then the type of tumor is called an MDT or main duct type. Therefore, the MDT form of the tumor can involve just the MPD or the MPD plus side branches. This is important because whenever the neoplastic change involves the main pancreatic duct, the chance of carcinoma is much higher than with small branch type.

Look for the "cystic" structures to be most easily seen on CT scan. Endoscopic ultrasound or MRI studies can tell us more about the irregularity of the lining of the cyst, suggesting more papillary changes and therefore more need to address these changes with resection.

The evolution of our understanding of these lesions has led to confusion because the first cases reported just the clinical forms of the disease without an explanation of the histology. The first clinical report was by Ohhashi in 1982 in Japan. The World Health Organization did not publish the first standardized histologic classification until 1996. Ohhashi described an "endoscopic triad" consisting of 1) a cystic dilatation of the main pancreatic duct; 2) a large amount of secreted mucus seen endoscopically; and 3) a dilated papillary orifice and swollen papilla, usually exuding mucus. Since some of these tumors did not exude mucus and were more of the papillary variety, the literature was filled with concocted terminology to best describe what the individual investigator was seeing. Therefore, one of the most common terms and the most understandable was "mucinous ductal ectasia."

My approach to the problem is aggressive in that if an IPMT is present, it should be resected no matter what estimation of malignant potential is present. Since most of my patients are symptomatic, the clinician is first faced with ridding the patient of the symptoms, which are abdominal pain, and a high frequency of recurrent pancreatitis. If you see a patient with idiopathic recurrent pancreatitis, consider IMPT as the cause as CT scan may not see a small cystic lesion. Another reason to become aggressive with these tumors is that many of them are malignant already, and the remaining IPMTs are premalignant. They all need to be removed. We have modern pancreatic surgery with mortality rates that approach zero. If the patient has a malignant IPMT, resection allows for prolonged survival and eradi-

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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00059-8

cates symptoms. In summary, resection is required in all patients if the patient is a surgical candidate.

This year at the annual meeting of the Society for Surgery of the Alimentary Tract, we presented a long-term follow-up of 63 resected patients with IPMT.[2] Abdominal pain was observed in 84% of them and a history of documented pancreatitis was observed in 54%. One quarter of these patients presented with jaundice, which was strongly associated with the presence of malignancy. Also strongly associated with the presence of malignancy was the presence of abnormal liver function tests.

If a predictor of malignancy were known, would that help the clinician decide on resection? The answer is no, because all of these lesions need to be removed. However, we sought predictors of malignancy in our 63 patients and found that a short duration of symptoms (15 vs. 35 months in benign cases) was associated with a malignancy. In addition, malignancy was also associated with elevated liver function tests (61% vs. 17%), an elevated CA 19-9 (81% vs. 14%), the main pancreatic duct being involved (73% vs. 43%), and the lack of gross mucus observed by endoscopy (66% vs. 35%). You can see in all of these numbers that even the benign form of the disease has had elevated predictors of malignancy. For instance, if the main pancreatic duct is not involved, 43% of these patients still had malignancy. These facts underscore that if an IPMT is present, it should be removed.

Since 52% of our cases were malignant, it is interesting to note that the 5-year survival rate with malignant IPMT after resection was almost 50% while the 5-year survival rate with benign disease approached 90%. It appears that the IPMT lesion when it is malignant has a better survival rate than ductal adenocarcinoma of the pancreas. Also interesting was that p53 over expression was noted only in malignant cases. About half of the malignant cases were p53 positive. If the actuarial survival of all of our cases were looked at just based on p53 staining (disregarding whether benign or malignant), then the 5-year survival rate was statistically different ($P = 0.0055$). The p53 positive patients had a 5-year survival rate of about 25% while the p53 negative tumors (this included half of the malignant tumors) had a 5-year survival rate of about 75%.

In summary, IPMTs should all be resected if they are documented to have intraductal papillary mucinous changes within the main pancreatic ductal system or its primary side branches. These are usually cystic lesions and most of them will be predominantly of the mucinous variety. Any IPMT that results in a biliary stricture with elevated liver function tests or jaundice is likely malignant, and there should be no question about resection. In those cases that present with recurrent pancreatitis due to mucus coming down the pancreatic ductal system, these cases usually have the primary cystic lesion in the head as well and therefore about three quarters of these patients require pancreaticoduodenectomy.

The main difficulty I see is not a decision of when to resect, but rather how much to resect. At frozen section, severe dysplastic lesions can be identified and these should be further excised until margins show no dysplasia. I do not chase hyperplastic changes on frozen section in the main pancreatic ductal system by extending resection for these benign changes. I am currently utilizing careful long-term follow-up to derive more objective guidelines.

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Hepatic Artery Embolization for Control of Symptoms, Octreotide Requirements, and Tumor Progression in Metastatic Carcinoid Tumors

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Hepatic artery embolization (HAE) has been utilized for treatment of advanced hepatic carcinoid metastases, with promising symptom palliation and tumor control. Our institution employs transcatheter HAE using Lipiodol/Gelfoam for treatment of carcinoid hepatic metastases, and this report presents our experience with twenty-four patients, examining symptom control, quality-of-life, octreotide dependence, and tumor progression. Twenty-four (11 male, 13 female, mean age = 59.4 ± 2.5 yr) patients with carcinoid and unresectable hepatic metastases, confirmed by urinary 5-hydroxyindole acetic acid (5-HIAA) measurement and biopsy, were treated with Lipiodol/Gelfoam HAE from 1993–2001. Median follow-up was 35.0 months. Before HAE, 14 patients (58.3%) had malignant carcinoid syndrome, with symptoms quantified using our previously reported Carcinoid Symptom Severity Score, and 13 patients (54.2%) required octreotide for symptom palliation. Following treatment, symptom severity, octreotide dose, and tumor response were measured. Asymptomatic patients did not develop symptoms or require following treatment. Hepatic metastases remained stable (n = 4) or decreased (n = 19) in 23 patients (95.8%). Mean pretreatment Symptom Severity Scores (3.8 ± 0.2), decreased to 1.4 ± 0.1 post-treatment ($P < 0.00001$), with 64.3% of patients becoming asymptomatic. Mean pretreatment octreotide dosages (679.6 ± 73.0 μg/d), decreased to 262.9 ± 92.7 μg/d ($P = 0.0024$) post-treatment, with 46.2% of patients discontinuing octreotide. There were no treatment-related serious complications or deaths. This study demonstrates that Lipiodol/Gelfoam HAE produces excellent control of malignant carcinoid syndrome, allowing patients to decrease or eliminate use of octreotide, while controlling hepatic tumor burden. (J GASTROINTEST SURG 2002;6:664–670)

KEY WORDS: Carcinoid tumor, embolization, combined modality therapy, gastrointestinal neoplasms, liver neoplasms, survival rate, quality of life

Carcinoid tumors are rare gastrointestinal tumors, with an incidence of 0.5–2.0/100,000,[1] and a prevalence of 0.7/100,000.[2] Carcinoid tumors represent a diffuse group of tumors arising from the neuroendocrine system that include neuronal and endocrine cells that share a common phenotype characterized by simultaneous expression of certain marker proteins and cell specific regulatory peptides.[3]

These tumors are typically characterized as having an indolent course. Most primary carcinoid tumors (>90%) develop within the gastrointestinal tract, and with the exception of rectal carcinoid, these tumors develop into sizeable primary tumors with relatively few, and vague abdominal symptoms. Only about 50% of carcinoid tumors occurring in the cecum, colon, and rectum develop any symptoms of obstruction or lower gastrointestinal hemorrhage.[4] Gastrointestinal carcinoid tumors develop extensive hepatic metastases that remain clinically silent until the liver's metabolic capacity is overtaken by serotonin and neuropeptides produced by these tumors.[5] When tumor burden overtakes hepatic metabolic function, patients develop malignant carcinoid syndrome, characterized by flushing, diarrhea, cardiac valvular damage, bronchoconstriction and asthma symptoms, and pellagra. Symptoms of malignant carcinoid syndrome are well controlled in the majority of patients using the somatostatin analogue octreotide, presently available in both short- and long-

Presented at the Forty-First Annual Meeting of The Society of the Alimentary Tract, San Diego, California, May 21–24, 2000 (poster presentation).
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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00044-6

acting injectable forms.[6] However, use of octreotide remains solely as a palliative measure, as this therapy has no significant effect upon serotonin and neuropeptide production[7] or reduction of hepatic metastases.[8] More recently, use of receptor-targeted therapy using radio-labeled metaiodobenzylguanidine (MIBG) has been demonstrated as effective for decreasing symptoms and carcinoid metabolite production.[9–11] Despite attempts at palliation using a variety of treatment of modalities, patients still are subjected to significant morbidity from their symptoms.[12]

Surgical management of metastatic carcinoid tumors and malignant carcinoid syndrome remains a significant challenge. Previous authors have advocated hepatic resection for resectable hepatic metastases, with results supporting palliation and prolonged survival in these patients.[13–19] Most patients have unresectable disease at diagnosis, leaving aggressive chemotherapy, cytoreductive procedures, and symptomatic control with octreotide, all with disappointing results and few patients cured.[12,20–23]

Trans-catheter hepatic artery embolization (HAE) of carcinoid metastases has yielded excellent palliation and cytoreduction in patients with unresectable hepatic disease,[24–30] and our own institutional experience with transcatheter selective HAE using Lipiodol/Gelfoam (Lipiodol: Laboratories Guerbet, Aulnay-sous-Bois, France; Gelfoam: Upjohn Company, Kalamazoo, Michigan) has been promising in providing cytoreduction in a number of primary and metastatic hepatic tumors.

Thus, faced with the significant challenge of management for unresectable hepatic carcinoid metastases, and our early successes with HAE in a small number of patients with carcinoid tumors, this study was undertaken to determine whether HAE would represent a valuable adjunct in the management of symptoms, octreotide requirements, and tumor burden in these patients.

METHODS

During the period from 1993–2001 24 (11 male, 13 female, mean age 59.4 ± 2.5 yr) patients were referred to our practice as candidates for management of carcinoid tumors and unresectable bilobar hepatic metastases. The diagnosis of carcinoid tumor was made based upon percutaneous or surgical biopsy confirmation of the primary tumors or their hepatic metastases revealing findings consistent with neuroendocrine tumors and by the presence of elevated urinary 5-HIAA. Tumors were deemed unresectable when their number, location, and aggregate volume mandated a resection volume that exceeded patients' hepatic reserve, and in patients whose associated comorbid disease precluded major hepatic resection. Eligibility for treatment included the above criteria, and the absence of portal vein occlusion prior to HAE.

Fourteen patients (58.3%) had symptoms of malignant carcinoid syndrome, and these patients' symptoms were assessed using the Carcinoid Symptom Severity Scale we have reported previously,[31] and a severity score was calculated for each patient prior to treatment. Table 1 summarizes the Symptom Severity Scale categories and scores.

Of those patients with malignant carcinoid syndrome, 13 (54.2%) required treatment with the somatostatin analogue octreotide in order to alleviate their symptoms. Daily dosages of octreotide prior to therapy ranged from 300–1071 μg/d (mean 679.6 ± 73.0; median 714.0 μg/d), with dosages targeted to optimize patients' symptoms and minimize undesirable side-effects. One patient with malignant carci-

Table 1. Carcinoid symptom severity scale

Score	Description	Description
1	No symptoms	Symptoms: None Frequency: None Lifestyle effects: None
2	Mild symptoms	Symptoms: Diarrhea, flushing, or wheezing Frequency: Up to 4 times daily Lifestyle effects: None to minimal
3	Symptoms impact daily living	Symptoms: Diarrhea, flushing, or wheezing Frequency: 5–7 times weekly Lifestyle effects: Restricts patient from leaving home for prolonged periods of time
4	Severe symptoms	Symptoms: Diarrhea, flushing, or wheezing Frequency: Multiple daily episodes Lifestyle effects: Symptoms require significant reorganization of daily activities to accommodate for these symptoms; patients rarely leave home, must be close to bathroom facilities and medical supplies.
5	Disabling symptoms	Symptoms: Diarrhea, flushing, and wheezing (severe) or of sufficient severity to warrant hospitalization for treatment of dehydration, electrolyte imbalance, refractory hypertension, or asthma Frequency: Numerous (>4) daily Lifestyle effects: Symptoms are disabling; patients are unable to leave home or require hospitalization

noid syndrome was unable to tolerate any dose of octreotide due to side-effects.

The remaining 10 patients (41.7%), while not exhibiting symptoms of malignant carcinoid syndrome, were included in this treatment protocol based upon evidence of progressive hepatic tumor burden as demonstrated by interval computed tomography (CT) or magnetic resonance imaging (MRI).

Prior to embolization treatment, all patients underwent repeat evaluation including abdominal and hepatic CT or MRI imaging, confirmation of elevated 5-HIAA levels, and, if indicated, echocardiography to assess for valvular damage or dysfunction. Patients were treated with selective transcatheter HAE using Lipiodol/Gelfoam as described previously.[24,26–31] Our standard cycle for initial embolization was four separate embolization sessions, alternating hepatic lobes, at 21–28 day intervals, and beginning with the hepatic lobe containing the heaviest tumor burden. Embolizations were performed as outpatient or short-stay (23 hour) patients in our institution, pursuant to our standard treatment algorithm.

Following completion of the initial embolization treatment cycle, patients were assessed at one, three, and six month intervals. During these visits, patients' symptoms were re-assessed using the Symptom Severity Scale, and hepatic tumor burden was assessed using repeat CT or MRI imaging. Additional embolization treatments were administered when patients exhibited worsening symptoms of malignant carcinoid syndrome, or when imaging demonstrated increasing hepatic tumor burden following treatment. Table 2 summarizes patient demographics, symptoms, octreotide requirements, and treatment profiles.

Patient symptom assessments were conducted through a self-assessment checklist and during physician interviews. All data are reported as the mean ± standard error of the mean. Intergroup comparisons were assessed using a two-tailed Student's *t* test, and *P* values <0.05 were considered significant.

RESULTS

Follow-up, as provided by outpatient clinic visits and telephone consultations, was maintained for all patients treated in this study. Mean follow-up for this series was 41.4 ± 5.7 months (median 35.0).

Table 2. Patient demographics and treatment results

Patient No.	Age at Dx (yr)	Gender	Race	No. Tx	Tx duration (mo)	Follow-up (mo)	Status	Pre-Tx symptom score	Post-Tx symptom score	Pre-Tx octreotide dose (μg/day)	Post-Tx octreotide dose (μg/day)
1	65.5	F	W	10	54.0	101.0	Alive	—	—	—	—
2	67.2	M	W	2	1.7	82.8	Alive	—	—	—	—
3	28.0	F	W	3	1.4	77.0	Alive	—	—	—	—
4	52.6	M	W	1	0.0	69.4	Alive	—	—	—	—
5	68.2	F	W	4	3.8	61.0	Alive	—	—	—	—
6	48.5	F	A	3	1.0	60.2	Alive	—	—	—	—
7	70.2	F	W	4	3.0	36.1	Alive	—	—	—	—
8	64.6	M	W	2	1.2	21.8	Alive	—	—	—	—
9	78.1	M	W	4	3.0	10.2	Alive	—	—	—	—
10	61.8	M	W	4	3.5	7.9	Alive	—	—	—	—
11	49.3	F	W	8	32.4	57.1	Alive	5	1	900	450
12	73.0	M	W	6	24.7	53.2	Alive	3	1	600	—
13	68.7	M	W	6	25.2	34.0	Alive	5	1	600	100
14	54.3	M	W	2	4.8	59.7	Alive	4	1	900	140
15	48.6	M	W	2	3.4	20.4	Alive	4	2	300	—
16	72.9	F	W	6	12.4	19.5	Alive	3	1	714	—
17	39.7	F	W	4	3.8	16.6	Dead*	4	2	1071	714
18	49.0	F	W	8	14.5	77.3	Dead*	4	2	900	1000
19	58.1	M	B	3	2.8	14.1	Dead	3	1	300	—
20	61.8	F	W	3	2.3	5.1	Dead	4	2	450	300
21	52.2	M	W	4	1.3	4.0	Dead	4	2	900	—
22	70.0	F	W	3	2.2	29.6	Dead	4	1	300	—
23	53.5	F	W	4	3.6	27.5	Dead	3	1	900	714
24	70.6	F	W	5	7.7	48.4	Alive	3	1	—	—

Dx = diagnosis; Tx = treatment; W = White; A = Asian; B = Black.
*Death from unrelated causes.

A total of 101 transcatheter selective HAE procedures were performed during this study. Each patient underwent multiple embolization treatments (mean 4.2 ± 0.4; median 4.0; range 1–10) over treatment intervals ranging from 1.2–54.0 months (mean 8.9 ± 2.6). After treatment, Lipiodol uptake was seen on CT scan in all patients. All patients treated with HAE experienced post-embolization syndrome symptoms (pain, nausea, fatigue, and anorexia). These symptoms were typically mild and transient, ending within the first 24 hours following treatment, and are in keeping with previous reports on this therapy.[32] There was no significant difference in the number of embolization treatments utilized in symptomatic vs. asymptomatic patients (mean 4.6 ± 0.5 vs. 3.7 ± 0.8; P = NS). There were no extra-hepatic complications or embolization-related deaths.

Following treatment, hepatic tumor burden was decreased in 19 (79.2%), and remained stable in four (16.7%) patients. One asymptomatic patient (4.2%) had an apparent increase in hepatic tumor burden following HAE. However, the patient's tumor burden and symptoms remained unchanged during subsequent 69.4 month follow-up.

Patient symptoms ranged from moderate to severe (range 3–5; mean 3.8 ± 0.2) prior to treatment, and were significantly reduced (range 1–2; mean 1.4 ± 0.1; $P < 0.00001$) following embolization. Nine patients (64.3%) were rendered asymptomatic following embolization treatment. Concordant with symptom severity, average daily octreotide dosages decreased significantly from 679.6 ± 73.0 μg/d pre-treatment to 262.9 ± 92.7 μg/d following embolization ($P = 0.0024$). Six patients (46.2%) had sufficient improvement in their symptoms, that octreotide treatments could be discontinued, and they remained asymptomatic. Post-treatment symptoms, octreotide use, and cytoreduction results are summarized in Table 2. During the initial phase of this study, symptom regression and recurrence were found correlated with decreased or elevated 5-HIAA levels respectively (data not shown). Thus, we did not routinely utilize 5-HIAA levels as a monitoring parameter following treatment.

There were seven deaths during the follow-up period, and six deaths were attributable to carcinoid disease progression as manifested by extra-hepatic abdominal or distant metastases. No deaths occurred during the 30-day period following the patients' final embolization treatment. The seventh death resulted from causes unrelated to their carcinoid tumor (esophageal perforation, patient number 17). Kaplan-Meier survival probabilities were calculated for all patients in our series, and for patients who presented with symptoms of malignant carcinoid syndrome (Figure 1). Five-year predicted survival was 71.5% for all patients, and 53.6% for symptomatic patients. All deaths, including the death not attributable to carcinoid disease progression, were included in the survival analysis, based upon the intent to treat these patients.

DISCUSSION

Two principal goals dominate the management of carcinoid tumors with hepatic metastases: symptom

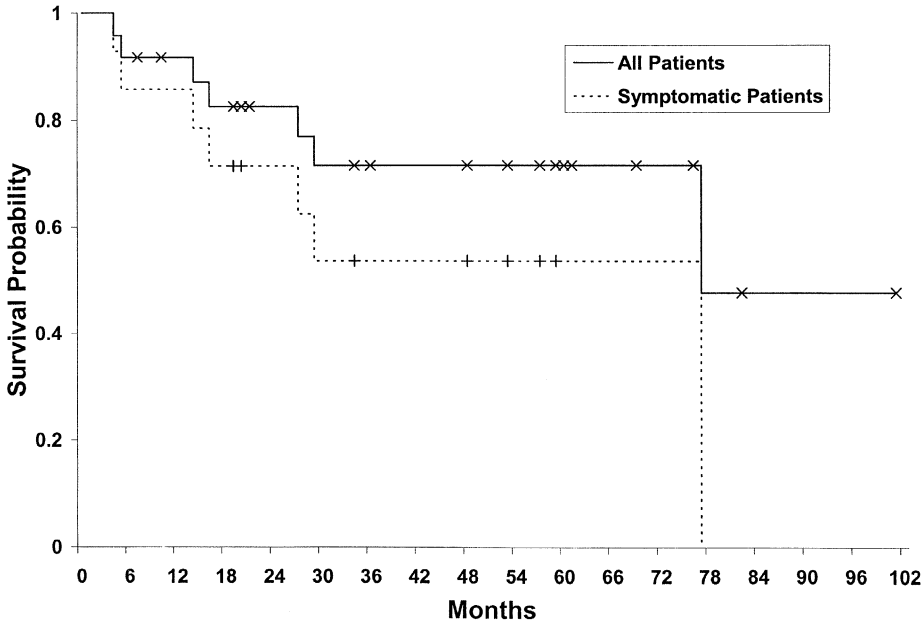

Fig. 1. Kaplan-Meier survival probabilities. Overall vs. symptomatic patients.

regulation and reduction of the tumor burden. Historical data suggest a five-year survival rate of less than 20% for patients with hepatic metastases.[33] Although safe in the hands of experienced surgeons, hepatic resection is rarely curative for these patients.[17,34] When complete resection of tumor and hepatic metastases can be achieved, this therapy clearly improves outcome, with five-year survival increasing to 79%.[15]

Unfortunately, as a result of the natural history of this disease, and the relative "silence" of the primary tumors and their metastases, the majority of patients diagnosed with carcinoid tumors have unresectable disease at presentation. Hepatic cytoreduction using open resection,[4,17,34,35] and cryotherapy,[36] have demonstrated some improvement in symptom control and survival. Radiofrequency ablation has been shown efficacious, and safer than surgical cytoreduction or cryotherapy, for decreasing tumor burden[36,37] and in our hands, for control of symptoms in patients refractory to embolization therapy.[31]

Allison et al. initially described use of percutaneous hepatic artery embolization for treatment of two patients with unresectable hepatic metastases, achieving symptomatic control of these patients' symptoms.[38] During the subsequent two decades, there have been a significant number of additional reports of modifications of this therapy utilizing combinations of synthetic alcohols, polyvinyl chloride, methacrylate, and various chemotherapeutic agents, and examining effects of this treatment upon symptom control, production of biochemical (5-HIAA) markers, cytoreduction and survival.* As carcinoid remains an extremely rare disease, the number of patients in these studies remains understandably low, yet the efficacy and safety of embolization therapy has steadily improved over time.

The goal of this study was to revisit transcatheter hepatic artery embolization for control of malignant carcinoid syndrome utilizing a standardized symptom severity score, previously developed at our institution, and using the requirement for ongoing octreotide as novel indicators of treatment success. Since all patients do not present with symptoms of malignant carcinoid syndrome, we also evaluated this therapy upon cytoreduction and disease progression as evaluated by interval CT and MRI imaging, and by survival outcomes analysis in our patient group as a whole compared to those patients presenting with malignant carcinoid syndrome, and thus presumably more advanced disease. Our institutional experience has focused upon HAE performed without addition of cytotoxic chemotherapeutic agents, termed "bland embolization." The anti-tumor effects of bland embolization are believed principally related to tumor ischemia induced by arterial obstruction, although several interesting reports have suggested a role for natural killer (NK) cell anti-tumor activity in patients undergoing embolization for carcinoid and other tumor types.[29.52–56]

In concordance with previous reports, our group of 24 patients with 35-month median follow-up, experienced significant palliation of symptoms, with 64.3% of symptomatic patients rendered entirely asymptomatic after treatment. Consistent symptom evaluations are afforded by use of the standardized Symptom Severity Score instrument, and provide a basis for quantifying response after treatment, and inter-patient comparisons. Octreotide dependence was likewise dramatically reduced in our symptomatic patients, with nearly half of these patients able to discontinue its use after treatment. Cytoreduction, as evaluated by serial CT and MRI imaging, was achieved in 79.2% of patients, with four of the remaining five patients demonstrating stable disease.

Our series confirmed previous reports of the "post-embolization" syndrome of pain, nausea, fatigue, and anorexia experienced by patients. However, there were no deaths or complications resulting from embolizations in our series, representing an improvement over previous reports using this therapy.[25] Kaplan-Meier survival analysis demonstrated a five-year survival probability of 71.5% for all patients, which decreased to 53.6% when patients presented with malignant carcinoid syndrome.

Together, our findings support use of HAE as primary therapy in patients with carcinoid tumors and unresectable hepatic metastases in both asymptomatic patients and those with malignant carcinoid syndrome. In cases where complete resection of primary and hepatic metastases is possible, we believe that surgical therapy should be employed. However, as the vast majority of patients are unlikely to have resectable disease at the time of diagnosis, we feel that selective cytoreduction does not offer any therapeutic advantage over HAE, and exposes the patient to the real, albeit small, risk of morbidity and mortality from the procedures.

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Long-Term Follow-Up of Patients With Familial Adenomatous Polyposis Undergoing Pancreaticoduodenal Surgery

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Adenomatous polyps and adenocarcinomas of the periampullary region are the most common upper gastrointestinal neoplasms encountered in familial adenomatous polyposis (FAP) patients. Tumors arising from the liver, biliary tract, and pancreas have also been reported. The purpose of this study was to review the clinical outcome of FAP patients after pancreaticoduodenal surgery for periampullary neoplasms. Of the 61 individuals participating in our prospective FAP registry, 8 underwent surgical resection of periampullary neoplasms between 1987 and 1998. The charts of these individuals were reviewed for clinical indications, type of pancreaticoduodenal surgery, postoperative complications, and outcome. Of the 8 patients identified, 7 had pancreaticoduodenectomy and 1 had duodenotomy with ampullectomy. The indications for surgery were periampullary cancer (3), severe dysplasia within a duodenal villous tumor (4), and solid-pseudopapillary tumor of the pancreas (1). At the time of pancreaticoduodenal surgery, patients ranged in age from 29–65 years, and all but one had undergone colorectal surgery, on average 16 years beforehand. Pancreatic ascites after a pylorus-sparing pancreaticoduodenectomy was the only surgical complication. At a median follow-up of 70.5 months (range 37–162), 2 patients had died, neither from their periampullary neoplasm. The patient treated by local excision subsequently developed gastric cancer arising from a polyp and went on to gastrectomy. Another patient developed confluent benign jejunal adenomas just beyond the gastroenteric anastomosis almost 12 years after pancreaticoduodenectomy for severe dysplasia of a duodenal villous adenoma. Pancreaticoduodenectomy is a safe and appropriate surgical option for FAP patients with duodenal villous tumors containing severe dysplasia or carcinoma. Postoperative morbidity was minimal and there was no perioperative mortality. Good long-term prognosis can be expected in completely resected patients although subsequent proliferative and/or neoplastic lesions may still be detected in the gastrointestinal tract with prolonged follow-up. (J GASTROINTEST SURG 2002;6:671–675)

KEY WORDS: Familial adenomatous polyposis, duodenal polyps

Familial adenomatous polyposis (FAP), an autosomal dominant disorder caused by mutations in the adenomatous polyposis coli (APC) gene,[1] has colorectal polyposis as its predominant feature. However, this generalized hyperproliferative growth disorder manifests in other organ systems, including the upper gastrointestinal tract. Benign and malignant lesions have been described in the stomach, duodenum, liver, biliary tract, and pancreas.[2]

With the advent of endoscopic and genetic screening leading to prophylactic colectomy in patients with FAP, there has been an increasing ratio of deaths attributed to extracolonic manisfestations compared with deaths from colorectal cancer.[3] Aside from metastatic colorectal cancer, desmoid tumors and periampullary or duodenal cancers account for the majority of deaths among patients with FAP.[4] Although greater than 90% of patients with FAP develop duodenal adenomas 10–20 years after diagnosis of colorectal polyps, progression to duodenal cancer occurs in less than 5%.[4,5] While rare in the general population, the risk of duodenal or periamp-

Presented at the Forty-Second Annual Meeting of The Society of the Alimentary Tract, Atlanta, Georgia, May 20–23, 2001 (poster presentation).
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1091-255X/02/$—see front matter
PII: S1091-255X(02)00045-8

ullary cancer is increased several hundred-fold in patients with FAP.[6,7] The aim of this study was to determine the long-term outcome of patients with FAP requiring pancreaticoduodenal surgery for premalignant or malignant periampullary neoplasms.

MATERIAL AND METHODS

A database search of individuals participating in the prospective FAP registry at Memorial Sloan Kettering Cancer Center was performed. Eight patients underwent pancreaticoduodenal surgery for periampullary neoplasms. Data retrieved from a thorough retrospective review of patient records included patient age and sex, date and type of colorectal resection, date of initial duodenal adenoma diagnosis, symptoms related to duodenal adenomas, family history of duodenal cancer, indication for pancreaticoduodenal surgery, procedure performed, postoperative complications, and clinical outcome.

One patient underwent a local excision through a duodenotomy for a 2 cm sessile adenoma at the ampulla, as well as an anterior gastrotomy for removal of adenomatous polyps. In the remaining seven patients, either classical pancreaticoduodenectomy or pylorus sparing pancreaticoduodenectomy was performed. There were no specific difficulties encountered with these procedures on reviewing the operative reports. However, surgeons who manage upper gastrointestinal neoplasms in patients with FAP should be cognizant of the potential complexity related to associated colonic and extracolonic manifestations, including colorectal polyposis and intraabdominal desmoid tumors.

RESULTS

Out of 61 individuals with FAP participating in the prospective Hereditary Colorectal Cancer Family Registry at Memorial Sloan Kettering Cancer Center, between 1987 and 1998, 8 patients (5 female, 3 male) underwent pancreaticoduodenal surgery for periampullary neoplasms (Table 1). The median age at diagnosis of duodenal adenomas was 41 years (range 25–65), and the median age at pancreaticoduodenal surgery was 43.5 years (range 29–65). Half of the patients had symptoms related to their duodenal adenomas. None had a family history of duodenal cancer.

Preoperative indications for surgery included periampullary cancer (3), severe dysplasia in a duodenal villous tumor (4), and solid-pseudopapillary tumor of the pancreas (1). Pancreaticoduodenectomy was performed in 7 patients, 3 with preservation of the pylorus. One individual had a transduodenal ampullectomy. No perioperative mortality was encountered. One patient developed postoperative pancreatic ascites without significant sequelae (Table 1, Patient 1). Previous colorectal surgery was performed in 7 of 8 patients on average 16 years before. Although identification of the superior mesenteric vein at the inferior border of the pancreas may be more difficult, there was no indication upon review of the operative reports that prior colectomy hindered subsequent pancreaticoduodenectomy apart from the typical issues related to reoperative surgery. In the patient with the pancreatic neoplasm, this lesion was addressed first, with subsequent prophylactic colorectal resection planned upon recovery because there was no evidence of cancer on initial colonoscopy. However, she did not return for follow-up after pancreaticoduodenectomy, and by the time colectomy was performed 14 months later, she had developed a rectal cancer.

At a median follow-up of 70.5 months (range 37–162), 4 patients had no evidence of recurrent disease with follow-up intervals of 64, 70, 81, and 118 months. One patient treated by pylorus sparing pancreaticoduodenectomy for a villous adenoma containing severe dysplasia subsequently developed jejunal adenomas distal to the duodenojejunostomy 133 months after initial operation. The patient treated by ampullectomy with known gastric polyps underwent subtotal gastrectomy for a gastric adenocarcinoma 35 months after duodenal surgery. Two patients are deceased, neither from their periampullary neoplasm. Mortality in these cases was attributed to metastatic colorectal cancer (at 71 months) and comorbid illness (at 37 months).

DISCUSSION

Over the past 20 years, the clinical significance of duodenal neoplasms in FAP patients has been highlighted by the impact prophylactic protocolectomy has had on significantly reducing colorectal related deaths in this patient population. In FAP patients followed to death after prophylactic colectomy, periampullary neoplasia accounts for 22% of deaths, an average 23.1 years after colorectal surgery.[8] Although duodenal polyps are found in over 90% of patients with FAP, progression through the adenoma/carcinoma sequence is uncommon. Lifetime risk of developing duodenal cancer was estimated at 4% by the age of 70 years in the Dutch Polyposis Registry and 3% in the Danish Polyposis Registry.[5]

Table 1. Pancreaticoduodenal surgery in patients with familial adenomatous polyposis (FAP)

Patient	Age (yr)/sex	Indication	Procedure	Pathology	Status	Follow-up (mo)
1	42 F	Severe dysplasia	PSPD	Adenoma	Small bowel adenomas distal to duodenojejunostomy at 133 months	162
2	43 F	Pancreatic neoplasm	PD	Solid-pseudopapillary tumor of the pancreas	Deceased from CRC metastases	71
3	65 M	Cancer (periampullary)	PSPD	Ampullary CA $T_1N_0M_0$	NED	118
4	56 M	Cancer (periampullary)	PD	Ampullary CA $T_2N_1M_0$	Deceased from other illness (no evidence of recurrence/ metastases)	37
5	44 F	Severe dysplasia	PSPD	Adenoma	NED	64
6	55 F	Severe dysplasia	LE	Adenoma	Gastric carcinoma arising from polyp at 35 months	37
7	29 F	Cancer (periampullary)	PD	Ampullary CA $T_1N_0M_0$	NED	70
8	35 M	Severe dysplasia	PD	Duodenal CA $T_3N_0M_0$	NED	81

PSPD = pylorus preserving pancreaticoduodenectomy; PD = pancreaticoduodenectomy; CRC = colorectal cancer; CA = carcinoma; NED = no evidence of disease; LE = local.

The mean age at diagnosis of duodenal cancer in patients with FAP is approximately 45–50 years, and both men and women are equally affected.[4,5,9] The mean age of patients in our study is 46 years and there is a slight preponderance of females (5:3) The 8 patients represent 13% of those FAP patients participating in our registry. However, this figure accounts for all patients undergoing pancreaticoduodenal surgery including those with premalignant duodenal villous tumors. Recent studies observed familial segregation in the development of periampullary malignancy, suggesting a possible association with certain APC mutations.[10,11] Although no definitive genotype-phenotype correlations have been firmly established, the incidence of duodenal polyps was found to be higher in patients with APC mutations in exons 10–15 and in exons 4–9[12] and severe upper gastrointestinal polyposis in cases with APC mutations between codons 1445 and 1578.[13,14] Interestingly, none of the patients in our series had any family history of duodenal cancers, but this may be attributed to the small sample size and/or incomplete family histories.

The treatment of duodenal neoplasms in patients with FAP is difficult because no consistent therapeutic guidelines exist. Spigelman's criteria, based on polyp number, size, histology, and dysplasia, are intended to grade severity of duodenal polyposis and to guide surveillance and treatment decisions (See Table 2).[15] Using this classification, initial recommendations for individuals in the low risk groups (stages 0–II) are screening endoscopy every 2–3 years and for those in the high risk group (stages III–IV), endoscopy with biopsy every 6–12 months. In a recent study, which combined data from two large FAP registries, 11% of patients were noted to have Spigelman stage IV disease and less than 10% of patients advanced to a more severe stage of polyposis between exams.[5] Other studies have also demonstrated limited progression of duodenal adenomatosis in patients with FAP.[11,15,16] In contrast, a Finnish study documented significant progression in 74% of patients undergoing repeated endoscopies.[17] Documentation of villous changes, severe dysplasia, and rapid growth during endoscopic surveillance has been proposed as indications for surgical intervention.[18–23] In our series, all but one patient had duodenal lesions with histologic evidence of severe dysplasia within a villous adenoma or

Table 2. The Spigelman classification for staging duodenal polyposis[15]

	Grade of duodenal disease (points)		
	1	2	3
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0 = 0 points; Stage I = 1–4 points; Stage II = 5–6 points; Stage III = 7–8 points; Stage IV = 9–12 points.

cancer. There was one patient with a pancreatic lesion who was found to have a solid-pseudopapillary tumor of the pancreas.

Local resection has been advocated for ampullary adenomas with severe dysplasia and carcinoma in situ in patients with FAP.[24] However, regular postoperative endoscopic surveillance is essential because of a high recurrence rate.[25–27] Furthermore, subsequent attempts to remove polyps may be hampered by initial local resection. In an analysis of benign duodenal villous tumors in 50 patients treated by transduodenal local resection, there was a recurrence rate of 32% at 5 years and 24% of recurrences were invasive adenocarcinomas.[27] Of 11 patients with associated polyposis syndromes, 7 (64%) developed a recurrence of which 4 (57%) were malignant.

Recurrent disease after local resection has prompted the reevaluation of pancreaticoduodenectomy for duodenal and periampullary neoplasms.[19,22] In addition, local resection is often inadequate therapy for invasive carcinoma, which may only be evident upon resection for suspected but unconfirmed duodenal malignancy.[22,28,29] Pylorus preservation and pancreas sparing procedures are suitable alternatives to classical pancreaticoduodenectomy.[22,28] Some surgeons prefer pylorus preservation because functional outcomes may be better, specifically in relation to reduction of biliary reflux.[21] This may be an important consideration, as bile adducts appear to have a role in adenoma formation.[15] Experience with pancreas sparing duodenectomy in polyposis patients is limited,[26,27] but has been associated with significant postoperative morbidity in at least one series.[27]

Patients without FAP who undergo pancreaticoduodenectomy for periampullary adenocarcinomas have a 5-year survival in the range of 20–70%.[30–33] Invasive duodenal cancer in patients with FAP has been associated with poor prognosis.[34] The mean survival in 4 patients was 13 months after diagnosis despite pancreaticoduodenectomy in 3 of these patients. However, in our cohort of patients, the long-term clinical outcome was remarkably good. At a median follow-up of 70.5 months, 4 of 7 patients undergoing pancreaticoduodenectomy remained free of disease while 2 became deceased due to causes unrelated to their periampullary neoplasm. The remaining patient developed recurrent adenomas in the jejunum 133 months after a pylorus preserving pancreaticoduodenectomy for a villous tumor with severe dysplasia. Therefore, in our experience, no one has died of his or her periampullary neoplasm subsequent to pancreaticoduodenectomy. This, together with our very low operative morbidity, would support an aggressive surgical approach in these patients, prior to a confirmed diagnosis of invasive carcinoma.

Clearly, awaiting symptomatic duodenal disease in FAP patients is likely to result in a poor outcome.[34] Endoscopic ablation by excision, sphincterotomy, coagulation, laser therapy, and photodynamic therapy may control upper gastrointestinal polyposis.[35] However, surgery is indicated if polyps are large (>3 cm),[19] exhibit villous change, or severe dysplasia.[20–23,27] Preoperative endoscopic ultrasound may add to the current armamentarium for diagnosis of lesions suspicious for malignancy and for characterizing the ductal systems. Our study, as well as others,[21] demonstrate that aggressive surgical management of premalignant lesions may be undertaken with little morbidity or mortality yet achieve excellent functional and oncologic outcomes. Thus, pancreaticoduodenal surgery for periampullary neoplasms in patients with FAP should be considered on a selective basis subsequent to evaluation by clinical history, preoperative diagnostic work up, and intraoperative findings.

CONCLUSION

Few FAP patients require pancreaticoduodenal surgery for periampullary neoplasms because progression from adenoma to carcinoma is infrequent. However, resection by pancreaticoduodenectomy is a safe and appropriate surgical option for FAP patients with large duodenal adenomas not amenable to endoscopic removal nor local excision/ablation or duodenal villous tumors of any size containing severe dysplasia or carcinoma. Pancreaticoduodenectomy may be preferred over local excision because of lower local recurrence rates, reduced requirement for endoscopic surveillance, and excellent long-term results. Although good long-term prognosis can be anticipated in completely resected patients, proliferative and/or neoplastic lesions may be detected in the remaining gastrointestinal tract with prolonged follow-up.

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Unusual Causes of Benign Biliary Strictures With Cholangiographic Features of Cholangiocarcinoma

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Focal strictures occurring at the hepatic duct confluence, or within the common hepatic duct or common bile duct in patients without a history of prior surgery in that region or stone disease, are usually thought to represent cholangiocarcinoma until proved otherwise. However, not uncommonly, patients undergo surgical exploration for a preoperative diagnosis of cholangiocarcinoma, based on the cholangiographic appearance of the lesion, only to find histologically that the stricture was benign in nature. Despite sophisticated radiographic, endoscopic, and histologic studies, it is often impossible before laparotomy to distinguish malignant from benign strictures when they have the characteristic radiographic appearance of cholangiocarcinoma. Even at the risk of overtreating some benign cases, most agree that aggressive surgical resection is the treatment of choice, given the serious consequences resulting from a failure to diagnose and adequately treat cholangiocarcinoma. Four patients who presented to our institution between February 1991 and June 2000 underwent laparotomy for a preoperative diagnosis of biliary tract malignancy based on clinical presentation and cholangiographic findings. The final pathology report in all patients showed marked fibrosis and inflammation of the biliary duct without evidence of malignancy. A review of the patient data and the relevant literature identified benign causes of focal extrahepatic biliary strictures associated with concomitant disease processes in two of the four patients. We present these cases and discuss the benign etiologies with emphasis on the role of surgery in both diagnosis and treatment. (J GASTROINTEST SURG 2002;6:676–681.)

KEY WORDS: Biliary stricture, cholangiocarcinoma, Sjogren's syndrome, idiopathic retroperitoneal fibrosis

In 1965 Dr. Gerald Klatskin[1] asserted that strictures of the bile ducts found in patients with no history of biliary tract disease should be considered neoplastic until proved otherwise. Other investigators have echoed the belief that in the absence of previous biliary surgery, focal strictures of the extrahepatic bile ducts on cholangiography represent cholangiocarcinoma.[2,3] However, several authors have reported cases in which patients underwent surgical exploration for a preoperative diagnosis of cholangiocarcinoma, on the basis of the cholangiographic appearance of the lesion, only to find histologically that the stricture was benign in nature. Verbeek et al.[4] reported a series of 82 patients with a preoperative diagnosis of hilar cholangiocarcinoma, all of whom underwent exploration; in 11 patients (13.4%) examination of the resected specimen showed a localized benign fibrotic lesion with no evidence of malignancy. Wetter et al.[5] also reported a series of 98 patients with a clinical and radiographic diagnosis of cholangiocarcinoma who underwent surgical exploration. Malignancies were found in 68 patients, whereas in eight patients the strictures were benign, including three patients with so-called idiopathic benign focal stenosis. In this series a diagnosis of benign disease was established in 30 cases (31%). Nakayama et al.[6] also reported postoperative histologic evidence of benign fibrosis in 14 (14%) of 99 patients undergoing radical resection for a preoperative diagnosis of cholangiocarcinoma.

Iatrogenic injury to the extrahepatic biliary tree incurred at the time of cholecystectomy or other upper abdominal surgery accounts for the majority of benign biliary strictures. Other causes such as stone disease, pancreatic pseudocyst, sclerosing cholangitis, and chronic pancreatitis may have radiographic

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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(01)00062-2

features and clinical presentations that allow them to be distinguished from their malignant counterparts. In contrast, isolated biliary strictures occurring at the hepatic duct confluence, or within the common hepatic duct or common bile duct in patients without a history of prior surgery in that region or stone disease, are usually thought to represent cholangiocarcinoma. Despite sophisticated radiographic, endoscopic, and histologic studies, it is often impossible before laparotomy to distinguish malignant from benign strictures when they have the characteristic radiographic appearance of cholangiocarcinoma.[7]

Biliary brushing and bile sampling at the time of endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography and cytologic examination for malignant cells is commonly employed in the initial evaluation of biliary strictures. Studies have shown bile cytology to have a 5% to 30% sensitivity, whereas brush cytology has been reported to have an overall 30% to 70% sensitivity for diagnosing malignancy, with an 80% sensitivity for diagnosing cholangiocarcinoma specifically.[8–19] Endobiliary forceps biopsy and endoluminal fine-needle aspiration have also been used to improve diagnostic accuracy, with an overall sensitivity for diagnosing malignancy of approximately 60% to 65% with either of these methods alone.[8,12,13,20,21] Combining these various sampling methods has increased the overall sensitivity negligibly.[7,22]

Imaging techniques such as magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) offer promise for differentiating malignant from benign causes of extrahepatic biliary obstruction, but their role in specifically diagnosing cholangiocarcinoma is still imprecise. A study comparing MRCP with EUS in diagnosing extrahepatic biliary obstruction as malignant or benign found a sensitivity of 91% and specificity of 94% with MRCP and respective values of 97% and 88% for EUS. However, there were only two cases of cholangiocarcinoma in the series.[23] Yeh et al.[24] reported accurate diagnoses of cholangiocarcinoma in 22 of 26 patients with specific perihilar biliary obstruction with the use of MRCP, indicating that this modality may have promise as the collective experience increases. Positron emission tomography with [^{18}F] Fluoro-2-deoxy-D-glucose (FDG-PET) also holds promise for accurate diagnosis of cholangiocarcinoma in patients with bile duct stenosis, demonstrating a sensitivity and specificity of 92% in one recent study.[25]

Failure to diagnose and adequately treat cholangiocarcinoma has serious consequences. Most authors currently agree that aggressive surgical resection, including hepatic lobectomy if necessary, is the treatment of choice, even at the risk of overtreating some benign cases.[5,6,26,27]

CASE REPORTS

Four patients who presented to our institution between February 1991 and June 2000 underwent laparotomy for a preoperative diagnosis of biliary tract malignancy based on clinical presentation and cholangiographic findings. The final pathology report in all cases showed marked fibrosis and inflammation of the biliary duct without evidence of malignancy.

Case 1. A 47-year-old woman in otherwise good health presented with jaundice and was noted to have a high-grade biliary stricture involving the proximal common hepatic duct extending to the area of the hilum, highly suspicious for a Klatskin tumor (Fig. 1). Brushings demonstrated amorphous debris, ulcerated biliary mucosa with focal necrosis, and markedly inflamed granulation tissue; no evidence of neoplasm was identified. The patient underwent resection of the extrahepatic biliary tree and gallbladder and reconstruction with a Roux-en-Y hepaticojejunostomy. The final pathology report demonstrated fibrosis and inflammation of the biliary tree with mucosal ulceration at the hepatic duct bifurcation without evidence of neoplasm. Chronic cholecystitis and

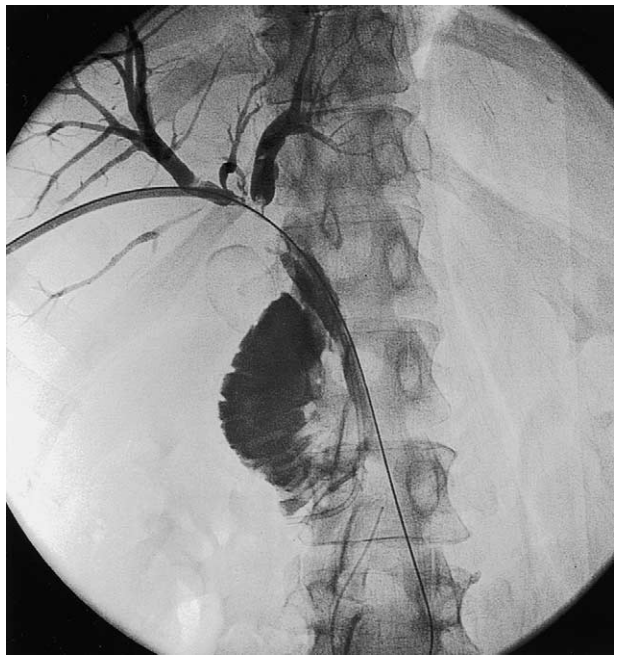

Fig. 1. Cholangiogram demonstrating a smooth, tapered filling defect at the confluence of the hepatic ducts.

cholelithiasis were also noted. The patient is well 2 years after her operation.

Case 2. A 61-year-old woman presented with jaundice and a tight 1 cm long stricture involving the common bile duct, 2 cm below the bifurcation of the right and left hepatic ducts. The patient had undergone an open cholecystectomy 16 years earlier. Brushings were negative for neoplasm. She underwent resection of the common bile duct, which was reconstructed with a retrocolic Roux-en-Y hepaticojejunostomy. The final pathology report demonstrated inflammation and fibrosis and was negative for neoplasm (Fig. 2). The patient is free of any evidence of malignancy or biliary stenosis 2 years after resection.

Case 3. A 54-year-old man with a history of Sjogren's syndrome, for which he was being treated with prednisone, presented with jaundice and was found to have a mass involving the ampulla of Vater and extending 1.8 cm up the common bile duct. Biopsies of this mass showed ampullary epithelium with active inflammation and reactive epithelial changes without evidence of atypia or neoplasm. The patient underwent a pylorus-sparing Whipple procedure as well as complete resection of the extrahepatic biliary tree because of possible neoplastic changes in the biliary epithelium on frozen-section report. The patient's biliary tree was reconstructed with bilateral intrahepatic cholangiojejunal anastamoses. The final pathology report on this specimen demonstrated a fibroinflammatory lesion with myofibroblastic proliferation and a mixed inflammatory infiltrate with plasma cells, lymphocytes, and eosinophils. Fibrosis and inflammation were noted without evidence of neoplasm (Fig. 3). The patient continues to do well 2 years after his operation. He continues to take prednisone for symptoms of Sjogren's syndrome.

Case 4. A 67-year-old man presented with jaundice and was noted to have a common hepatic duct stricture suspicious for a Klatskin tumor. He underwent biliary resection and reconstruction with a Roux-en-Y hepaticojejunostomy. The final pathology report showed bile duct epithelium with prominent spindle cells in the wall. Again there was no evidence of neoplasm. The patient subsequently developed ureteral obstruction and on investigation was found to have evidence of idiopathic retroperitoneal fibrosis. When last seen for a follow-up examination, the patient was doing well without recurrence 8 years after the original operation.

Based on this experience and a review of the literature, we sought to explore these unusual benign causes of biliary stricture formation and obstruction that mimic cholangiocarcinoma.

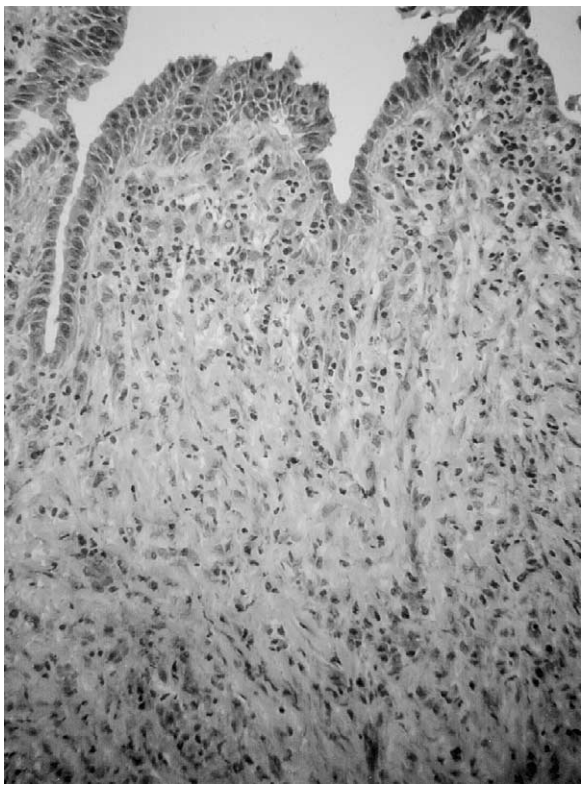

Fig. 2. Medium-power view of inflamed and regenerative bile duct epithelium. (Hematoxylin and eosin–stain; original magnification ×200.)

DISCUSSION

Patients with systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa, and Sjo-

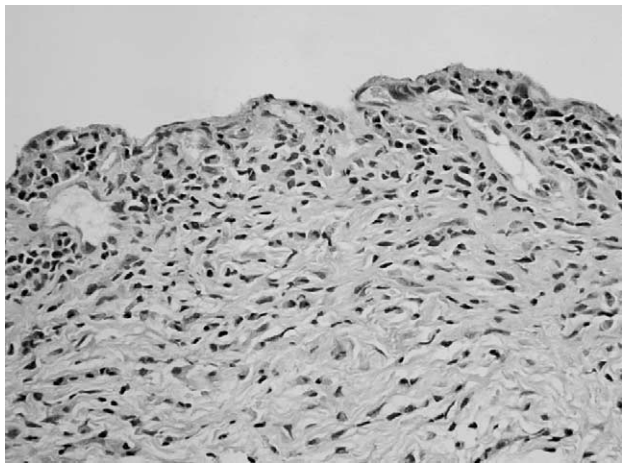

Fig. 3. High-power view of denuded bile duct luminal surface with large numbers of eosinophils infiltrating fibrous stroma. (Hematoxylin and eosin stain; original magnification ×400.)

gren's syndrome can present with biliary strictures that may mimic cholangiocarcinoma or pancreatic adenocarcinoma. The stricture is believed to result from inflammatory-mediated necrotizing vasculitis involving the fine axial arterial supply of the extrahepatic bile duct. In the case of Sjogren's syndrome, the immunologically mediated process can also affect the target organ directly, as evidenced by the glandular destruction characteristic of this disease.[28–31] Besides presenting as isolated extrahepatic strictures, these processes have also been reported to affect the gallbladder, resulting in acute acalculous cholecystitis, as well as the intrahepatic biliary system, resulting in a process resembling sclerosing cholangitis. In addition, the pancreatic arterial system may be affected, resulting in recurrent acute pancreatitis, chronic pancreatitis, or inflammation of the pancreatic head, with a radiographic appearance similar to that of a pancreatic tumor.[32–34]

In Sjogren's syndrome, the gastrointestinal and specific hepatobiliary manifestations of the disease are more common and appear better characterized than in other connective tissue disorders. Primary biliary cirrhosis affects 69% to 81% of the patients with Sjogren's syndrome. In addition, there is an increased incidence of chronic active hepatitis and cryptogenic cirrhosis. The complex of chronic pancreatitis and sclerosing cholangitis are also well described in patients with Sjogren's syndrome. The underlying pathophysiology appears to be direct destruction of target organs by autoantibodies. Antimitochondrial and anti–smooth muscle antibodies are detected in the sera of 11% of patients with this disease.[28,34]

Although well documented in the literature, the actual incidence of patients with benign extrahepatic biliary strictures resulting from an underlying connective tissue disorder is extremely low. In light of this, it is hardly justifiable to routinely screen for these diseases in patients who present with isolated extrahepatic biliary strictures without either a history of connective tissue disorder or obvious characteristic clinical stigmata. Those patients with suspected or previously diagnosed connective tissue disorders and an isolated extrahepatic biliary stricture with the cholangiographic appearance of cholangiocarcinoma present a unique diagnostic and therapeutic challenge. In patients suspected of having a connective tissue disorder, rheumatologic testing may provide confirmatory evidence, but the characteristic stricture remains malignant until proved otherwise. The same is true in patients with a diagnosis of connective tissue disorders and biliary strictures, as was the case in the patient described earlier in this report.

Some groups have reported regression of immunologically mediated biliary strictures after treatment with steroids or more potent immunosuppressive agents.[29,31,33,35] Patients with biliary strictures and known or highly suspected connective tissue disorders may benefit from a brief course of immunosupressants and repeat evaluation of the stricture for evidence of regression. In the absence of clear regression of a stricture suspicious for cholangiocarcinoma, the patient should be considered for surgical resection, both to establish a definite clinical diagnosis and also to relieve the obstruction.

In the case we presented, a diagnosis of Sjogren's syndrome had been established and was being treated aggressively with steroids when the patient presented for evaluation of the stricture. In light of this, and based on its radiographic appearance, which was consistent with biliary malignancy, a further trial of immunosupressants was unwarranted and the patient underwent resection.

In 1948, Ormond[36] described two cases of ureteral obstruction secondary to an inflammatory retroperitoneal process. Since that time additional cases of primary idiopathic retroperitoneal fibrosis, characterized by the transformation of fat tissue into a fibrous mass involving the small bowel, mesentery, duodenum, colon, urinary bladder, epidural space, and biliary tree, have been reported.[37,38] The commonly accepted pathogenesis is thought to involve an autoimmune process whereby antibodies are produced against ceroid, a polymer of oxidized lipid and protein. The inflammatory antigens pass through the adventitia of the aorta and other arteries, producing perivascular fibrosis.[37,39–42]

Although 70% of the cases of retroperitoneal fibrosis are considered idiopathic, a similar condition can result from a retroperitoneal malignancy–induced desmoplastic response, pharmacologic agents, and injury to the retroperitoneum.[37,39,42] The drugs most commonly associated with this condition include methysergide, ergotamine β-blockers (timolol, atenolol, propanolol), antihypertensive agents (α-methyldopa, hydralazine, reserpine), analgesics (aspirin, phenacetin, cocaine), and others such as haloperidol and bromocriptine.[43] Retroperitoneal injury from any inflammatory, immunologic, or traumatic process such as ulceratve colitis, radiation, or abdominal aortic aneurysm has also been associated with the development of retroperitoneal fibrosis.

Retroperitoneal fibrosis can involve the biliary tract either as an isolated process or as part of widespread involvement of the retroperitoneum and the peritoneal cavity.[39] Involvement of both the pancreatic head leading to common bile duct fibrosis and obstruction, as well as isolated involvement of the common hepatic duct and common bile duct, have been reported.[38,42] Bile duct strictures may be singu-

lar, resembling cholangiocarcinoma, or multiple as in the case of sclerosing cholangitis, supporting a possible link between these conditions.[37,44] Diagnosis of retroperitoneal fibrosis affecting the bile ducts is commonly made at the time laparotomy is performed with the intention of resecting either a presumed biliary or pancreatic malignancy.

Treatment of patients with suspected retroperitoneal fibrosis involving the biliary tree begins with decompression of the bile ducts, either surgically or endoscopically, followed by immunosuppressant therapy in order to both induce stricture regression and halt disease progression.[38] Some authors advocate reserving surgery for those patients whose lesions fail to regress after a 2- to 3-week trial of steroid treatment.[45] The downside to this approach is that tissue may not be obtained to make a definitive diagnosis and exclude malignancy, either as the primary cause of obstruction or as the inciting event leading to fibrosis and obstruction. In the patient presented earlier in this report, at the time his biliary stricture was evaluated, there was no other evidence to suggest a diagnosis of idiopathic retroperitoneal fibrosis. The diagnosis was made subsequently, after he developed ureteral obstruction. In patients without either a diagnosis of retroperitoneal fibrosis or clinical suspicion, a focal biliary stricture resembling cholangiocarcinoma on cholangiography should be resected both to provide definitive diagnosis and to relieve the obstruction.

Many benign processes can have cholangiographic features similar to those of cholangiocarcinoma. Because of the limitations of cholangiography and nonoperative investigation to definitively confirm or exclude a diagnosis of cholangiocarcinoma, some patients with benign lesions may require radical surgical resection. In this setting, most authors would agree that any lesion with the features of cholangiocarcinoma that cannot be definitively proved to be a benign process after conservative measures should be resected with the presumptive diagnosis of malignancy.

We thank Joel Greenson, M.D., Department of Pathology, University of Michigan Medical Center, for providing representative histologic sections.

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Analysis of Hepatic Resection of Metastasis Originating From Gastric Adenocarcinoma

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Few patients with metastatic gastric cancer have disease that is amenable to curative surgery. Thus far, little is known about liver surgery for metastases arising from gastric adenocarcinoma and prognostic factors. Of 73 patients operated on between 1980 and 1999 for noncolorectal, non-neuroendocrine hepatic metastases, 15 underwent liver resection for gastric adenocarcinoma metastasis. Ten patients underwent synchronous hepatic resection and five underwent metachronous hepatic surgery after a median disease-free interval of 10 months (range 6.1 to 47.3 months). None of the patients died within the first 30 days after surgery, and the in-hospital mortality rate was 6.7%. Among patients in the synchronous group, 26.7% experienced major complications mainly associated with gastric surgery. Overall median survival was 8.8 months (range 4 to 51 months); two patients survived more than 3 years. Univariate analysis revealed that the appearance of liver metastasis (synchronous vs. metachronous), the distribution of liver metastases (unilobar vs. bilobar), and the primary tumor site (proximal vs. distal) were marginally significant predictive factors regarding overall survival. Because of its high morbidity, synchronous liver resection for metastases originating from gastric adenocarcinoma is rarely followed by survival longer than 2 years. Primary tumor localization within the proximal third of the stomach and bilobar liver involvement appear to be predictive of poor outcome. On the other hand, curative resection of metachronous liver metastases may allow long-term survival in selected patients. (J GASTROINTEST SURG 2002;6:682–689.)

KEY WORDS: Liver, metastasis, gastric, cancer, resection, survival

The diagnosis of advanced gastric cancer goes hand in hand with a seriously impaired prognosis. Metastatic liver involvement, which occurs in up to 50% of patients with gastric cancer, makes long-term survival without treatment impossible[1]; median survival is reported to be approximately 6 months (range 2 to 4 months) with palliative chemotherapy. Surgery is the only treatment modality that offers the potential for cure. Morbidity and mortality have decreased remarkably as a result of improvements in perioperative management and surgical technique.[5–8] Precise staging is a prerequisite for a tailored treatment. If liver resection is being considered for metastatic disease, other sites of metastases should be ruled out. Liver imaging techniques, such as contrast-enhanced helical computed tomography and magnetic resonance tomography, have undergone immense technical refinements but still fail to detect malignant hepatic lesions in a remarkable proportion of patients. Intraoperative ultrasonography has been shown to substantially improve detection of liver metastases in resection candidates[9–11] and we have duplicated these findings at our institution.[12] This technique is not appropriate for screening, however. Ultrasound-guided resections have reduced the incidence of involved resection margins and made tissue-sparing, segment-oriented resections feasible, even for comparably large lesions.

On the other hand, hepatic metastases from gastric cancer, once recognized, generally are scattered throughout both lobes of the liver. Liver metastasis is frequently accompanied by peritoneal dissemination and/or gross involvement of lymphatic tissue under synchronous as well as metachronous condi-

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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(01)00075-0

tions.[13] Thus, in contrast to secondary hepatic lesions arising from coloretal metastases, curative resection of metastases from gastric cancer is not feasible in most cases.[3,14,15] Moreover, surgery for liver metastases arising from gastrointestinal carcinoma remains controversial, even in potentially resectable cases.[7,16–19] Because of the small number of suitable cases, only a few studies have been published.[7] Most reports dealing exclusively with surgical treatment of hepatic infiltration of gastric cancer originated in Japan.[3,15,20,21] European and American centers have generally reported on noncolorectal metastasis. However, most of these reports do not provide specific information about the treatment of secondary tumors originating from adenocarcinoma of the stomach.*

In an attempt to focus on this subject, we evaluated our experience with patients undergoing liver resection for hepatic metastasis of gastric adenocarcinoma. Because careful patient selection seems crucial in the surgical treatment of advanced malignancies, we analyzed several factors that had the potential to identify patients who might benefit from this surgery.

MATERIAL AND METHODS

Between 1980 and 1999, 14% of patients admitted to our institution for treatment of gastric adenocarcinoma already had hepatic metastasis at the time of diagnosis. Liver resection was considered in patients with hepatic metastasis, when complete tumor resection—metastasis, and primary tumor and lymph node involvement in synchronous disease—seemed possible and liver function was normal. Patients with evidence of other distant metastases or with severe comorbidity that increased their perioperative risk were excluded. We reviewed the records of 15 patients who underwent hepatic resection for secondary hepatic tumors discontinuously arising from gastric cancer. The group consisted of five women and 10 men ranging from 37 to 81 years of age (median 61.6 years).

This retrospective evaluation included assessment of the following: type of gastric resection, histopathologic pattern of the primary tumor, type of hepatic resection, interval between the primary operation and the liver resection, if appropriate, and several perioperative parameters such as the duration of the operation, amount of blood transfused, lengths of stay in the intensive care unit and hospital, perioperative complications, completeness of the resection, adjuvant therapy, and overall survival after hepatic surgery.

Operative death was defined as death occurring within 30 days of the operation; in-hospital death was defined as any death occurring before discharge. Morbidity included any type of complication, either surgical or nonsurgical. Complications considered life-threatening or requiring surgery or other interventional treatment and those that substantially prolonged the hospital stay were classified as major. Survival curves were calculated according to the Kaplan-Meier method. The log-rank test was used for univariate comparisons of survival between groups.

RESULTS

The characteristics of primary neoplasms are presented in Table 1. Because some patients had undergone primary surgery for gastric cancer elsewhere, data regarding primary tumors are incomplete. In the five patients who underwent metachronous liver resection, the median interval between gastric resection and the diagnosis of hepatic metastases was 10.1 months (range 6 to 47 months). In these patients there was no evidence of hepatic involvement at the time of surgery for the primary tumor. In the remaining 10 patients, the primary and secondary tumors were resected during the same operation (synchronous resection). None of the patients had any apparent distant metastasis other than hepatic metastases. The median diameter of liver metastases was 17.5 mm (range 3 to 200 mm). Solitary manifestations were found in eight patients and multiple manifestations in seven patients (unilobar in two and bilobar in five).

Regarding the type and extent of resection, nine patients had nonanatomic (perilesional) resections, three underwent bisegmentectomy (one in combination with a wedge resection), and three underwent right hemihepatectomy (with expansion to the central segment in two patients). In three patients with synchronous and one patient with metachronous liver resection (plus resection of the gastric remnant), splenectomy was also included in the procedure.

The overall mean duration of the operation was 276 minutes (range 135 to 540 minutes). On average, four units of erythrocyte concentrate were administered intraoperatively (range 0 to 12 units). Additional data regarding perioperative parameters are presented in Table 2. Postoperative complications occurred in 40% of patients in the metachronous group and in 50% of patients in the synchronous group (30% in direct association with concomitant

*References 2, 4, 6, 8, 16, 18, 23, and 24.

Table 1. Characteristics and treatment of primary tumors

	Synchronous manifestations of liver metastasis	Metachronous manifestations of liver metastasis
No. of patients	**10**	**5**
Primary tumor site		
Cardia	5	0
Fundus	1	1
Corpus	1	1
Antrum	3	2
Unknown	0	1
Lauren classification		
Intestinal	4	2
Diffuse	4	1
Unknown	2	2
Tumor staging		
2	5	1
3	1	1
4	3	2
X	1	1
Node staging		
1	3	3
2	4	1
3	2	0
X	1	1
Tumor grade		
1	1	0
2	2	1
3	5	2
4	1	0
X	1	2
Type of gastric resection		
Total	4	3
Subtotal	4	2
Proximal*	2	0

*Esophagectomy plus cardia resection.

gastric resection and/or splenectomy, respectively) (Table 3). Overall morbidity was 46.7%, and major complications were observed in four patients (26.7%). None of the patients died during the 30-day perioperative period. One patient died 52 days after gastrectomy, splenectomy, and hepatectomy, and two patients had reoperations for multiple complications such as bleeding, anastomotic failure, peritonitis, and pancreatitis. Thus the overall hospital mortality rate was 6.7%. During follow-up, two patients died of causes other than cancer (13.3%). One patient died of hepatic, peritoneal, and bone recurrences, and one died of locoregional recurrence. In the remaining 11 patients, the exact cause of death was unknown but was presumed to be related to recurrent or persistent disease. None of these patients were still alive at the time of this review.

The mean overall survival for all patients who were discharged was 15.7 months; the median survival was 8.8 months (range 4 to 51 months). Survival rates at 1, 2, and 3 years were 35.7%, 28.6%, and 14.3%, respectively. None of the patients survived more than 5 years after liver surgery. With respect to overall survival, the primary tumor site (proximal third vs. the distal two thirds of the stomach), the type of liver metastasis manifestation (synchronous vs. metachronous), and the distribution of liver metastases to one or both lobes were marginally significant indicators (Table 4 and Figs. 1, 2, and 3).

There was also a tendency toward improved survival in patients with a solitary metastasis (Fig. 4), "curative" (R_0) resection of hepatic tumors (Fig. 5), intestinal-type N0 and N1 staging, and G1 or G2 grading of the primary tumor (see Table 4). Almost no difference in survival was found with regard to the size of the metastases or the stage of the primary tumor (see Table 4).

DISCUSSION

Few patients with secondary hepatic lesions arising from gastric adenocarcinoma have a malignancy that is confined to a resectable portion of the liver. The resection rate is 10% or less.[14,15] At specialized treatment centers, the proportion of surgery for hepatic metastasis of gastric cancer is 7% to 12% of hepatic resections for all types of secondary malignancies.[5,8,15] In reports dealing with surgery for noncolorectal, non-neuroendocrine metastasis, the proportion of gastric cancers metastasizing to the liver ranges from 5% to 29%.[6,8,16,18,23] In these reports, the number of patients undergoing liver resection for metastasis of gastric cancer did not exceed 11. Two series from the Far East reported approximately 21 patients (Table 5). To our knowledge, ours is the largest Western study on surgical treatment of liver metastasis originating from gastric adenocarcinoma (see Table 5).

In the present series, 15 patients with synchronous or metachronous metastasis of gastric cancer to the liver were treated by resection. During the same period, a total of 59 patients underwent surgery for other noncolorectal, non-neuroendocrine liver metastases. Of the 14 patients who were discharged, only two survived more than 3 years. In both of them the primary tumor was advanced (T3N1, T4N1), and metastasis to the liver developed metachronous (after 6 and 26 months, respectively) and was confined to one lobe, and the resection margins of the liver were free of disease. However, malignant cells were closer than 10 mm to the resection plain.

Table 2. Results of liver resection for gastric cancer metastasis

	Synchronous manifestations of liver metastasis	Metachronous manifestations of liver metastasis
No. of patients	**10**	**5**
No. of metastases		
Solitary	5	3
Multiple	5	2
Type of liver resection		
Nonanatomic	8	1
Bisegmentectomy	1	2*
Right hemihepatectomy	0	1
Right hemihepatectomy with segment IV	1	1
Resection status		
Curative	5	5
Palliative	5	0
Morbidity	5	2
In-hospital mortality	1	0
Reoperations		
n	6	2
Patients undergoing reoperation	1	1
Duration of		
ICU stay (mean)	6.1 days	1.8 days
Total hospitalization (mean)	18.2 days	17.4 days

*In combination with wedge resection.

As reported by many investigators, secondary liver tumors arising from gastrointestinal adenocarcinomas have the worst prognosis among noncolorectal metastases after resection.* Confirming their data, overall survival in our series was disappointing (see Table 5). Long-term survival seems to occur in an almost unpredictable manner, in addition to being very rare. Most investigators who provide specific data on survival after hepatic resection for gastric metastases report a much longer median survival—up to 2 years—compared to what we observed. As shown in Table 5, the proportion of metachronous and complete resections and unilobar involvement was higher in almost all studies when compared with this series. On the other hand, the 3-year survival rate in our study was similar to other reports (see Table 5).

There are three possible reasons for the considerable differences in outcome among published series. First, in contrast to colorectal cancer, in the vast majority of patients with gastric cancer and liver involvement might reflect generalized disease. Because of the inaccuracy of available diagnostic tools, detection of early metastases is not yet possible. Some investigators have discussed whether to delay hepatic surgery for several months to see whether other metastatic manifestations would arise.[4,18] Because we know from our experience with liver transplantation for primary hepatic malignancies that metastases are able to set secondary metastases into the transplanted liver, we would not completely agree with this approach. Moreover, staging techniques must be improved. Second, in all published series—even those from highly specialized centers—the number of patients was severely limited (Table 5), as was also the case in our study. A type II error results, and thus the identification of statistically relevant predictive factors is hampered.

*References 6, 8, 16, 18, 19, and 23.

Table 3. Postoperative complications

Complications	No.
Bleeding	2
Pancreatitis	2
Anastomotic failure	1
Pneumothorax	1
Recurrent nerve palsy	1
Catheter-associated bacteremia	1
Pneumonia	1
Pulmonary congestion	1
Paralytic ileus	1
Wound separation	1
Patients with any complications	7 (46.7%)
Patients with major complications	4 (26.7%)
No. of reoperations	8
No. of patients undergoing reoperation	2 (13.3%)

Table 4. Median survival after liver resection for gastric cancer hepatic metastasis

Parameters (No. of patients)	Median survival (mo)*	Log-rank *P* value	Median survival after R0 resection† (mo)	Log-rank P value†
Primary tumor				
Proximal (6)/distal (8)	7.15/21.17	0.064	8.8/25.6	0.063
Diffuse (5)/intestinal (5)	9.1/16.79	0.481	9.0/16.8	0.764
T2 (6)/T3, T4 (7)	9.33/9.0	0.460	8.8/9.0	0.395
N0, N1 (5)/N2, N3 (7)	16.79/8.8	0.165	16.8/8.8	0.113
G1, G2 (3)/G3, G4 (8)	16.79/5.19	0.402	16.8/4.7	0.661
Liver metastasis				
Solitary (8)/multiple (6)	12.9/5.09	0.633	16.8/4.4	0.747
Unilobar (10)/bilobar (4)	12.9/4.93	0.052	16.8/4.0	0.001
Diameter <21 mm (7)/>20 mm (5)	9.0/8.8	0.463	16.8/8.8	0.827
Synchronous (9)/metachronous (5)	5.49/32.49	0.051	9.0/32.5	0.102
Liver Surgery				
Curative (10)/palliative (4)	12.9/5.0	0.169	—	—

*Results in 14 patients who were discharged from the hospital.
†Results in 10 patients with R0 liver resection.

Third, reports of noncolorectal metastases are based on very diverse groups of patients. In our opinion, these patients should be registered and evaluated prospectively by an international cooperative organization to collect sufficient data. We are further convinced that these cases should be treated at specialized centers.

Thus the question of whether the surgical success and the resulting quality of life are worth the price is still open to discussion. The consensus seems to be that there is no apparent value to surgery if residual disease remains, whether it is involvement of resection margins, other distant metastases, or peritoneal carcinosis.[16,18,19,22,25]

The lack of a significant difference in outcomes between patients treated curatively vs. noncuratively, as was found in this series, is a possible indication that, besides the small numbers of cases, there were more patients with residual disease that we were unable to detect. Highly sensitive techniques are still needed to reliably determine the extent of the disease. More sophisticated staging by means of intraoperative ultrasonography, as routinely used at our institution since 1996, has been reported to reveal the presence of hepatic lesions that go undetected preoperatively in a significant proportion of patients with liver tumors and may result in a changing of surgical strategy.[12] Highly sensitive screening tests for distant microscopic disease are not yet available. This is crucial, especially in the case of highly aggressive tumors such as gastric carcinoma.

In our study, patients with metachronous manifestations of liver metastasis experienced longer survival than patients who were initially seen with liver involvement. Despite the small number of patients, this difference was almost significant. Long-term survival after curative (R0) metachronous liver resection is possible.[8,14,25] Even after we excluded those patients with incomplete resections, we clearly observed a longer median survival in the metachronous group, but the difference was not significant (see Table 4). Perhaps this is a consequence of the small number of samples.

Several reports dealing with noncolorectal metastasis were unable to detect a significant difference in survival depending on the timing of the resection.[16,18,23] Akamo et al.[20] reported a median survival of 24 months in three patients undergoing metachronous resection (see Table 5). With regard to perioperative morbidity, our results confirm the observation of Bines et al.[25] that synchronous liver resection carries a higher risk. This may deepen the concerns regarding the use of aggressive liver surgery in conjunction with the treatment of gastric cancer under synchronous conditions.

When the primary tumor was located at the cardia or fundus, survival was shorter with marginal significance. The difference in survival with regard to the primary tumor site is highly significant when incomplete resections are excluded (see Table 4). It is assumed that adenocarcinomas of the gastroesophageal junction are biologically different from distal gastric malignancies. Until now this issue has not been discussed with respect to surgical treatment of gastric metastases to the liver. However, because of the ongoing increase in proximal gastric cancers in Western countries, it is our opinion that this point should be taken into consideration when selecting patients for liver surgery.

We were unable to confirm serosal infiltration of the primary gastric tumor as a prognostic factor, as

Table 5. Results of liver surgery for metastases originating from gastric adenocarcinoma: Review of the literature

Reference	No. of patients	Solitary metastasis (%)	Bilobar metastasis (%)	Metachronous resection (%)	Noncurative resection (%)	HAI (%)	Postoperative chemotherapy (%)	Morbidity (%)	30-day mortality (%)	In-hospital mortality (%)	Median survival (mo)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Okuyama et al.[3]	9	33.3	66.7	0	55.6	44.4	55.5	NR	0	11.1	8 (4 alive)	50	11.1	0
Habu et al.[2]	12	33.3	66.7	0	NR	NR	NR	NR	6	NR	10‡	33	NR	0
Bines et al.[24]	7	42.9	14.3	42.9	14.3	0	14.3	30	14.3	NR	16	57.1	14.3	14.3
Ochiai et al.[14]	21	71.4*	NR	38.1	0	19	85.7	NR	NR	NR	18	NR	NR	19
Seifert and Junginger et al.[8]	7	57.1	14.3	42.9	28.6	0	NR	NR	0	14.3	21 (3 alive)	71	14.3	0
Taniguchi et al.[15]	6	NR	NR	0	NR	0	NR	NR	0	NR	18.9	NR	NR	0
Miyazaki et al.[21]	21	33.3	14.3	47.6	NR	9.5	66.7†	NR	0	0	11 (5 alive)	45	19	11.1
Akamo et al.[20]	3	NR	NR	100	NR	0	0	NR	0	0	24.3	100	33.3	0
Present series	15	53.3	33.3	33.3	33.3	7.1	14.3	27	0	6.7	8.8	35.7	14.3	0

HAI = hepatic arterial infusion; NR = not reported.
*Proportion of patients with less than four metastases.
†Oral chemotherapy with fluorouracil.
‡Mean survival.

Fig. 1. Actual overall survival (Kaplan-Meier). Primary tumor site. Proximal third of the stomach (*dotted line*); distal two thirds of the stomach (*solid line*).

previously reported.[14] Neither the type of gastric cancer, according to Lauren's classification, nor the size of the liver metastases markedly influenced overall survival. According to previous reports,[14,21] the number of metastatic lesions alone appeared to play a minor role in this series. On the other hand, we found that the distribution of metastases to both lobes of the liver hampered overall survival (see Table 4). The difference was highly significant when only complete resections were included.

Fig. 2. Actual overall survival. Synchronous and metachronous manifestations of liver metastases. Synchronous metastasis manifestations and resection (*dotted line*); metachronous metastasis manifestations and resection (*solid line*).

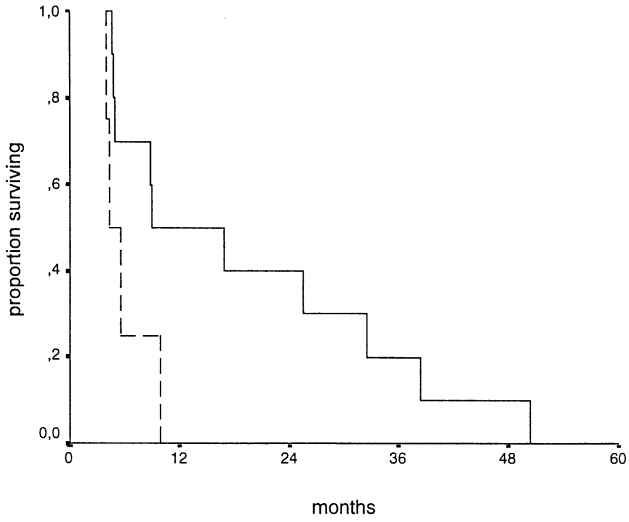

Fig. 3. Actual overall survival (Kaplan-Meier). Distribution of liver metastases. Bilobar liver metastasis (*dotted line*); unilobar liver metastasis (*solid line*).

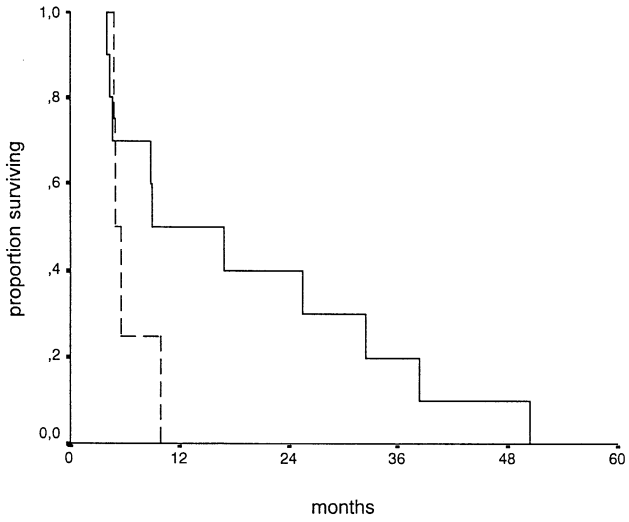

Fig. 5. Actual overall survival (Kaplan-Meier). Complete vs. incomplete resection. R1 and R2 resection (*dotted line*); R0 resection (*solid line*).

Reports from Japan[3,15,23] indicate that a locoregional chemotherapeutic regimen might improve surgical outcome. Gastric cancer metastases are reported to respond better than colorectal metastases.[15] In our series, only one patient received a postoperative hepatic arterial infusion and survived 38 months. In terms of adjuvant therapy, however, we are unable to draw any conclusions based on these data.

In concert with other reports, approximately one fourth of our patients experienced serious complications, which led to the death of one patient after approximately 2 months. These data confirm the observation that liver surgery has become safer and operative mortality has decreased far below 10% at specialized centers (see Table 5). This lowered surgical risk justifies the use of hepatectomy to treat selected patients with gastric cancer metastasizing to the liver, even in the face of an uncertain oncologic outcome and the absence of empiric data. The discussion about whether liver surgery should be performed in patients with limited chances of cure is ongoing, but information about patient selection is still lacking. Thus far, we conclude that surgery for liver metastasis arising from gastric adenocarcinoma is reasonable, if complete resection seems feasible after careful pre- and intraoperative staging. However, currently available diagnostic tools are not able to detect microscopic disease manifestations. In our study, survival of longer than 3 years was possible only when metastases appeared to be metachronous and were confined to one lobe, and if the primary tumor was located within the corpus or antrum. It is not yet possible to overcome the difficulty of clearly identifying patients who would benefit from hepatic resection for metastases arising from gastric adenocarcinomas. Patients with potentially curable noncolorectal, non-neuroendocrine secondary liver malignancies should be documented and evaluated in a prospective manner from multiple centers in order to obtain a sufficient number of patients for multivariate analysis.

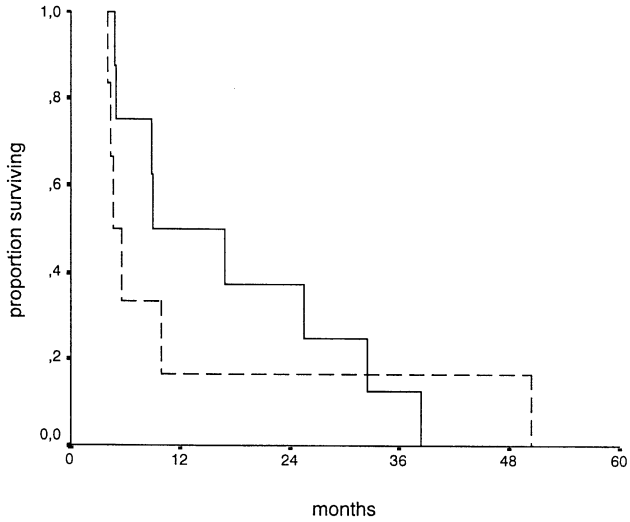

Fig. 4. Actual overall survival (Kaplan-Meier). Number of liver metastases. Multiple liver metastases (*dotted line*); solitary liver metastasis (*solid line*).

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Does Bone Change After Biliopancreatic Diversion?

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This prospective study evaluated bone changes after biliopancreatic diversion (BPD) consisting of a distal gastrectomy, a 250 cm alimentary channel, and a 50 cm common channel. Thirty-three consecutive patients had clinical, biochemical, and bone mineral density analysis before surgery and 4 and 10 years after surgery. Iliac crest bone biopsies and special tests including parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OH-D), 1,25-dihydroxyvitamin D (1,25-OH_2-D), bone-specific alkaline phosphatase (BAP), and osteocalcin were obtained at surgery and 4 years postoperatively. Over the years, with close metabolic surveillance, additional calcium and vitamin D were given as indicated. After BPD, serum levels of calcium and vitamin D were decreased and serum levels of PTH, BAP, and osteocalcin were increased. Bone turnover and mineralization were both increased. Mean osteoid volume ($P < 0.0007$) and bone formation rate in relation to bone volume ($P < 0.02$) were increased. Static measures of bone were altered as follows: cortical thickness decreased ($P < 0.01$) and trabecular bone volume increased ($P < 0.01$). Ten years after surgery, overall bone mineral density was unchanged at the hip and was decreased by 4% at the lumbar spine. Overall fracture risk, based on the Z score, was unchanged. Preoperative factors predicting bone loss included menopause, smoking, and preexisting osteopenia. An elevated level of 1,25-OH_2-D was also found to be a predictor of future bone loss ($r = 0.40$; $P < 0.002$). After surgery, a greater increase in bone markers and bone turnover was associated with an increased risk of bone loss. Although elevated osteocalcin levels were associated with overall bone loss ($r = 0.52$; $P < 0.002$), lower albumin levels were associated only with bone loss at hip level ($r = 0.44$; $P < 0.02$), whereas lower calcium levels were associated only with the loss at the lumbar spine ($r = 0.39$; $P < 0.02$). Ten years after surgery, bone loss at the hip continued to depend on albumin levels ($r = 0.37$; $P < 0.03$). We concluded that bone was relatively tolerant to the metabolic changes due to BPD. Provided that there is close surveillance for metabolic disturbances, the use of appropriate supplements, and the avoidance of malnutrition, the beneficial effects of surgery far outweigh the risk of postoperative bone disease. (J GASTROINTEST SURG 2002;6:690–698.)

KEY WORDS: Morbid obesity, biliopancreatic diversion, bone metabolism, calcium

Biliopancreatic diversion (BPD) is an efficient procedure for the treatment of morbid obesity. It preserves normal eating habits and results in an appropriate and sustained weight loss. Disturbances of gastric physiology and diversion of hepatic and pancreatic secretion both affect intestinal absorption and may reduce absorption of protein, calcium, and vitamin D. Consequently long-term bone damage may occur. Scopinaro et al.,[1–3] who first described the BPD procedure 20 years ago, used it in more than 1000 patients without gross clinically relevant bone damage. This is consistent with our own 15 years' experience.[4,5]

On the other hand, Compston et al.[6,7] evaluated bone histology 4 years after BPD and found damage similar to that described after intestinal bypass—that is, bone turnover was increased and mineralization was decreased. These changes represented a risk for osteomalacia, but the clinical significance of these findings remains unclear. Clinical manifestations of metabolic bone disease were rare after jejunoileal bypass.[8–12]

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Published by Elsevier Science Inc.

1091-255X/02/$—see front matter
PII: S1091-255X(01)00086-5

A clinical, biochemical, and radiologic study was undertaken in 33 consecutive patients about to undergo BPD. Evaluations were carried out before and 4 and 10 years after surgery. Bone biopsies with different bone markers and serum vitamin D measurements were obtained before and 4 years after surgery.

MATERIAL AND METHODS

Patient Population

Thirty-three consecutive patients who underwent BPD gave informed consent and participated in this study. We excluded patients with known kidney, liver, or bone disease, those with a history of gastric or intestinal surgery, and those receiving cortisone or anticonvulsant therapy. There were 26 women and seven men who had a mean age of 35 ± 8 years. Mean body mass index was 44 ± 6 kg/m^2, mean initial weight was 118 ± 17 kg, mean excess weight was 91% ± 25%, and mean waist-to-hip ratio, available in 12 subjects, was 0.87 ± 0.09. Among the men, two were diabetic, five admitted using alcohol occasionally, and none were smokers. Among the women, three were diabetic, four were postmenopausal, (3 were on hormone replacement therapy), two were taking birth control pills, and nine were smokers. Half of the patients (n = 16/33) said they were suffering from osteoarticular pain, and 11 patients had a history of bone fracture before surgery.

Method of Evaluation

Routine Follow-Up. Patients were seen in the clinic for follow-up every 3 months the first year, every 6 months the second year, and annually thereafter. Routine biochemical testing included serum levels of albumin, total calcium, phosphate, magnesium, alkaline phosphatase, and parathyroid hormone (PTH). Patients were given a multivitamin that contained 175 mg of calcium and 400 IU of vitamin D. Additional calcium (up to 2 g/day) and vitamin D (up to 100,000 IU/day) were given when serum calcium levels decreased to less than 2.15 mmol/L (normal = 2.15 to 2.50 mmol/L), or if bone pain was present.

Bone Evaluation. Bone condition was evaluated clinically, biochemically, and radiologically before surgery and again after a mean of 51 ± 3 months and 122 ± 4 months after surgery. Specimens for bone biopsy were obtained at the time of surgery and 4 years after surgery, along with serum for special biochemical bone marker studies. Because of technical difficulties, all components of the bone evaluation were not available for all patients. In six patients either the preoperative or postoperative biopsy was not of sufficient quality for histomorphometric analysis, and in five patients either the preoperative or postoperative bone density results were not available. Four years and 10 years after surgery, a formal evaluation and a written questionnaire were completed by all 33 patients. At 10 years, bone density results were not available in two patients because of pregnancy in one and lack of cooperation in the other.

Bone Biopsy. Bone biopsy specimens were obtained at the iliac crest with a Bordier trocar (9 mm) at the time of biliopancreatic surgery under general anesthesia. Follow-up biopsy specimens were obtained 4 years later from the contralateral iliac crest under local anesthesia. Declomycin, 900 mg, was given by mouth 11 days and 3 days before biopsy.[18] Specimens were embedded in methylmethacrylate, and 5-micron sections were prepared for histomorphometric analysis as previously described.[19] Bone activity was evaluated by measuring the percentage of osteoid volume, percentage of osteoid surface, osteoid thickness in micrometers, activation frequency per day, percentage of erosion surface, and the number of osteoclasts per 100 mm and the number of osteoblasts per osteoid surface. The following eight measurements were calculated to evaluate mineralization: percentage of single-line surface, percentage of double-line surface, mineralization application rate in micrometers per day, percentage of mineralization surface in millimeters, mineralization time in days, bone formation rate in relation to bone surface, bone formation rate in relation to bone volume, and bone formation rate at the cellular level to evaluate bone structure, the percentage of trabecular bone volume, wall thickness in millimeters, percentage of mineralized bone volume, and cortical thickness in micrometers were measured.

Some of the biopsies did not contain both internal and external cortices, particularly the initial biopsies in heavier patients. All biopsies were used for comparing bone turnover and mineralization, whereas only biopsies with both cortices were used for structural analyses (n = 10). Preosteomalacia was empirically defined when values one standard deviation more than the mean for the whole group were present for all three of the following: osteoid volume (>4.3%), osteoid thickness (>14.7 μm), and mineralization lag time (>22.7 days).

Bone Biochemistry. Special biochemical bone markers included 25-hydroxyvitamin D (25-OH-D), 1,25-dihydroxyvitamin D (1,25-OH_2-D), bone-specific alkaline phosphatase (BAP), and osteocalcin. These were measured by radioimmunoassay using commercial kits sold by Incstar Corporation (Stillwater, Minnesota) for vitamin D and osteocalcin, and by Hybritech Canada, (Scarborough, Onatario, Canada) for BAP.

Bone Radiometry. Bone mineral density (BMD) was measured in the lumbar spine from L_2 to L_4 and at the femoral neck (i.e., hip). Before surgery and 51 ± 3 months after surgery, measurements were obtained using a dual-photon absorptiometric device (DPA; Sophos, Sopha Medical, Buc, France) with a gadolinium source. At 10 years (122 ± 4 months) measurements were obtained using a dual-energy x-ray absorptiometric device (DXA; DPX-L, Lunar, Madison, Wis., software version 3.2). DXA is recognized as improving the precision and accuracy of BMD measurement.[13] Therefore all DPA values were adjusted to DXA levels by multiplying the DPA values by a factor of 1.15.[13] With the use of local normative data, the T and Z scores were calculated. The T score is the standard deviation (SD) from the mean for young normal subjects of the same sex and same ethnicity. The Z score is defined as the standard deviation from the mean predicted value for age-matched control subjects. Osteopenia was defined as 1 SD below either the T or Z score and osteoporosis as greater than 2.5 SD below.[14,15] Bone loss from aging was calculated from our reference group[13] and estimated to be approximately 8 mg/cm^2 per year or grossly 1% per year for this age group. This rate was used to recognize patients with abnormal bone loss. Fracture risk was evaluated from the Z score. Each standard deviation below the mean predicted value for age-matched control subjects doubled the risk of fracture.[16,17]

Type of Operation

The type of BPD used was the one described by Scopinaro et al.[2] It consisted of 65% distal gastrectomy, gastroenterostomy at 250 cm from the ileocecal valve, and ileoileostomy 50 cm from the ileocecal valve, creating an alimentary channel of 250 cm including a common channel of 50 cm.[4]

Statistical Analysis

Data are presented as mean ± standard deviation. Preoperative and postoperative data were compared by means of Student's t test or Wilcoxon's rank-sum test, with the use of SAS software. Results were considered significant if the two-tailed P value was <0.05, if the 95% confidence interval did not include zero. Correlations were explored between pairs of variables using Pearson's method. Multiple regression analyses were also performed to define the relative influence of different variables.

RESULTS

Clinical Findings

Four years after surgery, weight loss was 31% ± 9% of the initial weight and body mass index had fallen from 44 ± 6 to 30 ± 4 kg/m^2. From 4 to 10 years, patients gained a mean of 3 ± 9 kg ($P < 0.05$). The prevalence of diarrhea (>3 liquid stools/day) was the same at 4 years and 10 years. It was present in three patients at both evaluations, but over the years 5 (15%) of 33 patients required revision for diarrhea. This was done before 4 years in all but one patient. Common channels were lengthened from 50 to 100 cm and cured the diarrhea in four of five patients. Ten patients complained of bone pain before surgery, 11 at 4 years, and 19 at 10 years. Nonsteroidal anti-inflammatory drugs for osteoarticular pain were used frequently by two patients. One patient was receiving corticosteroid therapy for respiratory disease. Bone fractures occurred in eight patients (ankle [n = 2], rib, wrist, toe finger, tibia, and spine). These fractures healed normally. Six of these patients had already had a bone fracture before surgery. Four women were menopausal before surgery and seven others became menopausal during follow-up (n = 11/26). Half of them were on hormone replacement therapy.

Initially patients were given a multivitamin containing calcium (175 mg) and vitamin D (400 IU). If patients complained of bone pain, if serum calcium levels fell below 2.15 mmol/L, or if PTH levels increased to more than 100 ng/L, additional oral calcium (500 mg) and vitamin D (50,000 IU) were given. At 4 years after surgery, additional supplements had been given to one third of patients, varying the dosages up to 2000 mg of calcium and 100,000 IU of vitamin D per day. At 10 years, all patients had been advised to take additional supplements, but one third were considered noncompliant and admitted to having taken supplements rarely or having interrupted treatment for many months. Intramuscular vitamin D (Calciferol) had to be used in five patients and oral glucosamine sulfate (500 mg) in four.

Biochemical Findings

Four Years Postoperatively. Four years after surgery, mean values for calcium, 25-OH-D, and 1,25-OH_2-D were significantly decreased, and mean values for alkaline phosphatase, BAP, osteocalcin, magnesium, and PTH were increased. Albumin and phosphate levels were unchanged (see Table 1).

Bone pain was associated with an increase in osteocalcin ($r = 0.50$; $P < 0.05$) and a decrease in calcium levels ($r = 0.37$; $P < 0.02$). Diarrhea, weight

Table 1. Biochemical changes after biliopancreatic diversion

	Reference value	Before surgery	After 4 years	After 10 years	*P* value*
Calcium (mmol/L)	2.32 ± 0.18	2.26 ± 0.09 (n = 33)	2.16 ± 0.11 (n = 33)	2.19 ± 0.10 (n = 33)	0.0008
25-OH-D (ng/ml)	25.7 ± 3.6	28.5 ± 12.9 (n = 32)	17.5 ± 15.9 (n = 31)	—	0.006
1,25-OH_2-D (p/ml)	29.4 ± 6.5	40.0 ± 10.6 (n = 33)	34.8 ± 8.6 (n = 31)	—	0.03
Parathyroid hormone (ng/L)	45 ± 30	55 ± 13 (n = 33)	75 ± 35 (n = 32)	100 ± 63 (n = 33)	0.0001
Alkaline phophatase (U/L)	60 ± 30	79 ± 39 (n = 32)	98 ± 42 (n = 32)	115 ± 50 (n = 33)	0.003
Bone-specific alkaline phosphatase (μg/L)	12.2 ± 4.5	16.6 ± 7.9 (n = 33)	30.8 ± 15.3 (n = 31)	—	0.0001
Osteocalcin (ng/L)	2.89 ± 1.00	1.04 ± 0.66 (n = 33)	3.89 ± 1.56 (n = 31)	—	0.0001
Phosphate (mmol/L)	1.15 ± 0.35	0.97 ± 0.12 (n = 33)	1.04 ± 0.16 (n = 33)	1.05 ± 0.19 (n = 33)	0.05
Magnesium (mmol/L)	0.95 ± 0.30	0.84 ± 0.07 (n = 33)	0.88 ± 0.08 (n = 33)	0.84 ± 0.08 (n = 33)	NS
Albumin (g/L)	43 ± 7	40.7 ± 3.6 (n = 33)	41.7 ± 2.9 (n = 33)	40.7 ± 5.0 (n = 33)	NS

Data (mean ± SD) were obtained before and 4 years and 10 years after surgery in 33 consecutive patients. Note the decreases in calcium and vitamin D and the increases in PTH, alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcium, and phosphate at 4 years, whereas albumin and magnesium levels remain stable.
*Student's *t* test between paired data. Values before and up to 10 years after surgery were compared; NS = not significant.

loss, and fatigue were not correlated with any biochemical variable.

Ten Years Postoperatively. At 10 years, the only change was a slight increase in PTH and alkaline phosphatase levels. PTH levels increased from 75 ± 35 to 100 ± 63 ng/L ($P < 0.01$) and alkaline phosphatase levels increased from 98 ± 42 to 115± 50 U/L ($P < 0.01$). In nine patients the PTH level was above normal (>90 ng/L).

Radiologic Findings

BMD varied independently and disparately at spine and hip levels. At 4 years, BMD was increased at both sites in 12 subjects, decreased at both sites in seven, and varied in opposite directions in eight subjects. Overall, the mean value for BMD did not change at the lumbar spine, with a minimal decrease of 3% ($P < 0.012$) at the hip (see Table 2).

At 10 years postoperatively, the situation remained the same. When results before and 10 years after surgery were compared, no significant change at the hip and a minimal change of 4% at the lumbar spine ($P < 0.004$) were measured. Overall, the mean T and Z scores were unchanged for either site at both 4 years and 10 years. At the end of 10 years, nine patients had an increase in BMD, 13 had a decrease in BMD within the range expected for aging (i.e., less than 1% per year), and four patients had lost density at both the spine and the hip to a greater degree than would be expected for aging. Two of these patients had osteoporosis before surgery and two were menopausal. Although before surgery five patients were considered to have osteoporosis, 10 years after surgery there were six patients with osteoporosis, two of whom were newly diagnosed. There were no differences between those who gained and those who lost bone density with regard to the prevalence of fractures, hormone replacement therapy, compliance with taking supplements, or presence of diarrhea.

Histologic Findings

All measures of bone activity were markedly increased after surgery, except for the amount of resorption surfaces, which were also unexpectedly high before surgery. Many indices of bone formation were also increased (see Table 3). Static parameters of bone structure also changed. Trabecular bone volume increased from 16 ± 38 to 25 ± 72 ($P < 0.01$) and cortical thickness decreased from 1355 ± 419 to 992 ±

Table 2. Changes in bone mineral density after biliopancreatic diversion

	Before surgery	After 4 years	After 10 years	*P* value*
Spine				
BMD (g/cm^2)	1.151 ± 0.160 (n = 29)	1.190 ± 0.158 (n = 25)	1.103 ± 0.150 (n = 31)	0.004
Z score (SD)	−0.84 ± 0.83	−0.55 ± 0.81	−0.82 ± 1.13	NS
T score (SD)	−1.06 ± 0.98	−0.94 ± 1.02	−0.88 ± 1.25	NS
Hip				
BMD (g/cm^2)	0.943 ± 0.142 (n = 29)	−0.918 ± 0.152 (n = 28)	−0.906 ± 1.142 (n = 31)	NS
Z score (SD)	−0.66 ± 1.01	−0.67 ± 1.10	−0.83 ± 0.97	NS
T score (SD)	−0.98 ± 1.08	−1.16 ± 1.32	−0.84 ± 1.17	NS

Radiologic measurements of BMD before and 4 years and 10 years after BPD were obtained in 26 consecutive patients. Measurements were taken at the lumbar spine (n = 21) and at the femoral neck (n = 26) before and 51 ± 2.6 months and 122 ± 4 months after surgery. Z score represents the standard deviation (SD) from the mean predicted value for age-matched control subjects. T score represents the SD from the mean for young normal subjects.
*Student's *t* test between paired data. Values before and up to 10 years after surgery were compared.

399 ($P < 0.02$). One patient met the criteria for osteomalacia before but not after surgery (perhaps because of the calcium and vitamin D supplements). On the other hand, two siblings had osteomalacia after surgery. Initial biopsy results were available for only one of them and showed a preexisting abnormally long mineralization lag time of 26 days. In six others, levels of osteoid volume and thickness reached levels consistent with osteomalacia, but mineralization remained normal. The waist to hip circumference ratio (WHR) was the only anthropometric variable predicting a change in histomorphometric analysis. The higher the initial WHR, the greater the increase in osteoid thickness ($r = 0.63$; $P < 0.02$) and the decrease in trabecular wall thickness ($r = 0.99$, $P < 0.004$).

Table 3. Histomorphometric changes after biliopancreatic diversion

Indices	Reference value	Before surgery	After surgery	*P* value*
Turnover				
Osteoid surface (%)	13.7 ± 29.9	18.3 ± 10.9	42.9 ± 20.0	0.00001
Osteoid volume (%)	1.7 ± 3.0	2.2 ± 2.2	7.0 ± 5.0	0.0006
Osteoid thickness (μm)	12 ± 2.0	10 ± 5.0	14 ± 4	0.001
Erosion surface/bone surface (%)	4.5 ± 12.4	9.9 ± 6.0	10.0 ± 5.0	NS
Osteoblasts (%)	10 ± 26	5 ± 5	14 ± 9	0.0001
Osteoclasts (100 mm)	3.1 ± 7.7	2.3 ± 4.1	8.1 ± 8.0	0.004
Mineralization				
Single-line surface (%)	24 ± 48	15 ± 12	23 ± 14	NS
Double-line surface (%)	39.6 ± 70	39.6 ± 70	7.5 ± 7.7	0.05
Mineralization application rate (μm/day)	0.56 ± 0.2	0.71 ± 0.2	0.77 ± 0.25	NS
Mineralization lag time (days)	9.2 ± 23	16.1 ± 7	18.9 ± 6	NS
Bone formation rate/bone surface (mm^3/mm^2/yr)	0.01 ± 0.03	0.01 ± 0.01	0.03 ± 0.02	0.02
Bone formation rate/bone volume (mm^3/mm^2/yr)	0.22 ± 0.37	0.14 ± 0.02	0.37 ± 0.02	0.02
Bone formation rate/cellular unit (mm^3/mm^2/yr)	0.12 ± 0.4	0.04 ± 0.04	0.07 ± 0.05	NS
Structural				
Trabecular bone volume (%)	26 ± 6.4	16 ± 3.8†	25 ± 7.2	0.01
Wall thickness (μm)	42 ± 49	32 ± 7	31 ± 7	NS
Cortical thickness (μm)	911 ± 122	1355 ± 419†	992 ± 399	0.02

Values (mean ± SD) were obtained from bone biopsies taken before surgery and after a mean of 50 ± 3 months in 24 consecutive patients. Note the increased turnover as well as the increased mineralization process. Structurally, cortical thickness decreased and trabecular bone volume increased.
*Student's *t* test between paired data before and after surgery; NS = not significant.
†Significantly different from normal.

Increases in PTH levels were associated with an increase in both bone turnover and mineralization. The higher the biochemical markers, the greater the histologic bone loss as measured by decreased trabecular wall thickness. Bone loss was also associated with lower calcium and phosphate levels, and a decreased phosphate level was the sole indicator of slowing mineralization measured by the mineralization time ($r = 0.43$; $P < 0.005$) (Table 4).

Factors Associated With Bone Loss

Even if bone density remains related to age at both sites, age or sex do not appear to be significant factors for bone loss. Taking both sites together, menopausal women lost more bone than the other women (n = 4;15% ± 7% vs. n = 22 ; 5% ± 1%; $P < 0.06$). Smokers also lost more bone (n = 7; 11.4% ± 7.5% vs. n = 25; 4.3% ± 0.8%; $P < 0.05$) than nonsmokers.

At spine level, the lower the initial density, the greater the future bone loss ($r = 0.40$; $P = 0.02$) and patients with osteoporosis (n = 4) lost more bone than the others (n = 4; 10.2% ± 7.0% vs. n = 24; 1.8% ± 7.0%; $P < 0.01$). The greatest loss of BMD in an individual patient was 20% at the hip. BMD decreased from 0.832 to 0.632 g/cm^2. This occurred in a menopausal woman with osteoporosis who had not taken any supplemental calcium or vitamin D until a rib fracture occurred.

Among the initial biochemical data, the level of 1,25-OH_2-D was the only predictor of future bone loss. The higher the 1,25-OH_2-D level initially, the greater the future bone loss ($r = 0.47$; $P < 0.01$). It is noteworthy that after surgery, 1,25-OH_2-D was also higher when the rate of mineralization (measured by mineralization time) was slower ($r = 0.47$; $P < 0.02$).

At 4 years, multiple regression analysis showed that when age was excluded as a variable, the PTH level became the dominant factor influencing bone density at the hip ($P < 0.01$), whereas phosphate ($P < 0.03$) and osteocalcin ($P < 0.02$) levels were the best predictor of density at the lumbar spine.

Table 5 indicates among the 4-year data those measurements found to be predictors of bone loss at 10 years. It shows that increased histologic or biochemical activity was a strong predictor of future bone loss. Although among the 10-year data for PTH, alkaline phosphatase, calcium, and albumin levels, only albumin continued to be related to bone loss and only at the hip.

DISCUSSION

The decrease in calcium and vitamin D levels after BPD resembles that seen after jejunoileal bypass.[20–22] Four years after surgery, vitamin D concen-

Table 4. Correlation between biochemical and histomorphometric findings 4 years after biliopancreatic diversion

	PTH	OC	Alkaline phosphatase	BAP	Phosphate	Calcium
OV	+0.79*	+0.63†	+0.62†	NS	−0.58‡	NS
OS	+0.71*	+0.61†	+0.58‡	NS	−0.59‡	NS
AcF	+0.60†	+0.42‡	+0.49‡	NS	NS	NS
SL	+0.52‡	NS	NS	−0.48†	NS	NS
CF	+0.55†	+0.38‡	NS	NS	NS	NS
MS	+0.52	+0.43‡	NS	+0.50‡	−0.41‡	NS
MLT	NS	NS	NS	NS	−0.43‡	NS
BFR/BS	+0.74*	+0.55†	NS	+0.55†	NS	NS
BFR/BV	+0.71*	+0.57†	+0.41‡	+0.63†	−0.42‡	NS
BFR/BMU	+0.40‡	NS	NS	NS	NS	NS
WTh	NS	−0.74‡	−0.60§	−0.59§	+0.67‡	+0.75‡
CTh	NS	NS	NS	−0.74	+0.57	NS
TBV	NS	NS	NS	−0.65§	+0.56§	NS

Correlations between biochemical and histomorphometric variables were determined in 24 patients 50 ± 3 months after BPD. Pearson's coefficient correlation was used with its degrees of significance between serum levels of different markers and histomorphometric measurements. For measuring trabecular bone volume (TBV) and cortical width (CTh), only biopsies with both cortices (n = 10) were used. NOTE: The higher the level of PTH, osteocalcin (OC), alkaline phosphatase, and BAP and the lower the level of phosphate, the higher the bone turnover and mineralization rates and the greater the bone loss. AcF = Activation frequency per day; BFR/BMU = bone formation rate at cellular level; BFR/BS = bone formation rate in relation to bone surface; BFR/BV = bone formation rate in relation to bone volume; CF = calcification fraction; MLT = mineralization lag time; MS = mineralization surface; NS = not significant; OS = osteoid surface; OV = osteoid volume; SL = single labeled; WTh = wall thickness.

*$P < 0.0005$.
†$P < 0.005$.
‡$P < 0.05$.
§$P < 0.09$.

Table 5. Correlations between data obtained at 4 years and the final weight loss at 10 years

Data	*r* value	*P* value
Histologic data		
Mineralization lag time	0.62	0.001
Osteoid volume	0.59	0.003
Osteoid thickness	0.47	0.03
Biochemical data		
Osteocalcin	0.55	0.0001
PTH	0.45	0.02
Alkaline phosphatase	0.41	0.03
Albumin (Hip)	0.44	0.01
Calcium (spine)	0.38	0.02

Correlation between some of the histologic and biochemical data obtained at 4 years predicting the final weight loss at 10 years. Increased histologic or biologic activity increases the risk of bone loss.

trations were below normal in approximately half of the patients. Hyperparathyroidism, present in 30% after BPD, is in marked contrast with its reported absence after vertical banded gastroplasty[23,24] or after a short Roux-en-Y gastric bypass.[25] As expected, BPD compromises calcium and vitamin D absorption more than gastrectomy,[26–28] simple gastroplasty,[23,24] or gastric bypass.[25]

However, the condition of bone after BPD differs from what has been reported after jejunoileal bypass[8–10,12,29,30] and also differs from what Compston et al.[6,7] described after a different type of BPD. After jejunoileal bypass,[9,12,29,30] as in the series reported by Compston et al.,[7] mineralization was decreased. Bone formation rate was decreased, mineralization time was lengthened,[9,12] and trabecular bone volume was decreased.[29,30] In the present series, mineralization remained normal or was increased, and both bone formation rate and trabecular bone volume were increased.

Better postoperative nutritional status reflected in normal albumin, magnesium, and phosphate levels may explain the difference between BPD and jejunoileal bypass with regard to bone mineralization. Hypoalbuminemia was very common after jejunoileal bypass,[21,22,31] in contrast to our prevalence of only 3%. In the series reported by Compston et al.,[7] albumin levels were not reported, but half of these patients had a more severe type of BPD because of the absence of a common channel; a procedure with much greater impact on protein malabsorption.[2]

The importance of nutritional status to preserve the mineralization process is supported by the fact that in the present series, albumin level was the dominant marker of bone loss at 10 years. It is also in accordance with the findings of Parfitt et al.[8] who reported that 12 years after jejunoileal bypass, serum protein level was the best predictor of bone loss. In our series, as already noted by Compston et al.,[6] the phosphate level was the best indicator of the mineralization rate. The phosphate level, indeed, remained normal in our patients.

The finding that a higher level of 1,25-OH_2-D was a predictor of bone loss and was associated with slower mineralization in the postoperative period is compatible with the belief that a rise in this active metabolite means impairment of vitamin D metabolism.[32] Increased 1,25-OH_2-D has been associated with morbid obesity,[32] bariatric surgery,[33] and even partial gastrectomy.[26,28,34,35]

Ten years after surgery, the overall bone density remained remarkably stable. There were no significant changes at the hip and minimal changes at the spine. A 4% decrease over 10 years is less than what is predicted for normal aging. Our figure of 1% per year for aging, calculated from our reference group of 800 women taken from our own general population, could be questioned.[13] However, considering that 11 of the 26 women included in this series were menopausal, we believe that the 1% figure is quite conservative, because a 3% loss per year is frequently mentioned as the yearly rate of bone loss after menopause.

The relative tolerance of bone to different intestinal bypass operations is not new.[36–38] Rickers et al.[21] reported bone density to remain within 90% of its original level 4 years after jejunoileal bypass. As far as we are aware, only Parfitt et al.[8] have reported a substantial bone loss of 17%, measured at the forearm, 12 years after jejunocolostomy. It is recognized that osteomalacia is rare after jejunoileal bypass,[8,12] and it may even heal spontaneously.[39]

Unexpectedly, in one third of patients, bone density increased over the years after surgery. It is difficult to attribute this to changes in fat thickness or to variations in measurement devices, because the improvement was noted with both devices and when weight was stable. One third of our patients improved their bone density during the 10 years after surgery. We wonder whether increased physical activity, improved diet, and calcium and vitamin D supplements account for this beneficial effect.

The great majority of patients (85%) in this series did not lose more bone than expected for aging. Menopause, smoking, and preexisting low bone density represent risk factors for bone loss and suggest that more intense preventive medical treatment should be encouraged. After surgery, high levels of PTH and low levels of albumin and phosphate are indicators of bone loss and should trigger more aggressive medical treatment. Empirically, we try to maintain

PTH levels below 100 ng/L by increasing oral calcium and vitamin D supplements. Higher serum levels of albumin and phosphate are reassuring. Nutritional status remains the most important factor in the long term.

The present investigation concerned one type of BPD, the one suggested by Scopinaro,[2] and our conclusion is that, despite a 15% revision rate, the beneficial effects of this procedure on quality of life and other comorbid conditions far outweigh the risks of bone disease.[3,4] Over the past 10 years, the procedure has been improved; a more physiologic sleeve gastrectomy has replaced the distal gastrectomy and bile is returned at 100 cm from the ileocecal valve instead of at 50 cm. With these modifications revision is rarely necessary, and protein and calcium absorption are improved.[5] This will further ameliorate the overall outcome.[40]

CONCLUSION

We conclude that for most patients followed closely for metabolic disturbances, BPD represents a challenge to bone physiology but is not overtly detrimental. Despite frequent secondary hyperparathyroidism, which requires readjustment of calcium and/or vitamin D supplements, bone seems to tolerate this challenge. There remains a risk for bone loss that requires surveillance, but the beneficial effects of BPD on other types of morbidity and on quality of life far outweigh the risk of bone disease.

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Endothelins Induce Gallbladder Contraction Independent of Elevated Blood Pressure In Vivo in the Australian Possum

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Endothelin levels are elevated in shock, sepsis, and cholestatic jaundice, and an effect on biliary motility may be postulated. The aim of this study was to determine whether (1) endothelin-1 and endothelin-3 induce gallbladder contraction in vivo, (2) the response is caused by changes in blood pressure, and (3) the response is nerve mediated. Gallbladder pressure and blood pressure were measured in 38 anesthetized possums. Endothelin-1 or endothelin-3 (5 to 200 pmol/kg) was administered by close intra-arterial injection. Tetrodotoxin (9 μg/kg) or the mixed endothelin antagonist tezosentan was infused at a rate of 10 or 100 nmol/kg/min (close intra-arterial injection). Maximum changes in gallbladder pressure (% of carbachol-induced contraction) and blood pressure (mm Hg) were determined. Statistical analysis was carried out by means of repeated-measures analysis of variance and Kruskal-Wallis test. Both endothelin-1 and endothelin-3 induced dose-dependent increases in gallbladder pressure and blood pressure ($P < 0.05$), which were unaffected by pretreatment with tetrodotoxin. The endothelin-1–induced gallbladder pressure but not blood pressure was reduced by the higher dose of tezosentan ($P < 0.03$). The lower dose of tezosentan also produced a decrease in the endothelin-3–induced gallbladder pressure ($P < 0.02$) but not in blood pressure, whereas the higher dose reduced the blood pressure with no further reduction in gallbladder pressure ($P < 0.05$). Endothelins increase gallbladder motility in vivo, acting directly on the smooth muscle and independent of changes in blood pressure. (J GASTROINTEST SURG 2002;6:699–705.)

KEY WORDS: Gallbladder motility, endothelins, blood pressure

Endothelin (ET) is the term for a four-member family of potent vasoconstrictor peptides consisting of ET-1, ET-2, ET-3, and ET-4 (vasoactive intestinal constrictor).[1] Each ET peptide is composed of 21 amino acids and is synthesized as a larger precursor molecule, big ET. Although ET has been found to cause cholestasis in rats[2] and contract bile canaliculi in isolated rat hepatocytes,[3] there is a paucity of data concerning the distribution and function of ET in the biliary tree. ET immunoreactivity and messenger RNA have been detected in cultured human gallbladder epithelial cells,[4,5] and ET immunoreactivity is present in the bile ducts of sections of human cirrhotic livers.[6] In addition, we recently demonstrated ET immunoreactivity in the epithelium of chronically inflamed human gallbladders and normal possum gallbladders in organ culture but not in freshly fixed gallbladders from fasted or fed possums. The gallbladder muscle and nerves did not display ET immunoreactivity.[7]

ET-1 and ET-3 produce potent contraction of guinea pig,[8–12] possum,[14,16] rabbit,[13] and human[11,14–17] gallbladder muscle strips. This ET-induced gallbladder contraction was unaffected by tetrodotoxin (TTX)[8,11,14–17] and was blocked by the mixed ET antagonist tezosentan.[14–17] These data suggest that ETs act directly on gallbladder smooth muscle, but to date there are no reports on the effect of ET on the gallbladder pressure in vivo. Because ETs are potent vasoconstrictors, they might affect gallbladder motility via alterations in blood pressure.

The aims of this study were to determine the following: (1) whether ET-1 and ET-3 induce gallbladder contraction in vivo; (2) whether the gallbladder re-

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00011-2

sponse is mediated by changes in blood pressure by using a mixed ET receptor antagonist, tezosentan, to modify the ET-induced changes; and (3) whether the response is nerve mediated by blocking axonal transmission with TTX before ET administration.

METHODS

Preparation of Animals

Thirty-six fasted Australian brush-tailed possums (*Trichosurus vulpecula*) of either sex, with a weight range of 1.9 to 2.6 kg, were initially anesthetized with ketamine (20 mg/kg; Ketamil, Troy Laboratories Proprietary, Ltd., New South Wales, Australia) and xylazine (5 mg/kg; Rompun, Bayer Australia, Ltd., New South Wales, Australia) by intramuscular injection. Anesthesia was maintained with a continuous intravenous infusion of pentobarbitone sodium (10 to 20 mg/kg/hr; Nembutal, Rhone Merieux, Australia, QLD, Queensland, Australia) for the duration of the experiments. Each animal was killed at the completion of the experiment with a lethal dose of pentobarbitone sodium (Lethabarb; Virbac [Australia] Proprietary, Ltd., New South Wales, Australia). This study was approved by the Animal Welfare Committee of Flinders University of South Australia.

To measure gallbladder pressure and blood pressure and administer agents by close intra-arterial injection, possums were surgically prepared as previously described.[18] Briefly, the left femoral artery and vein were cannulated to monitor blood pressure and infuse physiologic saline solution and anesthetic, respectively. Body temperature was maintained at 37° C with a homeothermic heating blanket (Harvard Apparatus, Edenbridge, Kent, United Kingdom). The possums were artificially ventilated via a tracheotomy with a ventilator (Harvard Apparatus, Holliston, Massachusetts). A laparotomy was performed to enable access to the splenic artery and the gallbladder.

A polyethylene catheter (0.8 mm outer diameter × 0.4 mm inner diameter, 20 cm in length) was inserted into the splenic artery, just distal to its junction with the hepatic artery for close intra-arterial injection of ET-1, ET-3, TTX, and tezosentan. Gallbladder bile was then collected via a syringe with a 27-gauge needle, and the volume was noted. A small balloon attached to a polyethylene catheter was inserted through a small incision in the fundus of the gallbladder, and the incision was closed with a pursestring suture. The balloon was then filled with a volume of warm saline solution equivalent to the volume of gallbladder bile collected (2 to 2.5ml). The blood pressure and gallbladder balloon catheters were connected to pressure transducers (Transpac IV; Abbott Ireland, Silgo, Republic of Ireland). Pressure transducers were connected to a MacLab recording system (MacLab/8S; ADInstruments, New South Wales, Australia) with the software Chart v3.5.6/s ADInstruments).

At the end of the operative procedure, the abdomen was filled with warm saline solution (37° C) and covered with plastic wrap to minimize evaporation. A period of 30 minutes was allowed for all parameters to stabilize.

Experimental Design

Synthetic ET-1 and ET-3 (Auspep Proprietary, Ltd., Victoria, Australia) (in separate experiments) were dissolved in saline solution containing 0.01% bovine serum albumin (Sigma Chemical, St. Louis, Missouri). In preliminary experiments, we found that with ET-1 and ET-3, 5 pmol/kg was the threshold dose causing a gallbladder response, and at doses greater than 200 pmol/kg no further increases in gallbladder pressure were demonstrated but the responses were very long lasting. Furthermore, in animals receiving doses of ET greater than 400 pmol/kg, the blood pressure increase was extremely high, leading to sudden death most likely from a cerebral event. Consequently five graded doses of ET (5, 10, 50, 100, and 200 pmol/kg) were administered by close intra-arterial injection to establish the dose-response relationship for each peptide. A minimal recovery period of 30 minutes was allowed between doses for all parameters to return to preinjection levels. Thirty minutes after the highest dose, electrical field stimulation (70 volts, 0.1 msec duration, 30 Hz, 10 sec train) was performed with a bipolar stimulating electrode placed on the gallbladder to activate a neurally mediated contraction. Neural blockade was then achieved by close intra-arterial injection of TTX (9 μg/kg, Alomone Labs, Jerusalem, Israel). Electrical field stimulation was then repeated 10 minutes after TTX administration to confirm blockade of gallbladder nerves.[18] Repeat 50, 100, and 200 pmol/kg doses of ET-1 and ET-3 (in separate experiments) were then administered. All agents except tezosentan were administered as bolus injections of 500 μl over 30 seconds, followed by 1 ml of 0.9% saline solution delivered over 1 minute to flush the catheter. This protocol enabled simultaneous measurement of blood pressure and gallbladder pressure, with and without gallbladder neural blockade (6 animals for ET-1 and another 6 for ET-3, for a total of 12 animals).

In a second set of experiments, tezosentan was administered as a continuous infusion via the splenic artery at 10 or 100 nmol/kg/min after the initial set of graded doses of either ET-1 or ET-3 (groups of 6 animals per peptide per dose of antagonist, for a total

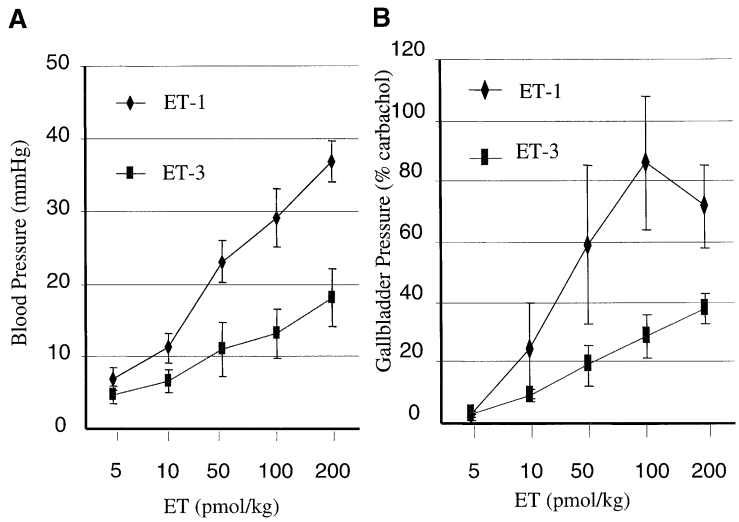

Fig. 1. Dose-response curves for ET-1 and ET-3. Blood pressure (**A**) and gallbladder pressure (% carbachol) (**B**). Data are expressed as mean ± SEM, n = 6.

of 24 animals). We chose to use tezosentan because our previous studies with possum gallbladder muscle strips[14–17] indicated that this antagonist was effective and that both ET-1– and ET-3–induced contractions involved receptor-subtype interactions. Preliminary experiments in vivo indicated that bolus injections of tezosentan only reduced the exogenous ET-induced response for a short time. Consequently tezosentan was administered as a continuous infusion, which was initiated 30 minutes before the repeated graded doses of ET-1 or ET-3 and continued until 30 minutes after the last ET administration.

Preliminary experiments also indicated that the infusion of tezosentan prior to application of ET did not influence the magnitude of the gallbladder contraction induced by carbachol (100 nmol/kg; Sigma Chemical), and the magnitude of the carbachol-induced gallbladder contraction was the same whether carbachol was administered at the beginning or end of the protocol. Fifteen minutes after the end of the tezosentan infusion, carbachol was injected and the magnitude of the resultant gallbladder contraction was used to normalize the ET-induced contractions and generate the group data.

Data Analysis

Changes in gallbladder pressure and blood pressure were analyzed. Mean arterial blood pressure and gallbladder pressure (mm Hg) were measured during a 1-minute period immediately before the administration of ET (control period) and during a 1-minute period of maximal response after ET administration (peak response period). The gallbladder pressure was expressed as the percentage of maximal gallbladder pressure induced by carbachol, and blood pressure was expressed in mm Hg. Group data were reported as mean ± SEM.

Statistical Analysis

Statistical analysis was performed on the raw data. For comparison of the dose-response data with and without TTX pretreatment, repeated-measures analysis of variance (SPSS 9.0.1, SPSS Inc., Chicago, Illinois) was used. For comparison of the dose-response data with and without tezosentan infusions, Kruskal-Wallis testing (nonparametric analysis) was performed. A P value of less than 0.05 was regarded as significant.

RESULTS

Both ET-1 and ET-3 induced dose-dependent increases in gallbladder pressure and blood pressure ($P < 0.05$). The maximal increase in gallbladder pressure was 86.0% ± 21.6% of the maximal contraction induced by carbachol, achieved with the ET-1 dose of 100 pmol/kg, and desensitization was evident above this dose (Fig. 1). In contrast, ET-1 administration increased blood pressure by a maximum of 37.0 ± 2.7 mm Hg, elicited by 200 pmol/kg. In comparison, the ET-3 responses were weaker, with the maximal increase in gallbladder pressure at 200 pmol/kg being 37.4% ± 4.8% of carbachol and the maximum increase in blood pressure at 200 pmol/kg being 18.0 ± 4.0 mm Hg (see Fig. 1). These changes in gallbladder pressure and blood pressure were TTX insensitive (Table 1).

Table 1. Neural blockade with TTX does not influence the ET-1– and ET-3–induced increase in blood pressure and gallbladder pressure

Dose (pmol/kg)	Blood pressure		Gallbladder pressure	
	− TTX	+ TTX	− TTX	+ TTX
ET-1				
50	23.0 ± 3.0	29.8 ± 7.3	59.2 ± 26.2	77.7 ± 27.6
100	29.3 ± 4.1	33.7 ± 7.2	86.1 ± 21.6	87.5 ± 22.0
200	37.1 ± 2.8	37.3 ± 4.5	71.8 ± 13.9	93.0 ± 10.3
ET-3				
50	10.8 ± 3.8	7.5 ± 4.1	19.1 ± 6.8	27.1 ± 7.3
100	13.1 ± 3.5	11.4 ± 3.2	28.2 ± 7.1	28.1 ± 8.6
200	18.0 ± 4.0	13.7 ± 5.2	37.5 ± 4.8	32.0 ± 9.4

Blood pressure is expressed as mm Hg and gallbladder pressure as percentage of carbachol-induced contraction. TTX (9 μg/kg) was administered by close intra-arterial injection. Data are presented as mean ± SEM, n = 6.

The ET-1–induced increase in gallbladder pressure was reduced ($P < 0.03$) by the high dose of tezosentan (Figs. 2 and 3). The response induced by 100 pmol/kg of ET-1 was 51.6% ± 8.0% and 26.6% ± 12.0% of carbachol in the presence of the low and high doses of tezosentan, respectively. It is important to note that the increases in blood pressure were not influenced by the infusion of either dose of tezosentan (see Figs. 2 and 3). The infusion of tezosentan alone did not significantly alter the gallbladder pressure or blood pressure.

The ET-3–induced increase in gallbladder pressure was reduced by both the low- and high-dose infusions of tezosentan ($P < 0.02$) (Figs. 4 and 5). The gallbladder pressure induced by 200 pmol/kg of ET-3, in the presence of both the low and high doses of tezosentan, were 19.4% ± 4.8% and 15.6% ± 4.1% of carbachol, respectively (Fig. 5). The ET-3–induced change in blood pressure was only reduced by the high dose of tezosentan ($P < 0.05$) (see Figs. 4 and 5). The blood pressure increase induced by 200 pmol/kg of ET-3 was 13.3 ± 2.4 mm Hg and 8.2 ± 2.0 mm

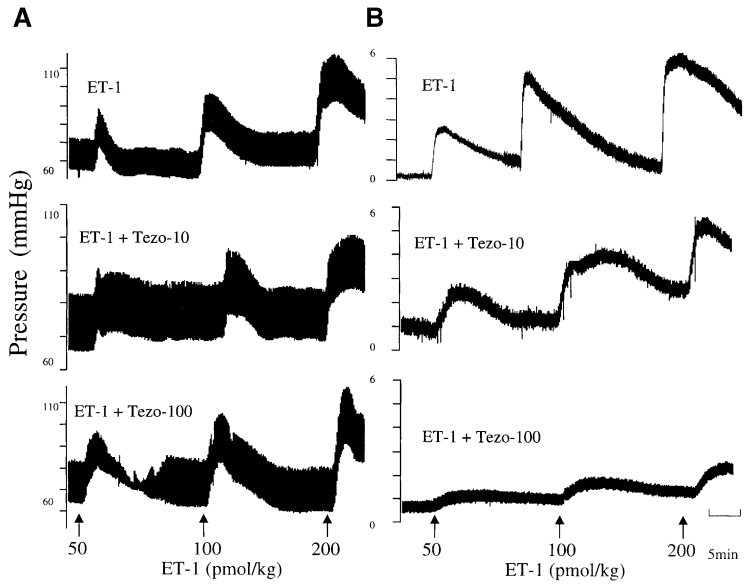

Fig. 2. Representative recordings illustrating the effect of tezosentan pretreatment on the ET-1–induced increase in blood pressure (**A**) and gallbladder pressure (**B**). In each panel, recordings for ET-1 only, (2) ET-1 + tezosentan infusion at 10 nmol/kg/min (*Tezo-10*), and ET-1 + tezosentan infusion at 100 nmol/kg/min (*Tezo-100*) are shown. ET-1 was administered as bolus close intra-arterial injections of 50, 100, and 200 pmol/kg. Both infusions of tezosentan had no effect on the ET-1–induced blood pressure (**A**) and the high-dose infusion of tezosentan reduced the ET-1–induced gallbladder pressure (**B**). Pressure is expressed as mm Hg.

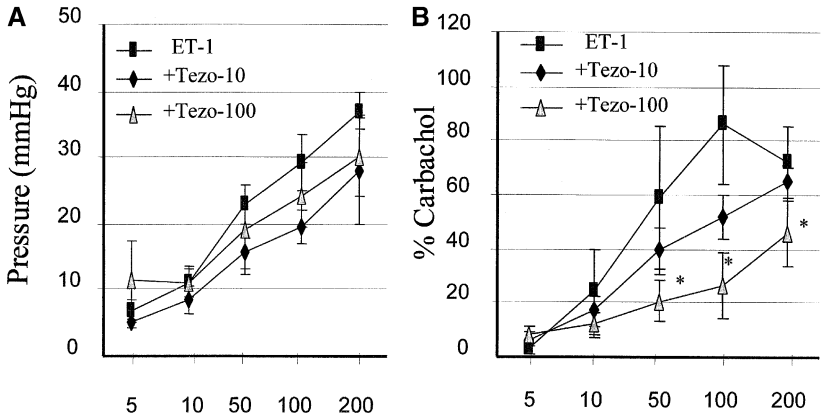

Fig. 3. Dose-response curves for ET-1 with and without tezosentan treatment. Tezosentan was infused at 10 nmol/kg/min (*Tezo-10*) and at 100 nmol/kg/min (*Tezo-100*). ET-1 was administered as bolus injections of 50, 100, and 200 pmol/kg. **A,** Tezosentan had no effect on the ET-1–induced blood pressure. **B,** Tezosentan (*Tezo-100*) decreased the ET-1–induced gallbladder pressure. Group data are presented as mean ± SEM, n = 6. $^*P < 0.05$.

Hg in the presence of the low and high doses of tezosentan, respectively (see Fig. 5). The reduction in the ET-3–induced gallbladder pressure produced by the infusion of either dose of tezosentan was not significantly different ($P = 0.2$).

DISCUSSION

This study has demonstrated for the first time that ET-1 and ET-3 cause potent dose-dependent, TTX-insensitive gallbladder contraction in vivo. Although ET-1 and ET-3 administration also caused

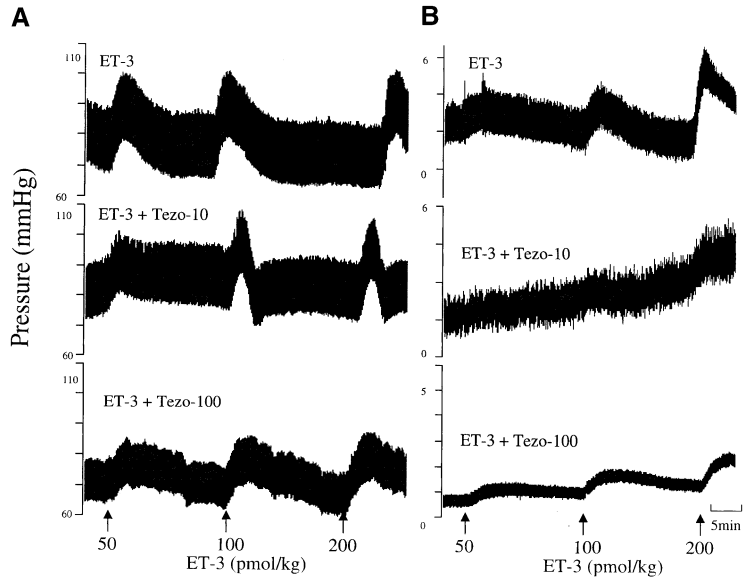

Fig. 4. Representative recordings illustrating the effect of tezosentan pretreatment on the ET-3–induced increase in blood pressure (**A**) and gallbladder pressure (**B**). In each panel, recordings for ET-3 only, ET-3 + tezosentan infusion at 10 nmol/kg/min (*Tezo-10*), and ET-3 + tezosentan infusion at 100 nmol/kg/min (*Tezo-100*) are shown. ET-3 was administered as bolus injections of 50, 100, and 200 pmol/kg. Both concentrations of tezosentan reduced the ET-3–induced gallbladder pressure. Pressure is expressed as mm Hg.

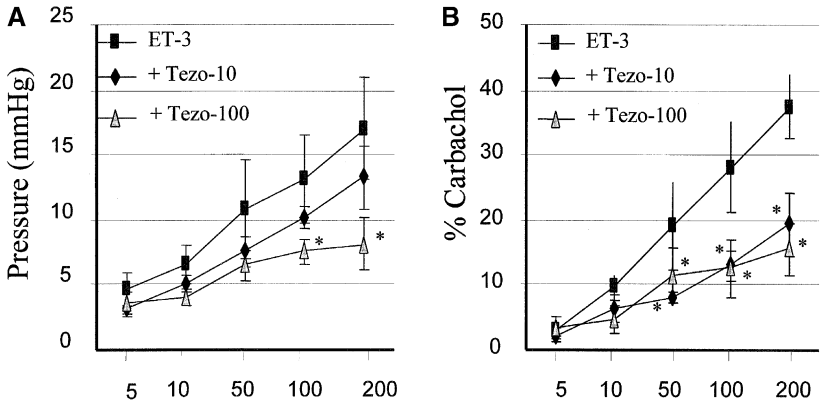

Fig. 5. Dose-response curves for ET-3 with and without tezosentan. Tezosentan was infused at 10 nmol/kg/min (*Tezo-10*) and at 100 nmol/kg/min (*Tezo-100*). ET-3 was administered as bolus injections of 50, 100, and 200 pmol/kg. **A,** The high-dose infusion of tezosentan decreased the ET-3–induced blood pressure. **B,** Tezosentan (*Tezo-100*) decreased the ET-3–induced gallbladder pressure. Group data are presented as mean ± SEM, n = 6. $^*P < 0.05$.

elevations in blood pressure, this response was independent of the gallbladder contractions, suggesting that ET-1 and ET-3 act directly on the gallbladder smooth muscle.

The increase in gallbladder pressure induced by ET-1 and ET-3 was not due to the simultaneous increase in blood pressure produced by these peptides. The independence of this response is demonstrated after ET blockade by the ET antagonist tezosentan. This mixed antagonist reduced the ET-1–induced gallbladder pressure increase without a significant change in blood pressure. Furthermore, the ET-3 induced–gallbladder contraction was inhibited by the administration of low doses of tezosentan, without a corresponding change in blood pressure, and a high dose of antagonist inhibited the blood pressure increase, without an additional reduction in gallbladder pressure. These results support the conclusion that elevations in blood pressure produced by ET are not responsible for the increased gallbladder pressure.

The findings in this in vivo study generally support those of our previous in vitro studies[14–17]— that is, with possum gallbladder muscle strips, both ET-1 and ET-3 produced gallbladder contraction, and ET-3 was less potent than ET-1. This in vivo study has shown that the magnitude of the ET-3 effects on blood pressure and gallbladder pressure are approximately 30% to 50% of those elicited by ET-1. Our previous muscle strip studies revealed that both ET receptor subtypes (ETA and ETB) mediate the ET-1–induced gallbladder contraction, whereas, ET-3 acts mainly via ETB receptors. A relatively high affinity to ETB by ET-3 has been reported in studies in other species.[9,10] In addition, our previous in vitro study also provided evidence for interaction between ET A and ETB receptor subtypes, presumably located on the smooth muscle, mediating the action of both peptides on gallbladder contractility.[14–17] Several previous in vitro studies have indicated that the effects of both peptides on gallbladder contractility are TTX insensitive.[8,11] We reported similar observations in our in vitro studies[14–17]; however, part of the ET-3–induced gallbladder muscle strip contraction was TTX sensitive. The reason for this difference is unclear, but discrepancies between in vitro and in vivo findings are often reported and may reflect the influence of the extrinsic nervous system, which is less likely to be active in muscle strips.

The role of ET in regulating gallbladder function is unclear. We have shown that ET is produced in the epithelial layer of the gallbladder wall, but not under normal physiologic conditions.[7] This finding supports a previous demonstration of ET secretion in cultured human gallbladder epithelial cells.[4] These investigators showed that the ET secretion was stimulated by the inclusion of glucose or cholecystokinin in the culture medium. However, we were unable to demonstrate, by immunohistochemical analysis, the induction of ET in the gallbladder harvested from possums in the early postprandial state where elevated levels of glucose and cholecystokinin were expected. Thus these finding do not support a physiologic role for ET in the regulation of gallbladder function.

On the other hand, a role in pathophysiologic states is more likely. The culture conditions under

which we were able to demonstrate induction of ET are similar to clinical scenarios that may be associated with ischemia of the gallbladder. Plasma levels of ET are elevated in patients with sepsis and shock.[19–21] In addition, patients with obstructive jaundice have been reported to have high plasma levels of ET.[22] Recently we have developed a possum model of acute cholecystitis using lipopolysaccharide instilled into the gallbladder lumen. Our preliminary studies indicate that by 4 hours after lipopolysaccharide instillation, gallbladder ET levels, measured by radioimmunoassay, were approximately 200 pg/mg tissue (wet weight). Hence the dose range we have used in the present study is of the same order as ET levels found in the possum gallbladder during the induction of acute acalculus cholecystitis.[17] The clinical relevance of our findings awaits the results of further clinical studies.

The results of this study indicate that both ET-1 and ET-3 act directly on the smooth muscle of the gallbladder to produce potent gallbladder contraction and that these changes are not influenced by the ET-induced changes in blood pressure. Our findings suggest that in conditions such as sepsis or ischemia, ET may be involved in the induction of gallbladder dysfunction.

We thank Dr. M. Clozel (Actelion Ltd., Allschwil, Switzerland) for donating the tezosentan compound. The cooperation of the National Parks and Wildlife Service of South Australia is also acknowledged.

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Biliary Complications After Hydatid Liver Surgery: Incidence and Risk Factors

Cuneyt Kayaalp, M.D., Khalid Bzeizi, M.D., F.R.C.P., Ali Eba Demirbag, M.D., Musa Akoglu, M.D.

The aims of this study were to determine the incidence and risk factors of biliary leakage and biliary fistulae after hydatid liver surgery and to suggest preventive precautions. From January 1999 to June 2000, 70 cysts were examined from 54 patients who were operated on for hydatid liver disease. Age, sex, primary or recurrent disease, liver function tests, number, location, content, radiological type, and diameter and cavity management techniques were examined with univariate and multivariate analyses for biliary complications. Biliary leakage occurred in 14 cysts (26%) from the patients. Purulent and/or bilious cyst content (61.9% vs. 2.0%; $P = 0.022$), male gender (40.9% vs. 10.4%; $P = 0.038$), and pre-operative raised alkaline phosphatase and gamma glutamyl transferase levels (34.6% vs. 11.4%; $P = 0.047$) were found as independent risk factors for post-operative biliary leakage. Nine instances of biliary leakage (16.7%) closed spontaneously within seven days. The remaining five instances of biliary leakage (9.3%) persisted for more than 10 days and were accepted as biliary fistulae. Stepwise logistic regression identified cyst content was the only risk factor for biliary fistulae (19% vs. 2%; $P = 0.036$). Described risk factors for post-operative biliary complications after hydatid liver surgery may be the guidelines for additional pre-operative or intra-operative radiological interventions of the biliary tract and for preventive procedures such as surgical biliary drainage. (J GASTROINTEST SURG 2002;6:706–712)

KEY WORDS: Echinococcosis hepatic, postoperative complications, bile duct, liver

Hydatid disease, particularly of the liver, is a significant surgical burden in areas such as the Middle East, the borders of the Mediterranean Sea, South Africa, Northern Canada, Australia, and New Zealand. In Turkey, the number of patients undergoing hepatic surgery for hydatid disease averages 3000 per year.[1]

Biliary complications are common post-operatively for hepatic hydatid cysts, which are associated with increased risk of morbidity. The incidence of these complications is variable from 2.6% to 28.6%.[2,3] The predisposing factors for biliary complications are not well defined, and there are conflicting results from the few published studies that have addressed this issue.[4,5] Our aim was to study the incidence and identify the risk factors of biliary complications in patients undergoing surgery for hepatic hydatid disease.

PATIENTS AND METHODS

This was a single center study where all patients who had surgery for hepatic hydatid disease between January 1999 and June 2000 were included for analysis. The diagnosis was made in all the patients by abdominal ultrasonography and computed axial tomography.

Surgical Details

After exploration of the abdomen, the area around the cyst was carefully isolated by gauze packs soaked in a scolicidal agent (0.5% cetrimide and 0.05% chlorhexidine combination; Savlex, Drogsan, Ankara, Turkey). The cyst was first aspirated and if the cyst content was clear, the aspirate replaced with the same amount scolicidal. After opening the cyst wall,

Preliminary results of this study were presented at the Tenth Anniversary of Eurosurgery, Istanbul, Turkey, June 20–24, 2000.
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 Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00046-X

all contents were removed and the cavity was then wiped with scolicide-soaked swabs. The cavity was observed carefully for sites of biliary leakage for 5 minutes and if present, the open biliary orifices were sutured with 3-0 silk.

After un-roofing the cysts by partial peri-cystectomy, obliteration of the cavity was performed by omentopexy,[6] introflexion,[7] or external drainage.[8] During introflexion, the edges of the pericystium were inverted into the cyst cavity. The edges of the un-roofed cyst sutured to the bottom of the cavity and also each other with absorbable sutures. The cavity management of the cyst was determined by the choice of the surgeons. All cavities were drained to prevent bilioma or biliary peritonitis.

Drains were removed on the third post-operative day, provided no biliary drainage was seen. Patients who had post-operative biliary drainage through the abdominal drains were accepted as having biliary leakage. Patients who continued with persistent biliary drainage more than 10 days post-operatively were accepted as having a biliary fistulae. Biliary fistulae that had a daily drainage <100 ml were treated conservatively and until spontaneous cessation. Biliary fistulae that had a daily drainage >100 ml were considered for endoscopic retrograde cholangiopancreaticography (ERCP) and naso-biliary drainage.

Data collected included age, sex, liver function tests, and whether the disease was primary or recurrent. The radiological types of the cysts were classified as uniocular (Gharbi Type I and II), multilocular (Gharbi Type III), and degenerated (Gharbi Type IV).[9] The number, location, diameter and content of the cysts, along with the cavity management technique, were all analyzed. All risk factors were evaluated by using both univariate and multivariate analysis.

For statistical univariate analysis, Pearson Chi-square and Fisher-exact tests were used, and for the hospital stay Mann Whitney U tests were used. A stepwise logistic regression model for multivariate analysis was used to simultaneously investigate the effects of several risk factors. SPSS 10.0.1 (Windows Release, Chicago, Illinois) was used for the statistical analysis. The statistical significance level was defined as $P < 0.05$.

RESULTS

A total of 68 patients who had surgery for hydatid liver disease during the period of the study were considered for analysis. Twelve patients who had a total peri-cystectomy or hepatectomy were excluded from the analysis, along with 2 more patients who had common bile duct exploration and biliary drainage. The remaining 54 patients (20 men and 34 women) were studied. The age range was 18–73 years (mean 42.6; SD 1.8).

In total, 70 cysts were treated surgically in 54 patients. The cyst cavity was obliterated in 28 cases (omentopexy in 13 and introflexion in 15). External drainage was performed in 42 cysts with no further procedures done to reduce the size of the cavity.

In 13 of 14 patients (26%) post-operative biliary leakage occurred. Nine (16.7%) closed spontaneously within 7 days with the amount of drainage varying between 50 to 300 ml. Only 5 patients (9.3%) had persistent biliary drainage (biliary fistula) more than 10 days and the amount of bile drainage was 50 to 200 ml. Two patients required ERCP and naso-biliary drainage that led to closure of the fistulae in 2 weeks. The remaining 3 patients were treated conservatively and the fistulae closed post-operatively at 5, 6, and 8 weeks, respectively.

Risk factors for biliary leakage and biliary fistula after hydatid liver surgery are summarized in Tables 1 and 2.

Age distribution was similar among the groups. Biliary leakage occurred more often in males (40.9% vs. 10.4%; $P < 0.01$) and this appeared to be as an independent risk factor. Although males had a higher risk of biliary leakage, gender was not a risk factor for biliary fistula ($P = 0.64$).

Seventeen patients (31%) had a recurrence of the hepatic hydatid disease during a period ranging from 2 to 14 years. This, however, did not seem to be a significant risk factor for biliary leakage compared with those presenting for the first time (18% for primary cysts vs. 25% for recurrent cysts; $P = 0.52$). Biliary fistula also occurred similarly in both primary and recurrent cysts (6% and 10%, respectively; $P = 0.61$).

Seventeen patients (31%) had a raised pre-operative alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT). Biliary leakage was seen more frequently in this group of patients, as compared with those with normal liver function tests (34.6% vs. 11.4%; $P = 0.02$). This was found in multivariate analysis as an independent risk factor for biliary leakage. Biliary fistulae was also observed more frequently in patients who had raised pre-operative ALP or GGT (2.3% and 15.4%, respectively), but the difference was significant ($P = 0.06$).

The incidence of biliary leakage for one, two, and three cysts was 20.5%, 33.3%, and 50%, respectively ($P = 0.46$). Biliary fistulae occurred similarly in the patients who had one, two, or three cysts ($P = 0.38$).

Thirty-four percent of the cysts were unilocular (Gharbi type I). The risk of biliary leakage was less in these group of patients (12.5%) compared to those with multilocular cysts (Gharbi III) and degenerated cysts

Table 1. Factors effecting biliary fistulae after hydatid liver surgery (univariated analysis)

Factors	Leakage (−)	Leakage (+)	Total	*P*
Age (yr)				
<40	30 (97%)	1 (3%)	31	0.37
≥40	35 (90%)	4 (10%)	39	
Gender				
Cysts (men)	20 (91%)	2 (9%)	22	0.64
Cysts (women)	45 (94%)	3 (6%)	48	
Primary	47 (94%)	3 (6%)	50	0.61
Recurrent	18 (90%)	2 (10%)	20	
ALP/GGT				
Raised	22 (85%)	4 (15%)	26	0.06
Normal	43 (98%)	1 (2%)	44	
Cyst number				
1	33 (89%)	4 (11%)	37	0.38
2	18 (95%)	1 (5%)	19*	
3	14 (100%)	0	14†	
Radiological appearance				
Unilocular	23 (96%)	1 (4%)	24	0.49
Multilocular	20 (95%)	1 (5%)	21	
Degenerated	22 (88%)	3 (12%)	25	
Diameter (cm)				
≤10	42 (93%)	3 (7%)	45	1.00
>10	23 (92%)	2 (8%)	25	
Content				
Bile and/or pus	17 (81%)	4 (19%)	21	0.02‡
Clear/degenerated	48 (98%)	1 (2%)	49	
Location				
Right lobe	46 (92%)	4 (8%)	50	<0.01‡
Left lobe	19 (100%)	0	19	
Caudate lobe	0	1 (100%)	1	
Operation				
External drainage	38 (90%)	4 (10%)	42	0.45
Introflexion	15 (100%)	0	15	
Omentopexy	12 (92%)	1 (8%)	13	

ALP = alkaline phosphatase; GGT = gamma glutamyl transferase.
*One of two cysts were resected by peri-cystectomy in three cases.
†Two of three cysts were resected by peri-cystectomy in two cases.
‡$P < 0.05$.

(Gharbi IV) (23.8% and 24.0%, respectively; $P = 0.52$). Risk of biliary fistulae was lower in the unilocular cysts (4%) and multilocular (5%) than degenerated ones (12%) ($P = 0.49$). Despite predominance of more biliary complications after multilocular and degenerated cysts, there was no significant difference among the groups.

Biliary leakage and fistulae risks of large cysts (>10 cm) were (20% and 8%, respectively) similar to the risks of small cysts (≤10 cm) (20% and 7%, respectively). Although caudate lobe cysts had a tendency toward biliary fistulae, location of the cyst in the right or the left liver was not a significant risk factor for biliary leakage or biliary fistulae in multivariate analysis.

In 30% of patients, the cysts contained bile and/or pus. These types of cysts were associated with significantly increased incidence of biliary leakage, when compared to the others (61.9% vs. 2.0%; $P < 0.01$). This was found in both univariate and multivariate analysis to be an independent risk factor for the biliary leakage. Bilious and/or purulent cyst content has also the raised risk of biliary fistulae (19% vs. 2%; $P = 0.02$) and it was the only independent risk factor for biliary fistula (Table 3).

Biliary leakage occurred in 1 of 15 cases that were treated by introflexion (6.7%) but was seen in 3 cases in the omentopexy group (23.0%). The remaining biliary leakage occurred in the external drainage group (23.8%). The operation type was not an independent risk factor for post-operative biliary leakage ($P = 0.08$) and fistula ($P = 0.45$) in this study. In the multivariate analysis, other factors were found much

Table 2. Risk factors for biliary leakage after hydatid liver surgery (univariated analysis)

Factors	Leakage (−)	Leakage (+)	Total	*P*
Age (yr)				
<40	28 (90%)	3 (10%)	31	0.07
≥40	28 (72%)	11 (28%)	39	
Gender				
Cysts (men)	13 (59%)	9 (41%)	22	<0.01*
Cysts (women)	43 (90%)	5 (10%)	48	
Primary	41 (82%)	9 (18%)	50	0.52
Recurrent	15 (75%)	5 (25%)	20	
ALP/GGT				
Raised	17 (65%)	9 (35%)	26	0.02*
Normal	39 (89%)	5 (11%)	44	
Cyst number				
1	29 (78%)	8 (22%)	37	0.86
2	16 (84%)	3 (16%)	19†	
3	11 (81%)	3 (19%)	14‡	
Radiological appearance				
Unilocular	21 (87%)	3 (13%)	24	0.52
Multilocular	16 (76%)	5 (24%)	21	
Degenerated	19 (76%)	6 (24%)	25	
Diameter (cm)				
≤10	36 (80%)	9 (20%)	45	1.00
>10	20 (80%)	5 (20%)	25	
Content				
Bile and/or pus	8 (38%)	13 (62%)	21	<0.01*
Clear/degenerated	48 (98%)	1 (2%)	49	
Location				
Right lobe	41 (82%)	9 (18%)	50	0.12
Left lobe	15 (89%)	4 (21%)	19	
Caudate lobe	0	1 (100%)	1	
Operation				
External drainage	32 (76%)	10 (24%)	42	0.08
Introflexion	15 (100%)	0	15	
Omentopexy	9 (69%)	4 (31%)	13	

Abbreviations as in Table 1.
*$P < 0.05$.
†One of two cysts were resected by peri-cystectomy in three cases.
‡Two of three cysts were resected by peri-cystectomy in two cases.

more important for biliary complications than cavity management techniques.

All cavity infections were diagnosed by purulent drainage from cavity drains or clinical findings of infection (fever >37.8 C and leukocytosis >10.000/mm^3) combined with imaging the cavities with abdominal ultrasound and CT. All the biliary fistulae (5 patients) resulted in cavity infections, along with two patients who had late cavity abscess and required laparotomy and drainage. The last two patients previously had transient biliary leakage. During the follow-up there was no evidence of recurrence or secondary sclerosing cholangitis.

The median hospital stay was 6 days (range 5–27). The hospital stay was longer in those who had a leakage (median 17; range 11–27) when compared with the non-leakage group (median 6; range 5–8) ($P < 0.01$).

DISCUSSION

Theoretically, hepatic hydatid cysts communicate with the biliary system in up to 80% of the cases.[3,10,11] In this study the incidence of biliary leakage was 26%. The apparent increase in incidence in our study is due to our criteria, which allowed for inclusion of patients with temporary leakage, alongside the persistent ones. The latter occurred in only 9.3% of the patients. We conclude that biliary leakage is under-reported in most studies than the expected rates.

Table 3. Independent risk factors identified by multivariated analyses

Risk factor for biliary leakage	*P* value	Relative risk	95% CI
Male	0.038*	4.1	1.794–93.279
Raised ALP/GGT	0.047*	3.2	1.248–78.464
Complicated content	0.022*	31.0	0.001–0.298
Risk factor for biliary fistula			
Male	0.880	1.5	0.382–10708.6
Raised ALP/GGT	0.198	7.5	0.744–327019
Complicated content	0.036*	9.5	1.411–2.E +13

Abbreviations as in Table 1.
*$P < 0.05$.

Most trials did not report the transient biliary leakage but only the persistent ones (Table 4). In some studies, contrary to expectations, rates of biliary leakage were reported lower than the biliary fistula (Table 4). Our observations are quite different. If the drain contents of the patients are followed closely and prospectively in the post-operative period, it can be noticed that biliary leakage is not so infrequent (16.7%). At least biliary leakage (26%) is much more than the biliary fistula (9.3%) and most of the leakage closed spontaneously (9 of 14 patients, 64% in our study). The thought that biliary leakage is not an important morbidity may be the cause of this under reporting. But biliary leakage, whether transient or persistent, can be the source of secondary cavity infections. Two of our secondary liver abscess cases that required surgical drainage had previous biliary leakage. Therefore, we thought that biliary leakage is not harmless and may cause secondary complications.

Table 4. Post-operative biliary leakage and fistula rates of the studies

Author	N	Biliary leakage	Persistent Biliary leakage
Ozmen et al.[2]	38	1 (2.6%)	NA
Langer et al.[3]	35	10 (28.6%)	NA
Demirci et al.[4]	260	51 (19.6%)	NA
Dawso et al.[5]	48	6 (12.6%)	4 (8.4%)
Little et al.[15]	39	3 (7.7%)	NA
Safioleas et al.[16]	132	6 (4.5%)	NA
Sayek and Onat[19]	100	6 (6.0%)	NA
Magistrelli et al.[20]	135	14 (10.4%)	NA
Gahukamble et al.[21]	35	8 (22.9%)	2 (5.8%)
Barros et al.[22]	212	8 (3.8%)	2 (1.0%)
Abu Zeid et al.[23]	20	2 (10.0%)	2 (10.0%)
Present study	54	14 (26.0%)	5 (9.3%)

NA = not available.

Although there was no difference among male and female patients as to biliary fistula, the risk of biliary leakage was higher among males in our study. Such gender difference was also noted in other studies related to hepatobiliary surgery. Brodsky et al.[12] reported that male gender was associated with more complications after laparoscopic cholecystectomy. Cohen et al. showed a raised operative and anesthesia risk for males, and Ziser et al. also noted that cirrhotic males had more frequent complications and mortality after surgical procedures than females.[13,14] This is, however, the first time that male gender was considered as a risk factor for increased biliary leakage rates after hydatid liver surgery. Predisposition of more biliary leakage in males may be the result of late presentation in males. Most fertile females have an abdomino-pelvic ultrasound performed during their pregnancies. Again, most females get abdomino-pelvic ultrasonography due to common gynecological problems such as over cysts and myoma uteri. It is well known that gallstone disease is also more common in females. Coincidental diagnosis of hydatid liver disease during these ultrasonographic examinations in females may result in the detection of more asymptomatic cysts in females. Males might be admitted to the hospital with more advanced disease and the possibility of ultrasonographic surveillance of females may protect them from more advanced disease when they are admitted to the hospital.

In our study, the recurrence of disease, which was seen in 31% of the patients, did not appear to be a predictive risk factor for biliary leakage. Little et al. also demonstrated no increase in the incidence of prolonged drainage in patients with recurrent hydatid disease.[15]

Increased serum level of ALP and GGT is considered a marker for communications between the hydatid cysts and bile ducts. Thirty-one percent of our patients had raised levels of both ALP and GGT. This ratio is similar to the findings of Langer et al.[3] (30%) and Safioleas et al.[16] (34%). As a new finding,

we found that pre-operative high serum ALP and GGT levels were significantly predictive for the presence of post-operative biliary leakage. It is routine practice in many centers to image the bile ducts (either pre-operative ERCP or intra-operative cholangiography) in patients who had cholelithiasis with a raised ALP and GGT. But, as far as we know, this is not a routine practice in hydatid liver disease and usually only jaundiced patients have pre-operative ERCP or intra-operative common bile duct exploration performed. This new finding is also important for the other treatment modalities of hydatid liver cysts excluding surgery for percutaneous treatment. It is well known that cysto-biliary communication is a contraindication for percutaneous treatment and this study shows that almost one-third of the cysts that have raised ALP and GGT levels result in biliary leakage. Therefore, we do not recommend percutaneous treatment for hydatid liver cysts that have raised ALP and GGT levels.

Multiple cysts occurred in 31.5% of our patients, similar to the reported incidence in the literature, which ranges from 29% to 38%.[4,16] Although it was not significant, we noted a tendency of increased risk of biliary leakage in patients with multiple cysts, and conclude that each hydatid cyst had its own potential for biliary complications, and cumulative risk of each cyst increases the complications. Further, we noted a slightly increased risk of the leakage in those with multilocular and degenerated cysts as compared with the unilocular cysts. This finding may support the idea that multilocular and degenerated hydatid cysts should not be treated by percutaneous treatment.[17]

Contrary to expectations, the size of the cyst does not appear to be of significance in the occurrence of biliary leakage and fistula in our study. It is a hypothesis that as the cyst enlarges it compresses the adjacent liver and stretches the bile channels in its immediate vicinity. Lateral openings develop in these over-stretched ducts, producing fistulae when the hydatid itself ruptures.[18] It is expected that risk of cysto-biliary communications increase when the cyst becomes larger. But this hypothesis has not been widely evaluated in the clinical studies. Other factors, such as the age of the cyst or anatomic location near to the large bile ducts, may be more important than the size of the cyst during its natural history in the liver.

The hydatid cysts appeared more commonly in the right lobe of the liver (70%) and this is in keeping with the previous reports in the literature.[4,16] We found no difference between right and left hepatic lobe cysts on biliary leakage and fistulae risk. Caudate lobe hydatid cysts may cause a higher incidence of biliary complications, but there are not enough cases to comment on caudate lobe hydatid cysts in our series and even in the previously reported trials.

In this study, the presence of bile and/or pus in hydatid liver cysts indicate communications between the cysts and the biliary system. Cyst content was the most important risk factor for post-operative bile leakage and the unique risk factor for the biliary fistula. Our findings support the previous reports by Langer et al.[3] who reported increased complications in patients with such complicated cysts. We believe that more studies are needed to focus on this topic about hydatid liver surgery.

The management of the cyst cavities is still controversial. Marsupialization was abandoned after the 1980s in our institute because of prolonged drainage and cavity abscess. Other approaches include external drainage and evacuation followed by obliteration of the cyst cavity (omentopexy or introflexion). Obliteration of the cyst cavity has been reported as having better results than external drainage alone in preventing the fistula formation.[2,4,16,19] These studies were retrospective and did not analyze data in regards to whether the patients had complicated or uncomplicated cysts. In our study, the type of operation did not appear to be a significant factor in the presence of leakage or the fistula. For patients without the risk factors identified in this study, we would suggest considering external drainage alone as the operation of choice given its safety and simplicity.

We have shown in this study that post-operative biliary fistulae in patients with hydatid disease is a complication seen in up to 9.3%. Multivariate analysis allowed us to determine the main causes of post-operative biliary complications and to eliminate the accompanying effects of the several risk factors, and the only risk factor for fistulae occurrence was the bilious and/or purulent cystcontent. The risk factors identified for biliary leakage are male gender, raised ALP and GGT, and the presence of bilious and/or purulent cysts. Despite spontaneous cessation, they can cause late cavity related complications such as secondary cavity abscess. Therefore, all biliary complications should be predicted, and if possible, prevented. Identifying the risk factors pre-operatively may help in optimizing the peri-operative management such as pre-operative ERCP and naso-biliary drainage[20] in the cases of raised ALP and GGT, especially in male patients. Identifying bilious and/or purulent cyst content during the operation may lead the surgeons to perform intra-operative cholangiography[2] and prophylactic internal or external biliary drainage[19] in these selected cases to prevent biliary leakage, fistula, secondary cavity infections, and prolonged hospitalization. These risk factors may also help the selection criteria for percu-

taneous treatment of hydatid liver cysts. Lastly, the myths that recurrent, large, externally drained, multilocular, or degenerated cysts cause more biliary complications should be changed because these are not the major determinants for post-operative biliary complications.

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Long Myotomy With Antireflux Repair for Esophageal Spastic Disorders

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This report presents the long-term subjective and objective results of esophageal myotomy and fundoplication by thoracotomy in the treatment of esophageal spastic disorders. From 1977 to 1995, a total of 16 patients with esophageal spastic disorders were referred to our unit and underwent a myotomy with an added partial (n = 12) or total (n = 4) fundoplication. The median follow-up was 6 years. Assessments included clinical evaluation, esophagogram, radionuclide emptying, manometry, 24-hour pH studies, and endoscopy. From the global results, patients with pure spastic disorders (n = 8) were compared to patients with spastic disorders with an accompanying epiphrenic diverticulum (n = 8). There were no deaths, and morbidity was minimal. Preoperative symptoms were similar in all patients with spastic disorders. After surgery, the clinical outcome was significantly better in patients with spastic disorders in the presence of a diverticulum. Delays in esophageal emptying persisted after surgery. Patients with pure spastic disorders showed more diffuse functional abnormalities. Patients with a diverticulum had dysfunction mostly in the distal esophagus. Both groups showed signs of coordination and relaxation abnormalities in the lower esophageal sphincter. Myotomy with antireflux surgery resulted in decreased propulsion and contraction pressure. The resting pressure and relaxation at the level of the lower esophageal sphincter improved, but the coordination abnormalities remained. Failure resulted from either reflux complications (n = 1) or obstruction (n = 4). Patients with spastic disorders plus a diverticulum showed better clinical results and improved esophageal function after surgery when compared to patients with pure spastic disorders. (J GASTROINTEST SURG 2002;6:713–722)

KEY WORDS: Esophageal spastic disorders, myotomy, diverticulum

Esophageal spastic disorders can be classified into diffuse esophageal spasm, hyperperistalsis, and hypertensive lower esophageal sphincter (LES). The function of the LES and its interaction with these poorly organized contractions remains unclear. When a diverticulum is identified in the distal esophagus, the spastic activity helps to explain the appearance of the diverticulum. However, the exact role of the LES with regard to its effect on the pathophysiology of this condition has yet to be clarified. Dysphagia and chest pain are the main presenting symptoms in patients with spastic disorders. Medical treatment is directed toward symptom control when these symptoms are attributed to high contraction pressures and poor propulsion. Investigation and management of any underlying psychogenic influences is also mandatory.

The role of surgery in the management of spastic disorders is limited to treatment of mechanical complications or uncontrolled symptoms related to the dysfunction. A long esophageal myotomy is the procedure of choice in these cases, with the upper limit of the myotomy and the preservation of the LES remaining areas of disagreement among surgeons.

The principal aim of the present study was to define the functional abnormalities that were present in 16 patients with spastic disorders, eight of whom had spastic dysfunction with no anatomic abnormalities and eight of whom had an epiphrenic diverticulum in association with the dysfunction. The secondary goal of this study was to report the clinical and functional results in this population before and after a long myotomy, which extended into the gastric wall and was intended to remove all of the LES effects.

Presented at the Forty-Second Annual Meeting of The Society for Surgery of the Alimentary Tract, Atlanta, Georgia, May 20–23, 2001 (poster presentation).

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00016-1

MATERIAL AND METHODS

Between 1977 and 1995, a total of 16 patients (5 men and 11 women), between the ages of 28 and 79 years, were referred to our unit by their physicians because they were not responding to conservative treatment. They were offered the option of surgical treatment for their idiopathic spastic disorders of the esophagus. Based on the classification of Richter and Castell, their findings were interpreted as showing one of the following: a pattern of diffuse spasm (n = 12); hyperperistalsis (n = 3); and hypertensive LES (n = 1). Patients were divided into two subgroups based on the presence or absence of an esophageal body diverticulum.

All patients underwent a cardiology workup to exclude myocardial ischemia as a cause of the chest pain. Preoperative and postoperative esophageal assessment included the following: clinical characteristics with evaluation of symptoms, esophagogram and radionuclide emptying, manometry, ambulatory 24-hour pH recording, and endoscopy. Symptoms had been present for 1 to 13 years (mean 5.8 years), and these patients had been managed conservatively before they were referred for surgery. Three patients had undergone prior surgery; two had a total fundoplication for what was then diagnosed as reflux disease, and one had a gastrectomy with a Billroth I reconstruction. Preoperative function in these patients was reviewed and results were compared to the tracings of a control group of 20 patients with no esophageal disease. The treated patients were then reassessed using their own preoperative evaluations as baseline in the assessment of postoperative results.

Operative Treatment

The indications for surgery in these 16 patients were persistent dysphagia with regurgitation and/or aspiration not responding to conservative treatment. Through a left thoracotomy above the eighth rib, all patients underwent a long myotomy of the manometrically diseased portion of the esophagus. The myotomy was planned to cover the area of dysfunction identified manometrically in the esophageal body. The length did vary. In patients with spastic disorders, it extended approximately 10 cm above the gastroesophageal junction to the area under the aortic arch. In patients with spastic disorders in the presence of a diverticulum, the myotomy covered only the area of the muscularis below the collar of the diverticulum. In all patients, the myotomy extended into the stomach approximately 1.5 to 2 cm, to ensure division of the LES area. A partial fundoplication (Belsey) was added in 12 patients, and a short total fundoplication was used as an antireflux procedure in four patients (Fig. 1). In one patient the long myotomy was combined with a Roux-en-Y reconstruction for coexisting alkaline gastritis resulting from a previous Billroth gastrectomy. When a diverticulum was present, it disappeared into the myotomy zone in four patients. In two patients the diverticulum was resected, and in two additional patients the diverticulum was suspended and attached to the layers of the transected muscle (Table 1).

Symptoms

Clinical assessment of symptoms recorded their presence or absence in the following four types of presentations: (1) dysphagia and/or slow emptying sensation; (2) regurgitation of fresh food; (3) chest pain; and (4) sour-tasting regurgitation and heartburn. Dysphagia is difficulty in swallowing with a blockage or poor emptying sensation identified either retrosternally or at the level of the sternal notch.

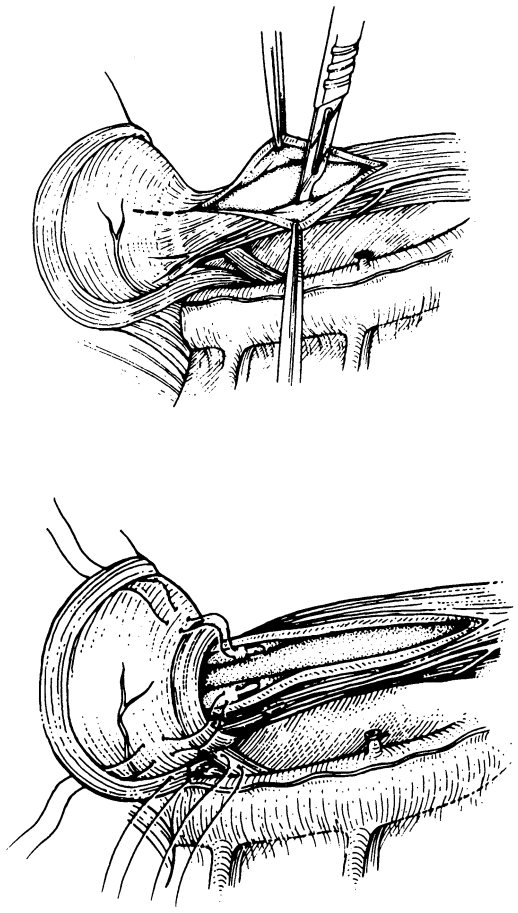

Fig. 1. The long myotomy should include the LES area (*top*). Belsey partial fundoplication as an antireflux repair (*bottom*).

Table 1. Operations performed in 16 patients

Operation	Diverticula (+)	Diverticula (−)
Myotomy + Belsey	7	4
Myotomy + Nissen	0	4
Myotomy + Roux-en-Y	1	0
Diverticulopexy	2	
Diverticulectomy	2	

Regurgitation is the bringing back of either fresh food or sour-tasting contents early or late after deglutition. Heartburn is a burning sensation beginning at the epigastric level and radiating toward the sternum and the neck. Chest pain is any discomfort or pain in the chest area related or unrelated to swallowing. In the evaluation of symptoms, the patient's sense of satiety is not recorded because this is considered a subjective measurement and can vary significantly according to the patient's psychological status. Symptoms regardless of their severity or duration were recorded simply as either present or absent. The objective measurements of the esophageal investigation were added.

Radiologic Findings

Standard barium esophagograms were obtained under fluoroscopic control with six frames printed per second. The presence of a hiatal hernia, diverticulum, gastroesophageal reflux, mucosal changes, stenosis, stasis, and abnormal motility were recorded for all patients preoperatively and in 15 patients postoperatively. Radiologic assessments were based on the anatomic abnormalities identified by the radiologist on the esophagogram and the upper gastrointestinal evaluation. Any irregularities seen on the mucosa (edema, irregular pattern, and the possibility of erosions or ulcers) were recorded as mucosal changes. A description of these anatomic abnormalities follows.

Stricture is defined as a narrowing of the esophageal lumen, and it can be identified at various levels without attempting to clarify its etiology. Abnormal motility is the presence of segmental contractions in the esophageal body, without any attempt at clarifying the type, quality, or strength of these contractions. Hiatal hernia is defined as sliding of part of the stomach above the diaphragm through the esophageal hiatus. Hiatal hernias are subdivided into four types according to the location of the gastroesophageal junction. In type I hernias, the sliding occurs when the gastroesophageal junction, along with some portion of the stomach, is displaced above the diaphragm. The anatomic orientation of the stomach remains the same. Type II is the paraesophageal hernia. In these hernias the gastroesophageal junction remains in a relatively normal position, but the stomach squeezes through the esophageal hiatus of the diaphragm alongside the esophagus and gastric cardia. Type III is a combination of the two preceding types of hernias, and type IV involves any abdominal organ besides the herniated stomach.[2]

Esophageal Emptying Scintiscan

Scintigraphic assessment of pharyngoesophageal and esophageal transit was performed with the patient in the standing and supine positions using the following methods. Data were acquired during a period of 2 minutes after the ingestion of 10 ml of water containing 1.0 mCi of ^{99}mTc sulfur colloid. The oropharynx and proximal, mid, and distal esophagus were studied. The objective parameter that was used as an indicator of the esophageal emptying capacity was the stasis of radioactive material at 2 minutes. Emptying studies were performed in all patients before surgery and in 15 of 16 patients after the operation.

Endoscopy

A standard fiberoptic system (FG34JH; Pentax Canada, Mississauga, Ontario, Canada) was initially used to assess the esophagus and gastroesophageal junction. Later on, this was replaced by a video endoscopy unit (GIF-130; Olympus Canada, Toronto, Ontario, Canada). Mucosal lesions were classified according to the MUSE system (metaplasia, ulcer, stricture, and erosions) as proposed by Armstrong et al.[3] Mucosal damage was graded according to the increasing severity of metaplasia, ulcers, stricture, and erosion, with a score ranging from 0 to 2 assigned for each of these aspects (Fig. 2). Barrett's esophagus was defined as the presence of any length of columnar-lined epithelium in the distal esophagus with a biopsy showing intestinal metaplasia (specialized epithelium).

Manometry

Esophageal motility studies were performed using a slow pull-through method with a triple-lumen polyvinyl catheter (MUI Scientific), each lumen having an internal diameter of 2.03 mm, with the orifice of 1.2 cm opening at 5 cm intervals and radially oriented at 120 degrees from each other. The motility tube was introduced via a nasoesophageal route and connected to external transducers (1290c; Hewlett-Packard Quality Monitor Systems, Inc., Colorado Springs, Colorado). Pressures were recorded on a four-

channel preamplifying physiograph (TA-11; Gould Fiber Optics, Millersville, Maryland). Constant perfusion was initially obtained using a mechanically driven perfusion system (3.8 ml/min; Harvard Pump, Harvard Apparatus Canada, Saint-Laurant, Quebec, Canada). A pneumohydraulic infusion pump (PIP-3; MuI Scientific Canada, Mississauga, Ontario, Canada) was subsequently employed, using pressures of 15 psi to study the esophageal body and the LES area. Ten voluntary swallows were recorded for each of the proximal and distal halves of the esophagus as well as for the LES area. A 2 ml water bolus was used for each swallow, leaving a 30-second quiescent period between swallows. Esophageal resting pressures and peak contraction pressures were recorded. The percentage incidence of primary peristalsis was noted. Tertiary waves in response to swallowing and spontaneous tertiary activity per minute were calculated in both the proximal and distal esophagus. In the LES, absolute resting pressure and closing pressure were recorded. After the intragastric pressures were subtracted from the intrasphincteric pressures, the LES gradient pressures between the esophagus and the stomach were calculated. Relaxation and coordination of the sphincter were assessed on all 10 swallows with the use of a station pull-through technique in the high-pressure zone.

Relaxation of the LES was interpreted as normal when the resting pressure of the sphincter fell to within 5 mm Hg above the resting intragastric pressure. The coordination of the sphincter was interpreted as normal when the opening phase of the sphincter totally encompassed the duration of the incoming wave in the distal esophagus. Results of these interpretations were then quantitated and expressed as the percentage of total swallows showing either normal relaxation or coordination.

24-Hour pH Recordings

The ambulatory pH recorder (Sandhill, RDL, Sandhill Scientific, Inc., Littleton, Colorado) has been used to assess acid reflux events since January 1987. After calibration, the antimony electrode was placed 5 cm above the LES previously identified and localized by manometry. The total number of reflux episodes, the number of reflux episodes lasting longer than 5 minutes, the time of the longest reflux episode, the total minutes, and the percentage of time with exposure to acid were computed.

Control Group

A group of 60 control subjects was used. Forty healthy volunteers in which motility studies were performed using a mechanically driven perfusion system (Harvard Apparatus Canada) formed the core of the normal population providing baseline control values in our laboratory. Twenty patients who showed no evidence of esophageal disease after undergoing a full esophageal assessment served as the control group. The only difference between the normal volunteers and the patient control group was the type of perfusion system used (mechanical vs. pressure driven). There were no differences in esophageal motor function between these two control groups.[4]

Statistical Analysis

Categorical data were expressed as proportions and analyzed by means of Fisher's exact probability test. Parametric data were expressed as mean ± SD, and Student's *t*-test or Wilcoxon rank-sum test was used for the comparison when appropriate. A two-tailed exact *P* value was provided unless it was greater than 0.25 or less than 0.001. $P < 0.05$ was considered statistically significant. Statistical analysis was performed by means of SPSS 7.5 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

There were no postoperative deaths. One patient had lobar atelectasis and another patient had an episode of pulmonary edema; both were treated successfully. The mean hospital stay was 8.4 days for both groups. We defined failure as persistent symptoms (presence of dysphagia with regurgitation and/or aspiration irrespective of severity) with evidence of reflux damage and/or obstruction to emptying.

Symptoms

Preoperatively the presenting symptoms were similar in all patients with spastic disorders whether or not a diverticulum was present. After surgery, the clinical outcome was significantly better in patients with spastic disorders in whom a diverticulum was present. Table 2 details the symptoms that were present before and after the operation in both groups.

Radiologic Findings

The results of the radiologic observations are summarized in Table 3. Eight patients had epiphrenic diverticula (one double). These diverticula showed a mean diameter of 5.4 cm (range 1.3 to 8.5 cm), six of which were left sided and three of which were right sided. Five patients had hiatal hernias (type 1 in 4 and type III in 1). Four of the hernias

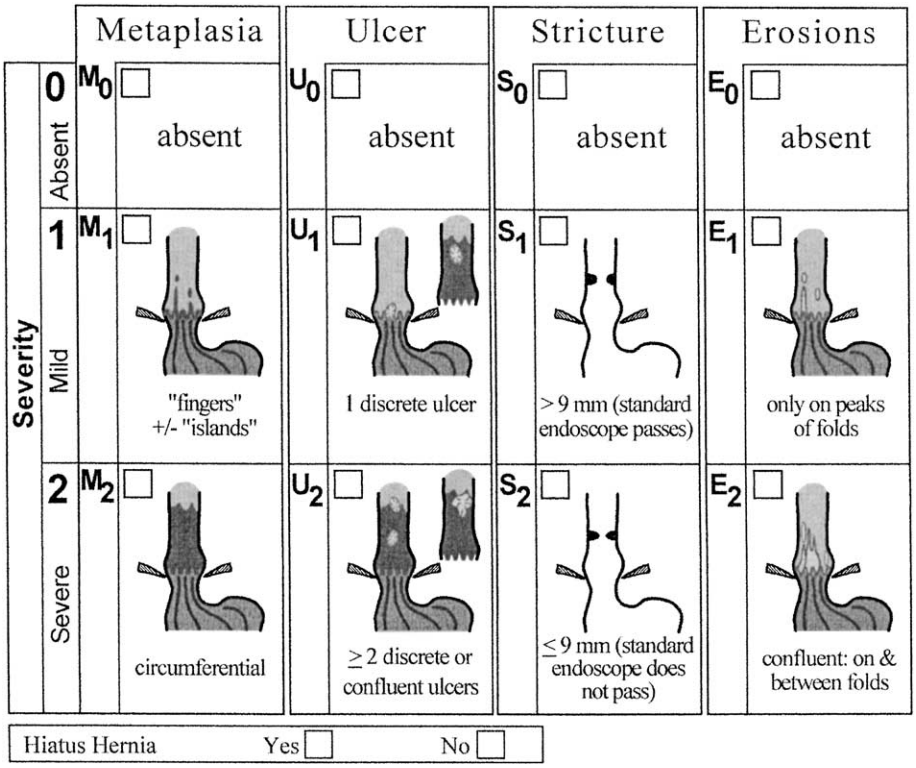

Fig. 2. MUSE system of Armstrong et al.[3] M = metaplasia; U = ulcers; S = stricture; E = erosions.

were identified in patients with diverticula. Tertiary waves observed preoperatively disappeared after myotomy. Stasis and dilatation remained after surgery. The long myotomy resulted in outpouching of the freed mucosa causing a wider esophagus. The antireflux effect contributed to esophageal stasis.

Esophageal Emptying Scintiscan

The capacity of the esophagus to empty a 10 ml liquid bolus is summarized in Fig. 3. Before the operation, emptying delays were significant in patients with spastic disorders when compared to the control population. Postoperatively all patients with spastic disorders continued to show significant esophageal retention of the 10 ml liquid bolus despite the myotomy and fundoplication.

Endoscopic Findings

Mucosal lesions in the esophagus in all patients with spastic disorders are summarized in Table 4. The nine diverticula were well outlined in the eight patients when the abnormality was present. All were located in the distal half of the esophagus, the most proximal being 28 cm from the incisors and the most distal being 35 cm from the incisors (mean 32.8 cm).

After the myotomy, five patients had esophageal widening in the operated area of the esophagus. Seven patients had evidence of stasis and food retention. One patient operated on for epiphrenic diverticulum and spastic motor dysfunction developed Barrett's esophagus with ulcers and stricture 9 years after the operation. In a second patient a diagnosis of columnar-lined esophagus was documented 3 years after her operation. Reoperation was not considered an option in these patients because of associated medical conditions.

Manometric Findings

The manometric results are summarized in Table 5. Esophageal body contraction abnormalities were more diffuse in patients with spastic disorders without a diverticulum—that is, dysfunction was seen in both the proximal and distal esophagus. When a diverticulum was present, the spastic activity was seen more frequently in the distal esophagus, whereas the propulsion was intact in the proximal half of the esophagus. The LES showed resting pressure slightly above the values for the control population. Abnormal relaxation was seen mostly in patients with spastic disorders without a diverticulum. Poor coordination in the opening and closing of the sphincter against the oncoming esophageal contraction was

Table 2. Symptoms in 16 patients before and after surgical treatment

Symptoms of spastic disorders	Diverticula (−)			Diverticula (+)		
	Preop	Postop	*P* Value	Preop	Postop	*P* Value
Dysphagia	8/8	3/8	0.026	7/8	1/7	0.010
Odynophagia	5/8	0/8	0.026	4/8	0/7	0.077
Regurgitation (food)	4/8	2/8	0.608	7/8	0/7	0.001
Chest pain	6/8	3/8	0.315	6/8	0/7	0.007
Heartburn	2/8	3/8	1	6/8	2/7	0.132
Regurgitation (sour)	3/8	4/8	1	6/8	2/7	0.132

present in all patients with spastic disorders. The operation reduced peristalsis and peak contraction pressure in the distal esophagus. At the LES level, resting pressures were decreased and the relaxation phase showed improvement. The coordination abnormalities remained.

24-Hour pH Recording

Twenty-four-hour pH studies were carried out in seven patients before and in 15 of 16 patients after the operation. Two patients with coexisting diverticula and hiatal hernias showed prolonged acid exposure before the operation, without mucosal damage. The LES pressure was normal in both of them. Overall, preoperatively there was more acid exposure in the esophagus of patients who had a diverticulum. After the operation, acid exposure increased significantly in the esophagus of patients who had pure spastic disorders without a diverticulum.

Follow-Up

The mean follow-up was 6 years and 9 months (range 1 to 14 years). Two patients were lost to follow-up: one in the early control period and one 7 years after the operation. Four patients, all from the group with pure spastic disorders without diverticula, had to be reoperated. Three of them underwent esophagectomy. Reconstruction was completed using a colon interposition graft in one patient and a gastric interposition graft in two patients. The indications for reoperation were progressive dilatation of the esophagus and dysphagia, 3.6 and 8 years, respectively, after the first operation. In one patient the fundoplication failed 4 years after the initial operation because of dilatation and dysphagia. This patient had undergone a Roux-en-Y gastrectomy, which was performed by another surgeon before the fundoplication failure. Numerous symptoms persisted in all four patients despite reoperation.

Table 3. Radiologic findings before and after surgery

Radiologic findings in spastic disorders	Diverticula (−)		Diverticula (+)	
	Preop	Postop	Preop	Postop
Stasis	3/8	4/8	2/8	3/7
Tertiary waves	7/8	0/8	3/8	0/7
Dilatation	2/8	6/8	3/8	5/7
Diameter (cm)	3.6 ± 0.4	5.5 ± 1.6	4.4 ± 1.8	4.6 ± 1.5

DISCUSSION

The functional characteristics and the management of esophageal spastic disorders are still controversial. The principal problem in patients with spastic disorders is one of diagnosis. The criteria suggested in the literature allow for a wide interpretation, a danger in itself. The manometric findings of simultaneous (tertiary) nonpropulsive waves in 20% to 30% of all esophageal wet swallows with the intermittent appearance of normal peristalsis are diagnostic of the diffuse spasm pattern. High-amplitude contractions may also be present. The LES may show increased resting pressures and poor relaxation in up to 30% of patients.[5,6]

We were conservative in the diagnosis of primary idiopathic spastic disorders in our group of patients. Sixty-three percent of all swallows in our patients with pure spastic disorders were nonpropulsive but without significant differences in peak pressure when compared to the control population. Similarly, the presence of abnormal contractions in the subgroup of patients with a diverticulum showed a high prevalence of nonpropulsive esophageal contractions. Here again, hypertensive pressures were seen occasionally, but overall the peak contraction pressures were no different from those in the control group.[7,8] The

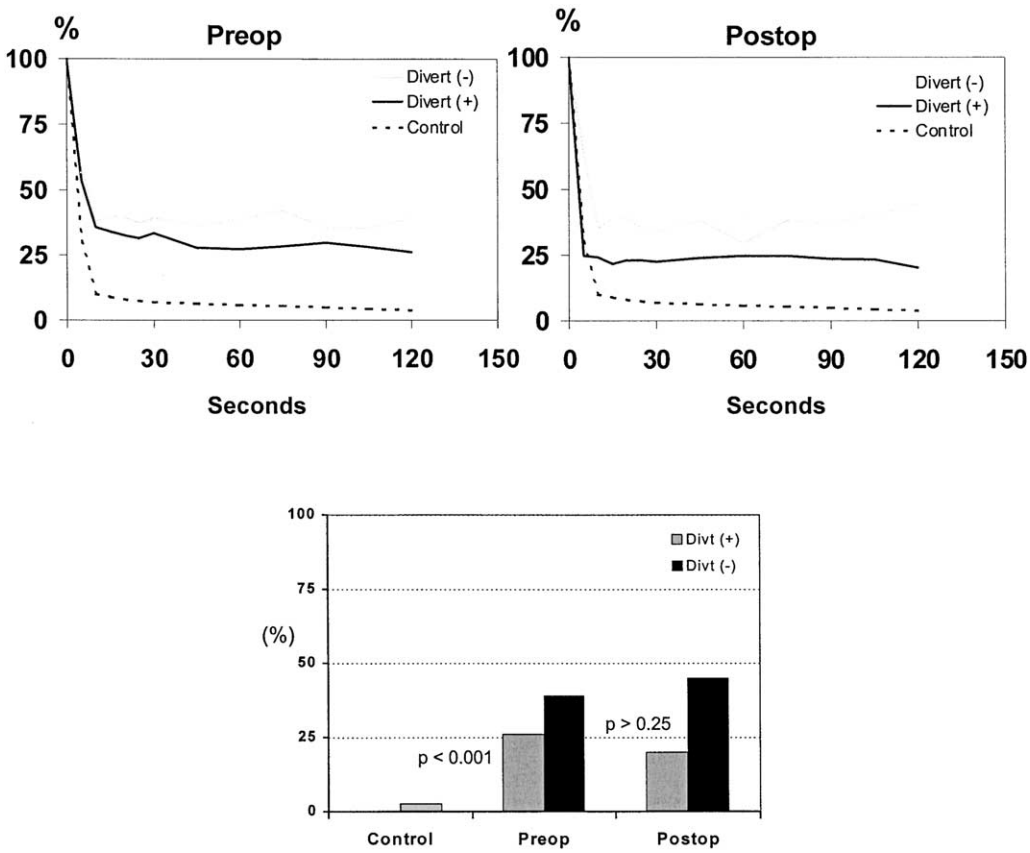

Fig. 3. Esophageal (single liquid bolus) emptying capacity (*top*) with esophageal stasis at 2 minutes (*bottom*).

main difference that could be observed in patients with spastic disorders with a diagnosis of diverticulum, as opposed to those who had pure spastic disorders with no diverticulum, was an intact propulsion in the proximal half of the esophagus. The other functional parameters were not found to be any different between the two subgroups studied. When looking at all 16 patients with spastic disorders, the LES resting pressures were found to be slightly increased. Coordination abnormalities of the LES were considered to be significantly more frequent than in normal subjects. Incomplete relaxation of the LES was seen more often in patients in whom a diverticulum was present.

A number of factors may have played a role in the interpretation of the functional abnormalities that were present. One of these was a history of total fundoplication where resistance to transit was added at the gastroesophageal junction. In both patients in whom this was done, the operation took place more than 3 years before the diagnosis of spastic disorder was made. Obstruction by the fundoplication was not a factor, and although reflux disease could have also been influential,[9,10] these two patients showed normal LES tone, no significant exposure to acid, and no mucosal damage.

The emotional factors that were present in these patients also most certainly influenced esophageal function. Clouse and Lustman[11] have clearly described the relationship between esophageal contraction abnormalities and emotional disturbances in patients affected by esophageal spastic disorders. Our group of patients all had evidence of a strong emotional overlay to their symptoms. Chest pain and dysphagia were the most frequent symptoms and were clearly influenced by individual perceptions. This remained evident during the follow-up after the surgical treatment.

Medical treatment may help to control the symptoms resulting from high contraction pressures and poor propulsion. This group of patients was treated for a mean period of 5.8 years before surgery was proposed as an alternative. The role of surgery is limited to treatment of mechanical complications or uncontrolled dysfunction. Surgical treatment for spastic disorders is not as successful as surgery for

Table 4. Endoscopic findings classified by the MUSE system

	Diverticula (−)		Diverticula (+)	
Grade	**Preop**	**Postop**	**Preop**	**Postop**
Metaplasia				
2	0	0	0	1*
1	0	0	0	1
0	8	8	8	6
Ulcer				
2	0	0	0	0
1	0	0	0	2
0	8	8	8	6
Stricture				
2	0	0	0	1*
1	0	0	0	0
0	8	8	8	7
Erosions				
2	0	0	0	0
1	0	0	0	0
0	8	8	8	8

*Same patient.

achalasia. The overall improvement rate in 42 patients with diffuse esophageal spasms and related disorders, as reported by Ellis,[12] was 70%. Their median follow-up period was 5.8 years. In an analysis of 19 patients undergoing myotomy for diffuse esophageal spasms, Eypasch et al.[13] found symptomatic improvement and improved swallowing in 80% of their patients. Henderson et al.[14] proposed total thoracic esophagomyotomy, including the LES, coupled with a short total fundoplication, as their approach of choice. This operation resulted in an improvement in 88% of their patients with a 5-year follow-up. The presence of a diverticulum is not an indication for surgery by itself. Some still recommend surgical treatment for all patients, emphasizing the risk of potentially serious complications if they were left untreated. Patients with a symptomatic epiphrenic diverticulum in association with an underlying motor disorder should be offered surgery.[15]

The choice of operation brings disagreement among surgeons; the length of the myotomy, the inclusion of the LES into the myotomy zone, and the addition of an antireflux valve at the end of an esophagus rendered atonic are some of the topics stimulating discussion.

Streitz et al.[16] support the elective use of myotomy. They suggest its use in the presence of dysmotility, preserving the normal LES. A recent report from the Mayo Clinic[17] analyzed the results of myotomy in 33 patients treated for an epiphrenic diverticulum. This report also emphasized the use of myotomy based on the recorded dysmotility and with preservation of the LES zone. These investigators observed 33% morbidity and a 9% death rate. Suture line leaks occurred in 18% of their group (6 patients). All of these leaks developed in patients who had a long myotomy with resection of the diverticulum while at the same time preserving the integrity of the LES. D'Ugo et al.[18] observed similar complications. The suggestion in these reports that the LES shows normal function may well result from the known difficulty in precisely assessing abnormalities in sphincter coordination. The intermittent nature of these abnormalities must also be noted. Based on the functional assessment of our patients, regardless of whether or not a diverticulum was present, myotomy remains the mainstay for treatment of motor dysfunction. In addition, however, we believe that the coordination dysfunction identified at the LES level should be taken into consideration, thereby justifying extending the myotomy to include the LES and 1 to 1.5 cm of the gastric muscularis. We have seen no complications at the level of the diverticulectomy transection line when this treatment philosophy is followed. When left intact, the lack of coordination in the sphincter, coupled with the occasional incomplete relaxation of the LES, may well be enough to explain abnormal esophageal outlet resistance and/or an obstruction causing undue pressure buildup and retention leading, on occasion, to leaks, sepsis, and even death. Belsey[19] suggested this approach early, with the addition of a partial fundoplication as an added antireflux maneuver. We also favor a partial fundoplication after documenting that a total gastric wrap, albeit a short one that is placed over a large inlaying Bougie, still resulted in obstructive symptoms over time.[20]

Treating the diverticulum should be viewed as treating the complication of the dysfunction. Where the diverticulum is small, intermittent, or wide and shallow, it will usually disappear in the myotomized zone. When the diverticulum is large and, especially if it shows a dependent portion, it should be resected taking care to protect the integrity of the esophageal lumen with an inlying Bougie while doing so if the size does not impose resection. The diverticulum can also be suspended to the thickness of the transected muscularis of the esophageal body.

Patients with pure spastic disorders respond poorly to surgical treatment. It is not clear whether the absence of an anatomic abnormality such as a diverticulum plays a role in selecting the population that may benefit from a myotomy. Only three of the patients in the group with pure spastic disorders were asymptomatic after treatment. In four patients, where an esophagectomy was finally offered for ei-

Table 5. Manometric results before and after the operation

Evaluation	Control	Preoperative		Postoperative		Preoperative vs. postoperative	
		Diverticulum (+)	Diverticulum (−)	Diverticulum (+)	Diverticulum (−)	Statistic	*P* value
Manometric recording							
Proximal esophageal body							
Peak pressure (mm Hg)	54.4 ± 19.72	55.9 ± 13.2	46.0 ± 9.9	48.0 ± 10.6	34.4 ± 12.5	$t = 2.668$	0.018
Primary waves (%)	96.6 ± 7.38	88.6 ± 21.0	48.8 ± 33.7	60.0 ± 26.7	61.4 ± 36.0	$z = 0.944$	>0.25
Tertiary waves (%)	3.4 ± 7.31	11.4 ± 21.0	51.2 ± 33.7	40 ± 26.7	38.6 ± 36.0	$z = 0.944$	>0.25
Spontaneous tertiary waves (min)	0.66 ± 0.85	1.94 ± 2.13	2.11 ± 1.86	0.40 ± 0.4	1.29 ± 1.27	$t = 1.785$	0.117
Distal esophageal body							
Peak pressure (mm Hg)	65.49 ± 23.09	70.1 ± 32.0	78.8 ± 37.4	35.0 ± 9.7	33.4 ± 10.3	$t = 4.784$	<0.001
Primary waves (%)	96.4 ± 7.83	61.4 ± 38.0	36.3 ± 42.4	30.0 ± 32.1	18.8 ± 34.8	$z = 2.408$	0.016
Tertiary waves (%)	3.6 ± 7.83	38.6 ± 38.0	63.7 ± 42.4	70 ± 32.1	81.2 ± 34.8	$z = 2.408$	0.016
Spontaneous tertiary waves (min)	0.72 ± 0.82	0.95 ± 1.0	2.0 ± 1.74	0.0 ± 0.0	0.76 ± 0.91	$t = 2.106$	0.068
Lower esophageal sphincter							
Resting pressure (mm Hg)	25.73 ± 6.25	35.1 ± 14.2	30.3 ± 8.1	20.0 ± 4.1	15.2 ± 5.3	$t = 6.198$	<0.001
Gradient pressure (mm Hg)	17.18 ± 5.94	23.1 ± 12.0	22.9 ± 9.7	8.2 ± 2.6	6.9 ± 4.2	$t = 5.880$	<0.001
Closing pressure (mm Hg)	61.25 ± 24.33	59.9 ± 19.9	55.4 ± 24.6	32.9 ± 6.9	29.0 ± 7.3	$t = 4.972$	<0.001
Relaxation (%)	98.63 ± 4.19	95.9 ± 5.3	63.9 ± 36.4	100 ± 0	100 ± 0	$z = 2.803$	0.005
Coordination (%)	75 ± 24.71	26.9 ± 38.7	18.5 ± 24.1	0 ± 0	0 ± 0	$z = 2.524$	0.012
24-hr pH monitoring							
Total No. of episodes	27.67 ± 23.6	48.3 ± 55.4	11.7 ± 2.5	41.3 ± 27.1	192 ± 353	$z = 1.970$	0.049
Time % of exposure	1.06 ± 1.22	10.0 ± 11.6	0 ± 0	6.3 ± 7.0	11.5 ± 12.2	$z = 0.415$	>0.25

ther symptoms of obstruction or complications of reflux multiple functional symptoms prevailed despite the removal of the esophagus.

Causes for failure over time are either reflux related or the result of obstruction with retention of food in the esophagus. Extension of the myotomy into the stomach may improve treatment of the motor disorders, but it certainly entails the risk of reflux complications. Despite a less than perfect protection against reflux, the partial fundoplication is still preferred for its less obstructive nature. The esophageal emptying capacity is altered with the dysfunction. It remains abnormal after reoperation, possibly influenced by the persistence of motor abnormalities, atony of the myotomized esophagus, and added resistance to emptying at the gastroesophageal junction. We have not assessed this emptying capacity with semisolids or with solid food.

CONCLUSION

Patients with pure spastic disorders, even after surgical treatment, remain more symptomatic, show more esophageal dilatation and retention, and show more acid exposure and reflux complications. They have a higher failure rate requiring reoperation, and despite esophagectomy they remain symptomatic.

Patients with spastic disorders, who also have an esophageal body diverticulum, usually demonstrate better proximal esophageal function. The LES in these patients shows good relaxation but poor coordination. Long myotomy and fundoplication in patients with spastic disorders reduces dysphagia and chest pain, decreases esophageal body contraction pressure, reduces peristalsis in the distal esophagus, decreases LES pressure, and improves the relaxation function of the LES.

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Megaesophagus Microbiota: A Qualitative and Quantitative Analysis

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Bacterial overgrowth in the esophageal lumen in patients with megaesophagus can be the cause of recurring pulmonary infections, infectious complications due to surgical or endoscopic procedures, and the development of dysplasia of the esophageal mucosa and cancer. Despite this, esophageal microbiota in the megaesophagus have never been studied. The aim of this study was to analyze qualitatively and quantitatively the microbiota in chagasic megaesophagus in comparison to the normal esophagus. Twenty-five patients (10 men and 15 women), ranging in age from 24 to 74 years (mean years), were prospectively studied from March to September 2000. Fifteen patients with chagasic megaesophagus were divided into three subgroups (n = 5 patients in each) according to the grade of esophageal dilation: MG1 = megaesophagus grade I; MG2 = megaesophagus grade II; and MG3 = megaesophagus grade III. Another group of 10 patients without esophageal disease served as a control group. Samples were collected using a method especially developed to avoid contamination with microorganisms of the oral cavity and oropharynx. In the control group, 40% of the cultures were positive with the genus *Streptococcus* predominating and concentrations varying from 10^1 to 10^2 colony-forming units/ml. In the megaesophagus group, 93.3% of the cultures were positive, with great variability in the bacteria and a predominance of various aerobic gram-positive bacteria (*Streptococcus* was most common) and anaerobic bacteria (*Veillonella* was most frequent) in concentrations that ranged from 10^1 to 10^5 colony-forming units/ml. The bacterial concentrations were generally more elevated in MG3 patients in comparison to MG1 and MG2 patients and the control group ($P < 0.05$). It was concluded that patients with megaesophagus have a variety of microbiota consisting mostly of aerobic gram-positive and anaerobic bacteria, in concentrations that varied according to the degree of esophageal dilation. (J GASTROINTEST SURG 2002;6:723–729)

KEY WORDS: Achalasia, megaesophagus, microbiota, microflora

From a microbiological viewpoint, the esophagus is considered an organ through which salivary secretions pass; it is therefore inhabited by transitory microbiota originating from the oral cavity and oropharynx. These transitory microbiota will be destroyed, for the most part, by the gastric acid secretions in the stomach.[1–3]

In patients with megaesophagus, the achalasia of the inferior sphincter and the body's motor disturbances induce progressive dilation of the organ causing difficulty in evacuating and chronic stasis.[4–7] In the stagnated contents, there is bacterial overgrowth of microorganisms from the oropharynx,[8] as demonstrated by Lau et al. and Finlay et al.[10] in patients with esophageal neoplasms. The stasis causes repetition of aspirative phenomena and chronic pulmonary infections,[1,11–13] and is responsible for aggravating the infectious complications related to the perforation of the esophagus in patients undergoing surgical or endoscopic procedures.[9,14,15]

Some investigators[15–19] have suggested that chronic esophagitis affects all of the mucosa of the organ, and is a consequence of stasis in addition to the action of bacteria in suspension in the lumen, which could favor the development of epithelial dysplasia. This could possibly be the first step in the develop-

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Supported by FAPESP (Fundação de Amparo á Pesquisa do Estado de São Paulo).
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1091-255X/02/$—see front matter
PII: S1091-255X(02)00028-8

ment of esophageal carcinoma, which is 33 times more frequent in these patients compared to the general population.[5,20] Although they have been exposed, the microbiota of the megaesophagus has never been studied. The intent of this study was to analyze qualitatively and quantitatively the microorganisms in suspension in the esophageal stasis liquid in patients with Chagas' megaesophageal disease.

PATIENTS

Twenty-five patients (10 men and 15 women), ranging in age from 24 to 74 years (mean 49.1 years) were prospectively studied. Fifteen patients with Chagas' megaesophageal disease comprised the megaesophagus (MG) group, with inclusion criteria as follows: plasma positive for Chagas' disease as tested by at least two methods, contrast-enhanced x-ray films of the esophagus demonstrating alteration in motor function and varying degrees of dilatation, and manometric examination of the esophagus demonstrating achalasia of the inferior esophageal sphincter and aperistalsis of the esophageal body. Patients with grade IV megaesophagus, according to the classification of Ferreira-Santos[21] and Rezende et al.[6] or the advanced classification of Pinotti et al.,[5] were excluded from the study (because of the large quantity of solid residue in the esophageal lumen, which could complicate the collection of material and increase the risks associated with the procedure); also excluded were those patients who had prior surgery for treatment of megaesophagus, patients with a nasogastric feeding catheter, patients with diabetes, alcoholism, or neoplasms, and patients who had taken antibiotics within the past 3 months.

The patients in the MG group were subdivided into three additional groups according to the degree of esophageal dilation:[6,21] five patients with megaesophagus grade I (MG1), five patients with megaesophagus grade II (MG2), and five patients with megaesophagus grade III (MG3).

Ten other patients with dyspeptic complaints who were undergoing upper digestive endoscopy served as a control group. Patients who had gastroesophageal reflux or other esophagogastroduodenal disease, patients with diabetes, alcoholism, or neoplasms, and patients who had taken antibiotics in the past 3 months were excluded from the protocol.

METHODS

The samples were collected in the Upper Digestive Endoscopy and Bronchoscopy Service of the Hospital das Clínicas of São Paulo University School of Medicine, using a method of collection that was developed especially for this research project. All of the patients who participated in this study filled out a consent form after the risks of the endoscopy procedure were explained to them in detail. The Ethics Commission for Research Projects Analysis of the Hospital das Clínicas of São Paulo University School of Medicine approved this form and the research protocol.

The patients were all outpatients and came directly to the ambulatory endoscopy clinic after fasting for 12 hours. The patients in the megaesophagus group were placed on a liquid diet for 2 days before the examination. After routine sedation for endoscopy, patients were placed in a left lateral supine position. Material for testing was collected prior to the endoscopic examination through a sterilized No. 14 Levine tube, which was passed through a No. 7.5 orotracheal tube that had also been sterilized. These tubes were introduced through the mouth into the inferior third of the esophagus with the Levine catheter placed inside the endotracheal tube to avoid contamination with microorganisms in the oropharynx. The catheter was then pushed until it reached the esophageal lumen, and the stasis liquid was then aspirated with a 20 ml syringe connected to its extremities. In the control group, this was performed by washing the esophageal lumen with 10 ml of sterile saline solution, after which the contents were then aspirated. It took 1 to 3 minutes to obtain the samples. One milliliter of the aspirated liquid was then transferred to a tube containing 9 ml phosphate-buffered saline solution for transportation.

The collected samples were transferred within 1 hour to the Microbiology Laboratory of the Institute for Biomedical Sciences at São Paulo University, where dilution, seriating, sampling, incubation, and identification of microorganisms were performed. Bacterial counts were expressed as colony-forming units (CFU) per milliliter, after normalization of data by $\log^{10}$ transformation. The differences in concentrations were compared among the microorganism groups; these differences were seen more frequently in the megaesophagus subgroups (MG1, MG2, and MG3), and in the subgroups compared to the control group. In sequence, the mean concentrations of the microorganisms that appeared with greater frequency were compared.

Statistical Analysis

To compare microorganism concentrations between groups, the Kruskal-Wallis one-way analysis of variance test for "k" independent samples was used. In addition, a multiple-comparison test was

used when necessary. This later test was used when the Kruskal-Wallis test showed no significant differences among the megaesophagus subgroups. When this was the case these subgroups were combined and considered a single group, which was then compared to the control group applying the Mann-Whitney test for two independent samples. In all analyses, $P < 0.05$ was taken as the level of significance.

RESULTS

Endoscopy

No procedure-related morbidity was observed in any of the 25 patients studied. No food stasis was observed after 2 days on a liquid diet and 12 hours of fasting. Stasis esophagitis was more common in the MG2 and MG3 subgroups. Lugol solution was applied in the megaesophagus subgroups, but no biopsy specimens were obtained because no unstained or poorly stained areas were observed.

Microbiotic Analysis

The frequency of the microorganisms found in the esophageal aspirate of patients in the control group and the megaesophagus group is presented in Table 1.

Both groups showed a predominance of aerobic gram-positive and anaerobic bacteria, with a greater percentage of positive cultures (93% vs. 40%) in the megaesophagus group ($P < 0.05$). Among the aerobic gram-positive bacteria, there was a predominance of the genus *Streptococcus*, which appeared in all positive cultures in both of these groups. Among the anaerobic bacteria, *Veillonella* was identified in 73.3% of the patients in the megaesophagus group.

There was a significant statistical difference when the total microorganism concentrations of subgroups MG1, MG2, and MG3 were compared, as well as in comparisons between subgroups MG1 and MG3 and between subgroups MG2 and MG3. There was no significant statistical difference between the MG1 and MG2 subgroups (Table 2). When the control group was added to the statistical analysis, differences between the control group and the MG2 subgroup and the control group and the MG3 subgroup were found (Table 2).

In a comparison between megaesophagus subgroups, specifically for aerobic gram-positive organisms, a difference between MG1 and MG3 was verified. When the control group was added to the statistical analysis, a statistical difference was noted between the control group and MG2 and also between the control group and MG3. The same evaluation was carried out for anaerobic bacteria, but no statistical difference between subgroups was observed. There was, however, a statistical difference between the control group and the MG3 subgroup (Fig. 1). For *Streptococcus* statistical differences were found between MG1 and MG3, between the control group and MG2, and between the control group and MG3. In the case of *Veillonella*, a statistical difference between the control group and the megaesophagus group was observed (see Table 2).

DISCUSSION

Patients with Chagas' disease develop digestive manifestations of luminal stasis and bacterial overgrowth, as has been demonstrated in segments of intestine from patients with megaesophagus[22] and megacolon[23]; however, until now, the alterations in eosphageal microbiata had not been studied.

Table 1. Frequency and concentration of microorganisms in control and megaesophagus groups

	Control group		Megaesophagus group	
Organism	Frequency (%)	Concentration (cfu/ml)	Frequency (%)	Concentration (cfu/ml)
Streptococcus	40	10^1	93	10^1 to 10^5
Staphylococcus	20	10^2	46	10^1 to 10^5
Corynebacterium	10	10^2	53	10^1 to 10^4
Enterococcus	0	0	33	10^2 to 10^5
Klebsiella	0	0	7	10^1
Veillonella	0	0	73	10 to 10^5
Lactobacillus	10	10^2	27	10^1 to 10^4
Peptococcus	10	10^1	4.0	10^1 to 10^4
Peptostreptococcus	0	0	33	10^1 to 10^2
Candida	0	0	13	10^3 to 10^4

Table 2. Multiple comparisons between concentrations (in absolute numbers) of microorganisms in groups and subgroups

Group	No.	Mean concentration (cfu/ml)				
		T[a]	G+[b]	A[c]	St[d]	Ve[e]
Control	10	16.0	5,0	20.33	4.0	0
MG1	5	308.182	290.0	334.615	242.0	204.0
MG2	5	1766.66	1500.0	2012.5	2440.0	8.0
MG3	5	26114.09	47900.0	11117.5	44020.0	20240.0
MG (MG1+MG2+MG3)	15	—	—	—	—	6817.33

a = total concentration; b = gram positive aerobic; c = anaerobic; d = *Streptococcus* sp. ; e = *Veillonella* sp.; CG = control group; MG1 = megaesophagus grade I; MG2 = megaesophagus grade II; MG3 = megaesophagus grade III; MG = megaesophagus group.

Lau et al.[9] and Finlay et al.[10] studied the esophageal microbiota of patients with esophageal neoplasms, with regard to the serious infectious complications (mediastinitis) that occurred when these patients were undergoing surgical procedures or endoscopy. They found a wide variety of bacteria with a predominance of gram-positive aerobic and anaerobic bacteria. Among gram-positive aerobic bacteria, *Streptococcus* was the most common and was identified in 100% of the patients.

Patients with megaesophagus also develop severe stasis and, often, are subject to infectious complications related to surgical or endoscopic procedures.[24] Borotto et al.[14] reported a risk of esophageal perforation that varied from 1.4% to 6% during forced dilation of the cardia, but according to Vaezi and Richter[25] this risk does not exceed 2.5% if a specific type of dilator (Rigiflex) is used. The severity is quite varied, ranging from the development of transitory bacteremia and small abscesses, which can be treated clinically once the patient is stable, to larger perforations, which may lead to the development of serious septic conditions that demand surgical treatment.[26] There are few reports in the literature regarding the incidence of esophageal perforation during surgical treatment of megaesophagus. However, this is a constant preoccupation among surgeons on several medical services, who routinely perform an esophageal wash with saline solution preoperatively, or administer oral antibiotics in an attempt to decrease the contamination in the esophageal lumen.[5] In those patients who have complications, adequate broad-spectrum antibiotic therapy is fundamental to therapeutic success.

In an attempt to acquire more information on the microbiota of the normal esophagus, Gagliardi et al.[27] studied the microbiota that were present in the esophageal wash of 30 patients without esophageal disease. Cultures were positive in 66.6% of their patients with a predominance of gram-positive aerobic bacteria, especially *Streptococcus*, which was found in 100% of the oropharynx cultures collected from 10 patients concomitantly. We used a similar model of collection in our study, with the difference being that the samples were collected before the endoscopy procedure, thereby avoiding the risk of esophageal contamination from microorganisms in the oropharynx during the introduction of the equipment, or even from microorganisms in the stomach during withdrawal. We believe that the subsequent difference in the percentage of positive bacterial cultures between our cases and those of Gagliardi et al. (40% vs. 66%) was due to the collection methods. We also believe that the endotracheal tube is essential in order to protect the Levine tube and to avoid contamination of the specimens, because we have performed a pilot study on microbiota of the normal esophagus with a polyvinyl tube without any protection and found almost 100% of positive cultures contained higher concentrations of microorganisms.

In 10 patients in the control group, we took samples from the mouth. There was a correlation between the bacteria found in the esophagus and bacteria found in the mouth, although in the latter a larger variety of microorganisms were found.

Analyzing these studies together, it is clear that microbiota found in normal esophageal contents are of the transitory type and consist of microorganisms in the oropharynx that are swallowed with the saliva. When stasis becomes a factor (neoplasm or achalasia), a proliferation of these microorganisms ensues, and the putrefaction process of stagnated victuals creates a propitious environment, with a low oxygen content for the growth of anaerobic bacteria with a predominance in patients with megaesophagus consisting of *Veillonella* (strict anaerobic).

It was also observed that there is an increase in the concentration of microorganisms in the more advanced phases of megaesophagus (mostly grade III), where dilation and therefore stasis are more evident. Despite the lack of a statistically significant difference in a comparison of concentrations of anaerobic bacteria among MG1, MG2, and MG3 subgroups, we believe that the concentration of microorganisms in the MG3 subgroup is larger than in MG2 and

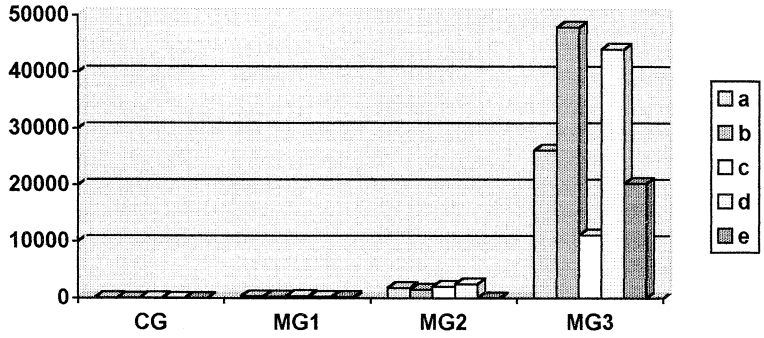

Fig. 1. CG = control group; MG1 = megaesophagus grade I; MG2 = megaesophagus grade II; MG3 = megaesophagus grade III. a = total concentration; b = gram positive aerobic; c = anaerobic; d = *Streptococcus* sp.; e = *Veilonella* sp. a: MG1 vs MG3; MG2 vs MG3; CG vs MG2; CG vs MG3. b: MG1 vs MG3; CG vs MG2; CG vs MG3. c: CG vs MG3. d: MG1 vs MG3; CG vs MG2; CG vs MG3. e: CG vs MG. $P < 0.05$.

MG1, because the absolute value of the mean posts was close to the minimum significant difference. In our experience, chagastic megaesophagus is a progressive disease and dilation usually follows the impairment of esophageal clearance. Thus we believe that the bacterial content remains stable at a given stage but increases with the degree of dilation.

Finlay et al.[10] performed antibiotic testing on all bacteria isolated from biopsy cultures of the mucosa in 12 patients with esophageal neoplasms, and found that 100% of the anaerobic bacteria were sensitive to metronidazole. The results of cultures of the aspirate from patients with megaesophagus were rather similar, with a predominance of aerobic gram-positive bacteria, mostly *Streptococcus* and *Staphylococcus* and anaerobic bacteria, with a predominance of *Veillonella*. In only one case was an aerobic gram-negative bacteria identified (*Klebsiella*). The use of antibiotics in cases of infectious complications must be focused on the more frequently occurring microorganisms, emphasizing the importance of coverage for anaerobic bacteria and therefore the use of metronidazole.

Recurring respiratory infections are another complication that affects patients with megaesophagus because of the repeated microaspiration of stagnated liquid. The incidence of aspiration pneumonia in patients with idiopathic achalasia is reported to vary from 10% to 24%. In fact, Black reported a 46% incidence of various respiratory symptoms in more than 500 patients. Camara et al.,[11] in autopsy studies, reported a 34% incidence of pneumonia and a 36% incidence of tuberculosis. These findings were corroborated by Howard et al.,[28] who reported a high incidence of atypical mycobacteriosis, particularly *Mycobacterium fortuitum*. The rapid growth of mycobacterium, which is resistant to most antibiotics, occurs as a result of its development in a greasy liquid medium secondary to the aspiration of fat microparticles in suspension in patients with achalasia. This oil, which is clarified with greater difficulty than other substances, impedes bacteria phagocytosis favoring infection.[1]

We believe that microorganisms in suspension in the stasis liquid are responsible for the development of respiratory infections with varying degrees of severity because of aspirative phenomena that can occur in the patients during regurgitation that is facilitated by decubitus; we also believe that antibiotic treatment must be directed toward the most frequently occurring microorganism. However, it is necessary to emphasize that often there are coexisting factors that cause changes in the microbiota in the mouth and oropharynx, and therefore produce the microbiota responsible for aspiration pneumonia. Such factors include prolonged hospitalization, chronic alcoholism, diabetes, and SNE's used for feeding.[29] It is important to note that the chronic malnutrition and immunosuppression that affects these patients contributes a great deal to the severity of this condition.[30] This could explain the high incidence of pulmonary infections from mycobacterium, facilitated by the aspiration of fat particles in suspension. In our study, no mycobacterium was identified on microscopic examination; despite this, no directed culture was performed.

Another aspect that has been thoroughly studied in megaesophagus is its relationship to esophageal carcinoma. The prevalence of squamous cell carcinoma in patients with chagasic esophageal disease varies from 2.0% to 8.6%, and in our population the prevalence was approximately 2.8%; the chance of developing carcinoma is 33 times greater than in the general population. Diagnosis of squamous cell carcinoma is usually delayed in patients with chronic dysphagia; often it is recognized only in the advanced stages.[20,31,32]

According to Loviscek et al.,[17] the pathophysiologic explanation would be chronic esophagitis due to stasis and bacterial overgrowth, which predisposes patients to the appearance of epithelial dysplasia and cancer. After performing histologic mapping of the esophageal mucosa in patients with megaesophagus

and cancer who were undergoing esophaogectomy, Yamamuro[20] concluded that the cancer could be multifocal and the mucosa considered as having a propensity for malignancy. But the relationship between microbiota and cancer remains open to question.

Hill[33] described bacterial production of carcinogens and promoters, not only in the digestive tract, but also in the urinary tract and genital area. Among them are the N-nitrous compounds, the formation of which was described by Calmels et al.[34–36] as the participation of the bacterial enzyme nitrate reductase. Its carcinogenic action in the esophagus has already been demonstrated in several experimental studies.[37, 38] Through clinical studies, several investigators[39–41] demonstrated the association between the changes in intra-gastric microbiota after prolonged use of blockers of acid secretion and the local production of N-nitrous compounds. In fact, Guadagni et al.,[42] studying patients who had a gastrectomy, concluded that hypochlorhydria, with consequent growth of the microbiota producer of nitrate and the formation of N-nitrous compounds in the gastric lumen, would act with synergism in carcinogenesis of the gastric stump. Using the same reasoning to study the pathophysiology of adenocarcinoma of the distal esophagus, Fein et al.[43] demonstrated in an experimental model of esophageal carcinogenesis the appearance of microbiota that were able to produce carcinogenic factors.

Despite the fact that this was not the initial objective of this study, we noted that the bacteria that appeared more frequently in cultures from patients in the megaesophagus group have the known capacity to metabolize nitrates and could therefore be involved in the process of endogenous production of nitrosoamines and, consequently, of carcinogenesis.[44] In this way it has opened up a wide field of research to explore the pathophysiology of esophageal cancer in patients with megaesophagus or idiopathic achalasia.

CONCLUSION

On the basis of our findings it can be concluded that patients without esophageal disease have a transitory microbiota consisting mostly of aerobic gram-positive bacteria from the oral cavity. However, patients with megaesophagus present with a wide variety of microbiota, constituted mainly of aerobic gram-positive and anaerobic bacteria in concentrations that correlate with the degree of esophageal dilation.

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Outcome of Laparoscopic Antireflux Surgery in Patients With Nonerosive Reflux Disease

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As many as 50% of patients with gastroesophageal reflux disease (GERD) have no endoscopic evidence of esophagitis (EGD negative). Laparoscopic antireflux surgery (LARS) provides effective symptomatic and endoscopic healing in patients with erosive GERD (EGD positive). The surgical outcome of patients undergoing LARS for EGD-negative GERD has not received wide attention. The objective of this study was to compare surgical outcomes between EGD-negative and EGD-positive patients. During the period from June 1996 to September 1998, all patients undergoing LARS for persistent GERD symptoms despite medical therapy, who were EGD-negative, were invited to respond to a questionnaire regarding their clinical status before and after LARS. To perform a comparative analysis, the same questions were posed to a randomly selected equal number of EGD-positive patients who underwent surgery during the same study period. LARS was performed in 255 patients during the study period; 59 patients (23%) had EGD-negative GERD, and 148 (58%) were EGD-positive. Forty-eight patients (19%) did not meet the entry criteria and were excluded from analysis. LARS provided effective symptomatic relief in patients with EGD-negative and EGD-positive GERD. There were no significant differences in patient satisfaction or symptom improvement between the two groups ($P = 0.82$). The surgical outcome of EGD-negative patients is similar to the outcome for patients with erosive esophagitis. LARS is a valuable treatment option for patients with persistent GERD symptoms regardless of the endoscopic appearance of the esophageal mucosa. (J GASTROINTEST SURG 2002;6:730–737.)

KEY WORDS: Gastroesophageal reflux, laparoscopic antireflux surgery, nonerosive reflux disease, outcomes

Gastroesophageal reflux disease (GERD) is a common disorder in American and European populations. It is estimated that approximately 40% of the United States population have symptomatic heartburn once a month, 14% have symptoms weekly, and 7% daily.[1–3] As many as 50% of patients have severe GERD symptoms but show no evidence of esophagitis on endoscopy nor do they suffer from nonerosive reflux disease (NERD).[4–6] With the advent of 24-hour pH testing, the spectrum of patients with these symptoms has been expanded. Some patients have symptoms but no endoscopic findings, yet pH parameters are abnormal. The lack of endoscopic findings in some of these patients may not be well understood or may be related to the effect of antisecretory medications. Despite the apparent healing effect of medications on the esophageal mucosa, many of these patients continue to be symptomatic. On the other hand, patients may have normal acid contact time but significant correlation of symptoms with episodes of reflux or a lower threshold for sensory perception in the esophagus.[7] Terms such as "irritable esophagus" and "acid-sensitive esophagus" have been recently used to refer to these patients.[7–10] There remains a group of patients that defies definition; symptoms are present in these patients but neither endoscopy nor pH studies correlate with those symptoms. These subjects most likely do not have GERD because therapeutic trials frequently fail to produce symptomatic relief.

Laparoscopic antireflux surgery (LARS) provides effective symptomatic and endoscopic healing in patients

Presented in abstract form at the Annual Meeting of the American Gastroenterology Association, Orlando, Florida, May 15, 1999.
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 Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00042-2

with erosive GERD.[11–13] Previous studies suggest that patients with NERD have a less than ideal response to medical treatment with H_2 receptor antagonists (ranitidine) or proton pump inhibitors when compared to those who have erosive disease.[14,15] In addition, physicians are more comfortable referring subjects for antireflux surgery with persistent erosive disease. Less information is available regarding the surgical outcome of patients who have persistent GERD symptoms but NERD on endoscopy. The purpose of our study was to examine our experience with the outcome of LARS in patients believed to have GERD (documented by pH testing) but without endoscopic findings of esophagitis (EGD negative or NERD) when compared with a similar cohort of patients with GERD but who had erosive disease (EGD positive).

METHODS

Patient Population

We searched our computerized records for all patients undergoing LARS during the period from June 1996 to September 1998 at our center. Consecutive patients undergoing LARS for persistent GERD despite medical therapy were included in the study. Patients with NERD were defined as having no visible mucosal break on endoscopy, or EGD negative. This group became the study population. To perform a comparative analysis, an equal number of patients with erosive esophagitis (any mucosal break, single or confluent, or EGD positive) were included in the study. These patients were randomly selected according to the number of order of surgery during the same study period. The study was approved by the institutional review board of the Mayo Clinic.

Preoperative data, including demographics, EGD results, esophageal motility studies, 24-hour pH monitoring, and postoperative follow-up time, were analyzed. Patients diagnosed with esophageal stricture, Schatzki's ring, a hiatal hernia $\geq$5 cm, or para-esophageal hernia were excluded from the study.

24-Hour Ambulatory pH Testing

24-hour pH monitoring was performed as previously reported.[16] GERD was defined as the percentage of time that the pH was <4 during the upright period, supine period, and during the total time. A DeMeester score greater than 14.8 indicates abnormal acid exposure at the ninety-fifth percentile.[16,17] Patients taking acid-reducing medications were asked to discontinue their use (proton pump inhibitors at least 7 days before testing and H_2 receptor antagonists 2 days prior to testing).

Questionnaire

All patients were contacted and interviewed postoperatively to evaluate their clinical outcomes. We used a slightly modified validated questionnaire to assess their clinical status before and after LARS.[18] The patients were not aware of the purpose of the study or the hypothesis.

The survey consisted of six questions evaluating satisfaction with the surgical procedure and with the patient's decision to have surgery. Satisfaction with the procedure was rated as follows: very satisfied, satisfied, acceptable, or not acceptable. Preoperative and postoperative GERD symptoms (heartburn, regurgitation, dysphagia, chest pain, and cough) were rated on the basis of five different grades of severity (none, minimal, mild, significant, and severe). The need for postoperative dilatation was also taken into consideration. Overall well-being before and after surgery was investigated using a scoring system ranging from 1 to 10 (1 = poor, 5 = moderate, 10 = excellent).

Statistical Analysis

Preoperative and postoperative symptoms were compared using the paired *t* test or Wilcoxon test; surgical outcomes in the two groups of patients were compared using the unpaired *t* test or chi-square test. A P value $\leq$0.05 was regarded as statistically significant.

RESULTS

During the study period, 255 patients underwent LARS at our center. Fifty-nine of the patients in this cohort (23%) had NERD. A total of 148 patients (58%) had erosive esophagitis. Forty-eight subjects (19%) were excluded from the study (esophageal stricture, Schatzki's ring, large hiatal hernia, or paraesophageal hernia).

Forty-two (71%) of 59 patients with NERD were available for interview, and 43 randomly selected EGD patients who answered the questionnaire served as a control group. Before patients were referred for LARS because of persistent GERD symptoms, 40 (95%) of 42 EGD-negative patients were taking acid suppressive medication; 36 (86%) were receiving proton pump inhibitors (primarily omeprazole) (20 to 60 mg), and four patients (10%) were taking ranitidine (600 to 1200 mg daily). 24-Hour ambulatory esophageal pH testing was done before surgery in 41 (98%) of 42 EGD-negative patients (one patient could not tolerate the pH probe). pH testing was abnormal in 36 (87.8%) of 41 of these patients. In five patients the diagnosis of GERD was

based on clinical history and symptomatic response to acid suppressive medication (2 of these subjects refused to stop taking acid suppressive agents, one patient could not tolerate the probe, and in the remaining two patients the requesting physician ordered the pH study on therapy). Thirty-eight (88%) of 43 EGD-positive patients had 24-hour ambulatory esophageal pH monitoring (in 5 patients no pH testing was done or the patients declined the test). Thirty-six (94.7%) of 38 had abnormal pH test results. The results of pH testing, manometry, and demographics are shown in Table 1. The only significant difference between the two groups was the DeMeester score, which was higher in the EGD-positive subjects. The percentage of time that the pH $\leq$ 4 in the upright position also showed a trend that nearly reached statistical significance.

Figs. 1 and 2 summarize the results of symptom scores before and after surgery in patients with EGD-negative and EGD-positive disease, respectively. LARS induced a significant symptomatic improvement in all of the symptoms evaluated. The only exception was dysphagia, which tended to occur more often after surgery in EGD-negative patients ($P = 0.06$).

Fig. 3 compares the symptomatic improvement noted between EGD-negative and EGD-positive patients. For the typical reflux symptoms of heartburn and regurgitation, no significant differences were noted. Cough was also equally improved in both groups. However, chest pain and dysphagia scores were significantly better in patients with EGD-positive GERD. EGD-negative patients had a more severe dysphagia score than EGD–positive patients after LARS ($P = 0.004$). Consequently, esophageal dilations were performed more often in these patients (38%) than in those who were EGD positive (14%).

Fig. 4 shows the mean scores for well-being before and after LARS in EGD-negative and EGD-positive patients. Both groups experienced a significant improvement in well-being after LARS ($P = 0.0001$). No significant differences were noted between the two groups (before LARS $P = 0.86$; after LARS $P = 0.74$). Satisfaction rate for EGD-negative patients was 90% and for EGD-positive patients 91% (data not shown on the graph). No significant differences were observed between the two groups ($P = 0.82$).

Table 1. Demographics, mean follow-up, pH results, and manometric findings

	EGD− (n = 42)	EGD+ (n = 43)	*P* value
Male:female ratio	1:1.7	1:1.2	0.9
Mean age (yr) (range)	60 (29–80 yr)	59 (30–77 yr)	0.6
Mean follow-up (yr) (range)	1.5 (4–30 mo)	0.9 (1–26 mo)	0.5
pH testing			
Mean DeMeester score	31.1 ± 18.7 (n = 30)	43.6 ± 47.8 (n = 31)	<0.01
Mean % time pH <4	9.5 ± 4.2	9 ± 16.7	0.1
Mean % time upright	7.2 ± 4.8	10 ± 13.7	0.07
Mean % time supine	9.7 ± 8.6	10.2 ± 23.5	0.4
Manometry			
Mean LESP (mm Hg)	10.4 ± 7.2	10.2 ± 6.2	0.4
Motility disorder (NEMD)	(8 patients)	(11 patients)	

LESP = lower esophageal sphincter pressure; NEMD = nonspecific esophageal motility disorder.

DISCUSSION

Endoscopy negative GERD occurs in 32% to 50% of patients evaluated for symptoms of reflux.[4–6] Patients who have EGD-negative GERD cannot be distinguished clinically from patients with erosive disease.[8] Symptoms suggestive of GERD correlate poorly with the presence or severity of esophagitis.[19–21] Surgical treatment of GERD is frequently prescribed for patients with persistent symptomatic disease coupled with objective endoscopic evidence of erosive disease. Less information is available about the surgical outcome of patients with persistent symptoms despite medical therapy without obvious erosive disease on endoscopy.

This study found that 23% of our patient population with symptomatic GERD referred for LARS had no evidence of esophagitis. Thus the prevalence of EGD-negative patients in our series is lower than that reported by other investigators.[4–6] The lower rates of nonerosive disease noted in our population may be explained on the basis of a referral or selection bias. Physicians are more comfortable referring for surgery those patients with erosive disease.[11,22] Indeed, the majority of patients undergoing surgery at our center had esophagitis that was grade II or higher. Medical treatment of erosive GERD results in control of symptoms and healing of esophagitis in 80% to 95% of the patients.[23–25] Surgical treatment (laparoscopic or open) induces symptomatic relief and healing of esophagitis in 90% of the patients,[11,12,26] and also in patients with complicated GERD.[27,28] Excellent outcome of surgery for these patients has been previously reported by several investigators.[29–31]

In contrast to the excellent results obtained with medical and surgical trials in patients with erosive

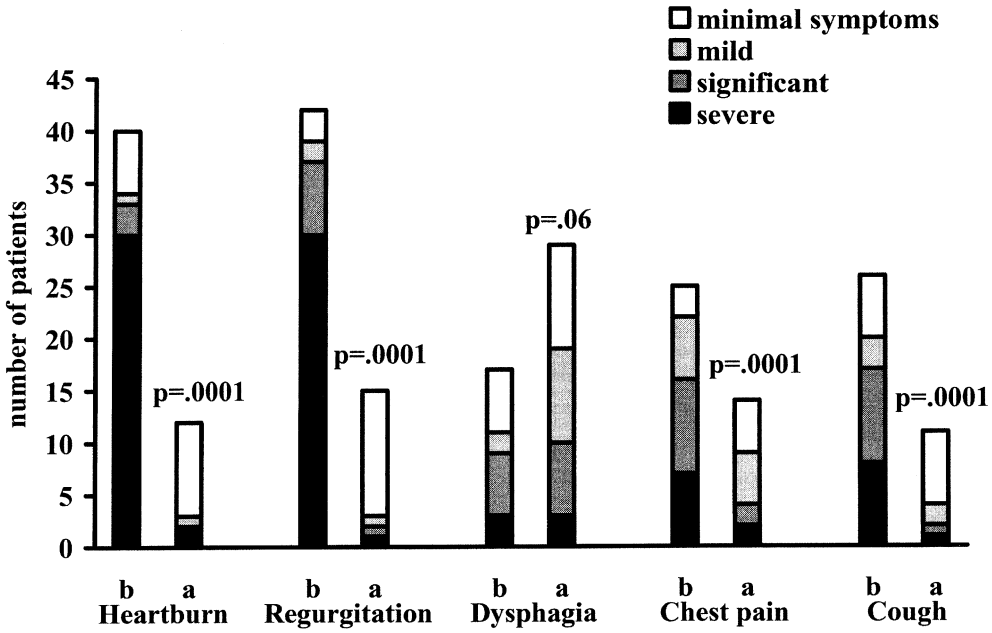

Fig. 1. Symptom scores before and after LARS for EGD-negative patients (n = 42). LARS = lapraroscopic antireflux surgery. b = before LARS; a = after LARS.

disease, the outcome of medical treatment of patients with EGD-negative GERD has not been as consistent. In a study of 283 patients with GERD (106 [37%] with normal endoscopy), subjects were randomized to ranitidine (150 mg twice a day) or placebo. Significantly greater symptomatic improvement was noted in the endoscopically abnormal group in comparison to the EGD-negative group.[15] An open multicenter European study involving 180 patients with EGD-negative GERD who were treated with famotidine (20 mg twice a day) showed that only 53% of patients achieved complete relief of

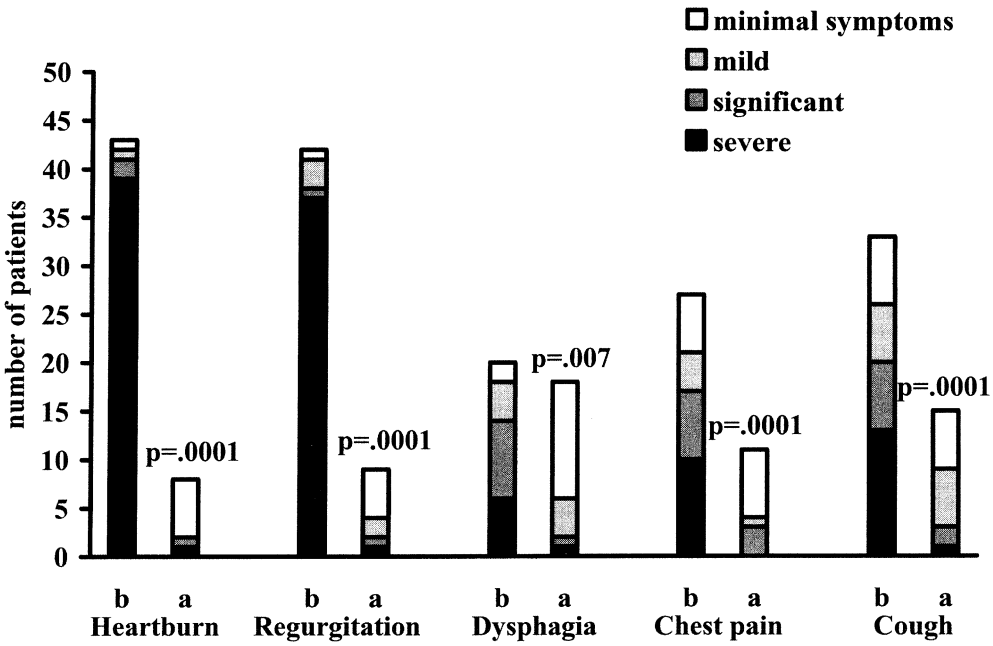

Fig. 2. Symptom scores before and after LARS for EGD-positive patients (n = 43). b = before LARS; a = after LARS.

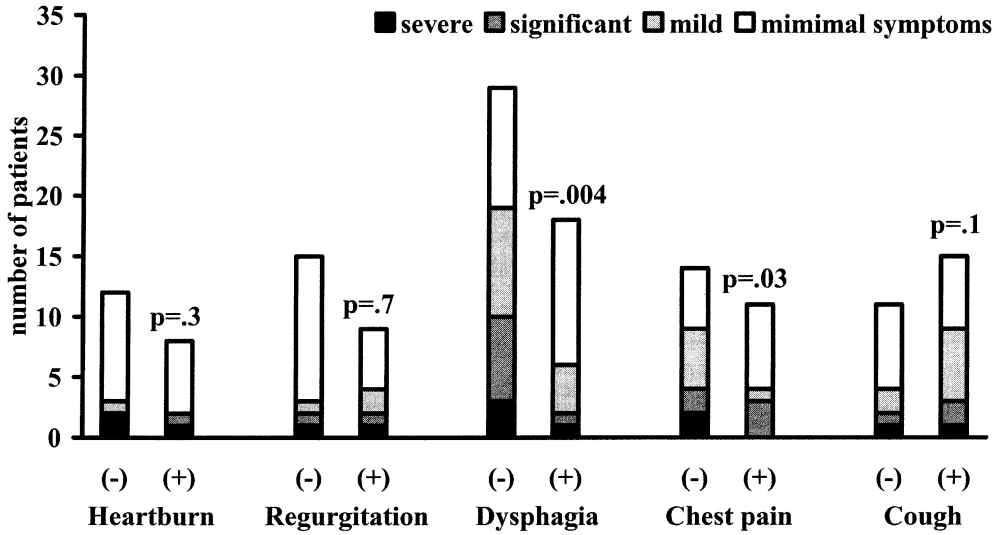

Fig. 3. Comparison of symptom scores between EGD-negative and EGD-positive patients after LARS. − = EGD-negative patients; + = EGD-positive patients.

symptoms.[32] A multicenter study of more than 500 patients from Australia, Holland, Norway, and England compared the efficacy of omeprazole (10 or 20 mg daily), to placebo in patients with erosive disease versus those with EGD-negative disease over a 4-week period. Significant therapeutic differences were noted between the study groups; among those treated with 20 mg per day of omeprazole, 48% of the patients with erosive disease showed improvement versus 29% of those with EGD-negative disease. The outcome for those on a lower dose of omeprazole (10 mg) was 31% and 27%, respectively. During clinical follow-up to 6 months, relapse developed more commonly in the EGD-negative group (90%) versus those with erosive disease (75%).[14] These differences in therapeutic outcome between EGD-positive and EGD-negative subjects prompted us to analyze our surgical experience in patients with GERD undergoing LARS stratified according to their endoscopic findings.

This study found that EGD-negative patients have the same significant relief of heartburn, regurgitation, cough symptoms, satisfaction with the surgical procedure, and well-being after surgery as their

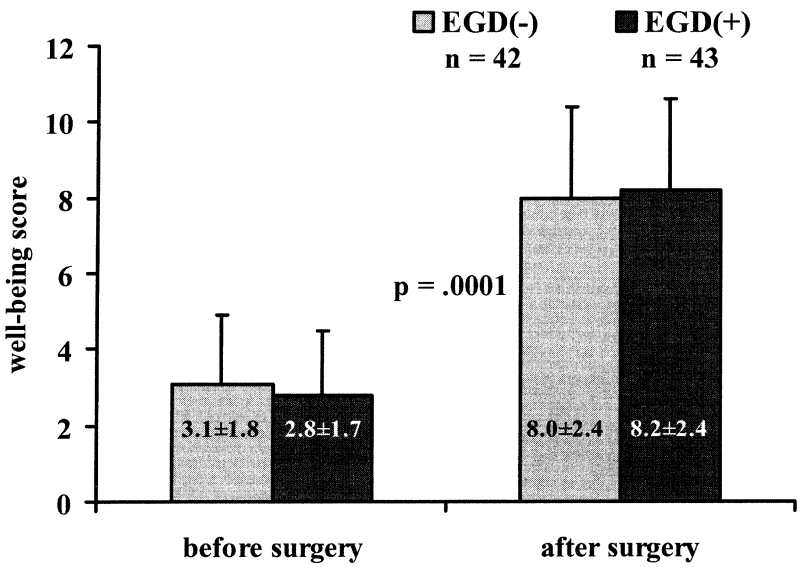

Fig. 4. Well-being scores before and after LARS in EGD-negative and EGD-positive patients.

EGD-positive counterparts. Our results indicate that surgery provides effective symptomatic control for patients with GERD regardless of the endoscopic appearance. These findings confirm the observations of Watson et al.[33] They compared the surgical outcomes in 59 patients without esophagitis and 148 patients with esophagitis. They found no significant differences in clinical outcome following LARS. This beneficial effect achieved by surgery in comparison with medical treatment may be due to the prevention of regurgitation of both acid and other non-acid-related compounds. Campos et al.[34] completed a multivariate analysis of factors predicting outcome after laparoscopic surgery for GERD. They noted that a successful surgical outcome is more dependent on the correct identification of the disease than on its severity (erosive disease or the magnitude of reflux on pH testing). Our study confirms the observations of Campos et al.[34] Indeed, in their study an abnormal 24-hour pH score was the single best predictor of outcome. The majority of our patients with EGD-negative (GERD) (88%) had an abnormal pH score.

Recent studies suggest that patients without esophagitis have an abnormal perception of acid in the esophagus (hypersensitive esophagus). These patients may even have normal pH scores but still show a significant association between their symptoms and the episodes of reflux.[35–40] It is also possible that nonacidic components in the refluxate may be responsible for symptoms in these patients.[10] Several investigators have raised the possibility that bile reflux may play an important role in certain patients with GERD.[36–40] An additional pathophysiologic feature of this disease might be an increased sensitivity of the mechanoreceptors in the esophagus.[10,41] Stress may also play a role in the genesis of symptoms in patients with EGD-negative esophagitis. Bradley et al.[42] found that patients with GERD who are chronically anxious and exposed to prolonged periods of stress may perceive low-intensity esophageal stimuli as painful reflux symptoms. The amplitude of esophageal contractions increases during psychological stress and might be a pain-producing mechanism.[43] Our study did not address this type of patient or explore the additional role of these mechanisms in the study outcome. However, based on the observations of Campos et al.,[34] it is unlikely that patients with a hypersensitive esophagus will have a favorable surgical outcome. These investigators reported that patients with normal pH test scores and atypical GERD symptoms have a less favorable surgical outcome than those with abnormal pH scores.

It is not clear why patients with EGD-negative GERD had a higher prevalence of postoperative chest pain and dysphagia and thus an increased rate of need for esophageal dilation. We speculate that the wrap at the lower esophageal sphincter is perceived by these patients as an enhanced resistance to flow by the same mechanism that contributes to explain the increased visceral perception in these patients.[10,41,44] The long-term follow-up of patients with postoperative dysphagia requires further study. Based on our previous published experience (including patients with both erosive and nonerosive disease), most patients with postoperative dysphagia require a mean of two sessions (range 1 to 5) of esophageal dilatation to resolve their dysphagia.[45]

It would be most informative to confirm the symptomatic response noted in our population by objective postoperative esophageal testing (pH, EGD, and esophageal motility). However, the retrospective nature of our study and the fact that postoperative esophageal testing is not routinely obtained in clinical practice, unless a patient fails to respond to treatment, preclude us from correlating symptom response with esophageal test results. It would also be of interest to know whether some of our patients who reported improvement were still consuming acid suppressive medications or promotilty agents. Although this information was not available during this study, data from our center indicate that as many as one third of patients undergoing LARS continue to consume acid suppressive agents postoperatively.[46] Surprisingly though, most of these patients continue to take these compounds despite reporting a successful surgical outcome.[46]

In conclusion, EGD-negative gastroesophageal reflux was shown in this study to be a prevalent disorder among patients undergoing LARS. This surgery provides effective symptomatic relief in patients with EGD-negative and EGD-positive gastroesophageal reflux. LARS is a valuable treatment option for patients with persistent gastroesophageal reflux regardless of the endoscopic appearance of the esophageal mucosa.

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APPENDIX

Questionnaire

Name: ID number:

1. Are you satisfied with the procedure?

   Very satisfied/satisfied/acceptable/not acceptable

2. Did you have the following symptoms before surgery?

State severity	None	Minimal	Mild	Significant	Severe
Heartburn					
Reflux of acid into the throat					
Dysphagia					
Chest pain					
Cough					

3. Did you have the following symptoms after surgery?

State severity	None	Minimal	Mild	Significant	Severe
Heartburn					
Reflux of acid into the throat					
Dysphagia					
Chest pain					
Cough					

4. Have you had any dilatation therapy since surgery? Yes/No
5. How was your well-being before surgery and how is your well-being now?

   Well-being before surgery: (1 = excellent; 10 = poor) 1 2 3 4 5 6 7 8 9 10

   Well-being after surgery: (1 = excellent; 10 = poor) 1 2 3 4 5 6 7 8 9 10

6. Are you satisfied with your decision to have surgery? Yes/No

Long-Term Response to Subtotal Colectomy in Colonic Inertia

G. Nicholas Verne, M.P. Hocking, R.H. Davis, R.J. Howard, M.M. Sabetai, J.R. Mathias, M.D. Schuffler, C.A. Sninsky

The purpose of this study was to determine the long-term outcome of patients who had previously undergone subtotal colectomy for severe idiopathic constipation at the University of Florida between 1983 and 1987. In addition, we aimed to determine whether preoperative motility abnormalities of the upper gastrointestinal tract are more common among those patients who have significant postoperative complications after subtotal colectomy. We evaluated 13 patients who underwent subtotal colectomy for refractory constipation between 1983 and 1987 at the University of Florida. Preoperatively, all patients exhibited a pattern consistent with colonic inertia as demonstrated by means of radiopaque markers. Each patient was asked to quantitate the pain intensity and frequency of their bowel movements before and after surgery. In seven patients an ileosigmoid anastomosis was performed, whereas in six patients an ileorectal anastomosis was used. Abdominal pain decreased after subtotal colectomy. Patients with abnormal upper gastrointestinal motility preoperatively experienced greater postoperative pain than those with normal motility regardless of the type of anastomosis. In addition, the number of postoperative surgeries was similar in those patients with abnormal upper motility compared to those with normal motility. Overall, the total number of bowel movements per week increased from 0.5 ± 0.03 preoperatively to 15 ± 4.5 ($P < 0.007$) postoperatively. The results of our study suggest that patients with isolated colonic inertia have a better long-term outcome from subtotal colectomy than patients with additional upper gastrointestinal motility abnormalities associated with their colonic inertia. (J GASTROINTEST SURG 2002;6:738–744)

KEY WORDS: Constipation, colectomy, colonic inertia, small bowel motility, myenteric plexus

Constipation is a common complaint that affects up to 34% of the general population.[1] The severity and duration of symptoms are often varied with a subgroup of patients who are refractory to all medical therapy. Motility disturbances, drugs, metabolic and endocrine abnormalities, malignancies, pelvic outlet obstruction, and a host of other abnormalities may cause constipation and should be entertained in the initial diagnostic evaluation.[2–6] In addition to fiber supplementation, treatment usually includes osmotic laxatives, misoprostil, colonic lavage solutions (i.e., Colyte), and prokinetic agents.[7] Other agents such as colchicine have also been shown to be effective.[8]

A subgroup of patients with severe idiopathic constipation fail to respond to these initial treatment measures. These are often young women who have significant abdominal discomfort that interferes with their social activities and ability to work.[9] Some patients may eventually require subtotal colectomy for relief of their obstructive symptoms.[10–12] Subtotal colectomy is usually effective for severe constipation; however, some patients may have significant postoperative complications.[13–17]

The purpose of this study was to determine the long-term outcome of patients who had extensive preoperative motility testing and underwent subtotal colectomy for severe idiopathic constipation at the University of Florida between 1983 and 1987. We chose to study patients who had surgery between 1983 and 1987 as they underwent extensive preoperative motility testing; silver staining on the myenteric plexus of the resected colon was performed in all of them. In addition, we aimed to determine whether preoperative motility abnormalities of the upper gas-

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Published by Elsevier Science Inc.

1091-255X/02/$—see front matter
PII: S1091-255X(02)00022-7

trointestinal tract were more common among those patients with significant postoperative abdominal pain and complications after subtotal colectomy. Finally, we compared postoperative results in those patients who underwent an ileosigmoid anastomosis vs. those who had an ileorectal anastomosis.

MATERIAL AND METHODS

We retrospectively evaluated 13 patients with a history of severe idiopathic constipation who had previously undergone subtotal colectomy between 1983 and 1987 at the University of Florida based on incapacitating symptoms of constipation, abdominal pain, and bloating. The studies were approved by the University of Florida Institutional Review Board and the Human Use Committee. Prior to colectomy, an extensive workup was performed to exclude diabetes mellitus, hypothyroidism, collagen vascular diseases, and systemic neurologic diseases. All patients underwent antroduodenal manometry before surgery to evaluate for motility disorders in the upper gastrointestinal tract. Patients were admitted to the Clinical Research Center after an overnight fast. Antroduodenal manometry was performed after an overnight fast. Gastroduodenal motor activity was measured with a semiconductor recording probe (Millar Instruments, Houston, Texas) that was placed into the small bowel perorally, under fluoroscopic guidance, such that the most proximal three ports (5 cm apart) were positioned in the antrum and the distal three ports (10 cm apart) were located in the duodenum with the most distal lead at the ligament of Treitz. Probe recordings were obtained for 24 hours.

Colonic transit was measured in all patients by asking them to swallow a capsule with 24 radiopaque rings (Sitz marker). Normal colonic transit was defined by passage of at least 80% of the markers within 5 days and all of the markers by day 7.[18–20] Slow-transit constipation or colonic inertia was defined by retention of six or more markers throughout the left colon, or in both the right and left colon on day 5. A predominance of markers in the rectosigmoid colon was considered suggestive of pelvic outlet dysfunction.[18–20] Preoperatively all of the patients exhibited a pattern consistent with colonic inertia with radiopaque markers noted throughout the colon. Anorectal manometry and defecography were performed in all patients to exclude pelvic floor abnormalities.[2,3] After colectomy, colonic tissue was evaluated with the use of both conventional staining techniques and silver staining (courtesy of M.D.S.) to delineate myenteric plexus abnormalities.

Each patient was asked to quantitate the severity of their pain on a scale of 0 to 10 (0 = none; 10 = most severe) and the frequency of their bowel movements during an office visit immediately before surgery. The severity of pain and frequency of bowel movements were documented in the patients' medical records by the surgeon. During our follow-up study, patients were again asked to rate the severity of their pain and the frequency of their bowel movements. In addition, patients were also questioned regarding episodes of fecal incontinence and their overall satisfaction with the surgery.

Data Analysis

All results are expressed as mean ± standard error of the mean (SEM). Paired and unpaired *t* tests were used for all comparisons. The level of significance was selected as $P < 0.05$.

RESULTS

A total of 13 patients were studied, all of them women who initially developed constipation between the ages of 10 and 58 years (mean 22.9 ± 4.5 years). Preoperatively all patients had intractable constipation with a mean stool frequency of 0.5 ± 0.03 bowel movements per week. In addition, all patients reported severe abdominal pain and bloating. Most patients noted intermittent pain that was located in the midabdomen and pelvic region. None of the patients had a dilated small bowel on preoperative barium studies, and none had any radiographic evidence of small bowel air-fluid levels preoperatively to suggest chronic intestinal pseudo-obstruction. Subtotal colectomy was performed in patients between the ages of 26 and 67 years (46.2 ± 3.5 years). Seven patients underwent an ileosigmoid anastomosis, whereas six underwent an ileorectal anastomosis because of redundant sigmoid colon, as shown on a preoperative barium enema. All of the operations were performed by the same surgeon at our institution.

During the preoperative evaluation, a total of nine patients had abnormal 24-hour antroduodenal manometric findings that included abnormal propagation of activity fronts, bursts of nonpropagated phasic pressure activity, sustained incoordinated fasting pressure activity, and failure of a meal to induce a fed pattern. These findings have been previously described in patients with small bowel dysmotility and intestinal pseudo-obstruction.[21] There were no small bowel motility abnormalities present that have been previously described in patients with mechanical bowel obstruction and/or adhesion disease.[22] All patients had delayed colonic transit with a pattern consistent with

colonic inertia by radiopaque markers, without evidence of segmental colonic motility abnormalities.[20–21] All patients had normal results of anorectal manometric and defecographic studies that excluded pelvic floor dysfunction. All patients had a normal anocutaneous reflex. The rectoanal inhibitory reflex was present in all patients after a fasting rapid distention of the rectal balloon with 60 cc of air. The mean basal and maximal squeeze sphincter pressures were 88.2 ± 9.4 mm Hg and 142.4 ± 13.1 mm Hg, respectively. The mean minimal rectal sensory volumes for initial sensation and urge to defecate as measured by slow ramp rectal balloon distention were 42.9 ± 5.9 cc and 86.3 ± 7.5 cc, respectively.

Microspic examination of resected colonic tissue with the use of hematoxylin and eosin staining was abnormal in 11 patients and included melanosis coli, hyperplasia of the myenteric plexus, and focal neuronal degeneration. All 13 patients had silver-staining abnormalities of the myenteric plexus that included a decreased number of axons and argyrophilic neurons, increased variably shaped naked nuclei within the ganglia, and morphologically abnormal argyrophilic neurons, as previously described in subjects with refractory constipation[23] (Fig. 1).

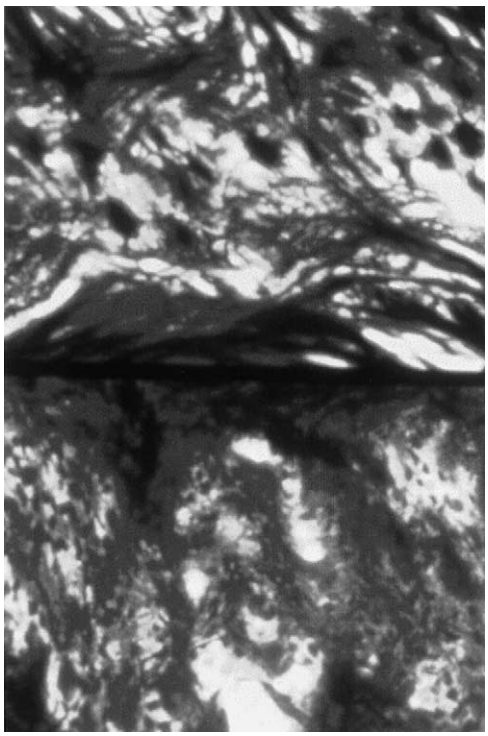

Fig. 1. Silver staining of a control colon showing normal argyrophilic neurons, processes, and nerve fibers (*top*). Silver staining of a colon from one of our patients with severe idiopathic constipation (*bottom*). Note the decreased number of argyrophilic neurons and neuronal processes (dendrites and axons).

Gastrointestinal Motility

Overall, abdominal pain scores decreased after subtotal colectomy (7.1 ± 0.8 vs. 4.8 ± 0.9) ($P < 0.05$ (Figs. 2–4). Patients with abnormal upper gastrointestinal motility preoperatively experienced higher mean postoperative pain scores (6.1 ± 1.0) than those with normal motility (2.0 ± 1.1) ($P < 0.04$) (Table 1). Overall, the mean duration of postoperative ileus was 5.2 ± 0.5 days. There was no significant difference in the number of days of postoperative ileus after colectomy in patients with normal preoperative upper gastrointestinal motility (4.5 ± 1.0) vs. those patients with abnormal motility (5.4 ± 0.6). There were more postoperative admissions after colectomy in patients with abnormal upper gastrointestinal motility (7.2 ± 2.6) than in those with normal motility (1.3 ± 0.5) ($P = 0.02$). However, the mean number of postoperative surgeries was similar in those patients with abnormal upper motility (2.4 ± 1.3) and those with normal motility (1.0 ± 0.6).

Surgical Anastomosis

Overall, the total mean number of bowel movements per week increased from 0.5 ± 0.03 preoperatively to 15 ± 4.5 ($P < 0.007$) postoperatively. Mean postoperative abdominal pain scores were similar in patients who had an ileosigmoid anastomosis (5.6 ± 1.4) and those who underwent an ileorectal anastomosis (4.0 ± 1.2) (Table 2). There was no significant difference in the mean number of bowel movements per week between those receiving an ileorectal anastomosis (18.0 ± 8.0) and those receiving an ileosigmoid anastomosis (12.4 ± 5.1). Of the five patients who had fecal incontinence postoperatively, four (80%) had undergone an ileorectal anastomosis. One patient ultimately was converted to an ileostomy because of the severity of the fecal incontinence. None of the patients developed dyschezia or evidence of obstructive defecation postoperatively. The number of postoperative admissions related to the colectomy were not significantly different in those who received an ileosigmoid anastomosis (7.6 ± 3.3) vs. those who had an ileorectal anastomosis (2.8 ± 1.5). Similarly the number of postoperative surgeries that were a result of the subtotal colectomy was not significantly different in those who had an ileosigmoid anastomosis (3.1 ± 1.6) vs. those with an ileorectal anastomosis (0.7 ± 0.3).

Most of the postoperative surgeries were done for adhesions that occurred 1 to 15 years after colectomy. None of the patients who had an ileosigmoid anastomosis required resection of the sigmoid colon.

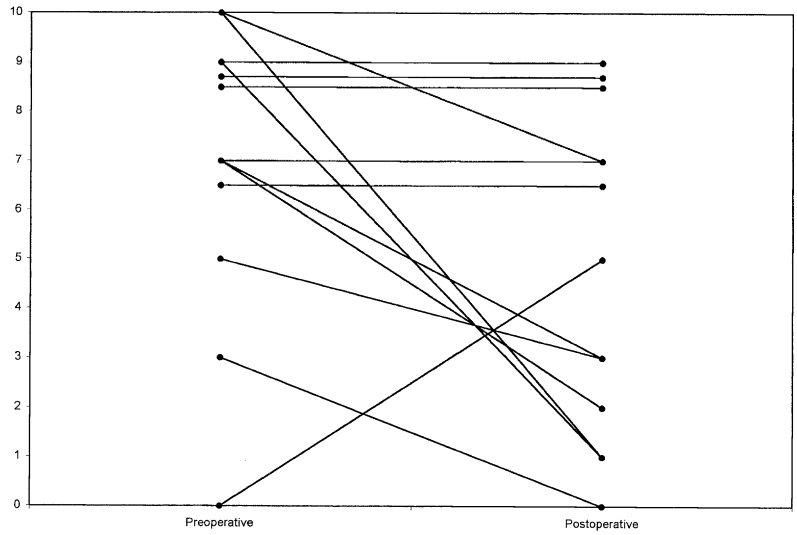

Fig. 2. Bar diagram illustrating the mean pain intensity scores preoperatively and postoperatively.

DISCUSSION

Severe idiopathic constipation is often refractory to most medical therapies. Subtotal colectomy is used to treat intractable symptoms and obstipation, and to improve the patient's quality of life. The etiology of severe idiopathic constipation is poorly understood; however, in our group of patients we demonstrated characteristic abnormalities of the myenteric plexus by means of silver staining techniques, which suggests a degenerative or developmental neurologic abnormality.[23] Some investigators using radioimmunoassays have demonstrated reduced concentrations of vasoactive intestinal polypeptide and colonic substance P in the colons of patients with idiopathic constipation.[24–27] A visceral neuropathy may also be present in these patients, as evidenced by reduced or absent neurofilaments.[28] Others have demonstrated a reduced release of acetylcholine within the colonic wall with the use of radiolabeling techniques.[29] It is not clear whether these changes are the cause or the result of the chronic constipation.

Our experience is similar to that of others who have reported that subtotal colectomy improves constipation in most patients; however, caution should be used as many patients may manifest substantial abdominal pain, obstructive symptoms, diarrhea, and fecal incontinence postoperatively.[30] Although the total mean pain scores decreased postoperatively,

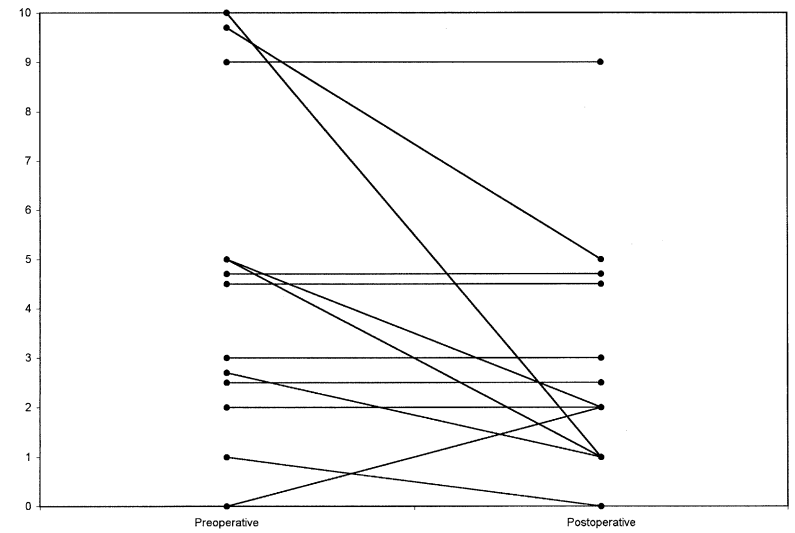

Fig. 3. Bar diagram illustrating the mean pain frequency scores preoperatively and postoperatively.

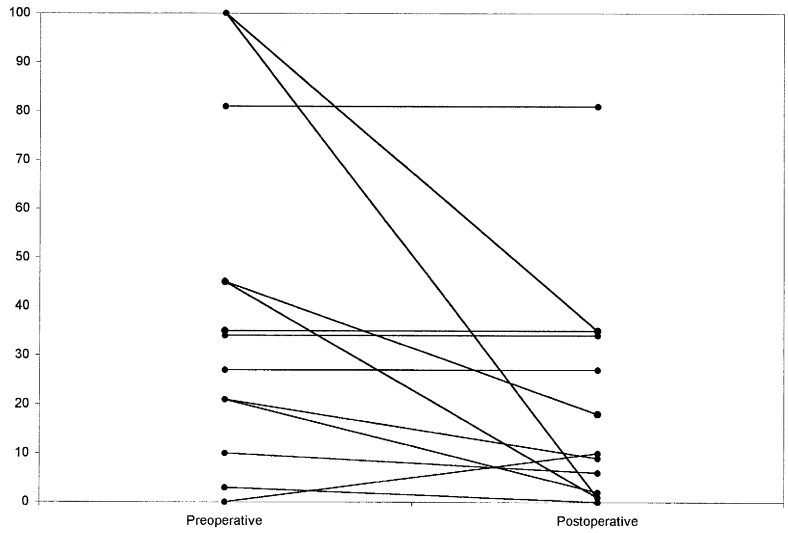

Fig. 4. Bar diagram illustrating the mean pain scores preoperatively and postoperatively.

some of our patients with motility abnormalities of the upper gastrointestinal tract did not experience an improvement of their pain. Upper gastrointestinal symptoms may persist after subtotal colectomy because of preexisting motility abnormalities of the stomach and small bowel.[31–33] Severe idiopathic constipation in some patients may be a manifestation of a more diffuse motility disorder affecting the entire gastrointestinal tract.[34–35] Detailed radiologic and manometric studies of the stomach and small bowel are important prior to subtotal colectomy.[36–37]

Some investigators have identified two distinct subgroups of patients: those who have predominantly colonic inertia and another group with generalized intestinal dysmotility, with colon predominance, who have a poor long-term response to abdominal colectomy.[38] Four of our patients (31%) had normal antroduodenal manometry and gastric emptying studies with no evidence of small bowel bacterial overgrowth preoperatively. In these patients the mean pain score postoperatively was 3.3 ± 2.3, compared with 27.4 ± 8.0 ($P = 0.08$) for the nine patients with evidence of preoperative gastric and small bowel dysmotility. Some of the postoperative pain in our subjects with antroduodenal manometric abnormalities could have been partially explained by the presence of bacterial overgrowth. The C^{14} D-xylose breath test was not performed postoperatively. In addition, the patients with normal foregut motility had a trend toward fewer postopera-

Table 1. Outcome by gastrointestinal motility

Category	Patients with normal preoperative motility (n = 4)	Patients with abnormal preoperative motility (n = 9)
Postoperative pain score	2.0 ± 1.1	6.1 ± 1.0*
Postoperative ileus (days)	4.5 ± 1.0	5.4 ± 0.6
No. of postoperative admissions	1.3 ± 0.5	7.2 ± 2.6*
No. of postoperative surgeries	1.0 ± 0.6	2.4 ± 1.3
Postoperative satisfaction (no. of patients)	3/4	8/9

Values for postoperative pain, postoperative ileus, postoperative admissions, and postoperative surgeries are the mean ± SEM.
*$P < 0.05$.

Table 2. Outcome by type of surgical anastomosis

Category	IRA	ISA
Postoperative pain scores	4.0 ± 1.2	5.6 ± 1.4
No. of postoperative bowel movements/wk	18.0 ± 8.0	12.4 ± 5.1
No. of postoperative admissions	2.8 ± 1.5	7.6 ± 3.3
No. of postoperative surgeries	0.7 ± 0.3	3.1 ± 1.6
No. of patients with fecal incontinence/total patients with IRA or ISA	4/6	1/7
No. of patients satisfied with postoperative result/total patients	4/6	7/7

IRA = ileorectal anastomosis; ISA = ileosigmoid anastomosis.
Values for postoperative pain, postoperative admissions, postoperative surgeries, and postoperative bowel movements are the mean ± SEM; $P < 0.05$.

tive admissions (1.3 ± 0.5) compared with the patients with upper tract dysmotility (7.2 ± 2.6) (P = 0.17). Of the four patients who did not believe their quality of life was improved, three had evidence of gastroparesis and manometric evidence of intestinal pseudo-obstruction on preoperative evaluation.

CONCLUSION

The results of our study suggest that patients with isolated colonic inertia may have a better long-term outcome from subtotal colectomy than patients with preoperative upper gastrointestinal dysmotility. One limitation of our study was the small number of patients who were included in our analysis. We recommend that patients presenting with severe idiopathic constipation have a gastric emptying test and antroduodenal manometry before being considered for subtotal colectomy. However, if gastric and small bowel motility abnormalities are present, subtotal colectomy can still be offered to the patient with the understanding that only the symptoms related to obstipation may be improved and that they may still have significant upper gastrointestinal tract symptoms. These results indicate that the majority of our patients with severe idiopathic constipation have long-term benefits from subtotal colectomy.

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Use of a Critical Pathway for Colon Resections

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Tremendous variation in patient care exists, both among medical centers and among individual surgeons, in the field of colon and rectal surgery. Clinical or critical pathways based on "best demonstrated practices" from the medical literature have led to improved outcomes for many disease entities. The objective of this study was to develop a pathway for elective colon and rectal resections, and then determine whether this led to any improvement in measurable outcomes. A critical pathway was developed for the care of patients undergoing elective colon and rectal surgery, by reviewing best demonstrated practices in the literature and then developing standardized order sheets, nursing flow sheets, and patient educational material. A patient satisfaction survey was also included in the evaluation process. After being informed of the positive results from the pilot study, surgeons were encouraged to use the critical pathway order sheets, patient information sheets, and flow sheets for their patients undergoing elective abdominal colon or rectal surgery. Between January 1995 and October 1998, the critical pathway was used for 263 patients, whereas for 122 patients this pathway was not used. For those patients in the critical pathway group, the hospital length of stay was shorter (5.5 vs. 8.2 days, including the day of surgery, $P = 0.001$), the time until a regular diet was tolerated was shorter (3.5 vs. 4.4 days, $P = 0.001$), the percentage of patients discharged home was greater (90% vs. 82%, $P = 0.038$), and the average hospital charges were less ($12,672 vs. $16,665, $P = 0.001$). These advantages did seem to be correlated with efforts at postoperative ambulation, but were independent of the type of postoperative pain control (patient-controlled analgesia vs. epidural analgesia). Patient satisfaction in the subset surveyed was slightly better for those in the critical pathway group than in those for whom the critical pathway was not used. Elective colon and rectal surgery appears to lend itself to uniformity of postoperative order sheets and clinical expectations. Shortened lengths of hospital stay, earlier resumption of a regular diet, and diminished hospital charges were found with the use of this critical pathway, with no diminution of patients' perceptions of satisfaction with the hospital experience. (J GASTROINTEST SURG 2002;6:745–752)

KEY WORDS: Colorectal surgery, perioperative management, clinical pathways, critical pathways

The development of critical pathways for a variety of medical and surgical conditions has been making an impact on the practicing physician for more than a decade. A critical (or clinical) pathway is defined as a sequence of events through which patients pass on their way from a state of illness (through surgery or some medical intervention) to the restoration of a desired outcome, usually wellness. The purpose of a critical pathway is to standardize the clinical practice of a group of specialists working to optimize care in a particular clinical scenario (e.g., myocardial infarction). This standardization is based on a "best demonstrated practice" model derived from the most recent literature on that particular clinical subject and is, by definition, fluid and evolving. In addition to standardizing clinical practice among physicians, critical pathways may define minimum standards for payors, define levels of cost-effectiveness, diminish process and outcome variation among physicians, and define a medicolegal "standard of care."

The benefits of a critical pathway are several. First, it makes all caregivers aware of the usual sequence of steps in the recovery from a clinical problem and defines expectation of patient progress over time. Second, it allows earlier recognition and intervention when a patient is not progressing in the usual manner. Third, it brings uniformity to orders and protocols reducing both physician and nursing errors. Finally, it allows more proactive discharge planning.

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00038-0

In comparing pathway and nonpathway approaches, a number of outcomes are generally examined including survival rates, readmission rates, lengths of stay, complications, and costs. In addition, some attempt to measure patient satisfaction has been an increasingly important factor to evaluate in recent years.

The purpose of this study was twofold: (1) to discuss the actual development of a critical pathway for colorectal resections as a process, as experienced at one institution, and (2) to evaluate the results of instituting such a critical pathway according to these outcome measures. We hypothesized that most measurable patient outcomes would improve in the presence of an established critical pathway for colon and rectal resections.

METHODS

This series comprised 385 patients who underwent elective colon resection between January 1995 and October 1998 at Northwest Hospital in Seattle. These cases were consecutive and inclusive. In 263 of these cases (68.3%), surgeons chose to use a critical pathway for patient management and monitoring. The remaining 122 patients were managed without using the critical pathway, and they were used as the control group in the series. Before the study, the critical pathway was developed by a committee that included physicians and representatives from the hospital's nursing staff, administration, care management, surgery, and research departments. An extensive review of the literature was first performed to identify best demonstrated practices for preoperative, intraoperative, and postoperative care specific to elective colon resection. Consensus on best demonstrated practices was established after a review of the literature and solicitation of opinions from all surgeons practicing colon and rectal surgery at the hospital. If more than one equally valid alternative was supported by the literature, and if no consensus could be achieved on a single alternative, then two or more equivalent options were included in the pathway. The pathway consisted of the following: standardized order sheets for preoperative and postoperative periods (Figs. 1 and 2, respectively); surgeon preference cards and instrument sets, which were standardized wherever possible; a progress note form; a patient information brochure; and a detailed patient instruction sheet at discharge. Extensive education of the hospital staff was carried out to explain the rationale for the critical pathway and the importance of its elements.

Key elements of the consensus critical pathway included the following:

1. Admission on the day of surgery after the patient had completed a mechanical bowel preparation, chosen by the surgeon, as an outpatient. In general, the sodium phosphate preparation was recommended, unless the patient had impaired renal function, in which case 1 liter of polyethylene glycol solution was used.
2. Check boxes on the pre- and postoperative order sheets for optional or equivalent choices.
3. Laboratory studies, chest radiographs, pulmonary function studies, and so forth, in accordance with American Society of Anesthesiologists (ASA) guidelines.
4. Standardization, as much as possible, of surgeon preference cards and instrument sets to facilitate nursing efficiency in the operating room and minimize costs.
5. Identification of a single operating room nurse or technician to act as a contact person in this phase of the pathway development.
6. Anesthesia consultations for input on development of the pathway, with particular attention to the use of regional anesthesia. The pathway did not, however, direct the type of anesthesia or analgesia offered to patients. This decision was generally left to the discretion of the anesthesiologist in consultation with the patient.
7. Attention to different methods of postoperative pain control, with equivalent choices available where consensus on a single practice could not be achieved. Check boxes were designed as reminders of common medical issues (steroids, glycemic control, antihypertensive therapy) that might need to be addressed in the postoperative phase.
8. The patient information brochure explained the anticipated sequence of events in lay terms for patients and their families.
9. Expected patient progress was tracked and documented. The data form consisted of a daily outline of expected patient progress in several functional categories (i.e., pain control, diet, activity), as well as space for nursing staff and physician notes to track an individual patient's progress relative to the designated pathway. Patients were discharged only after they were tolerating solid food, had adequate pain control (as judged by the patient) with oral medication alone, were able to ambulate independently for the planned discharge venue, and required no parenteral fluids or medication. No requirement for the patient to be passing flatus or stool was imposed.
10. Patients received a detailed instruction sheet on discharge that outlined the recommended

Initial Diagnosis: _____
Scheduled for: _____ on: _____
ALLERGIES: _____

☐ Code Status Form (M-409) completed.
Have patient sign op permit. Courtesy notification to Dr. _____ that pt has been admitted.

VITAL SIGNS

☑ Per unit protocol.

NUTRITION

☐ NPO *or* ☐ Clear liquids, encourage fluids. NPO after MN.

LAB/DIAGNOSTICS

☑ Obtain lab/diagnostics per Pre-Anesthesia Testing Guidelines (see protocol, "Preoperative Preparation").
In *addition* to above, obtain:

☐ CEA ☐ PT ☐ HFP (LFT's) ☐ CMP

☐ T&C _____units autologous blood. ☐ T&C _____ units PRBC's. ☐ Type & Screen ☐ Draw & Hold

☐ Other: _____

MEDICATIONs/IVs

☐ IV: Lactated Ringers at: ☐ 100cc/hr ☐ 200cc/hr. Use #18 or larger angiocath. Start IV at 1600 if patient is admitted the day before surgery.

☐ Ceftigyl 1.5 gm IV give in Pre-Surgical Area (PSA).

☐ Heparin 5000 units SQ pre-op if OK with Anesthesiologist. Give in Pre-Surgical Area (PSA).

☐ Triazolam (Halcion®) 0.125 mg PO hs prn sleeplessness; May repeat x 1.

☐ Zolpidem (Ambien®) 5 - 10 mg po q HS prn sleeplessness.

} ***PM admits***

☐ **For PM admit prep**: ☐ (Fleet PhosphoSoda®) 1 1/2 oz diluted in 4 oz clear liquid po at 1400 and 1800, plus bisocodyl 10 mg (Dulcolax®) 4 tabs po at 1800.

☐ Routine meds as taken at home: _____

_____

_____

PREPARATION

☐ IS instruction/pre-admit respiratory teaching.

☐ Page WOC (ET) Nurse for pre-op consultation.

☐ Povidone-iodine (Betadine®) shower evening before and morning of surgery (for PM admits).

OTHER

☐ _____

☐ _____

☐ _____

_____ _____
Date/Time Physician Signature

Fig. 1. Preoperative order sheet.

level of activity, expected postoperative course, and instructions for self-care and follow-up.

After development of the critical pathway, and a 3-month pilot period during which some fine-tuning was accomplished, the order sheets, patient information brochures, and data collection sheets were made available to any interested surgeon beginning in January 1995. After the three initiating surgeons described positive experiences with the pathway, within a few months of initiation, six of the eight remaining surgeons chose to use the critical pathway for all of their elective patients. Once a surgeon had begun to use the pathway, this use was voluntarily continued for all his or her subsequent patients.

Outcome data were collected concurrently by surgical case managers and summarized by the Northwest Hospital Department of Research and Development. The following data elements were recorded: age, sex, type of procedure, length of stay, number of

Surgical procedure: _____

Contact Dr. _____ for medical problems.

VITAL SIGNS

Per Postoperative Care protocol. Notify physician if: Systolic BP > 180 or < 90, Pulse > 120 or < 50, Respiration > 24, T° > 38.9°C.

ACTIVITY

Turn, cough, and deep breathe q 1-2 hrs post-op. Dangle day of surgery, up in chair for short periods. Ambulate with assistance TID starting day 1.

I & O

NPO, foley catheter, daily weight and I & O. Notify physician for urine output < 250 cc/shift (days/eves only).

☐ NG to low continuous suction. Follow GI Intubation protocol. ☐ Drains to self-suction. Record output q shift.

LAB

☐ Blood count and Electrolytes in AM x 1. ☐ BUN and Creatinine in AM x 1. ☐ CBC in AM x 1.

MEDICATIONs/IVs

IVs ☐ Finish current bottle at _____ cc/hr; then give D 5 ½ NS with 20 mEq KCl at _____ cc/hr.

☐ Other: _____

Analgesics

☐ Epidural per anesthesiology.

☐ IV PCA

Medication:	Mode Of Administration:	Parameters:
☐ Morphine 1 mg/mL.	☐ PCA only.	• Loading dose: 2 mL.
☐ Hydromorphone 0.2 mg/mL.	☐ PCA plus continuous @ _____ mL/hr.	• PCA dose: 1 - 2 mL.
☐ Other: _____		• Lockout: 8 - 10 min.
		• 4 hr limit: 40 mL.
		• For painful activities: prn bolus 2 mL.

☐ Ketorolac 30 mg IV now and 15 mg IV q 6 hrs x 72 hours.

☑ Naloxone 0.2 mg IV stat for RR < 8/min *AND* patient unresponsive. Repeat q 2-3 min prn until RR > 10/min *OR* 4 doses given.

☐ Other: _____

Antiemetics ☐ Prochlorperazine (Compazine®) 10 mg IM x 1. Call if ineffective.

☐ Droperidol 0.625-1.25 mg IV q 2-3 hrs prn.

☐ Trimethobenzamide HCl (Tigan®) 200 mg IM q 4 hrs prn.

☐ Other: _____

Antibiotics ☐ Ceftigyl 1.5 gm IV q 12 hrs x 2 doses. 1st dose at _____

☐ Other: _____

Other ☐ Heparin 5000 units SQ q 12 hrs (0900 and 2100).

☐ Famotidine (Pepcid®) 20 mg IV q 12 hrs.

☐ Other: _____

TREATMENTS

☐ Ostomy teaching (notify Wound Ostomy Nurse -WOC (ET) nurse).

☑ Sequential compression device until ambulating.

☑ Incentive spirometer q 1 hr while awake (10x/hr).

☐ Other _____

_____ Date/Time

_____ Physician Signature

Fig. 2. Postoperative order sheet.

ambulations per day, time when the patient was able to comfortably consume at least half of the served meal of a regular diet, day on which the Foley catheter was removed, whether the patient had received prophylaxis for deep venous thrombosis, hospital charges for each admission, disposition of patients after discharge, readmission rate within 30 days, ASA class, and type of anesthesia. Hospital charges were defined as the sum of all charges in a patient's account for the surgery stay, and were independent of payor contracts and reimbursement rates. This included operating room charges, laboratory fees, pharmacy, room charges, and so forth, defined by codes in the hospital's master charge structure. For patients undergoing surgery between January and April 1998, a telephone survey was also conducted to assess patient satisfaction with the critical pathway.

Statistical Analysis

We first compared patient demographics between patients managed using the critical pathway and

those managed without the critical pathway to determine whether these samples were representative of the same population. A nonparametric Mann-Whitney rank-sum test was used to compare the median age of these samples after the data failed a normality test. Sex distribution was compared using a Z-test of proportions, and the relative distribution of specific surgeries performed was compared by means of chi-square analysis. Analysis of variance was used to identify which outcome measures differed significantly between test and control samples.

RESULTS

No significant differences were found between the sample and control groups with regard to patient age, sex distribution, or type of surgery performed (Tables 1 and 2). Also, distribution of cases by ASA classification between groups did not differ significantly: 85.5% of the patients in the critical pathway group were ASA 2 or 3 compared with 88% of those in the non–critical pathway group.

Differences in outcomes measures between the sample and control groups are summarized in Table 3. We found no differences between the groups with regard to postoperative complications, death rate, or readmission rate within 30 days of surgery. We did find that patients managed by means of the critical pathway were transitioned to solid food sooner, had shorter hospital stays, incurred lower hospital charges, and were more likely to be discharged to home. The average length of stay was 5.5 days for those patients in the critical pathway group and 8.2 days for the control group, including the day of admission; this means that patients were discharged on postoperative day 4.5 and 7.2, respectively. In addition to differences in these outcome measures, we observed differences in clinical intervention measures, which reflect key components of the critical pathway. Our data indicated that larger proportions of the patients in the critical pathway group were ambulated more than three times per day, were given epidural anesthesia, received prophylaxis for deep venous thrombosis, and had their Foley catheters removed by postoperative day 3. Of these clinical interventions, we found that the number of days until solid food was tolerated was most strongly predictive of patient length of stay (Spearman rank correlation: $r = 0.734$, $P < 0.01$). We observed a moderate to weak negative correlation between length of stay and number of ambulations on postoperative day 1 ($r = -0.331$, $P < 0.01$).

Finally, in a consecutive sample limited to those patients who had surgery between January and April of 1998, we found patient satisfaction was higher for patients managed on the critical pathway (mean score 92%) compared to patients not on the pathway (mean score 86%, $P < 0.05$). In this satisfaction survey, patients were reached by telephone and invited to evaluate their satisfaction for eight aspects of their hospitalization, with possible scores ranging from 1 (very dissatisfied) to 5 (very satisfied).

DISCUSSION

The design and execution of a critical pathway for elective colon resections was initiated by colon and rectal surgeons from a single practice group whose primary motivation was to review best demonstrated practices for the perioperative period, and thereby provide the best possible care for their surgical patients, and to communicate this information to other surgeons practicing at the same hospital. No changes in the length of stay or cost savings were sought or expected. Because the administration of this particular hospital had been through positive experiences with previous critical pathways, they were eager to assist us by providing needed support with personnel and access to pertinent data. The results were very surprising to us, in that for every outcome measure examined, the pathway groups matched or exceeded the results of the control (nonpathway) group. Differences were particularly impressive for length of stay and total hospital charges.

The purpose of this study was to improve and assess our compliance with best demonstrated practices; as such, we collected data prospectively but did not randomize patients to the different groups. Although other investigators have reported reduced

Table 1. Patient demographics for 385 elective colon resections, 263 of which were managed using a critical pathway

	All cases	Pathway	Nonpathway	*P* value	Test
No. of patients	385	263 (68.3%)	122 (31.7%)		
Median age (yr)	67 (19–99)	68 (19–94)	66 (22–99)	0.957	Rank-sum
No. male	176 (45.7%)	128 (48.7%)	48 (39.3%)	0.107	Z-test

Table 2. Total of 385 colon resection surgeries, 263 of which were managed using a critical pathway

Description	All cases	Pathway	Nonpathway
Sigmoidectomy	71 (18.4%)	51 (19.4%)	20 (16.4%)
Right hemicolectomy	70 (18.2%)	52 (19.8%)	18 (14.8%)
Anterior resection of rectum	40 (10.4%)	36 (13.7%)	4 (3.3%)
Left hemicolectomy	22 (5.7%)	16 (6.1%)	6 (4.9%)
Excision of other portion of colon	17 (4.4%)	15 (5.7%)	2 (1.6%)
Cecectomy	11 (2.9%)	6 (2.3%)	5 (4.1%)
Rectal resection, not otherwise specified	10 (2.6%)	6 (2.3%)	4 (3.3%)
Anterior resection with colostomy	7 (1.8%)	5 (1.9%)	2 (1.6%)
Transverse colon resection	6 (1.6%)	3 (1.1%)	3 (2.5%)
Small-to-large bowel anastomosis	3 (0.8%)	0 (0.0%)	3 (2.5%)
Multiple segmental colon resection	1 (0.3%)	0 (0.0%)	1 (0.8%)
Abdominal proctopexy, with/without resection	1 (0.3%)	1 (0.4%)	0 (0.0%)

The distribution of these procedures between those managed using the critical pathway and those not managed with the pathway did not differ significantly ($P = 0.093$; chi-square analysis).

length of stay and charges after institution of critical pathways, we did not expect to find significant differences in outcome between the two groups. The critical pathway forms and program were simply offered to the surgeons for their use, without making any attempt to influence care patterns. By the last year of the data collection period, more than 90% of patients were placed on the critical pathway by their surgeons.

The Hawthorne effect is highly likely to have been a factor here, because the same nurses who were caring for patients on the critical pathway were also caring for the patients whose surgeons did not choose to use the critical pathway forms, data collection sheet, or patient information material. It is likely that the nursing care of the latter patients was closer to that given to the patients in the critical pathway group in terms of more aggressive attempts to ambulate and mobilize patients. If true, this would tend to diminish the differences seen between the two groups. It is unlikely that a truly prospective randomized study could be done with the same group of surgeons and nursing staff in a single hospital because it cannot be blinded to the caregivers and this could easily lead to inadvertent "crossing over" of the different means of caring for patients postoperatively. If two separate groups of surgeons and/or hospitals were to be used, many more unrecognized variables might be introduced, which could potentially confound interpretation of the data.

Hospital "charges" rather than hospital "costs" were used because they were calculated and used in a standard manner throughout the duration of the study. Hospital costs are often artificial figures, which may involve allowances for square footage of space of a

Table 3. Comparison of clinical outcomes and interventions for 263 colon resections managed using a critical pathway and 122 colon resections managed without the critical pathway

	All (n = 385)	Path (n = 263)	No path (n = 122)	*P* value	Test
No. with significant postoperative complications	24 (6.2%)	13 (4.9%)	11 (9.0%)	0.185	Z-test
No. of deceased	7 (1.8%)	4 (1.5%)	3 (2.5%)	0.785	Z-test
No. of readmitted within 30 days	36 (9.4%)	24 (9.1%)	12 (9.8%)	0.975	Z-test
Mean LOS (days)	6.4 (1–56)	5.5 (1–38)	8.2 (2–56)	0.001	Rank-sum
Mean days to solid food	4.1 (0–24)	3.6 (0–24)	5.3 (1–21)	0.001	Rank-sum
Mean charges	$13,937	$12,671	$16,665	0.001	Rank-sum
Discharged to home	334 (86.8%)	235 (89.4%)	99 (81.1%)	0.038	Z-test
No. ambulated >3×/day	110 (28.6%)	86 (32.7%)	24 (20.0%)	0.015	Z-test
No. with epidural catheter	289 (75.1%)	209 (79.5%)	80 (65.6%)	0.005	Z-test
No. receiving DVT prophylaxis	373 (96.9%)	260 (98.9%)	113 (92.6%)	0.003	Z-test
No. with Foley out by postoperative day 3	255 (66.2%)	192 (73.0%)	63 (51.6%)	0.001	Z-test

DVT = deep venous thrombosis; LOS = length of stay.

department, the relative share of utility use, and other factors, the calculation of which may change several times within any given year. No differences were seen between groups with regard to complications and readmission rates, suggesting that there were no adverse effects as a result of earlier postoperative feeding and earlier discharge. Finally, measurements of patient satisfaction with their pre-hospital, in-hospital, and post-hospital care showed a slight advantage for the patients in the pathway group.

Other investigators have addressed the benefits of the use of surgical critical pathways for colorectal surgery. Hawasli et al.[1] applied lessons learned from laparoscopic surgery to patients undergoing conventional colectomy with primary anastomosis and compared a group of 24 patients treated with an aggressive protocol with 30 historical control subjects, and reported that the hospital stay for protocol patients was 4 days as opposed to 8 days for the control group. Archer et al.[2] described their experience with a control group of 10 patients and an analytic group of 14 patients undergoing total colectomy and ileal pouch–anal anastomoses. They found a reduction in the length of hospital stay from 10.3 days to 7.5 days, and a reduction in mean hospital charges from $21,650 to $17,958 per patient for those in the critical pathway group. The percentage of patients discharged to home, as opposed to a transitional care facility, was not stated. Bradshaw et al.[3] reported a series of 36 study patients and 36 control patients in 1998, and noted the time to ambulation, types of analgesia used, time to first ambulation, and time to return of bowel function and discharge. The average length of stay was 6.0 days for patients in the control group vs. 4.9 days for the protocol patients. Hospital charge data and patient disposition at the time of discharge were not reported.

In the most recent study of this type, reported in 2000 by Basse et al.,[4] 60 consecutive patients were studied by means of a critical pathway that included continuous thoracic epidural analgesia, enforced early mobilization, and enteral nutrition, with a goal of discharging the patient within 48 hours. Three separate groups were identified for analytic purposes: group A, four patients with comorbid conditions that would preclude their discharge within 48 hours after surgery (3 of whom were, in fact, transferred back to their previous hospital department within 2 days); group B, three patients who had "precluding factors" identified during the surgical procedure (none were able to be discharged within the 48-hour period); and group C, 53 patients with no precluding factors, for whom the median (not the mean) length of stay was 2 days. Fifteen percent of the patients in this study required readmission, including two patients with anastomotic dehiscence. In a postoperative patient satisfaction survey, 73% of patients were satisfied with their postoperative care, but 27% believed that they had been discharged too early.

Several aspects of this critical pathway deserve emphasis. First is the use of routine early postoperative feeding. In recent years it has been demonstrated, in many studies, that routine use of nasogastric tubes is unnecessary.[5–7] The era of laparoscopic surgery brought with it the aggressive use of early postoperative feeding.[8,9] This has been shown to be safe and well tolerated in patients undergoing open colectomy as well.[10–12]

Another emphasis of the critical pathway is early and frequent ambulation. Although its effects have not been well documented in previous studies, we believe that patient mobilization is essential to minimize postoperative ileus and pulmonary complications. Several recent studies from Europe have suggested that aggressive mobilization is beneficial to patient outcomes, with regard to efforts to avoid what Moiniche et al.[13] have referred to as the "cascade of dependency." Critical to early mobilization is the commitment to optimizing pain control with liberal use of postoperative epidural anesthesia,[14–17] patient-controlled analgesia,[18] and nonsteroidal antiinflamatory drugs,[19] all of which are administered as part of the pathway.

Third, it is critically important to educate prospective patients and their families about the expected pre- and postoperative course in a specific fashion. Both verbal and written instructions are given to ensure that patients and their families understand the process and know what to expect throughout it. This degree of education and communication between patients and members of the health care team likely plays a role in increasing patient satisfaction.

A fourth and parallel emphasis of the pathway is that through its design and execution, it creates uniform expectations among all caregivers. The daily flow sheet is to be reviewed and notations made by all members of the health care team with specific goals to be achieved. Thus everyone (physicians, nurses, patients, and families) is on the "same page." A secondary benefit is the potential for earlier detection of problems when the clinical course is not progressing as expected.

A fifth important aspect of the critical pathway is that of preoperative discharge planning. Admission nurses contact patients and their families so that potential "at-risk" individuals can be identified and referred to surgical case managers to facilitate a smooth postoperative course after hospitalization (whether that be at home with visiting nurses or in a skilled nursing facility).

In the course of developing this critical pathway, reduction of expenditures was not one of our goals;

our intent was simply to streamline the approach to postoperative patient management and to avoid wasting hospital resources when it could be demonstrated that patients could receive adequate care at home. In the course of developing such a model we realized that, based on charge data, the average charges for those who were in the critical pathway group were nearly $3000 less than the charges for elective patients for whom this pathway was not used. This represents not an effort to save money, per se, so much as an effort not to waste resources.

Finally, it is extremely valuable to have a responsive hospital administration when developing a critical pathway. A partnership between the administration and physicians facilitates execution of the pathway and its ongoing monitoring and adjustments.

CONCLUSION

The literature on critical pathways is burgeoning, along with their use. Numerous studies looking at the use of pathways in the treatment of various in-patient medical illnesses (pneumonia, myocardial infarction), as well as various surgeries (e.g., vascular, cardiothoracic, and colorectal) have shown decreased lengths of stay, decreased costs/charges and, to a lesser degree, improved patient outcomes and satisfaction.[20–22] This study demonstrates the ability of a critical pathway in colorectal surgery to decrease length of stay and hospital charges while maintaining low readmission rates without compromising patient satisfaction. Such a pathway could be easily designed and implemented at any hospital with a motivated health care team and a supportive administration.

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Preoperative Predictors of Blood Transfusion in Colorectal Cancer Surgery

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Transfusion is associated with multiple risks and morbidities. Little is known, however, about preoperative predictors of transfusion in gastrointestinal surgery patients. To identify factors that influence transfusion practices, we analyzed hospital discharge data from colorectal cancer surgery patients in Maryland between 1994 and 2000 (n = 14,052). The primary outcome variable was whether or not patients received a blood product ("Any Transfusion"). Characteristics independently associated with an increased risk of receiving Any Transfusion included: advanced age (>80 yr: OR 2.3; 95% CI 1.9–2.9; 70–79 yr: OR 1.6; 95% CI 1.4–2.0 vs. <60 yr), moderate to severe liver disease (OR 2.5; 95% CI 1.5–4.2), mild liver disease (OR 2.1; 95% CI 1.5–2.9), diabetes with complications (OR 2.1; 95% CI 1.6–2.6), chronic renal disease (OR 2.1; 95% CI 1.4–3.0), female gender (OR 1.3; 95% CI 1.2–1.5), chronic pulmonary disease (COPD) (OR 1.3; 95% CI 1.1–1.4), and metastatic disease (OR 1.2; 95% CI 1.1–1.4). Patients at hospitals with an annual case volume in the highest quartile were at an increased risk for receiving Any Transfusion (OR 2.1; 95% CI 1.3–3.4) and those with surgeons in the highest volume quartile (>12 cases/yr) were at a decreased risk (OR 0.8; 95% CI 0.6–0.99). The association between greater surgeon case volume and low transfusion rates was seen in all but the very high volume hospitals (>74 cases/yr). Blood product transfusion was associated with a 2.5-fold (95% CI 2.1–3.1) increased mortality, 3.7 day (95% CI 2.1–3.1) increase in hospital length of stay, and a $7120 (95% CI $6472–$7769) increase in total charges compared to patients that did not receive Any Transfusion. This data can be used by providers in discussions with patients regarding the risks for transfusion and in identifying patients in whom strategies to reduce transfusions should be evaluated. (J GASTROINTEST SURG 2002;6:753–762)

KEY WORDS: Colorectal cancer, blood transfusion, outcomes

Although allogeneic blood product transfusions can be lifesaving in surgical patients, many transfusions are given for laboratory abnormalities without a well-defined benefit.[1–3] Recently, this practice has been scrutinized because of the morbidity and mortality associated with allogeneic transfusion.[4–9] In addition to the potential for transmission of blood borne pathogens,[10,11] blood product transfusion may be associated with an increased incidence of tumor reoccurrence in cancer patients,[12] immunosuppression,[5–8] and microcirculatory complications.[4,13] Despite these observations, little has been published regarding preoperative predictors of transfusion in gastrointestinal surgery patients.[14,15] Previous studies evaluating the association between patient characteristics and transfusions in high-risk surgical patient populations have been derived either from clinical trials[16] or from single institution series.[15,17–22] These studies may lack statistical power to identify other patient characteristics and such associations may not

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Dr. Berenholtz is supported, in part, by a grant from the Eugene & Mary B. Meyer Center for Advanced Transfusion Practices and Blood Research at Johns Hopkins University. Drs. Berenholtz and Pronovost are supported, in part, by a Clinician Scientist Award from The Johns Hopkins University.

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00043-4

be representative of the wide variety of patients who are operated upon in community and referral hospitals.

The goal of this study was to identify preoperative patient, surgeon, and hospital characteristics that are associated with an increased risk for perioperative blood transfusion in adult patients undergoing colorectal cancer surgery. By utilizing a statewide administrative database, we sought to identify preoperative predictors of transfusion that could be generalized to all colorectal cancer patients.[23] This information could be used by surgeons, anesthesiologists, and primary care physicians during preoperative risk-benefit discussions with patients and to identify the subset of patients who may benefit from interventions to reduce transfusion requirements.

METHODS

Patient Data

The Uniform Health Discharge Data Set maintained by the Maryland Health Services Cost Review Commission (HSCRC) contains patient discharge information from all 52 non-federal acute care hospitals in Maryland. After obtaining approval from our Institutional Review Board, we used the HSCRC database to identify adult patients (≥18 yr) with a primary procedure code for colorectal surgery (International Classification of Disease, 9th Revision, Current Modification [ICD-9-CM] 45.7x, 45.8, 48.4x, 48.5, 48.6x) and a primary diagnosis code for colorectal cancer (ICD-9-CM 15.3x, 15.41) between 1994 and 2000. These procedure and diagnosis codes accurately identify patients having colorectal cancer surgery.[24,25] We also abstracted information on the patients' age, gender, race, nature of admission, operating physician, hospital of admission, and as many as 14 secondary procedure and diagnosis codes. We excluded the records of patients who had neither a hospital nor an operating surgeon identified (n = 271).

Outcome Variables

The primary outcome variable was whether or not the patient received any blood product transfusion ("Any Transfusion"). Any Transfusion was defined as a transfusion of allogeneic packed red blood cells (PRBC), autologous RBC, fresh frozen plasma (FFP), or platelets. The HSCRC database classifies each type of transfusion as a dichotomous variable; the number of units of each product transfused is not available. Transfusion of blood product components is not mutually exclusive. Patients receiving any blood product component were classified as receiving "Any Transfusion." A recent analysis of coding of the HSCRC database at our own institution demonstrated that 92% of patients who had a code for blood transfusions actually received a transfusion.

Secondary outcome variables included whether the patient received specific blood product components, including allogeneic PRBC transfusions, autologous RBC transfusions, FFP transfusions, or platelet transfusions. We also evaluated the impact of transfusion on in-hospital mortality, hospital length of stay (LOS), intensive care unit (ICU) LOS, and total hospital charges. Total hospital charges were converted to 2001 dollars using the Consumer Price Index for Medical Services.[26]

Independent Variables

Using the primary procedure codes, we classified patients as having had a total colectomy (ICD-9-CM 45.8), a partial colectomy (ICD-9-CM 45.7x), or a rectal procedure (ICD-9-CM 48.4x, 48.5, 48.6x). Using the secondary diagnosis and procedure codes listed in the HSCRC database, we obtained information regarding patient characteristics, comorbid conditions, and complications. We adjusted for age, gender, race, comorbid diseases, hospital volume, operating surgeon volume, and severity of illness. Romano's modification of the Charlson comorbidity index was used to identify potentially important comorbid conditions that might impact transfusion requirements.[27,28] Because our specific aim was to identify predictors of transfusion, we included each disease in this index as an independent variable, rather than as a single comorbidity index.

As a proxy for severity of illness, we identified whether the patient was admitted through the Emergency Department (ED) versus elsewhere and whether the patient had a secondary ICD-9-CM diagnosis code for emergent surgery due to bowel obstruction (ICD-9-CM 560.89, 560.90) or perforation (ICD-9-CM 569.83). These variables have previously been validated in colorectal cancer surgery patients as surrogates for severity of illness.[24] We used the unique identification number of each surgeon and hospital within the HSCRC database to determine annual surgeon and hospital volume.

To determine cancer stage, we used secondary ICD-9-CM diagnoses codes to identify nodal involvement (ICD-9-CM 196-196.9) and organ metastasis (ICD-9-CM 197-198.89). If the patient did not have a secondary procedure code for metastatic disease, the cancer was assumed to be local.[25]

Statistical Analysis

We performed a descriptive analysis of patient characteristics and the primary outcome variable, Any

Transfusion. We performed unadjusted analyses to evaluate the relationship between the independent variables and each of the dependent variables. We used the Chi square test to evaluate the relationship between categorical dependent and categorical independent variables, and the *t* test to evaluate the association between continuous dependent variables and binary independent variables. Simple logistic regression was used to assess the association of categorical dependent variables and continuous independent variables. All predictor variables from the unadjusted analysis with a $P \leq 0.1$ were included in the adjusted analysis, in addition to apriori chosen clinically important patient variables, such as age (as a surrogate for patient illness severity). Hierarchical modeling was performed on all adjusted analysis in order to control for the artificially lowered

Table 1. Characteristics of study patients undergoing colorectal cancer resection in Maryland, 1994–2000

	% of patients with characteristic who received "Any Transfusion"* (N = 2,804)	% of patients with characteristic who were not transfused (N = 11,248)
Patient characteristics		
Age group (yr) (%)†		
<60	15‡	24
60–69	19‡	25
70–79	35‡	32
≥80	31‡	19
White (%)	79§	78
Female (%)	58‡	50
Severity of Illness (%)		
ED admission	29†	15
Bowel perforation	3.3†	1.6
Bowel obstruction	3.2	2.7
Surgical procedure (%)		
Total colectomy	1.8‡	0.9
Partial colectomy	7.9§	80
APR and other rectal procedures	19§	19
Comorbid disease (%)‖		
Old myocardial infarction	5	4
Dementia	2.7‡	1.4
Chronic pulmonary disease	16‡	12
Liver disease (mild)	2.0‡	0.9
Liver disease (moderate to severe)	2.2‡	0.8
Diabetes (mild to moderate)	15§	15
Diabetes with complications	2.8‡	1.3
Renal disease	1.8‡	0.7
Metastases from solid tumor	44‡	40
Hospital characteristics (cases/yr) (%)¶		
Low volume (<37)	26‡	29
Medium volume (37–56)	14‡	27
High volume (57–74)	24	23
Very high volume (>74)	36‡	22
Surgeon characteristics (cases/yr) (%)¶		
Low volume (≤4)	29‡	25
Medium volume (5–8)	26	25
High volume (9–12)	22‡	25
Very high volume (>12)	23	25

Overall, n = 14,052.
*"Any Transfusion" is defined as a transfusion of allogeneic PRBCs, autologous RBCs, FFP, or platelets.
†Cut points are based upon decades of life.
‡Unadjusted predictors with $P \leq 0.10$ included in adjusted analysis.
§ Nonstatistically significant predictor included in adjusted analysis.
‖ Comorbid diseases considered in this analysis are diseases in the Romano-Charlson index.
¶Cut points based upon quartiles.

variance estimates that resulted from the clustering of outcomes within a hospital.[29] Independent variables were not included in the adjusted analysis if they were collinear as determined by Spearman-rank correlation or if all patients with the given variable either did or did not receive a blood product transfusion.

Surgeon and hospital annual volumes are represented by categorical variables indicating quartiles of their distribution. A lowess smoother of each versus Any Transfusion was used to validate modeling hospital and surgeon volumes as quartiles.[30] Surgeon volume was defined as low (≤4 cases/yr), medium (5–8

Table 2. Characteristics of colorectal surgery patients in Maryland with and without "Any Transfusion," 1994–2000*

	Incidence of transfusion if condition present	Incidence of transfusion if condition absent	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted *P* value
Patient characteristic					
Age group (yr) (%)†					
<60	14	22	Referent	Referent	
60–69	16	21	1.2 (1.01–1.3)‡	1.1 (0.96–1.3)	—
70–79	21	19	1.7 (1.5–1.9)‡	1.6 (1.4–2.0)	<0.001
≥80	29	18	2.5 (2.2–2.9)‡	2.3 (1.9–2.9)	<0.001
White (%)¶	20	20	1.0 (0.9–1.2)	1.0 (0.7–1.3)	—
Female (%)	23	17	1.4 (1.3–1.5)‡	1.3 (1.2–1.5)	<0.001
Severity of illness (%)					
ED admission	32	17	2.3 (2.1–2.5)‡	2.2 (1.8–2.5)	<0.001
Bowel perforation	34	20	2.1 (1.6–2.7)‡	1.6 (1.2–2.1)	<0.005
Bowel obstruction	23	20	1.2 (0.96–1.5)	—	—
Surgical procedure (%)					
Total colectomy	32	20	1.9 (1.4–2.7)‡	—§	—
Partial colectomy¶	20	21	0.94 (0.9–1.0)	0.5 (0.3–0.7)	<0.001
APR and other rectal procedures¶	20	20	1.0 (0.9–1.1)	0.6 (0.4–0.9)	<0.05
Comorbid disease (%)‖					
Old myocardial infarction	24	20	1.3 (1.03–1.5)‡	1.2 (0.97–1.5)	—
Dementia	33	20	2.0 (1.5–2.6)‡	1.3 (0.9–1.8)	—
Chronic pulmonary disease	25	19	1.4 (1.2–1.6)‡	1.3 (1.1–1.4)	<0.005
Liver disease (mild)	37	20	2.4 (1.7–3.3)‡	2.1 (1.5–2.9)	<0.001
Liver disease (moderate to severe)	41	20	2.9 (2.1–4.0)‡	2.5 (1.5–4.2)	<0.001
Diabetes (mild to moderate)¶	21	20	1.1 (0.9–1.2)	1.1 (0.95–1.2)	—
Diabetes with complications	35	20	2.2 (1.7–2.9)‡	2.1 (1.6–2.6)	<0.001
Renal disease	39	20	2.5 (1.8–3.6)‡	2.1 (1.4–3.0)	<0.001
Metastases from solid tumor	22	19	1.2 (1.1–1.3)‡	1.2 (1.1–1.4)	<0.001
Hospital characteristics (cases/yr) (%)#					
Low volume (<37)	19	21	Referent	Referent	
Medium volume (37–56)	12	23	0.6 (0.5–0.7)‡	0.6 (0.2–1.5)	—
High volume (57–74)	21	20	1.2 (1.02–1.3)‡	1.2 (0.6–2.3)	—
Very high volume (>74)	29	17	1.8 (1.6–2.0)‡	2.1 (1.3–3.4)	<0.01
Surgeon characteristics (cases/yr) (%)#					
Low volume (≤4)	23	19	Referent	Referent	
Medium volume (5–8)	21	20	0.9 (0.8–0.99)‡	1.0 (0.8–1.2)	—
High volume (9–12)	18	21	0.75 (0.7–0.8)‡	0.8 (0.7–1.03)	—
Very high volume (>12)	19	20	0.8 (0.7–0.9)‡	0.8 (0.6–0.99)	<0.05

Overall, n = 14,052.

*"Any Transfusion" is defined as a transfusion of allogeneic PRBCs, autologous RBCs, FFP, or platelets.

†Cut points are based upon decades of life; OR for age are expressed relative to <60 years of age.

‡Unadjusted predictors with $P \leq 0.10$ included in adjusted analysis; adjusted results reported as odds ratio (OR) with 95% confidence intervals (CI).

¶Non-statistically significant predictor included in adjusted analysis.

§ Dropped from the analysis due to collinearity with the outcome variable.

‖ Comorbid diseases considered in this analysis are diseases in the Romano-Charlson index.

Cut points based upon quartiles.

cases/yr), high (9–12 cases/yr), and very high (>12 cases/yr). Similarly, hospital volume was defined as low (≤37 cases/yr), medium (37–56 cases/yr), high (58–74 cases/yr), and very high (>74 cases/yr). These thresholds for surgeon and hospital volume are consistent with previously published literature.[24,25]

To assess the interaction of hospital volume with surgical volume for patients receiving Any Transfusion, the groups were further subdivided into 8 groups according to both surgeon and hospital volumes (a 2×4 matrix). In this analysis, hospital volume was modeled as a dichotomous variable with a cut point of 74 cases/yr. This cut point was chosen based upon a crude analysis that demonstrated that surgeon volume did not influence transfusion rates in hospitals with an annual volume in the upper quartile, but did influence transfusion rates at low, medium, and high volume hospitals. Using this matrix, the adjusted analysis with hierarchical modeling was repeated for Any Transfusion. All reported *P* values are two-tailed and were considered significant if they were <0.05. All statistical analysis was performed using STATA (version 6.0 software; Stata Corp, College Station, Texas).

RESULTS

Between 1994–2000, 14,052 patients underwent colorectal surgery for cancer at 50 different hospitals in Maryland. The study population had a mean age of 69 yr (standard deviation = 12.5). Caucasians accounted for 79% of the patient population and 52% of the patients were female. Two percent of the patients underwent a total colectomy, 79% partial colectomy, and 19% rectal procedures. Eighteen percent of patients were admitted through the ED. Patients with congenital bleeding diatheses (i.e. Von Willebrand Disease, Hemophilia A, etc.) comprised 0.05% of the patient population. Table 1 outlines the demographic characteristics and comorbid conditions of patients with and without Any Transfusion.

The risk for Any Transfusion varied widely among hospitals. With the hospital as the unit of analysis, the median rate of Any Transfusion was 19% (interquartile range 3–31%). The variability was most dramatic at low patient volume hospitals (n = 26 hospitals), where rates of Any Transfusion ranged 0–100%, compared to very high patient volume hospitals (n = 5), where the range was 20–37%.

Primary Outcome Variable: Predictors of "Any Transfusion"

Patient, hospital, and surgeon characteristics associated with an increased risk for receiving Any Transfusion are included in Table 2. Factors associated with Any Transfusion in the unadjusted analysis included advanced age, female gender, ED admission, bowel perforation, total colectomy, history of prior myocardial infarction (MI), dementia, chronic pulmonary disease, liver disease, diabetes with complications, chronic renal disease, and metastatic disease. Greater hospital volume was associated with an increased risk of transfusion; however, greater surgical volume was associated with a decreased risk of transfusion.

Factors associated with Any Transfusion in the adjusted analysis are also included in Table 2. Female gender and advanced age were independently associated with an increased risk for transfusion. The risk of receiving Any Transfusion increased exponentially with increasing age: ≥80 yr was associated with a 2.3-fold increase in the risk of Any Transfusion compared to patients <60 yr. Admission through the ED and surgery for bowel perforation were also associated with an increased risk for Any Transfusion. Preoperative comorbid conditions that were independently associated with an increased risk for Any Transfusion in the adjusted analysis included chronic pulmonary disease, liver disease, diabetes with chronic complications, chronic renal disease, and metastatic disease. Hospitals in the highest volume quartile were associated with a 2-fold increased risk for Any Transfusion (OR 2.1, 95% CI 1.3-3.4). Patients with surgeons in the highest volume quartile had a decreased risk for transfusion (OR 0.8, 95% CI 0.6-0.99).

To evaluate time trends in transfusion practices, we repeated the unadjusted and adjusted analyses for Any Transfusion over the time periods 1994–1996, 1997–1998, and 1999–2000. Twenty percent of all patients received Any Transfusion during each time period. Patient, hospital, and surgeon characteristics associated with an increased risk for Any Transfusion in the adjusted analysis were consistent within each time period evaluated.

Secondary Outcome Variables

Impact of Transfusion. In-hospital mortality, hospital LOS, ICU LOS, and total hospital charges were increased for patients who received Any Transfusion when compared to patients who did not. Patients receiving Any Transfusion had a 2.5-fold increased risk of in-hospital mortality (OR 2.5, 95% CI 2.1–3.1), 3.7 day increase in average hospital LOS (95% CI 3.4–3.9 days), 0.9 day increase in average ICU LOS (95% CI 0.8–1.1 days), and $7120 (95% CI $6472–$7769) increase in total hospital charges compared to patients who were not transfused.

Predictors of PRBC, Autologous RBC, FFP, and Platelet Transfusions. Twenty percent of patients received an allogeneic PRBC transfusion (n = 2741), 0.2% received an autologous RBC transfusion (n = 38), 0.8% received a FFP transfusion (n = 119), and 0.2% received a platelet transfusion (n = 33). Factors associated with an increased risk for allogeneic PRBC transfusion in the unadjusted analysis included advanced age, female gender, ED admission, admission for a perforated bowel, prior MI, dementia, chronic pulmonary disease, mild liver disease, moderate-severe liver disease, diabetes with chronic complications, chronic renal disease, metastatic disease, and greater hospital volume. Greater surgeon volume, on the other hand, was associated with a decreased risk for PRBC transfusion. Total colectomy was associated with an increased risk for PRBC transfusion (OR 1.9, 95% CI 1.3–2.6), but was not included in the adjusted analysis because of collinearity with the outcome variable, allogeneic PRBC transfusion.

Table 3. Adjusted predictors of blood product transfusion for patients (n = 14,052) undergoing colorectal cancer surgery in Maryland, 1994–2000*

	Allogeneic PRBC (n = 2741)	Autologous RBC (n = 38)	FFP (n = 119)	Platelet (n = 33)
Patient Characteristics				
Age group (yr)†				
60–69	1.1 (0.95–1.3)	0.7 (0.3–1.5)	1.0 (0.5–2.0)	1.0 (0.2–4.1)
70–79	1.6 (1.4–2.0)‡	0.9 (0.4–1.8)	1.3 (0.7–2.2)	1.6 (0.4–6.4)
≥80	2.4 (1.9–2.9)‡	0.6 (0.2–2.1)	1.8 (0.97–3.2)	2.6 (0.6–11.4)
White	0.9 (0.7–1.2)	1.8 (0.6–5.6)	1.3 (0.7–2.5)	1.0 (0.3–3.6)
Female	1.3 (1.2–1.5)‡	0.6 (0.3–1.4)	1.0 (0.7–1.4)	0.7 (0.3–1.4)
Severity of illness				
Ed admission	2.1 (1.8–2.5)‡	0.7 (0.2–2.9)	3.1 (1.9–5.2)‡	4.0 (1.7–9.1)‡
Bowel perforation	1.6 (1.2–2.2)‡	—§	3.3 (1.5–7.3)‡	—
Bowel obstruction	—	—§	—	2.4 (0.96–5.8)
Surgical procedure				
Total colectomy	—‖	—‖	—‖	3.5 (0.9–14.5)
Partial colectomy	0.5 (0.3–0.7)‡	0.3 (0.04–1.5)	0.7 (0.2–3.0)	0.7 (0.2–1.7)
APR and rectal resections	0.6 (0.4–0.9)‡	1.2 (0.2–9.1)	1.2 (0.3–5.6)	—‖
Comorbid disease¶				
Old myocardial infarction	1.2 (0.96–1.5)	—	—	2.8 (1.1–7.4)‡
Dementia	1.2 (0.9–1.7)	—§	—	—§
Chronic pulmonary disease	1.3 (1.1–1.4)‡	—	—	2.3 (1.2–4.2)‡
Liver disease (mild)	2.0 (1.4–2.9)‡	—	5.9 (3.4–10.1)‡	7.0 (2.0–24.2)‡
Liver disease (moderate to severe)	2.6 (1.6–4.3)‡	—§	2.5 (1.02–6.2)‡	3.7 (0.8–18.2)
Diabetes (mild to moderate)	1.1 (0.96–1.2)	—	—	—
Diabetes with chronic complications	2.1 (1.6–2.7)‡	—§	—	—§
Renal disease	2.1 (1.4–3.1)‡	—§	3.0 (1.3–6.8)‡	—
Metastases from solid tumor	1.2 (1.1–1.4)‡	0.6 (0.3–1.3)	1.4 (0.98–1.9)	—
Hospital characteristics (cases/yr)#				
Medium volume (37–56)	0.6 (0.2–1.5)	0.4 (0.04–3.9)	1.3 (0.5–3.3)	1.0 (0.3–3.3)
High volume (57–74)	1.2 (0.6–2.3)	4.1 (0.8–20.3)	1.6 (0.6–4.2)	1.1 (0.4–3.0)
Very high volume (>74)	2.1 (1.3–3.4)‡	6.9 (1.4–33.2)‡	3.0 (1.4–6.4)‡	2.7 (0.8–8.7)
Surgeon characteristics (cases/yr)#				
Medium volume (5–8)	0.96 (0.8–1.2)	0.8 (0.3–2.1)	1.1 (0.6–1.8)	0.9 (0.4–2.0)
High volume (9–12)	0.8 (0.7–1.04)	0.7 (0.3–1.6)	1.1 (0.5–2.2)	0.8 (0.3–2.2)
Very high volume (>12)	0.8 (0.6–0.97)‡	1.4 (0.6–3.3)	0.9 (0.5–1.6)	1.0 (0.4–2.5)

APR = abdominal-perineal resection.

*Unadjusted predictors with $P < 0.10$ included in the adjusted analysis; adjusted results reported as odds ratios (95% confidence intervals).

†Cut points selected are based upon decades of life. Odds ratio are expressed relative to patients <60 years of age.

‡$P < 0.05$ in the adjusted variate analysis.

§ Excluded from adjusted analysis as no patient with the given independent variable received the specified blood product.

‖ Dropped due to collinearity with outcome variable.

¶Comorbid diseases considered in this analysis are the diseases in the Romano-Charlson index.

#Cut points based upon quartiles. Odds ratios expressed relative to low hospital volume (<37 cases/year) or low surgeon volume (≤4 cases/year), respectively.

Factors associated with an increased risk for autologous RBC transfusion in the unadjusted analysis included very high surgeon volume, very high hospital volume, and rectal procedures. Patients undergoing a partial colectomy were less likely (OR 0.2, 95% CI 0.1–0.3) to receive an autologous transfusion. ED admission was associated with a non-statistically significant decrease in the rate of autologous RBC transfusion (OR 0.3, 95% CI 0.1–1.1, $P = 0.06$), providing internal validation to the analysis.

Patient demographic and comorbid factors associated with an increased risk for FFP transfusion in the unadjusted analysis included advanced age, mild liver disease, severe liver disease, renal disease, and metastatic disease. ED admission, admission for bowel perforation, and greater hospital volume were also associated with an increased risk for FFP transfusion. Factors associated with an increased risk for platelet transfusion in the unadjusted analysis included advanced age, prior MI, chronic pulmonary disease, mild liver disease, moderate- severe liver disease, ED admission, admission for bowel obstruction, and very high hospital volume. Total colectomy was associated with an increased risk for platelet transfusion.

Characteristics associated with an increased risk for specific blood products in the adjusted model are included in Table 3. ED admission was associated with an increased risk for all blood product components except autologous RBC, providing internal validation to the study design. Similarly, emergent surgery for bowel perforation was associated with an increased risk for PRBC and FFP transfusion. Comorbid conditions that were associated with an increased risk for multiple blood products included chronic pulmonary disease (PRBC and platelets), mild liver disease (PRBC, FFP, platelets), moderate-severe liver disease (PRBC and FFP), and chronic renal disease (PRBC and FFP). Very high hospital volume was associated with an increased risk for PRBC, autologous RBC, and FFP transfusion.

Interaction of Hospital Volume and Surgical Volume. The interaction of surgeon volume and hospital volume is presented in Table 4. In an adjusted analysis that controlled for surgical procedure, patient demographics, comorbid conditions, metastatic disease, and nature of admission, greater surgeon volume was associated with a decreased risk for Any Transfusion at low, medium, and high volume hospitals. The same relationship was not observed at very high volume hospitals, where surgeon volume did not impact transfusion rate. For each level of surgeon volume, patients at hospitals that performed >74 cases/yr were at an increased risk for receiving Any Transfusion compared to patients at hospitals that performed <74 cases/yr.

To assess whether high volume hospitals included patients with more advanced cancer, we evaluated the association among hospital volume and both lymph node metastasis and organ metastasis. When compared with patients at low, medium, and high volume hospitals (≤74 cases/yr), patients at very high volume hospitals (>74 cases/yr) had neither an increased incidence of lymph node metastasis (OR 1.0, 95% CI 0.9-1.1) nor increased incidence of organ metastasis (OR 1.0, 95% CI 0.95–1.1).

DISCUSSION

Our study found that patient demographics, comorbid disease, and nature of admission could be used to identify patients at high risk for transfusion during the surgical management of colorectal cancer. In addition, we have identified several surgeon and

Table 4. Interaction of surgeon volume and hospital volume on rate of "Any Transfusion" for colorectal surgery patients in Maryland, 1994–2000*

	Hospital volume†	
	≤74 cases/yr (n = 10,552)	**>74 cases/yr (n = 3500)**
Surgeon Volume‡		
Low (%) (n = 3631)		
Total patients	21	5
Metastatic disease	44	43
OR (95% CI)	1.0 (Referent)	1.9 (1.3–2.8)¶
Medium (%) (n = 3510)		
Total patients	20	5
Metastatic disease	41	41
OR (95% CI)	0.9 (0.7–1.2)	1.9 (1.3–2.7)¶
High (%) (n = 3446)		
Total patients	20	5
Metastatic disease	41	41
OR (95% CI)	0.8 (0.6–0.99)¶	2.0 (1.3–3.2)¶
Very high (%) (n = 3465)		
Total patients	15	10
Metastatic disease	38	38
OR (95% CI)	0.7 (0.5–0.99)¶	1.8 (1.1–2.9)¶

Overall, n = 14,052.
*"Any Transfusion" is defined as a transfusion of allogeneic PRBCs, autologous RBCs, FFP, or platelets.
†Hospital volume is modeled as a dichotomous variable with a cut point of ≤74 cases per year. Hospitals with cases ≤74 cases per year include hospitals in the lowest three volume quartiles; hospitals with an annual volume >74 include hospitals in the highest volume quartile.
‡Surgeon volumes are based upon quartiles and are defined as follows: low (≤4 cases/year), medium (5–8 cases/year), high (9–12 cases/year), and very high (>12 cases/year).
¶*P* value <0.05 compared to low volume surgeons at hospitals with ≤74 cases per year.

hospital characteristics that are independently associated with an increased risk for transfusion. There is limited data regarding preoperative predictors for transfusion in patients undergoing gastrointestinal surgery.[14,15] Such predictors are important given the high incidence of transfusion in these patients and our findings that transfusion is independently associated with increased in-hospital mortality, hospital LOS, ICU LOS, and total hospital charges. In addition, the inclusion of a large number of patients, hospitals, and surgeons increases the generalizability of our findings.

We identified several comorbid diseases that are associated with an increased risk for blood product component transfusion. Patients with a history of liver and renal disease were more likely to receive Any Transfusion, allogeneic PRBC transfusion, and FFP compared to patients without these comorbid diseases. In addition, mild liver disease was also associated with an increased risk for platelet transfusion. The risk of receiving FFP and platelets in patients with mild liver disease was disproportionately elevated when compared to the risk of receiving allogeneic PRBCs. Patients with mild liver disease were much more likely to receive FFP (OR 5.9, 95% CI 3.4–10.1) and platelets (OR 7.0, 95% CI 2.0–24.2), than they were to receive allogeneic PRBCs (OR 2.0, 95% CI 1.4–2.9). These findings suggest that providers may be preemptively transfusing FFP and platelets based upon a clinical history of liver disease rather than clinical evidence of bleeding.

Our study provides additional support to a growing body of literature that female gender is independently associated with an increased risk for blood product transfusion.[19,20] Our study design precludes us from establishing a cause for this association. This trend may reflect the lower baseline hematocrit seen in women, which has previously been identified as an independent predictor for transfusion.[16,17,19,21] Given the increased morbidity and mortality associated with transfusion, the increased transfusion requirement for women warrants further investigation.

The variability in transfusion rates among hospitals in our study suggests that hospital organizational characteristics may impact transfusion practices. We found an association between hospital volume and risk for Any Transfusion, allogeneic PRBC transfusion, autologous RBC transfusion, and FFP transfusion. This association was most striking at very high volume hospitals where patients had a 2-fold increased risk for Any Transfusion, a 2-fold increased risk for allogenic PRBC transfusion, a 7-fold increased risk for autologous transfusion, and a 3-fold increased risk for FFP transfusion compared to patients at low volume hospitals. In contrast, very high volume surgeons were associated with lower rates of Any Transfusion and allogeneic PRBC transfusions. These seemingly contradictory results prompted us to examine how surgeon and hospital volume interact to influence transfusion rates.

Our study found that surgeon volume at low, medium, and high volume hospitals was independently associated with a decreased risk for Any Transfusion. Other studies have found an association between high surgeon volume and lower complication rates.[27,30] One explanation may be that more skilled, higher volume surgeons may lose less blood and patients would be less likely to require a transfusion. Surgeon volume, however, did not influence transfusion rates at very high volume hospitals, which suggests that the organizational structure of patient care at very high volume hospitals may impact transfusion practice. Very high volume hospitals are often affiliated with residency training programs and these physicians may have lower transfusion thresholds. It is also possible that the association of very high volume hospitals with increased transfusion rates, independent of surgeon case volume, could be due to patient severity of illness that was not accounted for in our analysis. This is less likely, though, because we did not find an increased incidence of lymph node metastases or organ metastases in patients at very high volume hospitals when compared to patients at low, medium, or high volume hospitals. The association among surgeon volume, hospital volume and transfusion warrants further exploration.

Institutional organizational structure might also influence autologous transfusion practice. We found that patients at very high volume hospitals were 7-fold (OR 6.9, 95% CI 1.4–33.2) more likely to receive an autologous transfusion compared to patients at low volume hospitals. One possible explanation for this association is that hospitals with high surgical volume may have the infrastructure and organizational support to arrange for patients to preoperatively donate autologous blood. Our study design does not allow us to determine which institutions have preoperative autologous donation services available. The impact of preoperative autologous service availability on transfusion practices warrants further investigation.

We have identified several limitations to our study. First, we used discharge data rather than medical records to evaluate the 14,052 patients included in the study, which limits the information that can be obtained. For example, we are unable to determine if other potential confounding factors such as intraoperative blood loss or anemia were present. We are also unable to determine the patients' hemoglobin prior to transfusion. A chart review of all patients

undergoing colorectal cancer surgery in the State of Maryland would have been very difficult and very expensive. Surgical patients are ideal populations to study with discharge data because specific patient populations are easy to identify and risk adjustment models appear to work well in these patients.[31] Despite these limitations, hospital discharge data provides an efficient means of analyzing outcomes from a large patient population at multiple hospitals that might not otherwise be possible.[23] In addition, the results are more generalizable and are not subject to the selection bias that can affect results from a single institution.

Second, the coding of secondary procedures and diagnoses may not be as accurate as the coding of the primary diagnosis and procedure code. In addition, complicated hospital stays may result in a "prioritization" of procedures and diagnosis. Previous studies have determined that the ICD-9-CM codes for transfusion accurately identify patients that received a transfusion, thus increasing our confidence in the validity of our dependent variables.[32,33]

Third, our ability to obtain detailed information about a patient's stay in the hospital is limited. For example, the database does not allow us to determine when the patient was transfused (i.e., preoperatively versus postoperatively) or the number of units transfused, thus preventing the evaluation of a dose response relationship. Despite these limitations, the study accomplished its goal of identifying patient demographics, comorbid conditions, and surgeon and hospital characteristics that were associated with increased transfusion. This data can be used by providers in discussions with patients regarding the risks for transfusion and in identifying patients in whom strategies to reduce transfusions should be evaluated.

CONCLUSION

We have identified several patient, surgeon, and hospital characteristics that are independently associated with an increased risk for blood product transfusion in patients undergoing colorectal cancer surgery in Maryland. Our study provides important information that healthcare providers can use during preoperative risk-benefit discussions with patients about the risks for transfusion. In addition, our study identified high-risk patients in whom strategies to reduce transfusions should be evaluated. Finally, this study suggests a relationship between hospital organizational structure and transfusion rates. Such a relationship warrants further exploration, as this may represent a potential opportunity to implement strategies to reduce blood product transfusions and the associated morbidity, mortality and costs.

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Does Neoadjuvant Chemoradiation Downstage Locally Advanced Pancreatic Cancer?

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Recent studies suggest that neoadjuvant chemoradiation can downstage locally advanced pancreatic tumors. There is limited evaluable data to support this approach. We review our experience with preoperative chemoradiation for surgically staged, locally advanced pancreatic cancer to determine whether patients are downstaged with multimodal therapy allowing for curative resection. A prospectively collected database from Memorial Sloan-Kettering Cancer Center was reviewed. Patients admitted between January 1993 and March 1999 with locally advanced pancreatic adenocarcinoma were identified (N = 163). Chemoradiation was administered to 87 (53.3%) of 163, and regimens varied from standard 5-fluorouracil/gemcitabine–based therapies to experimental protocols. Only three patients (3/87; 3.4%) had a sufficient clinical response on restaging to warrant reexploration. Of these, two thirds were unresectable on subsequent laparoscopy because of extensive vascular involvement or metastatic disease. Only one patient underwent a potentially curative resection, with a survival of 18 months despite negative margins and no nodal involvement. The overall median survival for all patients with locally advanced disease treated with chemoradiation was 11 months (6.5 months without multimodal therapy; $P = 0.004$). Although chemoradiation is associated with improved overall survival in locally advanced disease, it rarely leads to surgical "downstaging" allowing for potentially curative pancreatic resections. Novel multimodality approaches are required. (J GASTROINTEST SURG 2002;6:763–769.)

KEY WORDS: Pancreatic cancer, downstaging, locally advanced, chemoradiation

Conventional treatments for adenocarcinoma of the pancreas have had little impact on the natural history of the disease. Despite recent advances in multimodality therapy and surgical techniques, pancreatic cancer remains the fifth leading cause of cancer deaths in the United States, with a highly aggressive natural course and a dismal overall prognosis.[1–3] Approximately 80% to 90% of patients with pancreatic cancer have either clinically apparent metastatic disease on presentation or radiographic evidence of unresectability due to the locally advanced stage of the disease.[4–7] Of the remaining 10% to 20%, only half of these patients will undergo a potentially curative resection. Despite the dismal prognosis associated with the diagnosis of adenocarcinoma of the pancreas, surgical resection remains the only potentially curative option.[1,8–10]

Codivilla, in Bologna, is credited with reporting the first radical operation for carcinoma of the pancreas in 1898.[11] Today the standard surgical treatment for tumors of the head of the pancreas remains the pancreaticoduodenectomy, which was initially described by Kausch in 1913[11] and modified by Whipple et al.[12] in 1935. Despite improvements in operative techniques and perioperative management, which have reduced perioperative mortality rates to less than 5%, the overall disease-specific survival remains dismal, with a median survival of less than 20 months after surgical resection.[13,14] In reality, a survival benefit is realized only in those patients undergoing surgical resection of the primary tumor with negative margins (R0). Although actuarial survival rates of 20% to 30% are reported in the literature, a previous study from our institution documented an actual 5-year survival of only 10%.[1] The median survival of patients undergoing a pancreaticoduodenectomy with positive margins is 8 to 12 months, similar to the survival rates reported for patients treated with palliative chemoradiation alone.[15–18]

Various neoadjuvant and adjuvant multimodality approaches have been described with little impact on either disease-specific or overall survival.[9,19–25] Pa-

Presented at the Forty-First Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, California, May 21–24, 2000 (poster presentation).

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00017-3

tients with locally advanced disease at presentation rarely survive longer than 1 year. These patients are defined as being unresectable because of locally advanced disease when surgical exploration reveals extensive vascular involvement (other than portal vein), precluding complete resection with negative margins. Postoperative external-beam radiation therapy and concomitant chemotherapy with 5-fluorouracil (5-FU) have been shown to prolong survival in one study (Gastrointestinal Tumor Study Group),[23] but was not confirmed in others.[24–26] Controversy exists as to whether locally advanced disease can be downstaged and patients converted from unresectable to resectable disease status with current regimens of chemoradiation. Several recent studies have demonstrated the potential for downstaging disease by means of various regimens.[10,21,22,27–38] These studies are plagued with numerous difficulties including inclusion/selection bias and a lack of standardization in pretreatment staging criteria. Currently there are no prospective trials that demonstrate downstaging of surgically staged, locally unresectable pancreatic cancer. The present study was designed to review our prospectively accrued experience in patients who were surgically staged with locally advanced disease to assess the efficacy of current chemoradiation regimens in downstaging locally advanced pancreatic tumors from unresectable to resectable.

MATERIAL AND METHODS

A prospectively collected pancreatic database maintained by the Department of Surgery at Memorial Sloan-Kettering Cancer Center was reviewed. All patients identified with biopsy-proved, surgically staged, locally advanced pancreatic adenocarcinoma between January 1993 and March 1999 (N = 163) were included in this study. An analysis of clinical outcomes and associated factors was performed; clinicopathologic and operative details were reviewed from the databases and hospital records. Preoperative assessment in all patients included a high-resolution, contrast-enhanced, thin-cut CT scan of the pancreas. Tumors were defined as locally advanced based on intraoperative evidence (diagnostic laparoscopy ± ultrasound imaging, open laparotomy) of extensive vascular involvement precluding resection. In general, patients with localized portal vein or superior mesenteric vein involvement alone were considered resectable. However, patients with extensive retropancreatic venous involvement or encasement of the celiac axis, hepatic artery, or superior mesenteric artery were considered unresectable for cure.

After surgical staging, patients receiving combined-modality therapy were identified; specific regimens were noted and the results of follow-up were documented. As expected, the adjuvant chemotherapy regimens for locally advanced disease were predominantly 5-FU/gemcitabine based (N = 70). However, nonstandard adjuvant therapies ranged from an experimental combination of agents (cisplatin, mitomycin, Taxol, topotecan, and doxorubicin [N = 9]) to adjuvant intraperitoneal protocols (fluorodexyuridine, floxuridine [N = 4]). In addition, several patients received novel experimental agents (TNP-470, BB-2516, or DX-8951F [N = 4]), either alone or in combination with standard multimodality regimens. After chemoradiation, patients were restaged, usually within 6 to 8 weeks, using dynamic, thin-cut contrast-enhanced CT scans of the abdomen to determine the response to therapy. Radiologic response was defined, and only those patients considered to have a response that would potentially allow for an R0 resection were considered for surgical reexploration.

Descriptive statistical analysis was performed using a commercially available software package (SPSS 10.0 for Windows; Statistical Package for Social Sciences, SPSS, Inc., Chicago, Illinois). Survival was determined by the method of Kaplan and Meier[39] with a log-rank analysis. Univariate analysis was carried out by chi-square testing, and multivariate analysis was performed using logistic regression and Cox linear regression. Statistical significance was defined as $P < 0.05$.

RESULTS

Between January 1993 and March 1999, a total of 1020 patients were admitted to Memorial Sloan-Kettering Cancer Center with the diagnosis of pancreatic adenocarcinoma. Of these patients, 839 underwent surgical exploration, either laparoscopy (± ultrasonography) and/or laparotomy, with 302 patients undergoing potentially curative resections. On the basis of the intraoperative staging criteria as defined in Material and Methods, 163 patients were identified with histologically proved, locally advanced pancreatic adenocarcinoma, none of whom underwent resection. Patient demographics and follow-up data are presented in Table 1.

Of the 163 patients, 87 (53%) received chemoradiation regimens varying from standard 5-FU/gemcitabine–based therapies with or without radiation therapy (80.4%; N = 70) to several experimental protocols. Selection was not based on any randomization but rather on patient and/or physician preference. Patients were subsequently restaged on com-

Table 1. Demographic data

Total admissions for Pancreatic adenocarcinoma	N = 1,020
Surgically staged locally advanced disease	N = 163
Male:female ratio	89:74
Median age (yr)	66 (range 39–83)
Status of follow-up	
Alive with disease	13.5% (N = 22)
Died of disease	81.0% (N = 132)
Unknown	5.5% (N = 9)
Neoadjuvant chemoradiation	53.3% (N = 87)

A prospectively collected database of patients with histologically proven, locally advanced pancreatic adenocarcinoma treated at Memorial Sloan-Kettering Cancer Center from January 1993 to March 1999.

pletion of therapy, to determine responses to chemoradiation, and complete follow-up information was available in 85 patients (two foreign patients were lost to follow-up). The overall median survival for patients treated with multimodality therapy for locally advanced disease was 11 months, with a median follow-up of 7.3 months (for survivors, median follow-up was 16.5 months) (Fig. 1). In contrast, patients with locally advanced disease who received "best supportive care only" had a median survival of 6.5 months ($P = 0.004$). All patients were followed with CT scans of the abdomen during therapy to evaluate the status of their disease.

After restaging, three patients (3/87; 3.4%) demonstrated a sufficient radiologic response to chemoradiation to warrant surgical reexploration for possible resection (Table 2). Reexploration was performed by the original surgeon. Of those patients who showed a clinical response, two thirds were deemed unresectable on laparoscopic restaging because of biopsy-proved extensive vascular involvement or metastatic disease (peritoneal dissemination). The patient with extensive vascular involvement was still alive with disease at 16 months' follow-up, and the patient with metastatic disease survived 13 months. Only one patient had a sufficient objective response to preoperative chemoradiation on restaging to undergo a potentially curative pancreaticoduodenectomy. Despite negative resection margins on pathologic examination, with no lymph node involvement, the patient had a recurrence and survived for 18 months (from initial surgical staging as locally advanced) after developing widely metastatic disease.

DISCUSSION

Pancreatic cancer is a highly aggressive and generally lethal disease. In addition, conventional treatments have had little impact on the natural history of the disease.[1,3,8] Although overall survival rates remain dismal, complete (R0) surgical resection of the tumor with negative lymph nodes remains the therapeutic goal in patients with a potentially resectable pancreatic adenocarcinoma, offering the best hope for long-term survival.[3,6] Even with aggressive surgical resection and multimodality therapy, actual long-term survivors of pancreatic cancer are rare.[1]

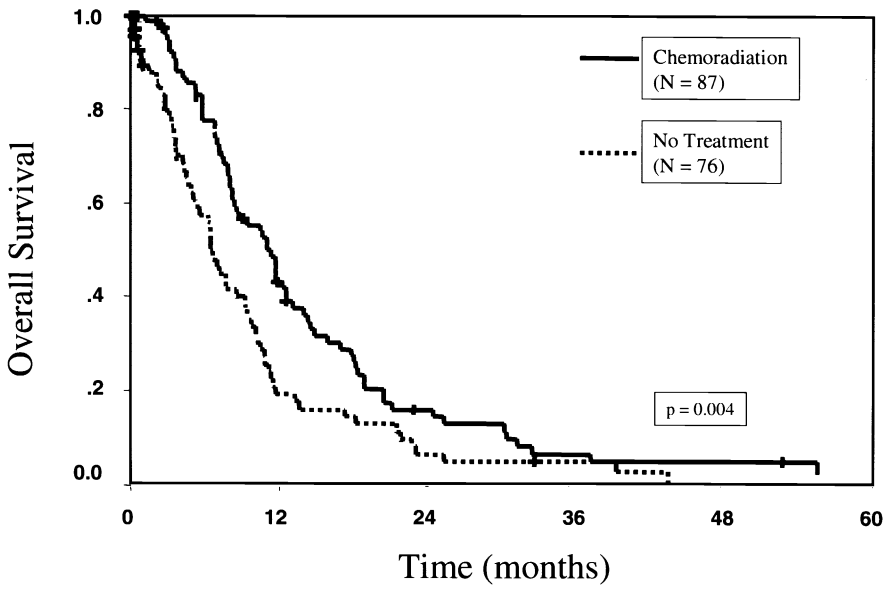

Fig. 1. Overall survival of patients with surgically staged, locally advanced pancreatic cancer treated with aggressive standard (5-FU/gemcitabine based) and experimental multimodal regimens, compared to those patients treated with best supportive care.

Table 2. Clinical responses to chemoradiation

	Patient 1	Patient 2	Patient 3
Age (yr)	62	67	52
Sex	F	M	M
Presenting symptom	Jaundice	Abdominal pain	Jaundice
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Location of pancreatic tumor	Head of pancreas	Neck of pancreas	Head of pancreas
Initial operative staging	Laparoscopy	Laparoscopy	Laparoscopy + laparotomy
Determination of locally advanced stage	PV/SMA involvement	SMA/celiac axis involvement	PV encasement
Chemoradiation	5-FU, RT	Cisplatin, Topotecan, RT	Gemcitabine, RT
Response	Decreased size and CA 19.9	Decreased size (80%)	Decreased size (>50%)
Restaging laparoscopy	Yes	Yes	Yes
Resection	No (PV/celiac axis involvement)	No (peritoneal disease, celiac node [+])	Yes (negative margins, 0/22 lymph nodes [−])
Subsequent chemoradiation	None	Doxorubicin, 5-FU	5-FU, RT
Survival	AWD (16 mo)	DOD (13 mo)	DOD (18 mo)*

AWD = alive with disease; DOD = died of disease; PV = portal vein; RT = external-beam radiation therapy; SMA = superior mesenteric artery. After restaging, these three patients underwent surgical reexploration for potentially curative resection.
*Time from initial diagnosis of pancreatic adenocarcinoma.

Because of the aggressive nature of the disease, most patients are initially seen with either metastatic disease or locally advanced disease, precluding a potentially curative surgical resection.[7,14] Locally advanced disease is generally defined on the basis of extensive vascular involvement (other than portal vein/superior mesenteric vein) or nodal involvement outside the region of surgical resection. Most patients can be adequately staged by means of modern CT or MRI techniques; however, some locally advanced disease still requires surgical staging, by means of either laparoscopy, with or without ultrasound imaging, or laparotomy.[1,40] In patients with locally advanced disease, external-beam radiation therapy and concomitant chemotherapy were shown to prolong survival in the adjuvant setting,[23] although this has not been confirmed in the adjuvant setting in the recent European Study Group for Pancreatic Cancer or European Organization for Treatment and Research of Cancer trials.[24–26] As a result, numerous groups have adopted the strategy of administering combined-modality therapy in the neoadjuvant setting for locally advanced disease in an attempt to enhance resectability rates, ultimately improving overall survival rates.* However, data to support this approach are limited, and the efficacy of these approaches is questionable. These studies have been criticized for their inclusion and selection bias, as well as for difficulties in defining locally advanced disease and standardizing the staging prior to treatment. To date, there are no prospective trials that have demonstrated the downstaging of surgically staged, locally unresectable pancreatic cancer.

Studies by Hoffman et al.[21,22] and Yeung et al.[38] at Fox Chase Cancer Center used an aggressive regimen of 5-FU/mitomycin/50.4 Gy radiation therapy to downstage patients with locally advanced pancreatic cancer; an improved median survival was seen in patients undergoing surgical resection (15.7 months; N = 24/53 patients) compared to patients with unresectable disease. The overall median survival was 9.7 months, and none of the patients demonstrated a complete response on pathologic examination. In this study, patients with both pancreatic and duodenal adenocarcinoma were included, and many of the patients (N = 10/53 patients) were staged as locally advanced at outside institutions using nonstandardized staging criteria. In a retrospective review from Duke University, by White et al.,[37] of 25 patients with biopsy-proved locally advanced pancreatic adenocarcinoma undergoing neoadjuvant chemoradiation (45 Gy radiation therapy/5-FU ± mitomycin C and/or cisplatin), eight patients underwent surgical reexploration after restaging, with resection in five patients. Preoperative staging was determined by radiographic or intraoperative evidence. Of the five patients who underwent resection, four had positive margins of resection. One patient underwent resection with negative margins and had a complete response, as demonstrated on pathologic examination; the patient developed distant metastasis and died of disease at 17 months. This patient was staged ini-

*References 22, 32, 34, 36–38, 41, and 42.

tially at a referring institution, and neither pretreatment nor post-treatment CT scans showed a definitive mass, which raises the issue of whether the tumor initially appeared to be locally advanced because of pancreatic inflammation.[37] A study by Todd et al.,[5] from UCLA, reported promising results with the use of an aggressive four-drug chemotherapeutic regimen in downstaging locally advanced pancreatic adenocarcinoma. The response rate was 39%, with six patients demonstrating a sufficient clinical response to warrant reexploration and four patients undergoing a potentially curative resection. The median survival of the six patients was 28 months, as compared to a median survival of 15.5 months for the entire group (N = 38 patients). Again, this study demonstrated inconsistencies in the original staging of the pancreatic tumor prior to chemoradiation, with inclusion of patients staged at outside institutions on the basis of both radiologic and surgical criteria. In addition, many of these patients had limited local venous involvement, suggesting that their responses could be related to tumor burden. A recent study by Snady et al.,[32] from Mt. Sinai Medical Center, examined 159 patients with locally unresectable disease treated with surgery alone, with or without postoperative chemoradiation (N = 91), vs. neoadjuvant 5-FU/streptozotocin/cisplatin/54 Gy radiation therapy followed by selective surgical resection (N = 68). In this trial, 30 patients in the multimodality group were clinically downstaged, with resection in 20 patients, leading to an improved survival in the multimodality group of 23.6 months median survival (compared to 14.0 months for the adjuvant treatment group; $P = 0.006$). Although the investigators concluded that neoadjuvant chemoradiation could result in downstaging of locally advanced pancreatic cancer and lead to improved survival, the initial staging of the patients within the trial lacked uniformity. The patients were staged initially at numerous centers, and resectability was determined on the basis of a combination of diagnostic tools: CT scans, angiography, endoscopic ultrasound imaging, laparoscopy, and/or laparotomy.[32] Several other studies have examined small numbers of patients who were deemed unresectable by a combination of surgical and radiologic staging methods, with overall partial response rates ranging from 20% to 60% and surgical resection rates ranging from 10% to 25%.[27,28,30,31,36] The numerous chemoradiation regimens are not standardized, and the staging criteria lack uniformity. A summary of these studies is presented in Table 3.

In the present study, after routine preoperative evaluation, patients underwent surgical staging by means of extensive laparoscopy or open exploration at our institution. In most instances, an extended multiport laparoscopic exploration was performed. Previous reports from Memorial Sloan-Kettering Cancer Center have outlined this procedure[40] and validated this technique as having greater than 90% accuracy in determining resectability, with a positive predictive value for determining unresectability of 100%.[40] In combination with thin-cut, contrast-enhanced CT scans of the pancreas, unresectability is proved with a high degree of accuracy and the diagnosis in each case is determined with histologic confirmation. After surgical staging, these patients underwent chemoradiation, as directed by our medical and radiation oncologists, consisting of either standard 5-FU/gemcitabine–based regimens, with or without radiation therapy, or a number of experimental protocols. Overall survival was improved in the patients who received therapy compared to those who were treated with best supportive care (11 months vs. 6.5 months; $P < 0.004$) (see Fig. 1). This improvement in survival may represent the efficacy of therapy and is consistent with results in other published reports.[2,9,43] The numbers within each group of patients treated with the various chemoradiation regimens were too small to determine whether any one regimen was more effective. A selection bias favoring the treatment group may exist. Despite this potential bias, the data in this study suggest that currently available chemoradiation regimens are not effective in downstaging surgically staged, locally advanced pancreatic cancer from unresectable to resectable with any discernible long-term improvements in overall prognosis.

The differences between our results and those from previously cited reports may lie in the definition of locally advanced disease. In this study, all patients were surgically staged, with histologic proof of unresectable disease. The intraoperative assessment was made by experienced pancreatic surgeons with extensive familiarity in vascular reconstructions. The issue is further complicated by the varying degrees of peripancreatic inflammation or pancreatitis seen at the time of the initial evaluation, which can resolve during the period of chemoradiation. However, these data suggest that patients who truly have either extensive venous or arterial involvement at the time of the original procedure rarely, if ever, respond sufficiently to current multimodal approaches, allowing for subsequent potentially curative resections. Our results in which only 3 of 87 patients were considered amenable to resection on restaging support this contention.

CONCLUSION

Although chemoradiation is associated with an improvement in overall survival for locally advanced

Table 3. Review of recent studies evaluating efficacy of neoadjuvant chemoradiation in the treatment of pancreatic adenocarcinoma

Reference	(N)	Chemo/RT	Response	Resection	Survival Advantage (months)	Comments
Snady et al.[32] (Mt. Sinai, 2000)	68	5-FU/CDDP STP 50.4 Gy RT	30/68	20/68	23.6 vs. 14	Initial staging at multiple centers Both OR/CT staging
Hoffman et al.[22] (Fox Chase, 1998)	53	5-FU MITC 50.4 Gy RT	0 CR	24/53	15.7 vs. 9.7	10 staged elsewhere Both pancreatic and duodenal cancers
Todd et al.[35] (UCLA, 1998)	38	5-FU/LV MITC Dipyridamole	14 PR/1 CR	4/6	28 vs. 15.5	26 staged OR 12 staged CT
Staley et al.[20] (MDACC, 1996)	39	5-FU 50.4/30 Gy RT/IORT	39% (>50%) PR	39	None	Not locally advanced All deemed resectable radiographically
Morganti et al.[42] (Italy, 1999)	20	5-FU/IORT 39.6 Gy RT	3 PR	9/20	18.5 vs. 8.3	12 locally advanced 8 radiographically resectable
Bajetta et al.[41] (Italy, 1999)	32	5-FUDR/LV 50 Gy RT	22PR	5/32	None	16 staged OR 16 staged CT
Present study (Memorial Sloan-Kettering Cancer Center, 2001)	87	80.4% 5-FU or Gemcitabine	3/87 PR	1/87	None	All staged OR

CDDP = cisplatin; CR = complete response to therapy; FUDR = floxuridine; IORT = intraoperative radiation therapy; LV = leucovorin; MITC = mitomycin C; PR = partial response to therapy; STP = streptozotocin.
Overall response rates and rates of potentially curative resection vary significantly; survival rates remain dismal with current treatment regimens.

disease, it rarely permits subsequent potentially curative pancreatic resections in adequately staged patients. Standardized multimodality therapies need to be evaluated by means of randomized prospective trials, and novel approaches are required for the treatment of locally advanced pancreatic cancer.

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Treatment of Ampullary Villous Adenomas That May Harbor Carcinoma

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Villous adenoma of the ampulla of Vater is a rare tumor. It is a deceptive tumor because it is a premalignant lesion and biopsies of the lesion are false negative in 25% to 56% of patients. The primary focus of this report is 23 of 30 patients with villous adenoma of the ampulla of Vater who underwent Whipple operations. Paraffin blocks from 22 patients were available. In eight patients, blocks of the biopsies and the corresponding resected specimens were available. Immunohistochemical studies using antibodies to p53 and Ki-67 were performed to determine whether accumulation of these antibodies in the biopsy specimens would identify false negative biopsies. There was one operative death. The 2-, 5-, and 10-year survival rates for the 22 patients surviving a Whipple operation were 74%, 57%, and 35%, respectively. Three patients died of cancer. The mean p53 expression index was increased in adenomas to 88 ($P = 0.001$) and in carcinomas to 114 ($P = 0.01$), compared with 12.6 for normal ampullary epithelium adjacent to tumor. Significant differences in the Ki-67 proliferation index were noted between normal adjacent epithelium (13%), adenoma (34%, $P = 0.0002$), and carcinoma (53%, $P = 0.034$), as well as between adenomatous epithelium and carcinoma (34% vs. 53%, $P = .012$). Villous ampullary adenocarcinoma was present in 65% of patients with villous adenoma (87% if patients with carcinoma in situ in resected specimens are included). Because of the high false negative rate of ampullary biopsies, and the inability to accurately stage these lesions, we recommend pancreaticoduodenectomy in most patients. Studies with p53 and Ki-67 markers suggest that they may be helpful in the recognition of ampullary villous cancer not identified on routine biopsies. (J GASTROINTEST SURG 2002;6:770–775)

KEY WORDS: Villous adenoma, ampullary

Villous ampullary tumors are deceptive. Carcinoma may be sequestered in large villous tumors or in the depths of a tumor not accessible to biopsy. The incidence of false negative endoscopic biopsy findings ranges from 25% to 56%.[1–4] Villous tumors of the ampulla of Vater are premalignant lesions,[5–7] and malignant transformation increases as the villous component increases.[2,7] Twenty-six percent[1] to 50%[8] of villous adenomas are malignant and 25% to 50% of malignant villous adenomas have invasive cancer in the resected specimen.[2] Sixty-five percent of our patients with villous adenoma had adenocarcinoma in resected specimens. If patients with carcinoma in situ are included, 87% of resected specimens were cancerous. One must be mindful of the malignant potential, the difficulty in preoperative staging, and the high rate of recurrence of ampullary villous adenomas.

Whether a villous ampullary lesion is malignant remains uncertain until after pancreaticoduodenectomy or transduodenal wide local excision. Despite the high malignancy rate for ampullary villous adenomas and the high recurrence rate after endoscopic removal, this procedure is frequently used in patients who can tolerate a curative operation.[9–12] There are, however, patients who are unsuitable for major surgery in whom endoscopic resection will cure small noninvasive or pedunculated lesions. In some patients, with slow-growing tumors,[4] repetitive endoscopic removal may control recurrent tumor for the remainder of the patient's life.

Because of the high rate of false negative biopsies and the high prevalence of carcinoma in ampullary villous tumors, one of the objectives of our study was to determine whether immunohistochemical analysis can identify patients with normal biopsy results who

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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00040-9

harbor carcinoma.[13] Younes et al.,[13] in contrast to others,[14] demonstrated that p53 is present throughout all stages of ampullary carcinoma. This suggests that the molecular events leading to p53 accumulation occur early in the progression to advanced stages of cancer. We examined the concordance of immunohistochemical staining for p53 and Ki-67[15] in endoscopic biopsies and villous adenocarcinoma of resected specimens from the same patients to determine whether retention of p53 and/or Ki-67 in benign biopsy specimens is indicative of cancer in ampullary villous adenomas in which case a major operation is required to eradicate disease.

METHODS AND PATIENTS

Between 1983 and 1999 we treated 30 patients (22 men and 8 women) with villous adenoma. The mean age was 66 years (range 44 to 76 years). The predominant, presenting symptoms included jaundice in 11 patients, pain in six patients, weight loss in six patients, pancreatitis in five patients, and anemia in four patients. Colon cancer was or had been present in 14% of these patients and colon polyps in 25%. No patient had familial polyposis or Gardner's syndrome. Twenty-nine of the lesions involved the ampulla of Vater, and one was located inferior to the ampulla. Biopsy specimens were obtained endoscopically in each case. Pancreaticoduodenectomy was performed in 23 patients. Endoscopic resection was performed in four patients. Transduodenal wide local excision and reconstitution of the pancreatic and bile ducts were performed in two patients. The results in these six patients are presented in Table 1. A seventh patient refused operation.

All microscopic slides were stained with hematoxylin and eosin and reviewed by two or more pathologists. Paraffin blocks of the biopsy and/or resection specimens were available from 22 patients. Paraffin blocks of four normal ampullas obtained from patients undergoing surgery for chronic pancreatitis were used as control specimens. Matched biopsy and resection tissue blocks were available in eight patients.

Sections 5 μ thick were cut from each available block, and antigen retrieval was performed using citrate buffer and steam for 20 minutes (pH 6). Antibodies directed against p53 (clone 12-1, Bio Genex, San Ramon, CA) and Ki-67 (Mib-1 clone, Dako Corp., Carpinteria, CA) were used as primary antibodies. After serial washes, secondary antibodies were incubated for 20 minutes, respectively. The signal was detected using avidin-biotin complex. Hematoxylin was used as a counterstain.

Positive nuclear staining was a positive signal for both antibodies. The percentages of cells carrying positive signals in the normal duodenal tissue, adenoma, and carcinoma (if present) were quantified. The initial biopsy specimens and the resection specimens were analyzed separately and in a blinded fashion. The percentage of positive cells was used as the sole discriminator of Ki-67 expression (proliferation index). Intensity of p53 was semiquantified using a scale of 1 to 3, with 1 corresponding to weak but detectable nuclear stain and 3 intense nuclear stain. The intensity value was multiplied by the percentage of positive cells to obtain a p53 expression index (intensity $\times$ percentage = p53 index).

Statistical analysis was performed using Student's *t* test.

RESULTS

Patients undergoing pancreaticojejunostomy were divided into three groups on the basis of their preoperative biopsy results. Group I included six patients whose biopsies showed villous and tubulovillous adenomas. Three of these patients, one with positive lymph nodes, had adenocarcinoma in the resected specimens. Group II consisted of five patients (group IIA) whose biopsies showed carcinoma in situ on the preoperative and resected specimens. None of these patients had positive lymph nodes. Seven patients (group IIB) had carcinoma in situ on their biopsy specimens and adenocarcinoma on the resected specimens. Six cancers were invasive. One patient had a positive lymph node. Five patients in group III had adenocarcinoma on their biopsy and resected specimens. All patients in group III had metastasis or invasive carcinoma at resection. Inaccurate preoperative diagnoses in 43.5% of patients were due to false negative biopsy findings (13%), and the diagnosis of carcinoma in situ rather than invasive carcinoma (30%). The final pathologic diagnoses in resected specimens were commensurate with the histologic findings on preoperative biopsy in 56% of all patients. The mean follow-up was 7 years (range 3 months to 15 years) for patients in group I, 8 years (range 0 to 11 years) for patients in group IIA, 7.5 years (range 2 to 16 years) for patients in group IIB, and 5 months (range 1 month to 11 years) for patients in group III. The follow-up for 22 patients surviving a pancreaticoduodenectomy is current in 12 patients (55%) for a mean of 10 years (range 2 to 16 years).

In the group undergoing pancreaticoduodenectomy IIA, there was one operative death (4%) due to multiorgan failure in a patient who had received ra-

Table 1. Endoscopic and transduodenal resections for villous adenoma

Patient	Biopsy diagnosis	Operation	Follow-up
1	Tubulovillous with carcinoma in situ	Endoscopic resection Carcinoma in situ	Endoscopic re-resections × 2 of recurrence Alive and well—1 yr
2	Villous adenoma with carcinoma in situ	Endoscopic resection Carcinoma in situ	Died within 1 yr—pulmonary complications, endoscopic re-resections × 1 of recurrence
3	Tubulovillous	Endoscopic resection Carcinoma in situ	Died—1 yr cause unknown
4	Tubulovillous with carcinoma in situ	Endoscopic resection Carcinoma in situ	Endoscopic re-resections × 2 of recurrence Alive and well—1 yr
5	Tubulovillous	Transduodenal resection of pedunculated tumor No carcinoma	Alive and well—1 yr
6	Tubulovillous with carcinoma in situ	Transduodenal resection had villous tumor at resection line No carcinoma	Alive and well—5 mo
7	Villous adenoma No carcinoma	No operation	No follow-up

diation therapy after a resection for colon cancer. This patient had carcinoma in situ on the biopsy and resection specimens. Seven patients died during the follow-up period. One patients in group I died of an unknown cause after 7 years, and one died of hepatitis within 3 months. In group IIB, one patient died of a stroke at 6 years, and one patient with cancer on the resected specimen died of metastatic cancer at 2.5 years. In group III, one patient died of liver cirrhosis and two patients with liver metastases died, one at 5 months (metastases existed at operation) and one at 2 years after operation. Fig. 1 represents the life-table analysis. Using the TNM staging system,[16] five patients undergoing a Whipple operation were classified as stage I, 13 as stage II, four as stage III, and one as stage IV. In 15 of 23 patients, the mean greatest dimension of tumors was 3 cm (range 1.2 to 8.0 cm). Based on this small sample, tumor size was not a predictor of malignancy invasion or outcome. Surgical complications in one patient each include intra-abdominal abscess, wound infection, gastrointestinal bleeding, pancreatic fistula, gastroparesis, and gastric outlet obstruction requiring gastroenterostomy.

The origin of ampullary villous tumors is frequently difficult to determine. In 13 of 15 patients with adenocarcinoma, tumor shown on the resected specimens appeared to originate in the ampulla and to extend into the bile and/or pancreatic ducts. This is in contrast to benign tumors, which rarely extend up these ducts.[3] The 2-, 5-, and 10-year survival rates for 22 surviving patients undergoing a pancreaticoduodenectomy were 74%, 57%, and 35%, respectively. This is comparable to the 3- and 5- year survival rates of 72% and 52% reported by Beger et al.[1] and the 5- and 10-year survival rates of 53% and 42% obtained by Chappuis et al.[17] in a series of 31 patients with invasive cancer.

In six patients undergoing endoscopic resection or transduodenal wide local excision for villous adenoma with carcinoma in situ, death occurred at 1 year from pulmonary insufficiency in one patient, and five patients recently treated have been followed for 1 year or less. None of the patients died of ampullary cancer, but three of four patients undergoing endoscopic removal required one or two endoscopic resections for tumor recurrence. Each of these patients had carcinoma in situ on their original biopsies.

In seven of eight patients tested for the immunohistochemical expression of p53 and Ki-67, the biopsy results from normal, adenomatous, and neoplastic tissues were similar to those obtained from corresponding tissue from resected specimens. Their expression increased moving from normal to adenoma to carcinoma tissue. p53 increased from normal ampullary epithelium to adenomas (13 vs. 88, $P = 0.001$) and carcinomas (13 vs. 114, $P = 0.01$). No significant difference in p53 expression was noted between adenomatous epithelium and carcinoma. Also noted was the difference in p53 expression between ampullary epithelium in control patients with chronic pancreatitis and normal ampullary epithelium adjacent to neoplastic tissues (4 vs. 14, $P = 0.03$).

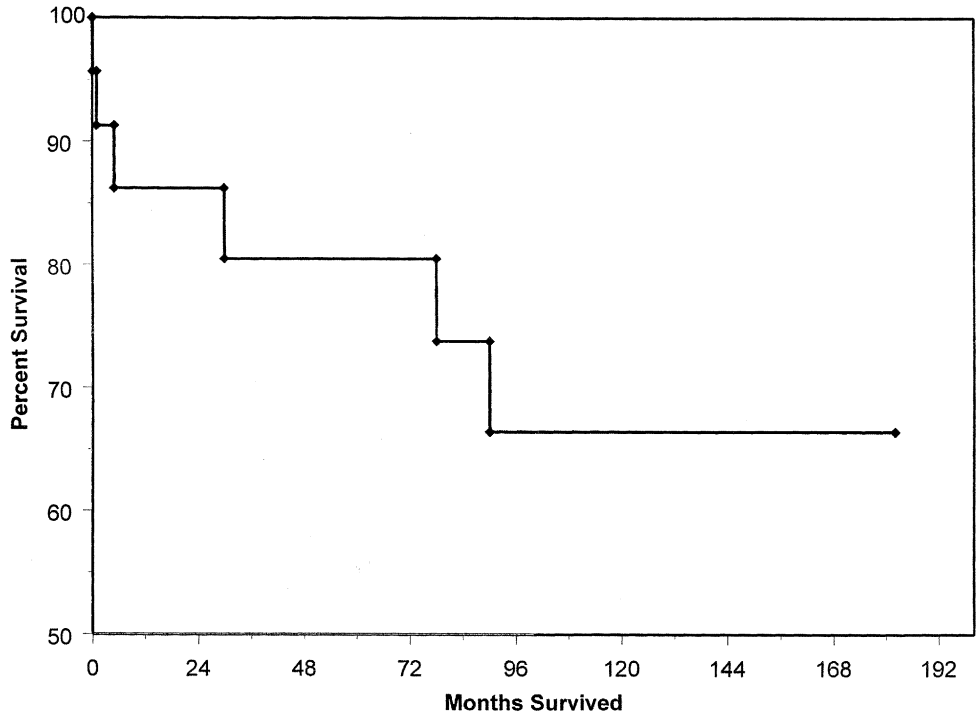

Fig. 1. Life-table analysis of 23 patients undergoing Whipple resection for villous adenoma of the ampulla of Vater.

Ki-67 expression is normally found at the base of crypts of ampullary epithelium. However, in adenomas, Ki-67 expression is seen not only at the base of crypts, but also in the surface epithelium. Significant differences in Ki-67 expression (proliferation index) were noted between normal ampullary epithelium and both adenoma (7% vs. 29%, $P = 0.0002$) and carcinoma (7% vs. 68%, $P = 0.034$), adenomatous epithelium and carcinoma (29% vs. 68%, $P = 0.012$), and ampullary epithelium from control patients and normal ampullary epithelium adjacent to neoplastic tissue (13% vs. 20%, $P = 0.03$).

DISCUSSION

Villous adenomas of the duodenum occur most commonly at the ampulla of Vater. If one looks closely at the periphery of ampullary adenocarcinoma, one will find areas of unequivocal villous adenoma at the margin in many.[18] Adenocarcinoma of the ampulla confirmed by pancreaticoduodenectomy resection was present in 15 (65%) of 23 of our patients, 20 (87%) of 23 if patients with carcinoma in situ are included. The unreliability of biopsies [1–4,19–21] from ampullary villous tumors and the inability to accurately stage these lesions preoperatively create management problems. Endoscopic ultrasonography (EUS) is of limited value in staging.[21] Recognition of tumor invasion by this means was accurate in 44% of patients and false positive for lymph node metastasis in 31%. Other investigators[22,23] noted the unreliability of EUS to recognize lymph node metastases. Although EUS may help stage villous tumors before operation, an accuracy rate of 78%[23] for defining the depth of tumor penetration is not reassuring, because complete resection is the important determinant of patient survival.[22] Menzel et al.[24] reported that small, high-frequency, flexible catheters may enhance the role of EUS in the examination of villous tumors of the ampulla of Vater.

Frequent cancer in villous tumors of the ampulla of Vater, a 46% recurrence rate after endoscopic excision,[3] and the inability to accurately stage tumors preoperatively leads us to agree with those who recommend pancreaticoduodenectomy for all patients with no contraindications to major operations.[1,3,4,17,22] Endoscopic or transduodenal local resection is adequate for T1 lesions. On the other hand, the adequacy of endoscopic or wide local excision cannot be confirmed at the time they are performed without serial frozen sections of the entire specimen.[25] Endoscopic or wide local resection should primarily be restricted to high-risk patients or patients with small pedunculated adenomas.[26] Although our six patients undergoing endoscopic resection or transduodenal wide

local resection have not developed adenocarcinoma, three developed recurrent adenoma with carcinoma in situ and required further local resection. Their follow-up was short, and as Ryan et al.[4] stated, years may pass in some patients before invasive cancer occurs. Inability to exclude tumor invasion in many patients after endoscopic or wide local transduodenal excision makes these procedures less acceptable in view of the low morbidity and mortality of pancreaticoduodenectomy. Endoscopic surveillance after endoscopic and wide local transduodenal resections of villous tumors in anticipation of performing pancreaticoduodenectomy for recurrent tumor may be a poor operative choice in good-risk patients.

Wide local transduodenal resection has been used by numerous investigators[1,17,27–29] and is an alternative to endoscopic resection or pancreaticoduodenectomy. It is nevertheless a major operation that requires reconstruction of the pancreatic and common bile ducts. The risk of leaving a small focus of residual tumor in a large lesion or in the depth of a tumor is a concern. Patients with positive margins after wide local resection have a survival of less than 3 years. The method devised by Rattner et al.[30] for obtaining negative tumor margins at the time of wide local excision was not helpful for ensuring a negative deep margin. We used the operation twice without complications. Follow-up was short, but the recurrence in one patient with a small pedunculated tumor was unexpected. The second patient had residual adenoma cells at the resection margin. If tumor at the resection margin is identified, or the benign nature at the resection line is uncertain, one has the option to proceed with pancreaticoduodenectomy or perform the procedure later for recurrent tumor.

Retrospective pathologic review of our data suggests that seven lesions resected by pancreaticoduodenectomy might have been successfully treated by transduodenal resection. It could not be determined at operation, however, that adequate margins could be obtained with a less radical operation. The extent of invasive tumor growth into the common and pancreatic ducts would have prevented successful use of wide local excision in the remaining patients. Beger et al.[1] recommended local resection for villous adenoma with carcinoma in situ, but in our experience 58% of patients with carcinoma in situ on their biopsies had adenocarcinoma on resected specimens.

Sixty-five percent of our group of patients who had a Whipple procedure (87% if patients with carcinoma in situ are included) harbored carcinoma in resected tumors. This is higher than the 63% among patients reported by Ryan et al.[4] and others. In our experience, tumors in 16 (70%) of 23 of patients would not have been completely removed by wide local excision. This fact, along with the difficulty of staging tumors preoperatively and our inability to evaluate their malignant potential, support our bias that pancreaticoduodenectomy is the treatment of choice.[4,27,30]

The observation made by Younes et al.[13] and confirmed by us, that p53 accumulation in biopsies reflects the likelihood of cancer in the depths of a villous adenoma, may help select the operation for a given patient. Our studies suggest that p53 overexpression and an increase in the Ki-67 proliferation index occur in all stages of preneoplastic and neoplastic development of villous adenomas and are part of the oncogenic pathways of ampullary lesions. The statistically significant differences in expression of p53 and Ki-67 in control normal ampullary tissue versus normal ampullary epithelium adjacent to adenomas indicate that differences occur early in neoplastic transformation before morphologic changes are observed in tissue stained with hematoxylin and eosin. We believe that these markers, as well as others, including telomerase,[31] and the ras family of gene mutations[32] with which we have no experience, may aid in early diagnosis of ampullary cancer. Our data suggest that p53 or Ki-67 overexpression may be indicative of carcinoma in situ or invasive carcinoma in the resected specimen. Although these studies were not helpful in the diagnosis of cancer in our patients, more data may provide reliable limits of these tests that will lead to a decrease in false negative biopsy results.

CONCLUSION

Villous adenomas of the ampulla of Vater are deceptive tumors because of their propensity to harbor malignancy not seen on routine biopsy examination. At the present time, pancreaticoduodenectomy is the safest treatment for most of these lesions. This study suggests that eventually biological markers may identify the ampullary villous tumors that do not harbor malignancies, thus making major operation unnecessary.

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Cholecystectomy, Liver Resection, and Pylorus-Preserving Pancreaticoduodenectomy for Gallbladder Cancer: Report of Five Cases

John R. Doty, M.D., John L. Cameron, M.D., Charles J. Yeo, M.D., Kurtis Campbell, M.D., JoAnn Coleman, R.N., Ralph H. Hruban, M.D.

Carcinoma of the gallbladder is an uncommon yet highly malignant disease with a poor overall prognosis. Surgical resection offers the only hope for cure in patients with this type of cancer, but resection is often impossible because of advanced disease at the time of presentation. Patients with locally advanced gallbladder cancer, however, may occasionally be amenable to management by adding pancreaticoduodenectomy to cholecystectomy and liver resection. A retrospective review of patient records at the Johns Hopkins Hospital identified five patients with gallbladder cancer with peripancreatic lymph node involvement, who were treated by surgical resection including pancreaticoduodenectomy. The preoperative evaluation, operative technique, pathologic findings, and outcome were reviewed for each patient. Follow-up was obtained via clinic visit or telephone contact. All five patients underwent resection of the gallbladder cancer with an operation that included pylorus-preserving pancreaticoduodenectomy to remove the peripancreatic lymph nodes. In addition, four of the five patients underwent a nonanatomic liver resection. There were no in-hospital deaths. Two patients had postoperative complications; one had persistent drainage from a T-tube site and one had an anastomotic leak from the hepaticojejunostomy. Four patients have died of recurrent tumor during follow-up at intervals ranging from 11 months to 23 months. The fifth patient is alive and free of clinical disease at 42 months after operation. Carcinoma of the gallbladder is a highly malignant disease that is often not amenable to surgical cure. There is a select group of patients, however, in whom adding a pylorus-preserving pancreaticoduodenectomy can result in a potentially curative operation by removing extensive regional spread to the peripancreatic lymph nodes. (J GASTROINTEST SURG 2002;6:776–780)

KEY WORDS: Pancreaticoduodenectomy, gallbladder cancer, radical cholecystectomy

Carcinoma of the gallbladder is an uncommon disease in the United States with approximately 5000 new cases diagnosed each year. It currently is the sixth most common gastrointestinal malignancy, yet most patients are not diagnosed before operative intervention.[1] Patients often present at an advanced stage, and younger patients are even more likely to have extensive disease at the time of diagnosis. Five-year survival remains poor for patients with advanced disease.

Radical operations have been used to treat advanced carcinoma of the gallbladder, although a review of North American studies as to the efficacy of these operations is disparate and inconclusive.[2] The most radical operations include extended cholecystectomy with wedge resection of the gallbladder fossa, various degrees of hepatic resection, and pancreaticoduodenectomy. Most such radical operations have been performed in Japan. Surgeons in the United States have been reluctant to add an extensive operation such as pancreaticoduodenectomy to an already major procedure for a disease with a dismal prognosis.

A review of patients with gallbladder cancer at the Johns Hopkins Hospital has identified a subset of patients with locally advanced disease that appeared to behave in a different manner. Rather than invading extensively into the liver, the cancer spread inferiorly to the porta hepatis lymphatics and presented as a peripancreatic mass, with the associated clinical find-

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Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00039-2

ing of obstructive jaundice. These tumors were amenable to surgical resection, utilizing a cholecystectomy, wedge resection of the liver, portal lymphadenectomy, and pancreaticoduodenectomy.

CLINICAL MATERIAL

A retrospective review of patient records at the Johns Hopkins Hospital was conducted to identify patients with advanced carcinoma of the gallbladder who had undergone standard surgical treatment plus pylorus-preserving pancreaticoduodenectomy. Five patients were identified, and operative records for each of these patients were reviewed. The final pathology report from each patient was reviewed and correlated with the operative findings. Follow-up was obtained either by individual clinic visit or by direct telephone contact, and was completed in all patients.

CLINICAL COURSE

Five patients at the Johns Hopkins Hospital underwent surgical treatment for advanced carcinoma of the gallbladder, which included pylorus-preserving pancreaticoduodenectomy, during a 3-year period from 1996 to 1999. Patient ages ranged from 45 to 80 years; there were three men and two women. Patient demographics and preoperative evaluation are summarized in Table 1. All patients presented with obstructive jaundice as the principal symptom. Two patients had undergone a prior cholecystectomy and were referred to our institution with a known diagnosis of gallbladder cancer. Preoperative imaging studies were applied in a selective manner and included ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography, and visceral angiography. Percutaneous transhepatic cholangiography with placement of a biliary stent was performed in all patients before surgery.

All patients underwent a potentially curative surgical resection with an additive pylorus-preserving pancreaticoduodenectomy. There were no in-hospital deaths. Details of the final pathology report for each patient are summarized in Table 2. Four patients underwent a nonanatomic wedge resection of the liver to encompass the gallbladder fossa. Three patients had resection of the extrahepatic biliary tree, and one patient had partial resection and repair of the portal vein to obtain a negative surgical margin.

Four patients had negative surgical margins of the pylorus-preserving pancreaticoduodenectomy specimen. The remaining specimen had a positive margin in the lymph nodes at the uncinate process. All patients had peripancreatic and periportal lymph node involvement to varying degrees. Two of the four patients with nonanatomic liver resection had no tumor in the liver specimen. The other two patients had tumor in the liver specimen but clear (although within 1 mm) margins.

The mean length of stay after surgery was 13.2 days (range 9 to 17 days). Two patients (20%) had complications after surgery. One patient had an anastomotic leak at the hepaticojejunostomy, and one patient had prolonged drainage from a T-tube site. Four patients underwent adjuvant therapy after surgery. Chemotherapy regimens included 5-fluorouracil/leucovorin (2 patients), 5-fluorouracil alone (1 patient), and VP-16/carboplatin (1 patient). Three had combined chemoradiation, all with 4500 cGy radiation therapy. One patient refused adjuvant therapy. The mean length of follow-up was 23 months (range 11 to 42 months). Four patients have died of recurrent tumor during follow-up at intervals ranging from 11 to 23 months. The fifth patient is alive and free of clinical disease 42 months after operation. This last patient received two cycles of VP-16/carboplatin and 4500 Gy of radiation over 34 fractions.

Table 1. Patient demographics and preoperative evaluation

Patient	Age (yr)	Sex	Presentation	Prior biliary operation	Preoperative imaging
1	65	F	Painless jaundice, nausea	None	ERCP, angiography, PTC/PBD
2	80	M	Painless jaundice	Laparoscopic cholecystectomy	ERCP, CT, PTC/PBD
3	75	M	Painless jaundice	None	US, CT, PTC/PBD
4	77	F	Jaundice, pruritis, abdominal pain	None	US, CT, angiography, PTC/PBD
5	45	M	Chronic cholecystitis	Open cholecystectomy, common bile duct exploration	US, CT, PTC/PBD

ERCP = endoscopic retrograde cholangiopancreatography; PTC/PBD = percutaneous transhepatic cholangiography with percutaneous biliary drainage; CT = computed tomography; US = ultrasound.

Table 2. Pathologic findings

Patient	Pathology	Peripancreatic nodes (positive/total)	Periportal nodes (positive/total)	PPPD margins	Liver margins	Perineural invasion	Vascular invasion	Survival (mo)
1	Well-differentiated adenocarcinoma of the gallbladder (2.1 cm) with separate 1.5 cm mass in retropancreatic region	4/17	0	Neg	No tumor	Pos	Neg	23
2	Moderately differentiated adenocarcinoma of the gallbladder (2.0 cm)	6/12	0	Neg	No tumor	Pos	Pos	17
3	Moderately differentiated adenocarcinoma arising from a villous adenoma in the gallbladder with 3 cm metastatic lesion in uncinate process	2/16	0	Positive at uncinate	Neg	Pos	Neg	11
4	Infiltrating adenocarcinoma of the gallbladder with small cell component (2.8 cm) and metastatic lesion in pancreas	1/1	0/4	Neg	N/A	Neg	Pos	42
5	Multiple foci of moderately differentiated adenocarcinoma of the gallbladder (largest 1.5 cm) in bile duct and peripancreatic tissue	10/18	0	Neg	Neg	Pos	Pos	21

PPPD = pylorus-preserving pancreaticoduodenectomy.

COMMENT

Gallbladder carcinoma remains a difficult challenge because of the advanced state of the disease at the time of presentation. Unfortunately, there are few specific symptoms attributable to early-stage gallbladder cancer, and when more classic symptoms of biliary obstruction occur, the disease has usually progressed to an incurable stage. The only persons who are diagnosed at an early stage are those found to have an incidental cancer at the time of laparo-

Table 3. Selected tabulation of pancreaticoduodenectomy for gallbladder cancer

Reference	Year	*n*	Operation	Stage*	Mortality	Morbidity	Outcome
Nimura et al.[4] (Nagoya University)	1991	14	PPPD and lobectomy or segmentectomy	N/A	21% (3/14)	N/A	1 yr = 50% 2 yr = 21% 5 yr = 10%
Matsumoto et al.[5] (Yamanashi Medical College)	1992	14	Classic PD only	II = 1 III = 1 IV = 12	7% (1/14)	57% (8/14)	N/A
Nakamura et al.[6] (Hamamutsu University)	1994	7	HPD	V	0	71% (5/7)	1 yr = 57% 1 yr = 27%
Shirai et al.[7] (Niigata University)	1997	17	Classic PD; 15 nonanatomic, 2 extended right	II = 1 III = 3 IV = 13	6% (1/17)	N/A	5 yr = 29%
Miyazaki et al.[10] (Saga Medical School)	1995	2	HPD (nonanatomic)	IV	0	0	1 yr = 50%
Totals		54			9% (5/54)	62% (13/21)	

PPPD = pylorus-preserving pancreaticoduodenectomy; PD = pancreaticoduodenectomy; HPD = hepatopancreatoduodenectomy.
*Series by Matsumoto et al., Shirai et al., and Miyazaki et al. report stage by American Joint Committee on Cancer classification; Nakamura reports stage by Nevin classification.

scopic cholecystectomy for gallstones. The advanced cases reported here represent a small fraction of all gallbladder cancers. During the 3-year time period of this report, there were only 10 patients who underwent any form of surgery at the Johns Hopkins Hospital for primary gallbladder cancer, and the five cases described herein represent 50% of these patients.

Data from the National Cancer Data Base Report on Carcinoma of the Gallbladder by Donohue et al.[1] show that more than two thirds of patients will present with American Joint Committee on Cancer stage III or IV disease at the time of diagnosis. Disturbingly, younger patients are more likely to present with advanced disease. Five-year survival data from this study report a 60% 5-year survival rate for stage I disease, with a rapid decline to 5% for stage III and 1% for stage IV.

Despite these dismal statistics, the same study demonstrated that surgical intervention resulted in improved survival for all stages of disease. Although standard radical cholecystectomy (to include hepatic wedge resection of segments 4 and 5, and hepatoduodenal lymphadenectomy) has not been conclusively shown to improve long-term survival, the number of patients is small. In select groups of patients, as evidenced by our series, more extensive surgical resection can improve the outcome for advanced gallbladder cancer. A more aggressive approach to all forms of gallbladder cancer has been advocated by several authors in Asia. Su et al.[3] recently reported a 15% 2-year survival rate in patients with gallbladder cancer, noting that the only long-term survivors were patients who had complete resection of their disease. Several other small series have been reported that describe radical surgical approaches for advanced gallbladder cancer. These series have advocated pancreaticoduodenectomy combined with aggressive liver resection, also known as hepatopancreatoduodenectomy. Results of these series are summarized in Table 3. In general, extended liver resection combined with pancreaticoduodenectomy has resulted in high morbidity and variable early mortality. Long-term survival, however, seems encouraging, with two series reporting 5-year survival rates as high as 10% and 29%.[4,7] The morbidity from these aggressive operations is either related to the extent of liver resection (hepatic failure) or to the known complications of pancreaticoduodenectomy (biliary or pancreatic anastomotic leak, gastrointestinal bleeding).

A less aggressive approach would be to perform a limited hepatic resection combined with pylorus-preserving pancreaticoduodenectomy.[7–11] This is a more logical approach for obtaining a curative resection for this disease without the attendant morbidity and mortality from a major liver resection. This approach is supported by data from Shirai et al.,[7] where the majority of patients had nonanatomic liver resection combined with "classic" pancreaticoduodenectomy (hemigastrectomy). Despite the absence of adjuvant therapy, 5-year survival was nearly 30%.

Pylorus-preserving pancreaticoduodenectomy has evolved into a safe operation with minimal operative mortality and a low rate of serious complications.[4] Adding pylorus-preserving pancreaticoduodenectomy to cholecystectomy and wedge resection of the liver should likewise be a procedure that can be done

with little mortality, and low morbidity, as demonstrated in this small series of patients. The operation should be performed for that small group of patients with gallbladder cancer who present with minimal local disease but have extensive nodal involvement of the periportal and peripancreatic regions. In three of our patients, the peripancreatic nodal involvement was so extensive, and the local gallbladder disease so minimal, that the primary lesion was thought to be in the pancreas. We believe that these patients represent a subset of patients with locally advanced gallbladder carcinoma that appears to behave in a different manner. Rather than invading extensively into the liver, the cancer spread inferiorly to the porta hepatis lymphatics and presented as a peripancreatic mass, with the associated clinical finding of obstructive jaundice. In addition, the presence of small cell features may indicate a more favorable prognosis, as noted in the patient with the longest survival of 42 months (patient 4, see Table 2). Since the submission of the original manuscript, we have identified an additional patient who presented in a similar manner to the other five patients and was found to have gallbladder carcinoma with small cell features and tumor primarily in the pancreatic region. This patient underwent successful cholecystectomy, liver resection, and pylorus-preserving pancreaticoduodenectomy and is doing well 1 year after surgery with no evidence of recurrence.

CONCLUSION

The addition of pylorus-preserving pancreaticoduodenectomy can be safe and effective in a select group of patients with carcinoma of the gallbladder and extensive nodal spread to the periportal and peripancreatic regions. Nonanatomic resection of the gallbladder fossa should also be performed in these patients with gallbladder cancer and can be done without the increased operative risk of a major hepatic resection. Additional resection of the extrahepatic biliary tree or portal vein can also be performed if necessary. Patients can be expected to recover quickly after this operation and do well during the postoperative period. Early results are encouraging and continued follow-up is necessary to determine long-term survival.

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Carcinoid and Chylous Ascites: An Unusual Association

Alan P. Kypson, M.D., Mark W. Onaitis, M.D., Jerome M. Feldman, M.D., Douglas S. Tyler, M.D.

Chylous ascites caused by carcinoid tumors is extremely rare. While carcinoid tumors usually have an indolent course, their association with chylous ascites is a harbinger of a poor outcome. (J GASTROINTEST SURG 2002;6:781–783)

KEY WORDS: Carcinoid, chylous, ascites, neuroendocrine

Lipid-rich lymph may accumulate in the peritoneal cavity as chylous ascites as a result of trauma or obstruction of the lymphatic system. The incidence of chylous ascites is exceedingly rare with just 28 cases diagnosed over a 20-year period at Massachusetts General Hospital.[1] The most common cause of this disruption is malignancy, followed by trauma (including surgery) and inflammatory disorders. Diagnosis of chylous ascites involves invasive surgical procedures, CT imaging, and paracentesis, with analysis of ascitic fluid revealing a concentration of trigycerides higher than that in the plasma. Treatment usually consists of correcting the underlying cause, although paracentesis may provide symptomatic relief.

Carcinoids are relatively rare neuroendocrine tumors arising from amine precursor uptake and decarboxylation (APUD) cells. Occurring most commonly in the gastrointestinal tract, these tumors are known to produce a variety of protein and peptide products, the most characteristic of which is serotonin. The association between carcinoid tumors and chylous ascites has only been reported in a few case studies.[1–4] Over the past 30 years, nine patients with carcinoid tumors and chylous ascites have been evaluated at Duke University Medical Center.

METHODS

Between 1970 and 2000, approximately 875 patients with carcinoid tumors were evaluated by one of us (J.M.E.) at Duke University Medical Center. A retrospective review of the medical records in this database was performed to record presenting symptoms, pathologic features, and survival. All patients submitted 24-hour urine samples and had blood drawn at the time of initial evaluation. Serotonin and 5-hydroxyindoleacetic acid (5-HIAA) were measured in the urine, and serotonin was measured in the serum and in platelets. All patients presenting with chylous ascites underwent paracentesis with subsequent biochemical analysis of the fluid. Standard statistical methods were used.

RESULTS

Demographic analysis of this cohort indicates a 2:1 male:female ratio. Of the nine patients, four had tumors of midgut origin, two had tumors of pancreatic origin, two had tumors of unknown origin, and one had a tumor of bronchial origin. Mean age at the time of diagnosis was 57 years with a range of (37 to 80 years). Average time from diagnosis to death was 15 months with only one patient alive past 5 years. The most common presenting symptom was diarrhea, which was present in seven of the nine patients. Other presenting symptoms included nonspecific abdominal pain in all patients. Interestingly, none of the patients exhibited other classic features of the carcinoid syndrome.

Table 1 shows the mean urinary 5-HIAA levels in both this cohort of patients and a cohort of 242 patients with non–ascites-producing metastatic gastrointestinal carcinoid tumors treated at Duke University Medical Center over the same time period. As demonstrated by these data, tumors of patients with chylous ascites do not produce more serotonin than those of patients without ascites.

Treatment of these patients was varied. Four in the series received chemotherapy. Of these, two were given streptozocin with no clinical response. The other two patients received ^{131}I-MIBG treat-

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1091-255X/02/$—see front matter
PII: S1091-255X(02)00014-8

Table 1. Urinary 5-HIAA levels in patients who had carcinoid tumors with and without chylous ascites

	5-HIAA (mg/24 hr)
Ascites	63.9 ± 61.5
No ascites	69.1 ± 169.2
P value	0.80

ment. Of these, one patient had a long-term clinical response and was alive at last follow-up 6 years after diagnosis. The other is alive at 8 months of follow-up. Palliative shunts were placed in three of the patients with marginal results.

Survival analysis reveals a dismal prognosis for these patients. As shown in Fig. 1, those patients who had chylous ascites as a component of their symptomatology had markedly worse overall survival (11% at 5 years as opposed to 50%) compared to those patients who had metastatic carcinoid tumors without ascites.

However, as carcinoid-induced chylous ascites is thought to occur either from obstruction of lymph nodes by tumor or from intense mesenteric reaction blocking uptake of peritoneal fluid, we classified metastatic disease as to whether it was limited to the lymph nodes and mesentery (regional metastases) or extended to the liver or other distant sites. As shown in Fig. 2, although those patients with regional disease survive longer than those with distant disease, those with regional disease and chylous ascites do not. In fact, their survival chances are significantly worse than even those with distant metastatic disease.

DISCUSSION

Chylous ascites, leakage of lipid-rich lymph, is rare, with an incidence of approximately 1 in 20,500 patients.[1] The vast majority of cases result from lymphoma with the remaining etiologies including inflammatory processes, trauma, and congenital causes. Carcinoid tumors are also rare, with an incidence of approximately three cases per million population. Patients presenting with both of these conditions are extremely rare, but they comprise approximately 1% of those with carcinoids who have been seen at Duke University Medical Center over the past 30 years. Although this experience hardly constitutes a large series, it does allow us to draw some conclusions.

Although ascites and nonspecific abdominal pain are the main presenting symptoms in this group of patients, all but two had severe diarrhea, presumably secondary to serotonin overproduction. The proportion of patients in this series with diarrhea is higher than that in patients who have metastatic carcinoid tumors without ascites despite our finding of similar urinary 5-HIAA levels. Chylous ascites itself does not cause diarrhea[1]; in fact, diarrhea was not noted in any of the 28 cases reviewed. Perhaps some other active peptide was produced by the tumors in our series. Diarrhea in the presence of chylous ascites should at least raise the suspicion of a carcinoid tumor.

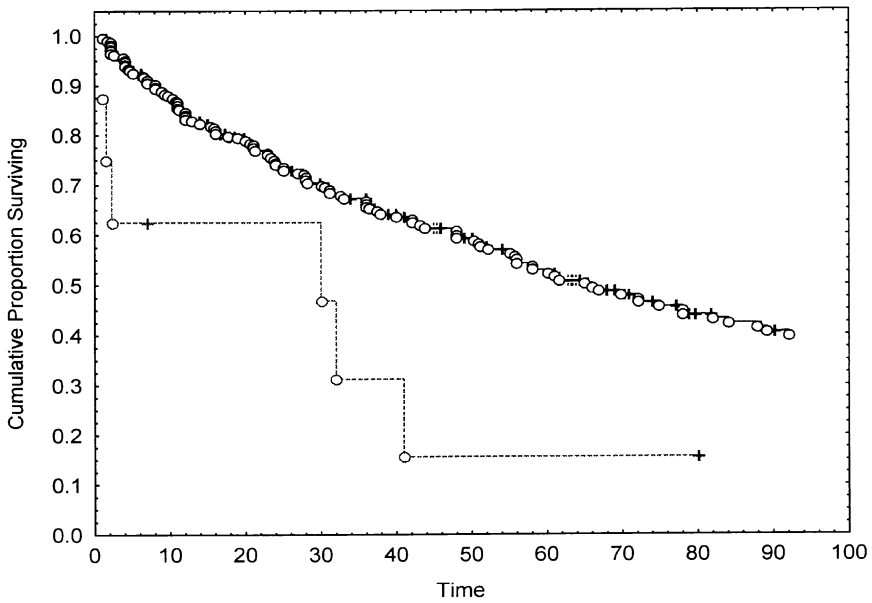

Fig. 1. Survival of patients who have metastatic carcinoid tumors with and without chylous ascites. Cumulative proportion surviving (Kaplan-Meier analysis). ○ = complete; + = censored; —— no ascites; - - - ascites. $P = 0.01$.

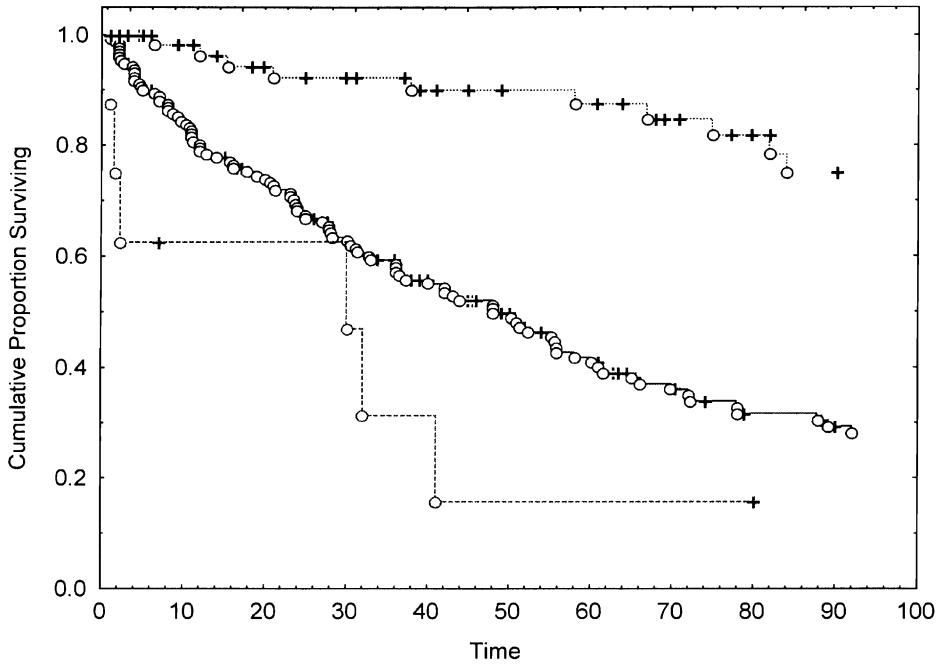

Fig. 2. Survival of patients with carcinoid tumors who have regional metastases, distant metastases, and chylous ascites. Cumulative proportion surviving (Kaplan-Meier analysis). ○ = complete; + = censored; —— distant; - - - regional; - – - ascites. $P < 0.01$.

Chylous ascites is a harbinger of a poor outcome in the setting of other diseases and also portends a grave outcome among patients with carcinoid disease. Although carcinoid disease often follows an indolent course, particularly in those patients with carcinoid tumors of midgut origin,[5] it is clearly more aggressive in those patients presenting with chylous ascites. The formation of chylous ascites, regardless of evidence for distant metastasis, may identify patients with particularly aggressive tumors. In these patients, early and aggressive treatment with ^{131}I-MIBG should be considered, as it led to clinical responses in our series.

CONCLUSION

Chylous ascites in the setting of a carcinoid tumor is an extremely rare event. Nevertheless, when a patient has chylous ascites and diarrhea, carcinoid tumors should be included in the differential diagnosis. Those who have this rare association have a much worse prognosis than those with other gastrointestinal carcinoid lesions and warrant an aggressive treatment approach.

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The American Hepato-Pancreato-Biliary Association (AHPBA)

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AHPBA MEETINGS

Two very successful meetings were conducted in 2001. In February, the third biannual "Americas" meeting was held at the Eden Roc Hotel in Miami, Florida. It included a hands-on postgraduate course on radiofrequency ablation and two and one-half days of papers, lectures, and symposia. In November, the annual Surgical Forum was held in conjunction with the American Association for the Study of Liver Diseases (AASLD). Topics discussed included intraductal papillary mucinous tumor and mucinous cystic neoplasm (M. Sarr), biliary injuries (W. Chapman), and hepatocellular carcinoma in cirrhosis (S. Helton).

FUTURE MEETING PROFILE

November 2002: AHPBA-AASLD Surgical Forum

Hepatic protection/living donor transplantation/hilar cholangiocarcinoma. Course Director: Steven M. Strasberg, M.D., Washington University at St. Louis, St. Louis, Missouri.

Protection of the Liver in Hepatic Surgery. Moderator: Pierre Clavien, University of Zurich, Zurich, Switzerland.

1. Evaluation of the cirrhotic and diseased liver prior to surgery (Jean Emond, Columbia Presbyterian Hospital, New York, New York).
2. Evaluation of minimal functional mass in liver surgery (Nicholas Vauthey, M.D., Anderson Hospital, Houston, Texas).
3. Portal vein embolization prior to surgery (*debate format*) (Jacques Belghiti, Hospital Beaujon Paris, France *vs.* Ravi Chari, Vanderbilt University, Nashville, Tennessee).
4. Protective strategies during liver injury (Pierre Clavien, University of Zurich, Zurich, Switzerland).
5. New "bloodless" techniques of liver transection/avoiding inflow occlusion (Steven Strasberg, M.D., Washington University at St. Louis, St. Louis, Missouri).

Living Donor Liver Transplantation: Why? How? Who? When? Moderator: Myron Schwartz, Mount Sinai School of Medicine, New York, New York.

1. Applied liver anatomy: Lessons learned from living donor transplantation (Amadeo Marcos, M.D., University of Rochester, Rochester, New York).
2. Hepatic regeneration in donor and recipient after living donor transplantation (Kim Olthoff, M.D., University of Pennsylvania, Philadelphia, Pennsylvania).

Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00048-3

3. Advanced hepatobiliary surgical technique in living donor transplantation (Masatoshi Makuuchi, M.D., University of Tokyo, Tokyo, Japan).
4. Living donor transplantation: When is it better than cadaveric? When is it worse? (Charles Miller, M.D., Mount Sinai School of Medicine, New York, New York).

Hilar Cholangiocarcinoma. Moderator: Theodore N. Pappas, M.D., Duke University Medical Center, Durham, North Carolina.

1. Preoperative imaging and staging of cholangiocarcinoma (William Jarnigan, M.D., Memorial Sloan Kettering Cancer Center, New York, New York).
2. Surgical resection for cholangiocarcinoma (Bryan Clary, M.D., Duke University Medical Center, Durham, North Carolina).
3. Palliative bypass for cholangiocarcinoma (Henry A. Pitt, M.D., Medical College of Wisconsin, Milwaukee, Wisconsin).
4. Transplantation in the management of cholangiocarcinoma—screening, diagnosis, and the Mayo Clinic experience (Gregory Gores, M.D., Mayo Clinic, Rochester, Minnesota).
5. Transplantation in the management of cholangiocarcinoma—staging, operative considerations, and the UCLA experience (Ronald W. Busuttil, M.D., UCLA, Los Angeles, California).

For information about this meeting and online registration go to AASLD.org

OTHER FUTURE MEETINGS

February 2003: 4th AASLD Biannual "Americas" Meeting, February 27–March 2, 2003. This will again be held at the Eden Roc Hotel in Miami, FL. The first day will be a postgraduate course chaired by C. Wright Pinson. Make this one with the family! Visit AHPBA.org for more information.

May 2004: 6th World Congress IHPBA Biannual Meeting, Washington, DC, May 27–June 2, 2004. The AHPBA hosts the IHPBA.

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Colorectal Surgery, October 25–26, 2002; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Introduction to Laparoscopic and Percutaneous Radio-Frequency Thermal Ablation of Renal Tumors, November 1, 2002; The University of Texas Southwestern Medical Center at Dallas. Cost: $795. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery Mini-Fellowship Program, November 3–8, 2002; February 23–28, 2003; April 20–25, 2003; June 22–27, 2003; August 24–29, 2003; October 26–31, 2003; The University of Texas Southwestern Medical Center at Dallas. Cost: $12,500 (team of 2 physicians and 1 nurse); $6,250 (physician); $1,000 (nurse). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): GERD—Medical/Surgical Management, November 15–16, 2002; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@ utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery, January 24–25, 2003; May 30–31, 2003; September 26–27, 2003; The University of Texas Southwestern Medical Center at Dallas. Cost: physicians ($300, lecture only; $1050, lecture and lab); UTSW and SCMIS Alumni ($250, lecture only; $950, lecture and lab); nurse ($175, lecture only; $375, lecture and lab). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Ventral Hernia, March 7–8, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Diagnostic Laparoscopy & Ultrasonography, April 11–12, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Management & Percutaneous Ablation of Small Retinal Tumors, July 25–26, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Management of CBD Stones, August 15–16, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Splenectomy, November 14–15, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

Published by Elsevier Science Inc.
1091-255X/02/$—see front matter
PII: S1091-255X(02)00047-1