SSAT/AGA/ASGE State of the Art Conference on Pancreatic Neuroendocrine Tumors

Consensus Statement

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Ever since the initial description of a pancreatic neuroendocrine (NE) tumor by Nicholls in 1902 the management of these very interesting and diverse neoplasms continues to evolve.[1,2] Although they are relatively uncommon, occurring in approximately one of every 100,000 people,[1] the treatment of NE tumors usually involves multiple modalities and a close collaboration between many different disciplines. As detailed in these review articles written as part of The Society for Surgery of the Alimentary Tract "State of the Art" conference, the treatment of patients with pancreatic NE tumors depends on the tumor histology and the degree of tumor involvement. The conclusions regarding the clinical management of patients with pancreatic NE tumors based on this multidisciplinary conference are illustrated in Figure 1.

As summarized by Dr. Robert Jensen from the National Institutes of Health in the first article entitled, "Pancreatic NE Tumors: Overview of Recent Advances and Diagnosis,"[3] the diagnosis of pancreatic NE tumors begins with the comprehensive history, physical examination, and biochemical screening. Most of these tumors secrete high levels of chromogranin A, which can be detected in the serum. In addition, biochemical testing should involve screening for other gastrointestinal peptides depending on the particular clinical syndrome. Localization of these tumors can often be achieved with high-resolution abdominal computed tomographic scan. Several recent studies have shown that somatostatin receptor scintigraphy is very sensitive in detecting occult disease with the majority of pancreatic NE tumors except for insulinomas. In cases of gastrinomas or other tumors involving the head of the pancreas, endoscopic ultrasound is very useful.

Treatment of primary pancreatic NE tumors is based on whether it is confined (localized) or metastatic. In the case of localized tumors, resection of the primary neoplasm is indicated, as detailed by Dr. Jeffrey Norton from Stanford University in the second article entitled, "Surgery for Primary Pancreatic NE tumors."[4] Enucleation of these tumors, especially in the case of insulinomas, is the preferred treatment. However, if the tumors are large or if the tumor is believed to be malignant, surgical resection may consist of distal pancreatectomy or pancreaticoduodectomy. In most cases, intraoperative ultrasound is useful to help delineate the number of tumors present and the degree of tumor involvement. In patients with inherited syndromes such as multiple endocrine neoplasia type I, special considerations must be taken before surgical resection, especially for gastrinomas. In the case of gastrinoma, duodenotomy is indicated to resect any submucosal tumors, which may be present.

In the third article, Dr. Bryan Clary from Duke University describes the treatment of choice for patients who present with isolated NE liver metastases.[5] Many studies have shown that patients with pancreatic NE tumors can have isolated metastases to the liver and can benefit from both a palliative and survival standpoint with complete tumor resection. In patients with isolated, resectable NE tumor liver metastases, resection of the primary tumor along with resection of the hepatic metastases can be performed. In the case of multiple hepatic lesions, multiple resections versus resection plus ablative technologists with thermal or cold modalities may be indicated. However, if the NE tumors are diffusely spread throughout the liver, hepatic artery embolization has been shown to be potentially a beneficial modality. Another potential option for patients with diffuse NE liver involvement is observation and/or somatostatin analogs to palliate symptoms from hormonal secretion.

In the fourth article entitled "Therapy with Radiolabeled Somatostatin Peptide Analogs for

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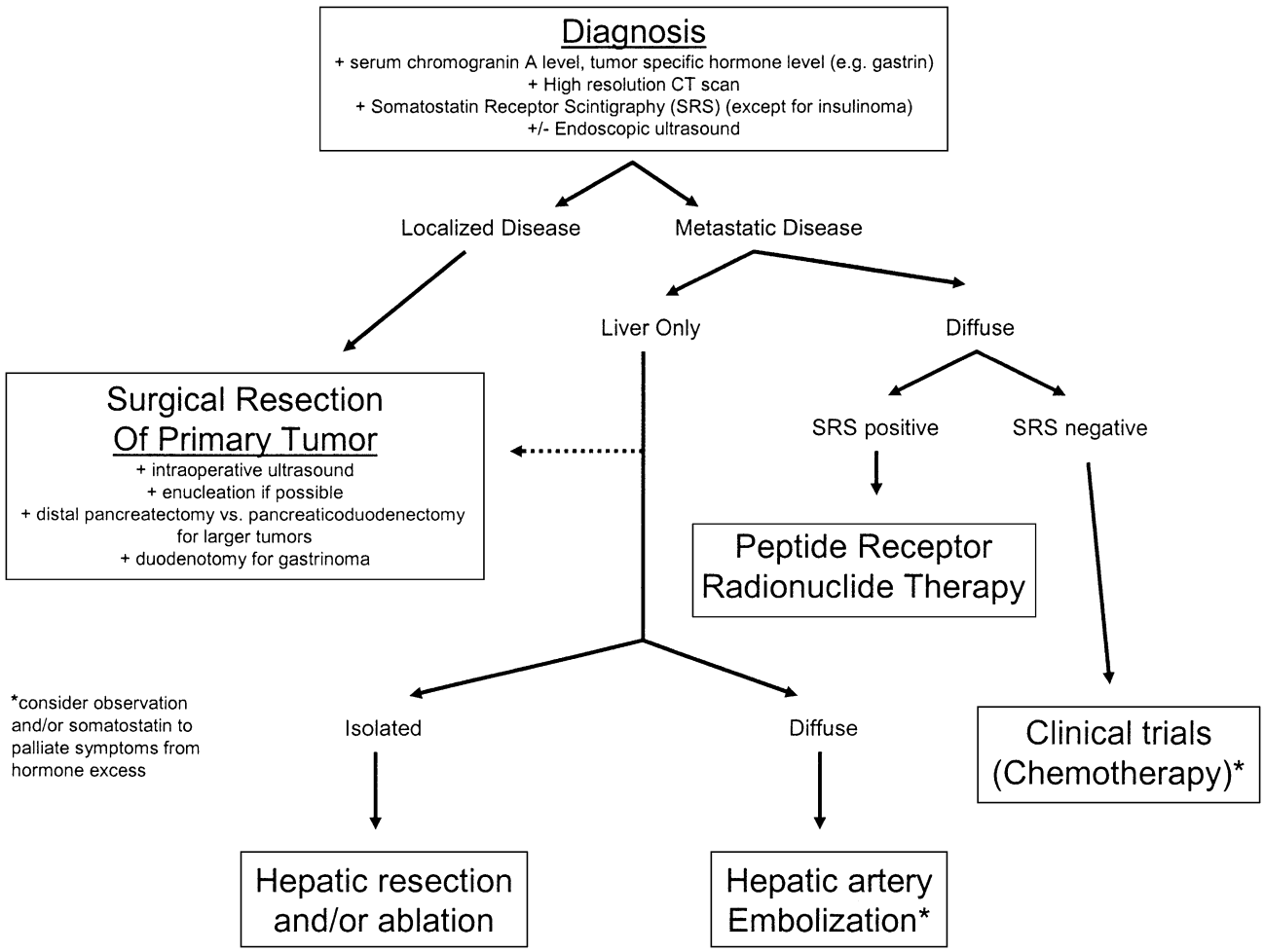

Fig. 1. Algorithm for treatment of patients with pancreatic neuroendocrine tumors. CT = computed tomographic scan. *See text for details.

Metastatic NE Tumors,"[6] Dr. David Bushnell from the University of Iowa describes a relatively new treatment for patients with pancreatic NE tumors that have metastasized to multiple sites in the body. Peptide receptor, radionucleotide therapy, or radiolabeled somatostatin therapy has been shown by many investigators to control NE tumor growth and reduce hormone secretion. In patients with widely metastatic disease in which their tumor can be visualized on somatostatin receptor scintigraphy, the therapy of choice would be peptide receptor, radionucleotide therapy.

Last, in the fifth article entitled "Therapeutic and Palliative Options for Diffuse NE Metastatic Disease,"[7] Dr. Kyle Holen from the University of Wisconsin summarizes the data regarding chemotherapy for patients with widely metastatic NE tumors who are not candidates for peptide receptor, radionucleotide therapy. Unfortunately, the experience with multiple regimens of chemotherapy has been disappointing to date. Standard chemotherapy regimens are generally not useful in this disease, and new studies should incorporate novel mechanisms of action. Thus, we highly encourage patients with metastatic NE tumors to consider enrollment in ongoing clinical trials. Another option would be observation with somatostatin analogs for palliation. However, there are several available strategies currently being tested that may result in durable treatment for these patients. It is hoped that with the maturation of ongoing clinical trials and directed laboratory research, we will find a tolerable and effective treatment for patients with diffuse metastases from pancreatic NE tumors.

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Pancreatic Neuroendocrine Tumors: Overview of Recent Advances and Diagnosis

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Pancreatic neuroendocrine (NE) tumors are seen in 0.5% to 1.5% of autopsies; however, less than 1 of 1000 cause symptoms, and therefore they are uncommonly seen by surgeons/clinicians, occurring with an incidence of 5 to 10 per million year in clinical series.[1,2] Pancreatic NE tumors are divided into 11 established classes that include those functional tumors causing a distinct clinical syndrome (gastrinomas, insulinomas, VIPomas, glucagonomas, somatostatinomas, GRFomas, ACTHomas, NE tumors causing carcinoid syndrome, NE tumors causing hypercalcemia [PTHrPoma], NE tumors secreting renin) and nonfunctional (NF) NE tumors (PPomas). NF NE tumors almost invariably secrete chromogranins (Cg), and in many cases, other products (neuron-specific enolase, human chorionic gonadotropin subunits, neurotension, pancreatic polypeptide, ghrelin), but these cause no distinct clinical syndromes and thus, NF pancreatic islet cell tumors (PICTs) symptoms are entirely the result of the tumor per se. Pancreatic NE tumors resemble carcinoids histologically and in their secretion of multiple peptides/amines, their biologic behavior, and many aspects of their tumor biology.[3,4] Except for insulinomas, which are uncommonly malignant (5%–15%), the other pancreatic NE tumors show predominantly malignant behavior (60%–90%).[1–3,5] Recently, there have been important advances in many aspects of pancreatic NE tumors that can affect surgical management including the following: in diagnosis, defining their natural history; identification of prognostic factors; in understanding their pathology; in their molecular pathogenesis, in localization modalities including endoscopic ultrasound, somatostatin receptor scintigraphy (SRS), and positron emission tomography (PET) scanning; increasing understanding of the importance of multiple endocrine neoplasia type 1 (MEN1) in patients with pancreatic NE tumors; and advances in treatments including surgical approaches.[1,2,4–9] A few of these important areas that pertain to the management of pancreatic NE tumors are briefly reviewed next.

DIAGNOSIS

Diagnosis is made by demonstrating elevated serum hormone levels with inappropriate hormone secretion, such as hypergastrinemia with increased acid secretion in gastrinomas causing Zöllinger-Ellison syndrome (ZES).[1,2,10] A recent prospective study of 261 patients with ZES shows the diagnosis should be suspect in any patient with peptic ulcer disease with diarrhea; without *Helicobacter pylori*, with a peptic ulcer disease complication, with prominent gastric folds, or with any other endocrinopathies. The diagnosis of ZES is becoming more difficult because of the widespread use of proton pumps inhibitors can mask symptoms leading to suspicion of ZES,[11,12] as well as cause hypergastrinemia in patients without ZES.[11] Recent studies report serum CgA is elevated in 70% to 95% of all pancreatic NE tumors, and so is a useful serum marker, especially for identifying NF pancreatic NE tumors.

NATURAL HISTORY

The natural history of pancreatic NE tumors is largely unknown because of their rarity and tendency to present late in their course.[3] However, studies of patients with gastrinomas have provided important insights, because these tumors frequently present early in their course and effective treatment for the acid hypersecretion exists, so their long-term course can be studied.[3] Because their growth behavior resembles that of other less common pancreatic NE tumors, it is likely the information from their study is pertinent to the other pancreatic NE tumors. Two long-term studies of patients with ZES involving 185[13] and 212[14] patients were recently published that identified important prognostic factors and growth patterns. These studies, as well as others,[3,4,15–17] show that 25% to 40% of pancreatic NE tumors demonstrate aggressive growth, whereas the majority demonstrate and indolent growth pattern.[3,13–16] Tumor-related deaths occur in the group demonstrating aggressive growth, so it is important

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to identify them, so aggressive treatment can be considered. One-half of all deaths are the result of tumor progression. Important prognostic factors are the presence or development of liver metastases, extent of liver metastases, development of bone metastases, or ectopic Cushing syndrome. Liver metastases are associated with large primary tumors (>3 cm), female gender, higher hormone levels, pancreatic gastrinomas, lack of MEN1, and certain flow cytometry features of the tumor.[3,13–15] Lymph node metastases alone, in may studies, are not associated with decreased survival.[13,14,17,18] In patients with liver metastases, the most important factors determining survival are tumor growth rate and the extent of tumor spread.[16]

PATHOLOGY

Studies of the pathology of pancreatic NE tumors have provided a number of insights that can have important effects on management. Recent studies show duodenal gastrinomas are two to 5 times more frequent than pancreatic tumors, are small (70% are <1 cm), and, in MEN1, are invariably multiple and can only be identified with a duodenotomy.[8,17,19] Similarly, duodenal somatostatinomas, nonfunctional duodenal tumors, and GRFomas occur in nonpancreatic locations, whereas the other pancreatic NE tumors almost always occur only in the pancreas.[1,5] Duodenal gastrinomas with ZES are submucosal in location and associated with lymph node metastases in 40% to 60%; therefore, laparoscopic resection is not recommended.[8] NF pancreatic NE tumors are usually diagnosed late in their disease course, with 70% to 90% of patients showing metastases at presentation.[1,5,20] However, in a recent large multicenter study of 184 patients with NF NE tumors,[20] only 35% of the patients were asymptomatic with the tumor detected by imaging during routine examinations, and only 38% had liver and/or lymph node metastases.[20] Molecular studies demonstrate the pathogenesis of pancreatic NE tumors is generally different from gastrointestinal adenocarcinomas, became alterations of common tumor suppressor genes (*retinoblastoma*, *p53*) or oncogenes (e.g., *Ras*, *Jun*) are uncommon.[4,9] Alterations in the *MENIN* gene (25%–40%) and $p16^{INK4a}$ (30%–90%) are frequent; however they do not have prognostic significance.[4,8] Overexpression of epidermal growth factor and hepatocyte growth factor receptor,[21] HER-2 expression,[22] and high chromosome 1 loss of heterozygosity (LOH) (34%–59%) have been shown to be associated with a poor prognosis.[4,8] Furthermore, comparative genomic hybridization and allelotyping studies show frequent chromosome 3p or 3q LOH (6%–47%), or chormosome 6q LOH (18%–68%), and their presence is associated with malignant behavior.[4]

DIAGNOSTIC IMAGING

Recent studies show SRS is the most sensitive method to localized the PICT primary and extent at one time including liver, bone, and lymph node metastases.[23,24] The use of SRS will change management in 19% to 47% of patients with pancreatic islet cell tumor.[23] Helical computed tomography with contrast shows high sensitivity for liver metastases in man studies and allows better anatomic localization than SRS but is less sensitive for small primaries and distant disease.[23–25] Endoscopic ultrasound with cytology is helpful for identifying pancreatic NE tumors, especially NF pancreatic NE tumors, but frequently misses extrapancreatic pancreatic NE tumors and is not helpful for distant disease.[8,26] PET scanning using [^{18}F]fluorodeoxyglucose for nonfunctioning islet cell tumors is insensitive because of their low proliferative rate generally.[27] However, recent PET studies using ^{11}C-labeled DOPA or 5-hydroxytrtryptophan show it is more sensitive than SRS or computed tomography scans for localizing the extent of pancreatic NE tumors or carcinoid tumors.[27] At the present, the experience with this imaging modality is limited in pancreatic NE tumors, but these studies[27] suggest it may be a very useful imaging modality in staging *PICT* extent.

MEN SYNDROMES

MEN1 is present in 20% to 30% of patients with ZEZ[7,11] and in less than 15% of patients with other pancreatic NE tumors, except GRFomas, in which up to 33% had MEN1.[5] The recognition of MEN1, which is caused by a defect in a 10-exon gene on 11q13,[4,28] is particularly important with patients with ZES or NF pancreatic NE tumors because the tumors are frequently multiple and less aggressive, and complete surgical cure is uncommon.[8,29] Pancreatic NE tumors also occur in von Hippel Lindau disease (usually NF), von Recklinghausen's disease (NF duodenal somatostatinomas), and, rarely, patients with tuberous sclerosis.[5] Each of the advances discussed has an influence on the surgical approach currently recommended and the general approach to a patient with a pancreatic NE tumor.

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Surgery for Primary Pancreatic Neuroendocrine Tumors

Jeffrey A. Norton, M.D.

The goal of surgery for primary pancreatic and duodenal neuroendocrine (NE) tumors is to cure the patient. Surgery is the only treatment modality that can result in cure. Cure is obtained by finding and removing the primary tumor and all lymph node metastases. Lymph node metastases do not seem to negatively affect survival, but they may decrease the cure rate.[1,2] Further, lymph node primary gastrinomas have been described, so that patients may be cured by only removing lymph nodes.[3] Multiple endocrine neoplasia type 1 (MEN1) is an important variable affecting the ability to cure patients with NE tumor.[4–6] The presence or absence of MEN1 should be determined preoperatively by accurate history and blood sampling for associated endocrine tumors. In patients with possible, but not definite, MEN1, the *MENIN* gene should be sequenced from peripheral white blood cells to accurately diagnose its presence. MEN1 has a significant impact on the number and extent of primary tumors. Multiple duodenal and pancreatic NE tumors are commonly present in patients with MEN1.[4–6] Decision making and planning for surgery should take into account the presence of MEN1. Further, the clinical presenting symptoms of the patient are also important. Generally, patients have a recognizable clinical syndrome or a pancreatic mass. Patients who present with a clinical syndrome generally have a smaller, more difficult-to-localize pancreatic NE tumor. Clinical syndromes from insulinoma or gastrinoma are diagnosed biochemically. Even if there is no identifiable tumor on preoperative imaging studies, patients with these syndromes and biochemical evidence for the diagnosis should undergo exploratory surgery to find and remove the tumor. In recent studies in patients with insulinoma and gastrinoma without an imagable tumor, most (>90%) have the tumor identified and removed during surgery.[7,8]

LOCALIZATION STUDIES

The extent of the NE tumor should be identified preoperatively by accurate imaging studies. Pancreatic and liver protocol computed tomography (CT),[9] somatostatin receptor scintigraphy (SRS; octreoscan),[10] and endoscopic ultrasound (EUS)[11] have each been shown to be useful in prospective studies. Pancreatic NE tumors appear bright on arterial phase CT scans because these tumors have increased vascularity.[9] CT accurately measures tumor size and relationship to vital blood vessels like the superior mesenteric vein, superior mesenteric artery, and celiac axis. Computed reconstruction of CT images can facilitate localization of small tumors (Fig. 1). Pancreatic NE tumor size has important prognostic information, because tumors greater than 4 cm have a 25% to 40% probability of developing liver metastases.[2] Studies have clearly demonstrated that liver metastases are the rate-limiting step for survival with pancreatic NE tumors. If liver metastases develop, the patient has a higher probability of death from the tumor.[2,12] SRS is the best study to determine the extent of tumor.[10] It images NE tumors based on the density of type 2 somatostatin receptors (Fig. 2). Approximately 90% of NE tumors will be seen on SRS. It is more sensitive than CT and magnetic resonance imaging combined. Insulinomas are

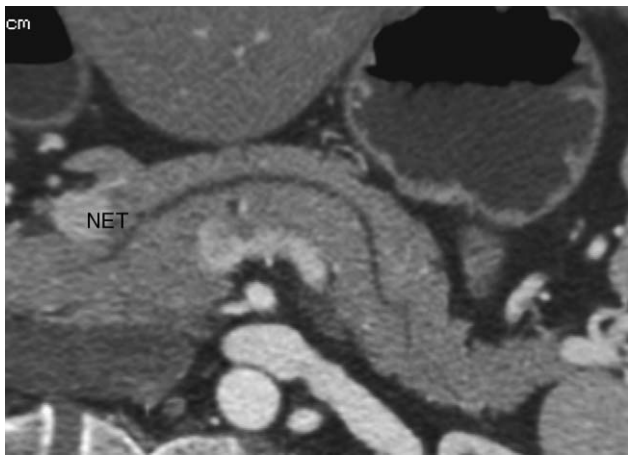

Fig. 1. Computer reconstruction of a computed tomography (CT) scan of a pancreatic neuroendocrine tumor (NET) within the head of the pancreas. This is an insulinoma.

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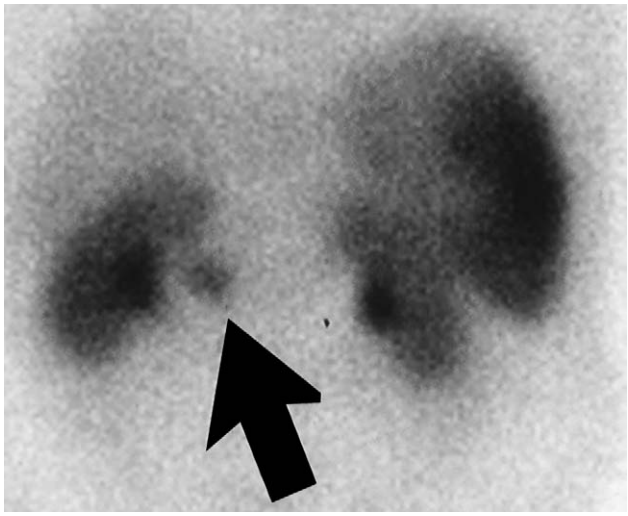

Fig. 2. Somatostain receptor scintigraphy (SRS) of a small neuroendocrine tumor within the duodenal wall (*arrow*). This is a duodenal gastrinoma.

the one pancreatic NE tumor that is often not imaged on SRS. EUS has been very sensitive (90%) at identifying pancreatic NE tumors.[11] Tumors appear sonolucent compared with the more echo-dense pancreas. EUS has been used to image small primary pancreatic NE tumors like insulinomas (Fig. 3). Needle aspiration biopsies of the tumor can be performed with endoscopic ultrasound guidance. Specimens can be sent for cytology or diluted in heparinized saline, and the specific hormone associated with the clinical syndrome (e.g., insulin for insulinoma) can be measured.

False-positive results that may occur with EUS-identified lymph nodes are biopsied, while a diagnosis of accessory spleens may be reduced in frequency with biopsy.

CURE RATE WITH SPORADIC NEUROENDOCRINE TUMORS AND FAMILIAL NEUROENDOCRINE TUMORS (MULTIPLE ENDOCRINE NEOPLASIA TYPE 1)

In general, functional NE tumors within the pancreatic head and duodenum are enucleated and excised, respectively, without performing a pancreaticoduodenectomy. NE tumors within the tail of the pancreas may be either excised or resected according to the size and relationship to the pancreatic duct. In patients with sporadic NE tumors, these surgical procedures provide a cure rate as high as 100% for insulinoma,[8] and 40% for gastrinoma.[7] Because sporadic insulinomas are generally small, benign, and uniformly distributed throughout the entire pancreas, surgery requires precise tumor localization to allow removal of the tumor with preservation of normal pancreas and spleen. Intraoperative ultrasound is essential for intraoperative localization and excision of insulinoma (Fig. 4). In our most recent series,

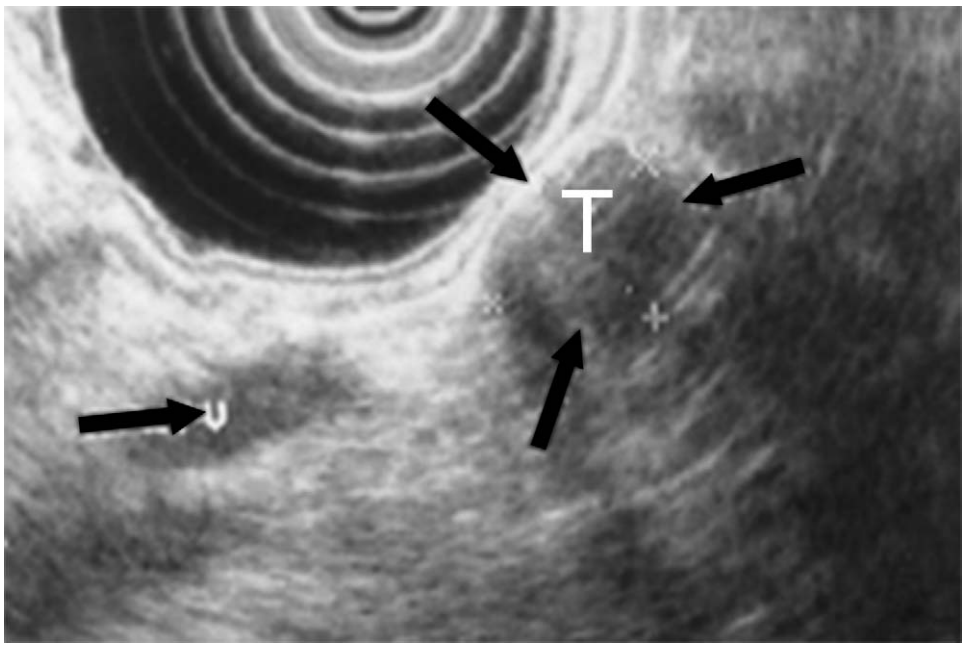

Fig. 3. Endoscopic ultrasound performed with the probe in the stomach. A sonolucent pancreatic neuroendocrine tumor (T) is identified within the tail of the pancreas. Its relationship to the splenic vein (V) is demonstrated. This is an insulinoma.

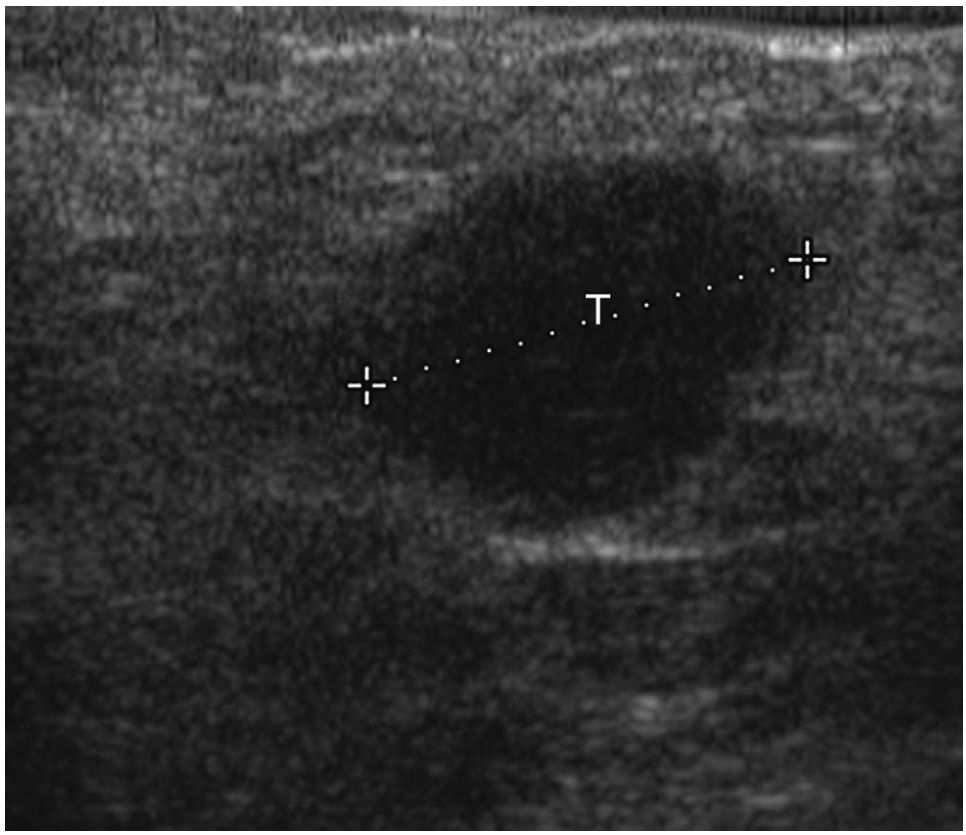

Fig. 4. Intraoperative ultrasound of a small sonolucent neuroendocrine tumor (T) within the tail of the pancreas.

the use of intraoperative ultrasound results in a surgical cure rate of 100% and on operative mortality of zero.[8] In gastrinoma surgery, duodenotomy (opening the duodenum) has increased both the tumor detection rate and the cute rate in patients with Zollinger-Ellison syndrome (ZES).[13] It seems that opening the duodenum and palpating with a finger inside and outside the duodenal wall allow accurate detection and excision of duodenal gastrinomas. This operative maneuver has increased the long-term cure rate from 34% in our earlier series to approximately 50% recently.[13] These results, coupled with no mortality and low morbidity (<15%) with surgery, strongly support routine surgical exploration and local excision of gastrinomas. The operation is safe and has resulted in cure in 50% of patients.[7,13] The reported cure rate for nonfunctional pancreatic NE tumors is approximately 50% at 5 years.[14] These tumors are usually larger (>4 cm) at detection and they require resection (pancreaticduodenectomy or distal pancreatectomy and splenectomy) rather than enucleation for removal.

NE tumors in patients with MEN1 are multiple within both the pancreas and duodenum. In patients with MEN1 with a clinical syndrome, the major question is which of the many tumors is causing the syndrome. Before 1990, it was not appreciated that the majority of gastrinomas in patients with MEN1 and ZES were located in the duodenum.[4–6] Despite this better understanding of the location of the primary gastrinoma in these patients, the surgical cure rate in patients with MEN1 gastrinoma remains very low (0%–10%) without pancreaticoduodenectomy.[4,5,7] This is different than insulinoma in patients with MEN1, which is usually a dominant CT-imagable pancreatic NE tumor. Hypoglycemia is cured by tumor excision in the majority of patients with MEN1 with insulinoma.[15,16]

ROLE OF PANCREATICODUODENECTOMY

Most centers with considerable experience in the management of patients with pancreatic NE tumors do not recommend proximal pancreaticoduodenectomy (Whipple operation) unless the primary tumor in the head of the pancreas or duodenum is locally advanced and large (>4 cm).[17,18] However, a number of small series have reported the use of Whipple

resection in patients with gastrinoma with or without MEN1. In a high proportion of these cases, pancreaticoduodenectomy has resulted in cure of gastrinoma even in the setting of MEN1. This has resulted in the opinion that Whipple resection may provide a better chance of cure and increased survival, especially in patients with MEN1, in whom long-term cure with the standard operation is rarely achieved.[19–21] In the largest series involving 12 patients with ZES, of whom three had MEN1, 92% of the patients were cured post-Whipple resection.[19] Because of these results, some recommend that Whipple resection be performed in patients with a large pancreatic head or duodenal tumor that cannot be enucleated; with multiple duodenal tumors; or with multiple lymph nodes with a duodenal or pancreatic head tumor; or if the patient is not cured after removal of a duodenal or pancreatic head NE tumor with or without lymph node metastases by the standard operation.[19–21]

At present, before the more frequent use of Whipple resection is recommended, a number of issues need to be studied. First, a study should demonstrate that Whipple resection increases the long-term cure rate in patients with NE tumor with and without MEN1. Second, the long-term complications of Whipple resection and their frequency need to be carefully assessed. This is an important point because patients with NE tumor currently live a long time and have an excellent quality of life. Furthermore, the presence of lymph node metastases is not a justification for Whipple resection, because such metastases have not been shown to decrease survival.[1,2] Third, ultimately, it will need to be established that a Whipple resection extends survival in patients with NE tumors. This will be difficult, because for sporadic NE tumors the 10-year survival is 95% and in ZES/MEN1 it is 86%.[7]

CONCLUSIONS

Currently, surgery for insulinoma is curative in nearly every patient, even those with MEN1, and future direction seems to be to make it more cosmetically acceptable and less morbid by trying to accomplish the same procedure laparoscopically. Surgery for gastrinoma and nonfunctional NE tumors is curative in approximately 50% of patients. Duodenotomy is indicated during surgery for gastrinoma, because it increases tumor detection and cure rate. Patients with MEN1 with gastrinoma remain a challenge. With our current approach in these patients, the cure rate is low, but the long-term survival remains excellent. The role of routine pancreaticoduodenectomy for sporadic and MEN1 NE tumors is currently unclear. It may increase cure rate, but it may also increase morbidity in patients with a low, long-term tumor death rate.

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Treatment of Isolated Neuroendocrine Liver Metastases

Bryan Clary, M. D.

The development of metastases is a frequent outcome in the majority of pancreatic neuroendocrine (NE) tumors, with insulinomas (<15%) and GRFomas (<30%) as exceptions. In addition to regional nodes, the liver is the most common site of metastatic disease, and in most patients it is the hepatic tumor burden that dictates outcome. The majority of patients with hepatic involvement have numerous lesions and frequently have very large metastases often in precarious locations. In determining the relative value of treatment strategies for the management of isolated liver metastases arising from pancreatic NE tumors, it is important to define the goals of therapy and to have a clear understanding of the natural history of these heterogeneous malignancies, including their prognoses and the manner in which they can adversely affect quality of life. The latter issue relates not only to their hormonal profiles but also to the volume and location of disease.

The general purpose of medical interventions is to provide a better opportunity for long-term survival in association with an acceptable quality of life. Even in the presence of distant metastases, death is not always imminent, and the quality of life is often well preserved, which is in stark contrast to patients with metastatic adenocarcinomas arising from the pancreas and other upper gastrointestinal sources. This fact is especially true for patients with nonfunctioning pancreatic NE tumors and for those in whom medical therapy is successful in combating the consequences of the excess hormone production (i.e., gastrinomas). Given the rarity of these tumors, the literature addressing the role of aggressive local interventions for the management of hepatic NE tumor metastases is limited to small to modest-sized retrospective, single-institution series. In addition, these reports typically include patients with carcinoid tumors who are thought to have similar prognoses.[1]

It is the purpose of this brief review to provide guidance on the role of local therapies for isolated hepatic metastases. These are, for the most part, limited to resection (partial hepatectomy and liver transplantation), thermal ablation (cryoablation and radio frequency ablation), and selective arterial embolization strategies. A discussion of the natural history of these malignancies, the role of systemic therapies for metastatic disease, and the surgical treatment of the primary tumors has been aptly provided by other members of this symposium. Although heterogeneous in nature, the role of aggressive local treatment strategies and the technical issues involved are similar for most metastatic NE tumors, and as such, the discussion that follows is technique specific and not disease specific in design. Given required constraints, the references are less than complete and as such are a starting point for interested individuals seeking more information on this topic.

RESECTION WITH "CURATIVE" INTENT

The role of hepatic resection has been a source of significant controversy due, in part, to the paucity of data on which to guide clinical decisions and to the evolving concept of resectability that is influenced not only by technical factors as they relate to the future liver remnant but also by the perceptions of individual surgeons, advances in surgical technique and perioperative care, and availability of nonresection treatment strategies including ablation and embolization. Improvements in surgical and anesthetic techniques and the perioperative management of these patients have led to significant reductions in the morbidity and mortality after partial hepatectomy. Even in series reporting a significant percentage of complex hepatectomies, perioperative mortality is approaching 1% to 3% in patients without underlying liver dysfunction.[2] It is clear that morbidity and mortality are directly related to the postoperative liver remnant function, the most important determinant of which is the extent of liver resection. In patients likely to require large volume resections, thereby leaving small liver remnants (e.g., those with lesions

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located adjacent to vascular structures or in whom multiple lesions exist in disparate locations), a number of strategies exist that have been reported in an attempt to extend the limits of resection. In addition to transplantation, these strategies include parenchyma-preserving, segmental approaches to resection, incorporation of concomitant wedge excisions or thermal ablations for small tumors outside the perceived safe field of resection, and the use of either preoperative portal vein embolization[3] or staged resections[4] to induce hypertrophy of the future liver remnant.

The rationale for resection in patients with hepatic metastases is suggested by the favorable long-term survival reported in patients undergoing hepatic resection. Whereas patients with untreated hepatic metastases have a 5-year survival of approximately 20% to 40%,[5,6] numerous reports have documented survivals of 45% to 90%[1,5–7] in patients undergoing resection. In addition, these reports demonstrate that these procedures can be carried out with minimal mortality and acceptable morbidity. Improvements in symptoms, including those related to excess hormone production, occur after resection in more than 90% of patients. It is also clear from these studies that surgery fails to be "curative," because metastases ultimately recur in almost all patients. It is unlikely that a randomized trial will be completed evaluating the value of hepatic resection in these patients. The excellent survival and symptom control suggest that patients with disease amenable to complete gross resection should be offered exploration. The definition of "resectability" is somewhat arbitrary, incorporating technical, patient, disease, and tumor factors. The essence of this definition lies in the technical ability to leave an acceptably functioning remnant in a manner consistent with a high probability of perioperative survival and an appropriate functional outcome. Relative contraindications to partial hepatectomy include medical comorbidities, rapidly progressing intrahepatic disease, progressive extrahepatic disease, and the inability to leave an appropriate liver remnant.

Many patients, because of an extensive distribution of disease within the liver, are not candidates for complete resection by partial hepatectomy. Transplantation has been reported as an alternative to partial hepatectomy. The published experience with transplantation is even more limited and involves fewer than 150 patients. Patients included in these reports seem to have a larger hepatic tumor burden than those undergoing "curative" partial hepatectomies.[8–12] Despite the large tumor burden present in many of these patients and although actual 5-year disease-free survivors are rare in these series, 5-year survival ranges from 36% to 80%. These results are, in general, less favorable than transplantation for other indications, and under current allocation guidelines, these patients are unlikely to receive cadaveric transplants. The availability of grafts afforded by living donation presents the only realistic possibility of transplantation, in these patients. Given the difficult prognosis after transplantation, this modality of therapy, especially when using living donors, should be reserved for very selected circumstances.

DEBULKING STRATEGIES

In patients in whom complete resection in not feasible because of extensive intrahepatic disease or the presence or the presence of irresectable extrahepatic disease, resection to accomplish debulking may still be of significant benefit,[1] but should be done on a very selective basis. An example would be patients with extreme hormonal symptoms unresponsive to other therapies. Another group of irresectable patients who might benefit from "debulking" include those in whom one or more of the tumors resides in a location that will adversely affect short-term quality of life such as those a butting the hepatic hilum where biliary obstruction is likely or those invading adjacent structures including the colon and duodenum.

In the population of patients with extensive hepatic disease only where ablative strategies can be used to treat the irresectable tumors, then a combination of resection and ablation can be appropriate versus ablation alone. Ablative strategies include tumor embolization and thermal ablation. Hepatic artery embolization (HAE) with or without local instillation of chemotherapy has been reported in patients with neuroendocrine metastases. In patients with symptoms of excess hormone production, HAE has a very high rate of response (>90%) with a median duration of response in excess of 15 months.[13] It is unusual for embolization to achieve a complete tumor response, because the periphery of the tumor commonly is spared. For this reason, embolization of irresectable tumors threatening vital structures, such as the hepatic hilum, in the absence of significant hormonal symptoms is generally not helpful, because the periphery of the tumor abutting these structures remains intact. HAE is generally well tolerated, although a postembolization syndrome of nausea, pain, and fever is seen in up to 70% of patients. Mortality is also a risk of tumor embolization and approaches 2% to 6% in the reported series, not dissimilar to resection.

Both cryotherapy[14] and radiofrequency ablation[15] have been reported to be of benefit in these diseases. Historically, cryotherapy has been performed through an open laparotomy incision and is associated with a morbidity rate of approximately 30% and a mortality rate of 5%. Data exist suggesting better efficacy in those tumors adjacent to large vascular structures when compared with radiofrequency ablation (RFA) and in larger tumors. In addition, multiple lesions can be treated simultaneously with cryoablation, whereas with current RFA technology, this is not possible. RFA can be accomplished percutaneously, laparoscopically, or by a standard laparotomy incision. The former two routes have been associated with minimal morbidity, rare mortality, and short hospital stays and, when resection is not a component of therapy, are preferable. Five-year survivals approach 50% in patients with NE tumors treated with thermal ablations. Thermal ablation has inherent limitations. Most RFA series demonstrate local recurrences of 10% to 20% with median follow-up of less than 2 years. Lesions larger than 3 to 4 cm and those adjacent to sizeable vessels are at greatest risk. In addition, complete ablations cannot be performed in lesions immediately abutting vital structures. Patients with iatrogenic biliary-enteric anastomoses (including sphincterotomies) seem to be at significant risk for hepatic abscesses. This is especially in the pancreatic NE tumor population, in whom patients with prior pancreaticoduodenectomies are frequently encountered.

SUMMARY

Data guiding the appropriate management of patients with hepatic metastases arising from NE primaries, including pancreatic NE tumors, are limited. Long-term survival seems to be enhanced in those patients undergoing resection when it is done with a curative intent and potentially when performed as a debulking procedure. Symptoms, including those arising from hormone production, and pain are effectively treated with locally aggressive treatments including resection, thermal ablation, and tumor embolization. Given the lack of effective chemotherapy, the limited duration of response with hormonal therapy, the often indolent oncologic nature of these diseases, and the increasingly safe profile of these local options, locally aggressive treatments remain an important component of care.

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Therapy With Radiolabeled Somatostatin Peptide Analogs for Metastatic Neuroendocrine Tumors

David Bushnell, M.D.

Neuroendocrine (NE) tumors typically synthesize and secrete a variety of bioactive monoamines and peptides, which can cause debilitating symptoms. Therapy of metastatic NE malignancies, including the large subset of gastrointestinal and pancreatic NE tumors, was enhanced dramatically with the introduction over a decade ago of the somatostatin analog octreotide (Sandostatin, Novartis, East Hanover, NJ), into clinical practice. Unfortunately, nearly all such tumors will eventually become resistant to the effects of octreotide, and therapeutic options have been limited for patients with disseminated disease.

Because of the presence of somatostatin receptors (SSTRs) on the cell surface membrane, the large majority of NE tumors bind peptide analogs of somatostatin. ^{90}Y-DOTA-Phe1-Tyr3-octreotide (^{90}Y-SMT 487 [OctreoTher], Novartis) is a radiopharmaceutical that targets SSTR and is currently under investigation for treating patients with receptor positive NE tumors. It is similar in structure to ^{111}Inpentetreotide (Octreoscan), which is used in routine clinical practice to image NE tumors. Unlike ^{111}In, which emits gamma rays, ^{90}Y emits beta particles that have the potential to kill tumor cells by indirectly and irreparably damaging the structure of DNA. Although there are more clinical efficacy data available for ^{90}Y-DOTA-Phe1-Tyr3-octreotide, other somatostatin peptide analogs, some with better tumor targeting properties, coupled with different radionuclides, most notably ^{177}Lu, are undergoing clinical testing. The concept of using beta-emitting radiolabeled peptide molecules to target related receptors on cancerous cells is referred to now as PRRT (peptide receptor radionuclide therapy).

Results from clinical trials with Y-90-DOTA-Phe1-Tyr3-octreotide in patients with metastatic NE tumors have been very encouraging, and a non-disclosure agreement for this radioactive drug was recently filed by Novartis. The tumor response data for this group of patients, including our own experience, indicate an overall response rate (partial remissions + complete remissions) in the range of approximately 20% to 35%.[1–3] Moreover, there is very good evidence that, in addition to tumor shrinkage, PRRT leads to a significant reduction in morbidity with improved quality of life for these patients.[4,5] Several studies have found 60% to 70% of subjects experience notable improvement in both systemic and local tumor-related symptoms.[4–6] Information regarding the effect on mortality is limited at this time.

Although all NE tumors have the potential for favorable outcome after PRRT, in our experience and that of others, pancreatic islet cell tumors show the best response to this form of treatment, with overall response rates ranging between 30% and 50%.[6] Often the systemic symptoms related to the substances elaborated by these tumors are nearly completely eradicated. We have witnessed dramatic reductions in the insulin/glucose ratio and need for supplemental glucose in two of our four patients with insulinoma treated with three cycles of ^{90}Y-DOTA-Phe1-Tyr3-octreotide at our institution. As expected, those tumors that show the greatest uptake on a diagnostic imaging procedure with Octreoscan or similar radiolabeled peptide are more likely to respond to therapy with ^{90}Y-DOTA-Phe1-Tyr3-Octreotide.[7] Larger tumors respond better to ^{90}Y agents and smaller tumors respond better to the ^{177}Lu-labeled SSTR peptide.[8] This is consistent with the longer particle pathlength of the higher-energy beta radiation coming from ^{90}Y.

Currently, radiation exposure to the kidneys is the dosage-limiting factor for nearly all PRRT, including treatments using ^{90}Y-DOTA-Phe1-Tyr3-octreotide. This is because the kidney tubules efficiently reabsorb and retain these radiolabeled peptides.[9] Cationic amino acid solutions infused at the time of treatment inhibit this reabsorption, leading to a corresponding reduction in renal radiation exposure of approximately 20% to 30%.[10–12] A small fraction of patients who have received PRRT even with concomitant amino acid infusion have developed renal insufficiency, usually beginning 6 to 12 months after the last therapy cycle.[13] There is

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a relatively wide range of renal radiation exposure from treatment with radiolabeled SSTR peptides over a population of patients. Consequently, individualized assessment of expected kidney radiation exposure before the actual treatment makes it possible to maximize the administered radioactive peptide dosage for a given individual, while limiting the likelihood of renal radiation toxicity.[14]

Acute or subacute side effects from PRRT are minimal and consist largely of mild reversible bone marrow suppression and occasional short-term nausea or vomiting associated with the amino acid solution. Some patients may also feel lethargy or malaise for a few days to a week after a treatment cycle.

The procedure associated with PRRT typically consists of first performing a scan to determine whether the tumor sites concentrate sufficient radiotracer to achieve therapeutic radiation levels with a subsequent treatment. At the present, this is most often accomplished using the radiopharmaceutical Octreoscan. If the scan does not show adequate tumor targeting, then the individual is not treated. Treatments generally consist of two to four cycles separated by 6 to 9 weeks to allow for bone marrow recovery. Amino acid solutions are administered concomitantly over a 4-hour period at the time of ^{90}Y-DOTA-Phe1-Tyr3-octreotide infusion to help minimize renal radiation exposure to this organ, as noted earlier. Therapy with both the ^{90}Y- and ^{177}Lu-labeld SSTR peptides are typically performed on an outpatient basis.

^{90}Y-DOTA-Phe1-Tyr3-octreotide and other radiolabeled SSTR analogs are effective in treating patients with metastatic pancreatic NE tumors that no longer respond well to Sandostatin. Side effects are limited primarily to mild reversible bone marrow suppression and a low incidence of chronic renal insufficiency. The future of PRRT might well include usage of radioactive cocktails aimed at targeting different subtypes of SSTRs and attempts to upregulate SSTR expression in tumor cells. Combining different radioisotopes with variable beta particle energies for more effective treatment of patients with tumors of differing sizes will also likely generate interest.

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Therapeutic and Palliative Options for Diffuse Neuroendocrine Metastatic Disease

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Neuroendocrine (NE) tumors include a range of rare and diverse neoplasms arising from the NE system. These tumors are characterized histologically by the presence of neurosecretory granules.[1] The tumors react positively to silver stains and to markers of NE tissue including neuron-specific enolase, synaptophysin, and chromogranin.[2,3] NE tumors include bronchial carcinoid tumors, medullary carcinomas of the thyroid, catecholamine-secreting tumors, pituitary tumors, merkel cell carcinomas, and pancreatic NE tumors. The gastrointestinal and pancreatic NE tumors include pancreatic islet cell tumors and carcinoid tumors, which have the highest incidence.[4] Despite being the most common NE tumors, gastrointestinal and pancreatic NE tumors represent only 2% of all gastrointestinal malignant neoplasms.[5] The incidence of patients with carcinoid tumors is estimated to be approximately 0.5:100,000, and that of pancreatic NE tumors is approximately 0.4:100,000.

The most important task a clinician must perform to correctly treat and prognosticate patients with NE tumors is differing between low-grade or high-grade tumors. In general, a pathologist is able to make this distinction by assessing mitotic rate and differentiation of the tumor cells. Low-grade NE tumors frequently show bland cytologic atypia, low proliferative rate, and benign or low-grade malignant behavior. On the contrary, high-grade tumors exhibit a highly atypical morphology with elevated proliferative index and behave in a highly malignant fashion, often presenting with local invasion and early metastases. They generally have a very poor prognosis. To date, Ki-67 staining has been the most helpful prognosticator in determining a high-grade versus low-grade tumor, although recent evidence supports the use of high-resolution allelotyping in determining tumor grading.[6] This review focuses on pancreatic islet cell systemic therapies, as well as therapies for all low-grade NE tumors.

BIOLOGIC THERAPIES: HORMONES AND IMMUNE MODULATORS

For patients who become symptomatic from hormonal hypersecretion, somatostatin analogs, including octreotide, are efficacious.[7] α-interferon has also been shown to improve symptoms of hormonal hypersecretion in patients with carcinoid and pancreatic NE tumors both alone and in combination with somatostatin analogues. Although both somatostatin analogs and α-interferon can result in tumor stablization, neither agent is considered very effective in controlling tumor growth. Tumor regression has been reported in approximately 10% to 15% of patients treated with interferon in phase II studies, but tumor regression has been reported to occur only in approximately 5% of patients treated with somatostatin analogs. A recent study by Faiss et al.,[8] compared lanreotide (a somatostatin analog) with α-interferon or the combination in a randomized fashion for patients with previously untreated disease. There were 25 patients treated in the lanreotide arm, 27 patients in the α-interferon arm, and 28 patients, in the combination arm. Although the study was underpowered to show a true difference between the arms, the response rates were similar and similarly disappointing: 4% (lanreotide), 4% (α-interferon), and 7% (combination).

CHEMOTHERAPY: NITROSOUREAS AND DACARBAZINE COMBINATIONS

Cytotoxic chemotherapy is a therapeutic consideration in patients who are symptomatic secondary to tumor bulk or who have rapid progressive disease. In general, the response to chemotherapy has had limited success in patients with low-grade NE tumors. Multiple chemotherapeutic agents have been assessed alone or in combination for patients with advanced tumors, with response rates in recent

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prospective trials no higher than about 20%.[1] In pancreatic NE tumors, streptozocin combined with doxorubicin has been reported to generate responses in 69% of patients.[9] The determination of response in this study, however, was probably overestimated given that a response determination by physical examination was acceptable. Further, World Health Organization or Response Evaluation Criteria in Solid Tumors criteria were not in common use at the time. Cheng and Saltz[10] at Memorial Sloan-Kettering Cancer Center retrospectively analyzed patients at their institution treated with the streptozocin/doxorubicin combination described by Moertel et al.[9] In their series, they noted a response rate different than that reported by Moertel et al.,[9] only 6% as determined by standard computed tomography criteria.[10] Conflicting reports, however, can be found in the literature with a recent retrospective review claiming a 40% response rate with fluorouracil, cisplatin, and streptozocin. It was not clear in this study whether all patients were confirmed to have a low-grade tumor.[11]

Trials in other low-grade NE tumors have had equally disappointing results. In a trial by the Eastern Cooperative Oncology Group, 118 patients with metastatic carcinoid tumors were randomly assigned to receive either streptozocin and cyclophosphamide or streptozocin and fluorouracil.[12] The reported response rates were fairly high, 33% for streptozocin plus fluorouracil and 26% for streptozocin plus cyclophosphamide; however, they were measured by either tumor regression (not by response evaluation criteria in solid tumors or World Health Organization criteria) or a decrease in urinary 5-HIAA. Both regimens, expectedly, were associated with substantial toxicity. A follow-up trial to improve on the toxicity in the Eastern Cooperative Oncology Group trial increased the interval between cycles of streptozocin plus fluorouracil from 6 to 10 weeks.[13] Although the longer interval between cycles resulted in less toxicity, the response rate decreased to 22%. In an attempt to increase this response rate and perhaps the survival, the Southwest Oncology Group evaluated in 56 patients a combination of fluorouracil, doxorubicin, cyclophosphamide, and streptozocin.[14] This regimen produced a response rate of 31%. Similar to the previous trials, however, the response rate reported was not performed to today's standards and toxicities were significant.

The use of other alkalating agents, such as dacarbazine, in combination with fluorouracil and other antineoplastics has shown clinically meaningful response rates in multiple clinical trials. Unfortunately, the high rates of neutropenia, diarrhea, hospitalization, and fever significantly limit the use of these combinations, particularly those with relatively asymptomatic disease. Clearly, more active regimens in this disease are needed.

CHEMOTHERAPY: RECENTLY REPORTED STUDIES

Efforts to find better-tolerated therapies have been universally disappointing. There is a long list of therapies that have shown little activity in this disease. The most recent treatments studied in a prospective design that have shown no responses include bortezomib,[15] gemcitabine,[16] hydroxyurea/5-fluorouracil,[17] paclitaxel,[18] and docetaxel.[19] There are many further studies that are completed or are near completed, but have yet to be published. These abstracts again highlight how resistant these tumors are to chemotherapy. They include (but are not limited to) imatinib (4% response rate),[20] EPO906 (no reported partial or complete responses),[21] irinotecan (no responses),[22] 7-hydroxycoumarin (3% response),[23] thalidomide (0% response),[24] capecitabine (no radiographic responses reported),[25] topotecan (5% response),[26] and endostatin (0% response),[27] to name a few. The take-home message from these studies is that standard chemotherapies are generally not useful in this disease, and new studies in this disease should incorporate therapies with novel mechanisms of action.

CHEMOTHERAPY: STUDIES IN PROGRESS

Agents that target the EGF receptor and pathway have made significant headway into the therapy for those with lung, colon, and other cancers and may also be useful in those with low-grade NE tumors. Currently under investigation is gefitinib, a well-tolerated, oral, small-molecule tyrosine kinase inhibitor affecting the intracellular domain of the EGF receptor. This trial is currently open through the phase II consortium, a collaboration of six cancer centers in the United States. Also affecting this pathway, downstream from gefitinib, is BAY43-9006, an oral, potent raf kinase inhibitor. The BAY43-9006 trial will also be run through the phase II consortium and is expected to open soon.

CCI-779 is a cell cycle inhibitor that acts by binding to FK506-binding protein-12, forming a complex that interacts with the "mammalian target of rapamycin." This results in the inhibition of signal transduction pathways that are required for progression through the G_1 phase of the cell cycle. The phase II study in low-grade NE tumors has recently

opened at the Princess Margaret Hospital in Toronto, and at other cancer centers in North America. Other agents under investigation include antiangiogenesis agents (bevacizumab, PTK787) and SOM230, a somatostatin peptidomimetic with inhibitory effects on the growth hormone/insulin-like growth factor I axis.

CHEMOTHERAPY: FUTURE THERAPIES

Preclinical studies are ongoing by Chen et al.[28] and others to elucidate new pathways that might inhibit tumor growth and cause cellular differentiation. Unlike most solid tumors, NE tumors rarely possess raf mutations. A raf-inducible construct in pancreatic NE tumors has been shown to inhibit tumor growth in vitro and decrease chromogranin expression.[29] Activating raf-1 has also been shown to induce cellular differentiation for these tumors.[30] Studies are under way to find agents that might work by activating raf-1 for development as possible medical treatments for NE tumors. Further preclinical studies looking at novel agents affecting EGFR or angiogenesis are also in progress.

Unfortunately, efforts are somewhat hindered because of the lack of any substantial funding targeted for this rare disease. The efforts now under way in preclinical and clinical testing should find more tolerable and effective treatments for patients affected by this as yet incurable affliction.

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Long-term Outcome of Esophagectomy for High-Grade Dysplasia or Cancer Found During Surveillance for Barrett's Esophagus

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Endoscopic surveillance is recommended for patients with Barrett's esophagus to detect high-grade dysplasia (HGD) or cancer. We studied the outcome of esophagectomy in a cohort of patients who developed HGD or cancer between 1995 and 2003 while under surveillance for Barrett's. Outcomes were measured by analysis of clinical records, symptom questionnaire, and SF-36 (version 2). In 34 patients, mean surveillance time was 48 months (range, 4–132); the mean number of endoscopies was 10 (range, 3–30). Preoperative diagnosis was HGD in 9 patients (26.5%), carcinoma in situ in 16 (47%), and adenocarcinoma in 9 (26.5%). There was no esophagectomy-related mortality; 10 patients (29%) had complications. At mean follow-up of 46 months (range, 13–108), SF-36 (version 2) results showed quality of life scores equal to or better than those of healthy individuals. Incidence and severity scores (VAS 1–10) for postoperative symptoms were reflux, 59% (2.8); dysphagia, 28% (3.7); bloating, 45% (2.6); nausea, 28% (2.1); and diarrhea, 55% (2.5). Twenty-nine patients (85%) have no clinical, radiographic, or endoscopic evidence of recurrent esophageal cancer or metastasis. One patient has metastatic disease. Endoscopic surveillance in Barrett's patients yields malignant lesions at an early, generally curable, stage. Esophagectomy is curative in the great majority and can be accomplished with minimal mortality and excellent quality of life. (J GASTROINTEST SURG 2006;10:341–346)

KEY WORDS: Barrett's esophagus, esophagectomy, esophageal cancer, outcomes of esophagectomy, Barrett's surveillance, esophageal dysplasia

Rates of esophageal and gastric cardia cancers in the United States have risen over the past two decades, in part as a result of the rise in the prevalence of Barrett's esophagus (BE).[1] Five-year survival rates after esophagectomy in these patients are typically 25% or less because the tumors are diagnosed at an advanced stage.[2,3] BE is a premalignant condition present in 10–20% of patients undergoing endoscopy for gastroesophageal reflux disease.[4] Dysplasia develops in 3.3% of patients per year and advances into esophageal adenocarcinoma in 0.5–1.5% of patients per year.[5,6] Current strategies to improve survival for patients with BE emphasize early detection of high-grade dysplasia (HGD) or esophageal cancer through routine endoscopic surveillance. This strategy assumes patients who develop HGD or cancer will be found at an earlier, curable stage.

Esophagectomy has been recommended for patients with esophageal cancer as well as for those with HGD because HGD is associated with a

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40–60% chance of harboring or developing cancer.[7] Previous reports have indicated that esophagectomy is associated with morbidity of 50–60% and mortality rates of 12%.[8,9] Because of these risks, the role of esophagectomy for HGD and early carcinoma has been questioned, and alternate management such as endoscopic ablation and photodynamic therapy has been recommended. These alternatives are not without risk as invasive cancer may be present or develop despite these treatments.[7]

Our study sought to determine whether a surveillance program did in fact yield patients with cancer at an early stage and, more specifically, what were the short and long-term outcomes of esophagectomy in these patients with special attention to their symptomatic outcome, survival, and quality of life.

MATERIAL AND METHODS

One hundred forty-two patients underwent esophagectomy at the University of Washington Medical Center over a 9-year period (February 1995 to February 2003). Thirty-eight (27%) of these patients had been enrolled in an endoscopic surveillance program for at least 4 months (range, 4–132 months) prior to their diagnoses of esophageal adenocarcinoma or HGD. A minimum of three surveillance endoscopic examinations with biopsies were required to be included in the study; thus, all patients who had cancer detected during their first endoscopy were excluded.

Staging

Standard guidelines for esophageal cancer staging were used based on the American Joint Committee on Cancer staging of esophageal cancer.

Assessment

Each patient was contacted by letter and/or by telephone and invited to participate in this study, which was approved by our Institutional Review Board (03-6810-E01). Each patient was evaluated using these three tools:

Symptom Questionnaire. We developed a questionnaire that focuses on the gastrointestinal symptoms associated with the postesophagectomy state. These include regurgitation/reflux, dysphagia, postprandial diaphoresis, abdominal pain, bloating, nausea, diarrhea, and hoarseness. Each symptom is evaluated with regard to frequency on a scale from 0 to 4 (0, never; 1, average once per month; 2, average once per week; 3, average once per day; 4, several times per day) and severity with a scale from 0 to 10 (0, none; 2, mild; 5, moderate; 8, severe; 10, worst).

Quality of Life Questionnaire. The SF-36 (version 2) survey was administered to determine each patient's current quality of life. Standard questions were asked in seven areas: Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, and Role-Emotional.

Medical Records. The medical records of the patients who agreed to participate in the study were studied to determine preoperative and postoperative endoscopic examinations, pathology reports, operative intervention, postoperative complications, cancer staging, and current status of the disease. Operative mortality was defined as death within 30 days of operation.

RESULTS

Between February 1995 and February 2003, 38 patients (84% males; median age, 61 years; range, 35–80 years) who were undergoing routine surveillance for BE were diagnosed with either esophageal adenocarcinoma or HGD and subsequently underwent esophagectomy. We were able to establish contact with 36 patients (95%); however, two patients refused to participate in the study (no interest and lack of time). Thus, there were 34 study participants.

Barrett's Surveillance

Each patient had a known diagnosis of BE and was enrolled in a surveillance program for at least 4 months (median, 36 months; range, 4–132). All patients underwent at least three endoscopic procedures prior to their operation (median, 10; range, 3–30). Three patients had short-segment BE defined as less than 3 cm in length, while the rest had long-segment disease (mean, 6.6 cm; range, 3–16). Nine patients (26.5%) were initially diagnosed with HGD on endoscopic surveillance and 25 (73.5%) were found to have either intramucosal carcinoma or invasive adenocarcinoma. Table 1 describes the preoperative and postoperative staging.

Table 1. Preoperative and postoperative staging

	Preoperative stage	Postoperative stage
LGD	0	1
HGD	9	14
CIS	16	9
T1 N0	7	7
T2 N0	1	1
T3 N0	0	1
T1 N1	1	1

LGD = low-grade dysplasia; HGD = high-grade dysplasia; CIS = carcinoma in situ.

Esophagectomy

Thirty patients were approached via a transhiatal route, three underwent a left thoracoabdominal, and one underwent an Ivor-Lewis approach. Seven patients had had an antireflux operation prior to esophagectomy, 56 months (mean interval) prior to their esophagectomy. They developed HGD 4.2 years (mean interval) after their antireflux procedure on surveillance endoscopy. Patients had good symptom control postoperatively, with only two patients taking medication for mild symptoms.

One patient in our cohort received neoadjuvant chemotherapy prior to esophagectomy for clinical stage T1 N1 M0 disease. The median length of hospital stay after operation was 9 days (range, 7–18). All patients had at least one postoperative esophagogram to evaluate the esophagogastric anastomosis. Only one contained leak was noted, which healed without reoperation. Postoperative complications occurred in 10 patients (29%): diaphragmatic hernia (two patients), wound infection (two patients), pulmonary embolus, gastrointestinal hemorrhage, anastomotic leak, laryngeal nerve palsy, intraabdominal hemorrhage, and pleural effusion (one patient each). Six patients developed anastomotic strictures requiring esophageal dilation, only two of which were retrospectively found on their initial postoperative esophagogram. There was no operative mortality, and at 18 months after their respective operations, all patients were alive.

Pathology

Final pathologic examination of the specimens revealed the following: one patient had low-grade dysplasia, 14 patients had HGD, 9 patients had carcinoma in situ, 7 patients had stage I disease, 2 patients had stage IIA disease, and one patient had stage IIB disease (Table 1). The single patient who had low-grade dysplasia on final pathologic examination received neoadjuvant chemotherapy for a clinical T1 N1 M0, biopsy-proved adenocarcinoma. Occult adenocarcinoma was found in one patient who was thought preoperatively to only have HGD (3%).

Table 2. Frequency and severity of postoperative symptoms

	No. of patients	Frequency (scale 0–4)	Severity (scale 0–10)
Reflux or regurgitation	59%	1.6	2.8
Diarrhea	55%	1.9	2.5
Bloating	45%	1.2	2.6
Nausea	28%	1.4	2.1
Dysphagia	28%	3.0	3.7
Postprandial diaphoresis	17%	1.4	0.6
Abdominal pain	17%	1.0	2.4
Hoarseness	7%	1.5	1.5

Frequency score: 0 = never, 1 = average once per month, 2 = average once per week, 3 = average once per day, 4 = several times per day.
Severity score: VAS scale from 0 to 10 (0 = none, 2 = mild, 5 = moderate, 8 = severe, 10 = worst).

Postoperative Symptoms

Table 2 summarizes the frequency and severity of each of the gastrointestinal symptoms reported by our patients. The most frequently reported postoperative symptoms were reflux, diarrhea, and bloating. The severity for all postoperative symptoms was mild. Twenty-one patients (56%) were taking antireflux medication.

Postoperative Quality of Life

Figure 1 summarizes the results of quality of life assessments from the SF-36 version 2 survey. Our patients scored at or above the average quality of

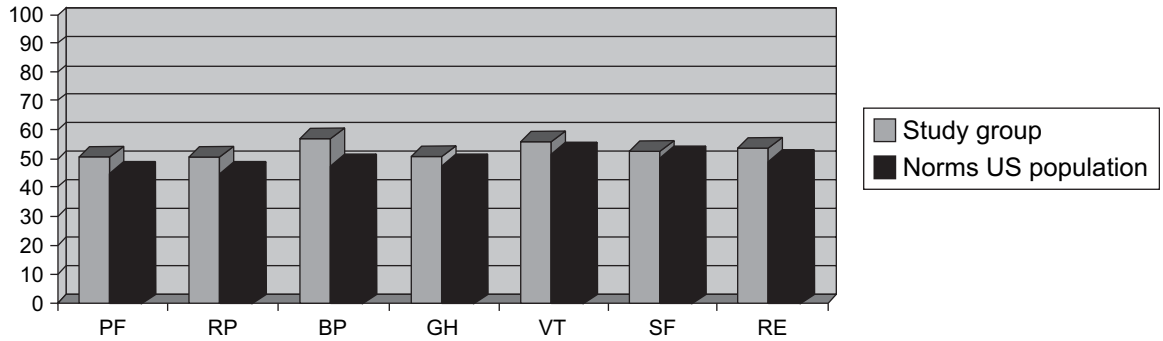

Fig. 1. SF-36 version 2 scores compared with national averages. PF = Physical functioning, RP = Role physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role emotional.

life reported by national averages in 1998 in all seven areas tested.[10]

Survival and Follow-up Cancer Surveillance

The mean postoperative follow-up time was 46 months (range, 13–108 months). Thirty (88%) patients are alive. Four have died; three from conditions unrelated to esophageal cancer (tongue cancer, coronary artery disease, renal failure) and one from unknown cause. One patient developed metastatic esophageal carcinoma to the pleura and was still alive at 28 months postoperatively. The remaining 29 (85%) patients have no clinical, radiographic, or endoscopic evidence of recurrent esophageal cancer or metastasis. Kaplan-Meier acutuarial survival curve for all patients in the study is shown in Figure 2. Twenty patients (62%) have had at least one upper endoscopy performed postoperatively for cancer surveillance. Of those, only one patient had evidence of grade II esophagitis on endoscopy. Six (18%) patients have had both upper endoscopy and computed tomography scanning for surveillance. No evidence of new or recurrent disease was found in these patients.

DISCUSSION

Our experience suggests that for patients who are found to have progression to HGD or adenocarcinoma during surveillance for BE, esophagectomy is safe and effective. The morbidity and mortality from the operation are low, and the long-term survival is high compared with previously reported rates, which were primarily for patients with advanced lesions. Postoperative symptoms related to esophagectomy are common and expected but are mild and do not interfere with the quality of life, which appears to be excellent.

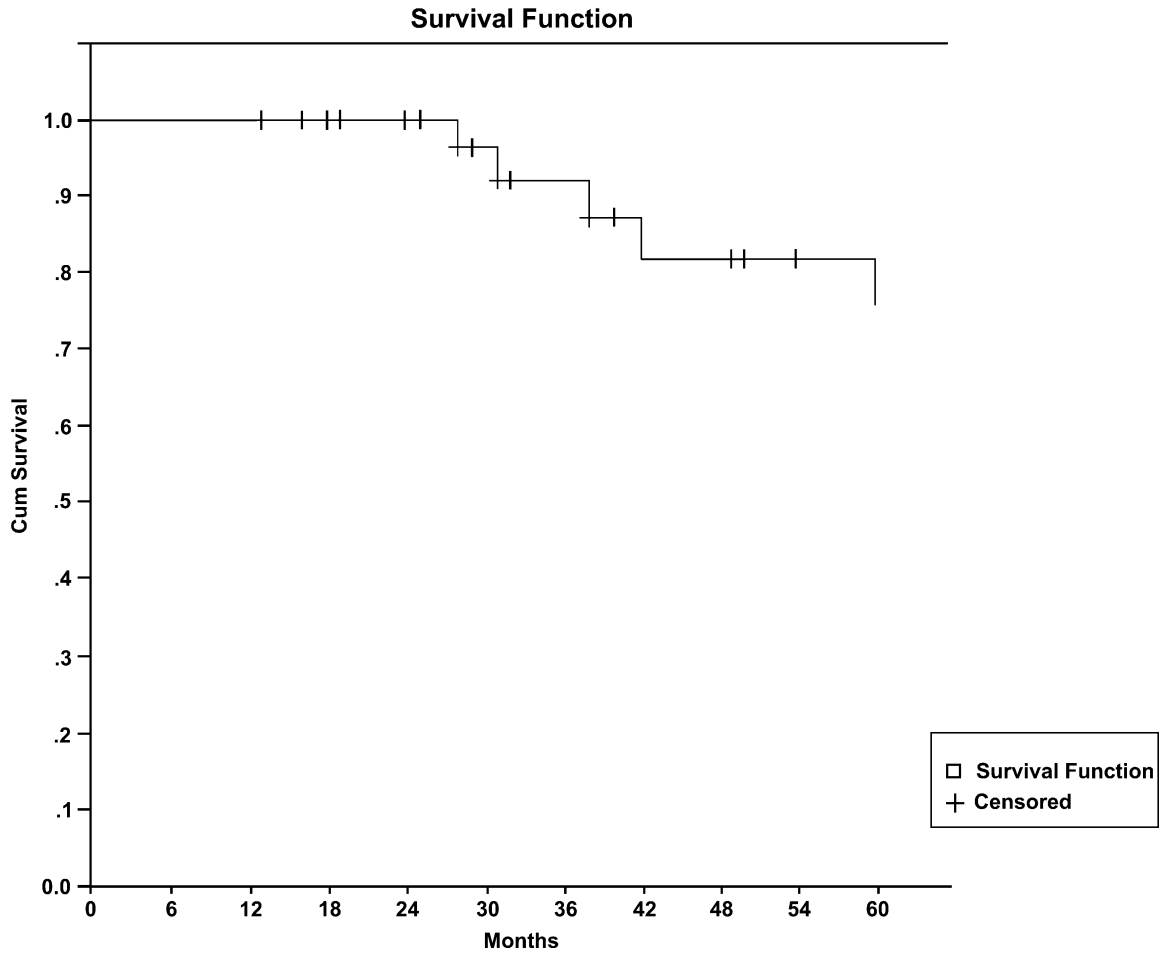

Fig. 2. Kaplan-Meier survival curve of 34 patients after esophagectomy for high-grade dysplasia or cancer found on surveillance for Barrett's esophagus.

Surveillance

The findings of our study support the recommendation that endoscopic surveillance for BE yields patients whose esophageal cancer is at an earlier and curable stage. Indeed, 9 of 19 patients in whom the final pathologic diagnosis was cancer had carcinoma in situ, and only 1 of the 19 patients had lymph node metastasis. These findings resulted in an 88% survival at 44 months with only one patient developing metastasis from esophageal cancer. Our data also show no operative mortality and a morbidity rate of 29%. These favorable results are, in part, a reflection of our patient population, who tended to have earlier stage cancers or only HGD and were, generally, in good health. It is important to note that in only one patient did the final pathologic diagnosis show cancer when the endoscopic biopsy had suggested HGD. The results of the Seattle Barrett's Project and the accuracy of biopsy in these patients have been previously reported: biopsy is accurate and the strategy yields early, curable tumors.[11] Thus, we do not necessarily recommend total esophagectomy for all patients with HGD. The age of the patient, the risk for a major operation, the extent of BE, and the difficulties obtaining appropriate endoscopic specimens must all play a role in the decision to remove the esophagus.

Quality of Life

As less invasive therapies to treat HGD gain popularity, the issue of quality of life after esophagectomy becomes increasingly important. Ultimately, the efficacy of a lesser form of therapy (endoscopic mucosal resection, photodynamic therapy, and others) has to be weighed against its potential risks as well as its ability to produce a permanent cure from the actual (or at-risk) cancer. Our study shows that in patients under endoscopic surveillance for BE who are judged to need an esophagectomy on the basis of cancer or the risk of developing it, esophagectomy can be performed safely with subsequent excellent quality of life. We selected the SF-36 version 2 survey to measure quality of life in these patients. This survey is a standardized health assessment tool that permits group comparisons in several areas covering general health, daily activities, work, emotional problems, social activities, depression, pain, and vitality.[12] Items in the SF-36 version 2 survey represent multiple indicators of health, including behavioral dysfunction and function, distress and well-being, and favorable and unfavorable self-evaluations of general health status. We compared our study group (88% males; mean age, 60 years) with the 1998 U.S. national population (males; mean age, 65 years).[10] We were surprised to see that in every area, our patients reported excellent quality of life that, in fact, exceeded the scores observed in the normal population. The SF-36 version 2 was developed to measure the effects of chronic illness, and it is possible that our results reflect the emotional impact of having survived a major operation for cancer or the near certainty of being cured from the cancer as opposed to the impact of a chronic condition that, one could argue, our patients no longer had. On the other hand, our patients are carefully instructed on the effects of total esophagectomy and on the gastrointestinal symptoms they are likely to have after esophagectomy, prior to the operation. It is possible that the relative absence of these symptoms or the mild nature that they reported contributed to a feeling of health that was unreal.

Long-term Functional Result

Even with excellent survival rates and quality of life after esophagectomy for HGD or cancer detected on Barrett's surveillance, we recognize that there are consequences associated with the reconstructed gastrointestinal tract. One example is reflux of duodenal and gastric content that can lead to symptoms or even pathologic changes. More than half of our patients experienced either reflux or regurgitation and were taking antireflux medication for this symptom. However, the imputed frequency was less than once per week and the severity as assessed by the patients was mild. Thus, despite the relatively large number of patients who experienced the symptom, based on the severity reported and on the results of the SF-36 version 2 reported, these symptoms did not appear to negatively affect their lives. Dresner et al.[13] reported that 83% of postesophagectomy patients with gastric conduit had evidence of abnormal exposure to both acid and bilirubin during 24-hour pH testing. Several factors likely contribute to this including loss of the lower esophageal sphincter and other natural antireflux mechanisms, positive intra-abdominal pressure combined with negative intrathoracic pressure, and impaired esophageal remnant and gastric motility.[14] Ongoing reflux after esophagectomy can also lead to Barrett's development in the remnant esophagus. For this reason, we encourage patients to follow up with annual endoscopy.

Symptoms of diarrhea and bloating were also commonly reported by our patients. Fifty-five percent described diarrhea following esophagectomy, with an average frequency of approximately once per week. This symptom may be secondary to the

concomitant vagotomy performed during the operation. The pathogenesis of postvagotomy diarrhea is not entirely clear but may be related to the passage of unconjugated bile salts from the denervated biliary tree into the colon, stimulating secretion. In addition, 45% of our patients reported bloating following esophagectomy with an average frequency of once per month. While bloating tends to be a fairly nonspecific symptom, it may be related to other conditions. For instance, reflux or regurgitation can lead to frequent swallowing, promoting ingestion of air and, ultimately, bloating. These postesophagectomy symptoms, while commonly reported in our patients, tended to be mild.

CONCLUSION

The findings of our study strongly support endoscopic surveillance in the setting of BE to identify those patients who develop HGD or carcinoma. The findings suggest that, when, indicated, esophagectomy for esophageal cancer or for selected patients with HGD can be carried out with minimal morbidity and mortality by a group who performs a large number of such operations. Survival after esopagectomy is excellent; gastrointestinal symptoms are usually mild and do not interfere with the quality of life.

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Pancreaticoduodenectomy in the Very Elderly

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It is estimated that by 2050, there will be a 300% increase in the elderly population (≥65 years) and a corresponding increase in elderly patients presenting for surgical evaluation. Surgical decision-making in this population can be difficult because outcomes in the elderly are poorly defined. We reviewed 2698 consecutive pancreaticoduodenectomies (PDs) at our institution over a 35-year period (April 1970 through March 2005), with the last 1000 resections being done in the last 4 years. Data collected included surgical indication, mortality (defined as 30-day or in-hospital mortality), complications, and survival. Patients were divided by age into three groups (<80, 80−89, and ≥90 years) and evaluated using multiple logistic regression. Two hundred seven patients ≥80 years old underwent a PD (7.7% of 2698). Patients 80−89 years of age had a mortality rate of 4.1% (8 of 197) and a complication rate of 52.8% (99 of 197), whereas patients ≤79 years of age had a mortality of 1.7% and a complication rate of 41.6% ($P < 0.05$). There were no perioperative deaths among the 10 patients ≥90 years of age, and their complication rate was 50% (5 of 10). One-year survival for patients 80−89 years of age was 59.1%, and that for patients ≥90 years was 60%. Age was not an independent risk factor for perioperative mortality and morbidity following PD after adjusting for preoperative comorbidities. We demonstrate that PD can be safely performed in patients over 80 years of age and conclude that age alone should not be a contraindication to pancreatic resection. The advent of improved surgical outcomes and an aging population will likely result in a significant increase in the number of PDs performed in the next few decades. (J GASTROINTEST SURG 2006;10:347–356)

KEY WORDS: Elderly, pancreaticoduodenectomy, pancreatic cancer, octogenarian, nonagenarian

The expanding elderly population is creating new demands on the healthcare system. According to current estimates, there will be a 53% increase in the population over 65 years of age in the United States within 15 years[1] and a 300% increase worldwide by 2050.[2] The most rapidly growing segment of the geriatric population in the United States is persons over the age of 85 years. This group alone is slated to increase six-fold by 2050.[3] The rapid increase in the number of elderly persons in the United States is attributed to two factors. First, medical and public health interventions, such as new medications, cardiac catheterizations, and cancer screening, have resulted in an increased life expectancy. On average, life spans have increased by approximately 10 years over the last half-century.[1] Second, the large group of individuals born between 1946 and 1964 ("baby boomers") are now approaching retirement age.[4] The result of the two factors has been a new generation of elderly Americans and new public attention to the impending problems of social security allocation, rising Medicare costs, and prescription drug coverage for the elderly. Furthermore, the new population distribution is placing new demands on American surgery. For example, Etzioni et al.[5] described the impending impact of the aging population on the surgical workforce. Using national discharge and census data, they forecast that surgical volume in general surgery will increase by 28% from 2001 to 2020 and conclude that new strategies must be developed to manage the new workload.

Surgeons are beginning to observe the predicted influx of elderly (>65 years) and very elderly (>80 years) patients presenting for surgical evaluation. Given the poorly understood contribution of a surgical procedure to morbidity and mortality in this population, the decision to recommend an operation

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to these patients can be difficult.[6] While there are large series of very elderly patients undergoing cardiothoracic[7–9] and vascular[10] procedures, there are few studies that have analyzed outcomes of very elderly patients following major intra-abdominal surgery. A previous report from Johns Hopkins looked at a small group of patients 80 years of age and older (n = 46) who underwent a PD and concluded that age alone should not be a contraindication to resection.[11] To further evaluate the risk of performing a major intra-abdominal operation in this population, we evaluated the morbidity and mortality of a large cohort of patients ⩾80 years who underwent a pancreaticoduodentomy (PD) and compared their outcomes to those of younger patients.

METHODS

The records of 2698 patients who underwent PD between April 1970 and March 2005 at the Johns Hopkins Hospital were reviewed. Data were extracted from the Johns Hopkins PD database and electronic records. Outcomes were compared between three patient groups according to age: under 80 years (n = 2491), between 80 and 90 years (n = 197), and 90 years or older (n = 10). Institutional review board approval to perform the described study was obtained.

A PD was performed in all patients by 24 different surgeons. The most common type of PD was a pylorus-preserving PD without extended retroperitoneal lymph node dissection.[12] As a matter of practice, a classic PD has been reserved for lesions that involve the distal stomach or first portion of the duodenum. Vagotomy, tube gastrostomy, tube jejunostomy, prophylactic octreotide, and total parenteral nutrition were not used routinely.

Demographic characteristics, past medical history, intraoperative data, histological diagnoses, pathology data, and patient outcomes were compared between the three patient age groups. Detailed pathological data were collected in patients who had pancreatic adenocarcinoma, including American Joint Committee on Cancer (AJCC) stage, positive lymph nodes, tumor diameter, margin status, and histological grade.[13] Perioperative mortality, defined as 30-day or in-hospital death, and perioperative morbidity were evaluated. Complications of PD were categorized and tabulated. Long-term survival of all patients was analyzed and was also examined separately among patients with pancreatic adenocarcinoma. Survival data were compared across age groups and against age-matched controls in the general population.[3]

Comparison of continuous variables was performed using the Mann-Whitney rank sum test, and comparison of categorical variables was performed using a χ^2 test. Multivariate logistic regression was used to determine clinical predictors of perioperative mortality and morbidity. The overall meaningfulness of age as an independent contributor to the outcome of death or a complication was evaluated by a simple logistic regression model using a pseudo r^2 analysis. Long-term survival data were compared using the Kaplan-Meier method. Results are reported as median values, unless indicated otherwise. Statistical significance was accepted for $P < 0.05$. Data analysis was performed using Intercooled Stata Version 7.0 (Chicago, IL).

RESULTS

PDs (2698) were performed at the Johns Hopkins Hospital between April 1970 and March 2005. This group included 2491 patients under 80 years of age, 197 patients between 80 and 89 years, and 10 patients 90 years or older. Over the 35-year period, PDs performed on the very elderly increased both in number and as a percentage of total annual surgical volume (Fig. 1). The annual distribution of patients 80 years of age and older who underwent PD is indicated in Figure 2. In 1 year (2003), 26 PDs were performed on patients 80 years of age or older. Currently (in 2005), approximately 9% of all patients who undergo a PD at Johns Hopkins are 80 years of age or older.

Demographics

The median age of the entire cohort of patients (n = 2698) is 65 years of age. Median age within each of the three age groups is 64 (<80 years group), 82 (80−89 years group), and 90 (⩾90 years group) (Table 1). The three age groups had approximately equal numbers of males and females. The older patient group (80−89 years) had a significantly greater proportion of white patients compared to the younger cohort. All 10 patients ⩾90 years old were white, although this did not achieve statistical significance due to a small sample size.

Comorbidities

The most common comorbidities in the 80- to 89-year-old group (Table 2) included hypertension (48.5%), coronary artery disease (25.9%), diabetes mellitus (17.5%), and chronic obstructive pulmonary disease (COPD) (10.8%). Compared to the <80 group, the 80- to 89-year-old group had significantly

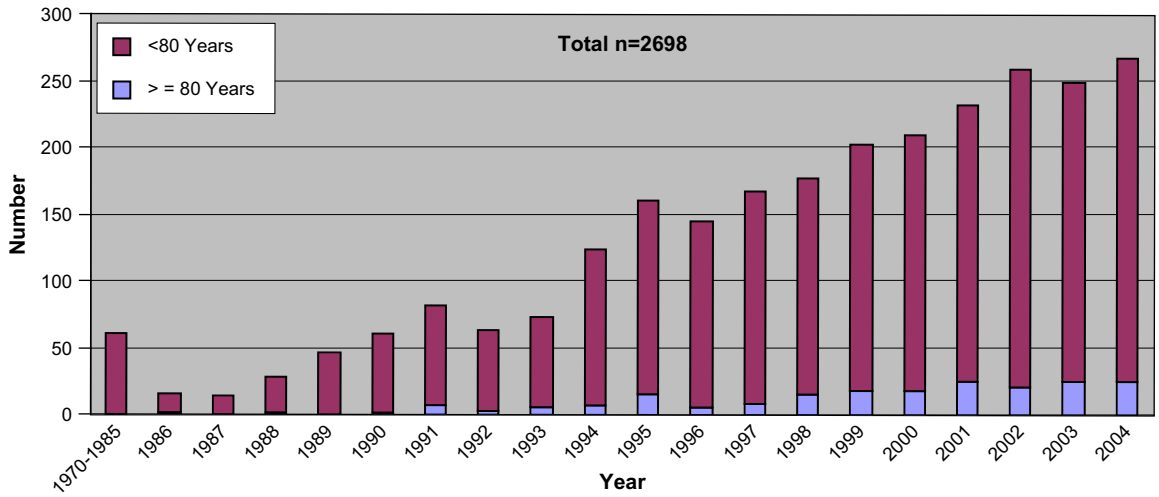

Fig. 1. Pancreaticoduodenectomies performed at Johns Hopkins annually by age group.

greater incidences of coronary artery disease ($P = 0.048$) and hypertension ($P < 0.001$), COPD ($P < 0.001$), peripheral vascular disease ($P = 0.003$), and other medical/surgical history ($P < 0.001$). The 80- to 89-year-old cohort had significantly lower incidences of chronic pancreatitis ($P < 0.001$), alcohol abuse ($P < 0.001$), and tobacco use ($P = 0.002$). In the ⩾90 group, the incidence of peripheral vascular disease was greater than the <80 group ($P = 0.01$).

Pathology

Patients in both of the older cohorts had a higher proportion of malignant disease than patients in the <80 years group (Table 3). The percentages of cases with cancer in each group were as follows: 75% of patients <80 years old, 85% of patients ages 80–89 (p = 0.002), and 100% of patients >90 years old ($P = 0.07$). Periampullary cancers comprised 66.7% of cases in the group <80 years, 82.7% of cases in the 80- to 89-year-old group ($P < 0.001$), and 100% of cases in the ⩾90 group ($P = 0.03$).

The distribution of the different subtypes of periampullary cancers in the 80- to 89-year-old group were as follows: 53.3% pancreatic cancer (includes ductal adenocarcinoma and intraductal papillary mucinous neoplasms [IPMNs] with invasive cancer), 14.7% ampullary cancer, 10.7% distal common bile duct cancer, and 4.1% duodenal cancer. The remaining three malignancies in the 80- to 89-year-old

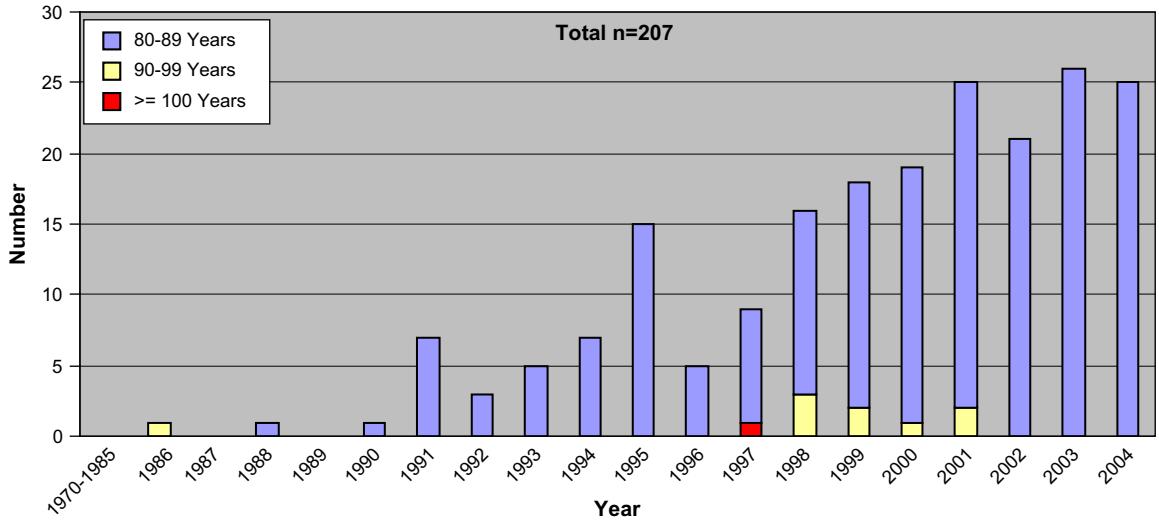

Fig. 2. Pancreaticoduodenectomies performed on patients >80 years of age at Johns Hopkins annually.

Table 1. Demographic characteristics of patients undergoing pancreaticoduodenectomy, categorized by age

	<80 yr (n = 2491)	80–89 yr (n = 197)	≥90 yr (n = 10)
Median age, yr (range)	64 (15–79)	82 (80–89)	90 (90–103)
Gender, male, n (%)	1351 (54.2)	95 (48.2)	4 (40)
Race, white, n (%)	2160 (86.7)	183 (92.9)*	10 (100)

*$P < 0.05$ compared with patients <80 yr.

group included a cystadenocarcinoma, a malignant neuroendocrine tumor, and a gallbladder cancer metastasis. All 10 specimens in patients ≥90 years were periampullary cancers; the cancer subtypes included 20% pancreatic cancer, 20% ampullary cancer, 30% distal common bile duct cancer, and 30% duodenal cancer.

Thirty of 197 (15%) resections in the 80- to 89-year-old group were for benign disease. Pathological diagnoses included 12 IPMNs, 6 cystadenomas, 5 tubulovillous adenomas, 3 with chronic pancreatitis, 1 with lymphoplasmacytic sclerosing pancreatitis, 1 with a duodenal diverticulum, 1 with a retention cyst, and 1 with focal papillary duct hyperplasia. None of the pathological diagnoses in the >90 group were benign.

Table 2. Past medical history of patients undergoing pancreaticoduodenectomy, categorized by age

Medical history, n (%)	<80 yr (n = 2491)	80–89 yr (n = 197)	≥90 yr (n = 10)
Coronary artery disease	301 (19.1)	38 (25.9)*	4 (44.4)
Myocardial infarction	168 (7.2)	15 (7.7)	1 (11.1)
Hypertension	837 (35.9)	94 (48.5)*	3 (33.3)
Diabetes mellitus	434 (18.6)	34 (17.5)	0 (0)
COPD	112 (4.8)	21 (10.8)*	1 (11.1)
Peptic ulcer disease	113 (4.9)	10 (5.2)	0 (0)
Peripheral vascular disease (includes history of CVA)	106 (4.6)	18 (9.3)*	2 (22.2)*
Acute pancreatitis	117 (5.0)	5 (2.6)	1 (11.1)
Chronic pancreatitis	161 (6.9)	1 (0.5)*	0 (0)
Pseudocyst	20 (0.9)	0 (0)	0 (0)
Inflammatory bowel disease	18 (0.8)	3 (1.6)	0 (0)
Alcohol abuse	329 (14.1)	9 (4.7)*	0 (0)
Tobacco use	609 (26.2)	31 (16.2)*	1 (11.1)
Other (includes medical and surgical history)	1856 (79.3)	178 (91.3)*	8 (89.9)

COPD = chronic obstructive pulmonary disease; CVA = cardiovascular accident.
*$P < 0.05$ compared with patients <80 yr.

For patients with pancreatic cancers (includes ductal adenocarcinoma and IPMNs with invasive cancer), the staging was similar in younger and older patients (Table 4). The American Joint Committee on Cancer (AJCC) cancer staging distribution in the 80- to 89-year-old group was 0% stage 0, 7.9% stage I, 86.9% stage II, 5.3% stage III, and 0% stage IV. The two patients in the ≥90 group had stage II cancers. The median number of positive nodes in all three age groups was two. The median tumor diameter in the <80 group and the 80- to 89-year-old group was 3 cm. The median tumor diameter in the ≥90 group was 1.6 cm. The proportion of cancers with positive margins was 41% in the <80 group and 42% in the 80- to 89-year-old group. The two pancreatic cancers in the ≥90 group had negative margins. The distribution of histological grades in the 80- to 89-year-old group was as follows: 4.0% well differentiated, 54.5% moderately differentiated, 39.6% poorly differentiated, and 2% undifferentiated/anaplastic. In the ≥90 group, one cancer was moderately differentiated and one cancer was poorly differentiated.

Intraoperative Parameters

Mean operative times were 6 hours 30 minutes in the <80 group, 5 hours 53 minutes in the 80- to 89-year-old group ($P < 0.001$), and 5 hours 38 minutes in the ≥90 group ($P = 0.07$) (Table 5). Although the operative times were shorter in both of the older cohorts compared to the <80 group, statistical significance was achieved in just the 80- to 89-year-old group.

Mean blood loss was 992 ml in the <80 group, 943 ml in the 80- to 90-year-old group ($P = 0.3$), and 428 ml in the ≥90 group ($P < 0.05$). Although both of the older cohorts experienced less intraoperative blood loss than the <80 age group, statistical significance was achieved in only the ≥90 group. The mean transfusion requirement was 0.98 unit in the <80 group, 1.25 units in the 80- to 89-year-old group ($P = 0.04$), and 0.56 unit in the ≥90 group ($P = 0.3$).

The type of resection, extent of resection, and frequency of major vessel resection were consistent across the three age groups (Table 5). In the 80- to 89-year-old group, 76.1% of the procedures were pylorus-preserving, while 23.9% involved a classic resection with distal gastrectomy; 94.9% of the resections were partial pancreatectomies, while 5.1% were total pancreatectomies; and 2.6% of the procedures involved a partial resection of a major vessel.

Table 3. Histologic data of patients undergoing pancreaticoduodenectomy by age

Histology, n (%)	<80 yr (n = 2491)	80–89 yr (n = 197)	≥90 yr (n = 10)
Malignant	1854 (74.8)	167 (84.8)*	10 (100)
Periampullary cancer	1661 (66.7)	163 (82.7)*	10 (100)*
Specific diagnosis			
Pancreatic ductal adenocarcinoma	1014 (40.7)	94 (47.7)	2 (20)
Ampullary adenocarcinoma	257 (10.3)	29 (14.7)	2 (20)
Distal bile duct cancer	218 (8.8)	21 (10.7)	3 (30)*
Duodenal adenocarcinoma	102 (4.1)	8 (4.1)	3 (30)*
Chronic pancreatitis	219 (8.8)	3 (1.5)*	0 (0)
IPMN	96 (3.9)	12 (6)	0 (0)
IPMN with invasive cancer	70 (2.8)	11 (5.6)*	0 (0)
Cystadenocarcinoma	9 (0.4)	1 (0.5)	0 (0)
Cystadenoma	83 (3.3)	6 (3.1)	0 (0)
Periampullary adenoma	74 (3)	5 (2.5)	0 (0)
Malignant neuroendocrine tumor	100 (4)	1 (0.5)*	0 (0)
Benign neuroendocrine tumor	32 (1.3)	0 (0)	0 (0)
Gastrointestinal stromal tumor	22 (0.9)	0 (0)	0 (0)
Metastatic disease	23 (0.9)	1 (0.5)	0 (0)
Other	171 (6.9)	5 (2.6)*	0 (0)

IPMN = intraductal papillary mucinous neoplasm.
*$P < 0.05$ compared with patients <80 yr.

In the ≥90 group, 70% of the procedures were pylorus-preserving while 30% involved a distal gastrectomy. All of the resections in patients ≥90 years were partial pancreatectomies, and there were no major vessel resections in this group.

Table 4. Tumor staging of the pancreatic cancers in patients undergoing pancreaticoduodencectomy by age*

	<80 yr (n = 1084)	80–89 yr (n = 105)†	≥90 yr (n = 2)
Stage (AJCC, 2002)‡			
Stage 0, n (%)	1 (0.2)	0 (0)	0 (0)
Stage I, n (%)	44 (7.0)	6 (7.9)	0 (0)
Stage II, n (%)	563 (89.1)	66 (86.9)	2 (100)
Stage III, n (%)	17 (2.7)	4 (5.3)	0 (0)
Stage IV, n (%)	7 (1.1)	0 (0)	0 (0)
Positive nodes (median)	2	2	2
Tumor diameter (cm)	3	3	1.6
Positive margin, n (%)	321 (41)	30 (42)	0 (0)
Differentiation§			
Well, n (%)	44 (4.2)	4 (4.0)	0 (0)
Moderate, n (%)	581 (55.6)	55 (54.5)	1 (50)
Poor, n (%)	420 (40.2)	40 (39.6)	1 (50)
Undifferentiated/ anaplastic, n (%)	0 (0)	2 (2)	0 (0)

AJCC = American Joint Committee on Cancer.
*Pancreatic cancers include ductal adenocarcinomas and intraductal papillary mucinous neoplasm (IPMNs) with invasive cancer.
†$P < 0.05$ compared with patients <80 yr.
‡Statistical analysis performed on early stage (I and II) versus late stage (III and IV).
§Statistical analysis performed on low grade (well and moderate) versus high grade (poor and undifferentiated/anaplastic).

Postoperative Morbidity and Mortality

Perioperative mortality was 1.7% in the <80 group, 4.1% ($P = 0.02$) in the 80- to 90-year-old group, and 0% in the ≥90 group (Table 6). The overall morbidity rates were 41.6% in the <80 group, 52.8% ($P = 0.002$) in the 80- to 89-year-old group, and 50% in the ≥90 age group. The most common complications in the 80- to 89-year-old group were delayed gastric emptying (15.4%), pancreatic fistula (10.7%), and wound infection (10.3%). Compared to the <80 group, the 80- to 89-year-old group had a significantly higher incidence of cardiac morbidity ($P = 0.006$) and pneumonia ($P < 0.001$), an expected association, given the higher prevalence of hypertension, peripheral vascular disease, and COPD seen in this population. Multivariate logistic regression was performed for patients ≥80 to determine the predictors of increased mortality and complications. After adjusting for age and common medical comorbidities, there was an increased mortality in PD patients with coronary artery disease ($P = 0.003$) and COPD ($P < 0.001$). Age alone did not result in increased perioperative mortality in patients >80 years of age ($P = 0.07$) or an increase in complications ($P = 0.06$); however, age approached statistical significance with both of these outcome variables. As a next step to measure the overall independent contribution

Table 5. Intraoperative data of patients undergoing pancreaticoduodenectomy, categorized by age

Intraoperative factors	<80 yr (n = 2491)	80–89 yr (n = 197)	⩾90 yr (n = 10)
Operative time, mean	6 hr 30 min	5 hr 53 min*	5 hr 38 min
Intraoperative blood loss, mean (ml)	922	943	428*
Transfusions, mean (units of PRBCs)	0.98	1.25*	0.56
Type of resection, pylorus-preserving (vs. classic), n (%)	1902 (76.7)	150 (76.1)	7 (70)
Extent of pancreatectomy, partial (vs. total/completion), n (%)	2352 (94.9)	187 (94.9)	10 (100)
Vessel resection, n (%)	67 (2.7)	5 (2.6)	0 (0)

PRBCs = packed red blood cells.
*$P < 0.05$ compared with patients <80 yr.

of age to outcome, we used logistic regression modeling with pseudo r^2 analysis. We found that age contributed less than 1% to the outcome of death (pseudo $r^2 = 0.009$, 0.9%) or a complication (pseudo $r^2 = 0.003$, 0.3%). By comparison, coronary artery disease (pseudo $r^2 = 0.050$, 5.0%) and COPD (pseudo $r^2 = 0.038$, 3.8%) have a greater impact on the outcome of death.

Survival Analyses

In the <80 cohort, the overall 1-, 2-, and 5-year survival rates for all pathological diagnoses were 78.6%, 59.9%, and 43.1%, respectively, with a median survival of 40 months (Fig. 3). In the 80- to 90-year-old age group, the 1-, 2-, and 5-year survivals were significantly decreased (59.1%, 45.8%, and 24.4%, respectively, $P < 0.001$). The median survival in this group was only 19 months. In the ⩾90 age group, the 1-, 2-, and 5-year survival rates were 60.0%, 25%, and 0%, respectively, with a median survival of 15 months; these survivals are significantly lower ($P = 0.002$), as compared to the <80 group. Of note, a single centenarian (age 103) underwent a PD for a duodenal cancer and had an uncomplicated postoperative course. The patient lived 1.6 years after surgery.

Table 6. Postoperative data of patients undergoing pancreaticoduodenectomy by age

Postoperative event/ course	<80 yr (n = 2491)	80–89 yr (n = 197)	⩾90 yr (n = 10)
Mortality, n (%)	42 (1.7)	8 (4.1)*	0 (0)
Complications, n (%)	984 (41.6)	104 (52.8)*	5 (50)
Specific complications, n (%)			
Reoperation	89 (3.7)	11 (5.6)	0 (0)
Small bowel obstruction	11 (0.5)	0 (0)	0 (0)
Ulcer	16 (0.7)	2 (1.0)	0 (0)
Delayed gastric emptying	321 (13.6)	30 (15.4)	2 (20.0)
Pancreatic fistula	244 (10.3)	21 (10.7)	0 (0)
Pancreatitis	32 (1.35)	0 (0)	0 (0)
Cardiac	53 (3.6)	12 (8.3)*	1 (12.5)
Pneumonia	27 (1.1)	11 (5.6)*	1 (10)*
Sepsis	49 (2.1)	3 (1.5)	1 (10)
Intra-abdominal abscess	144 (6.1)	8 (4.1)	0 (0)
Lymph leak	20 (1)	2 (1.2)	0 (0)
Cholangitis	55 (2.3)	8 (4.1)	0 (0)
Bile leak	73 (3.1)	2 (1)	0 (0)
Wound infection	218 (9.3)	20 (10.3)	1 (10)
Postoperative lengh of stay, days, median (range)	10 (4–388)	11 (5–48)	12 (9–101)

*$P < 0.05$ compared with patients <80 yr.

Survival analysis was also performed for individuals who had a PD for pancreatic adenocarcinoma, which represents the largest subgroup of pathological diagnoses (Fig. 4). In the <80 cohort, the overall 1-, 2-, and 5-year survival rates were 66.5%, 37.7%, and 19.3%, respectively, with a median survival of 18 months. The 80- to 89-year-old group with pancreatic cancer had a significantly decreased overall 1-, 2-, and 5-year survival (44.5%, 33.0%, and 11.9%, respectively) compared to the younger cohort ($P = 0.002$), with a median survival of 11 months. There were two patients >90 years of age who underwent PD for pancreatic cancer, including a 92-year-old who lived 4.6 years after resection and a 90-year-old who lived 7 months after resection.

The 80- to 90-year-old patients who underwent PD had reduced long-term survival compared to age-matched controls in the general population who did not have surgery (U.S. Census). However, the declining slope of the survival curve of the patients who underwent PD decreases with time and eventually becomes parallel to the survival curve of the general population. The postoperative time point in which the incidence of death in patients undergoing PD in the 80- to 89-year-old group becomes statistically indistinguishable from age-matched controls in the general population is 25 months ($P = 0.08$). Figure 5 depicts the long-term

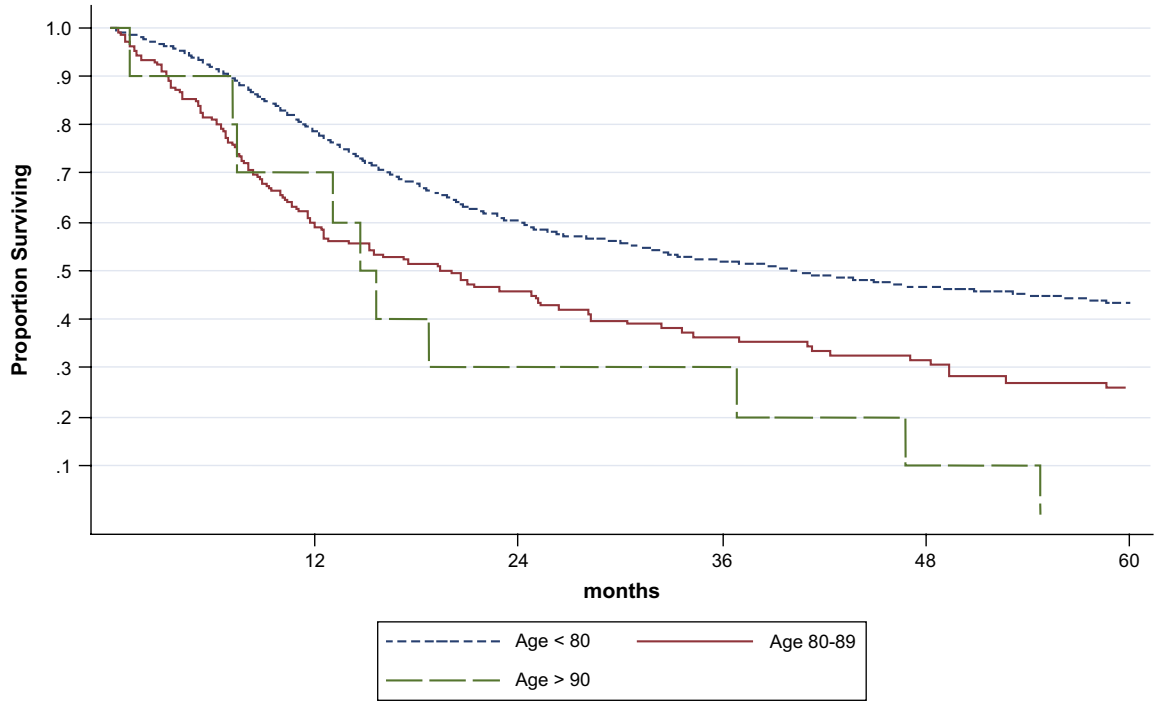

Fig. 3. Actuarial survival curves comparing patients under 80 years of age undergoing pancreaticoduodenectomy (n = 2340, median survival = 40 months, 5-year survival = 43.1%) to patients aged 80−89 (n = 187, median survival = 19 months, 5-year survival = 24.4%, $P < 0.001$) and over 90 (n = 10, median survival = 15 months, 5-year survival = 0%, $P = 0.002$).

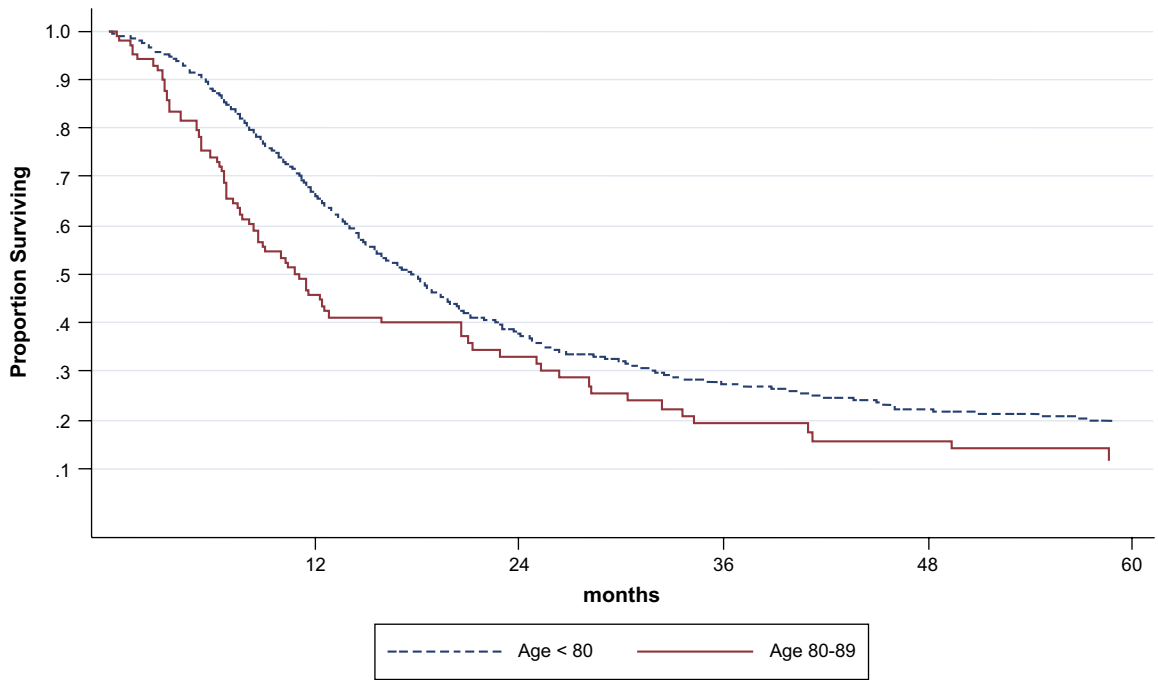

Fig. 4. Subset of patients with pancreatic cancer: actuarial survival curves comparing all patients under 80 years of age (n = 1022, median survival = 18 months, 2-year survival 37.7%) to patients aged 80−89 (n = 102, median survival 11 months, 2-year survival 33.0%, $P = 0.002$).

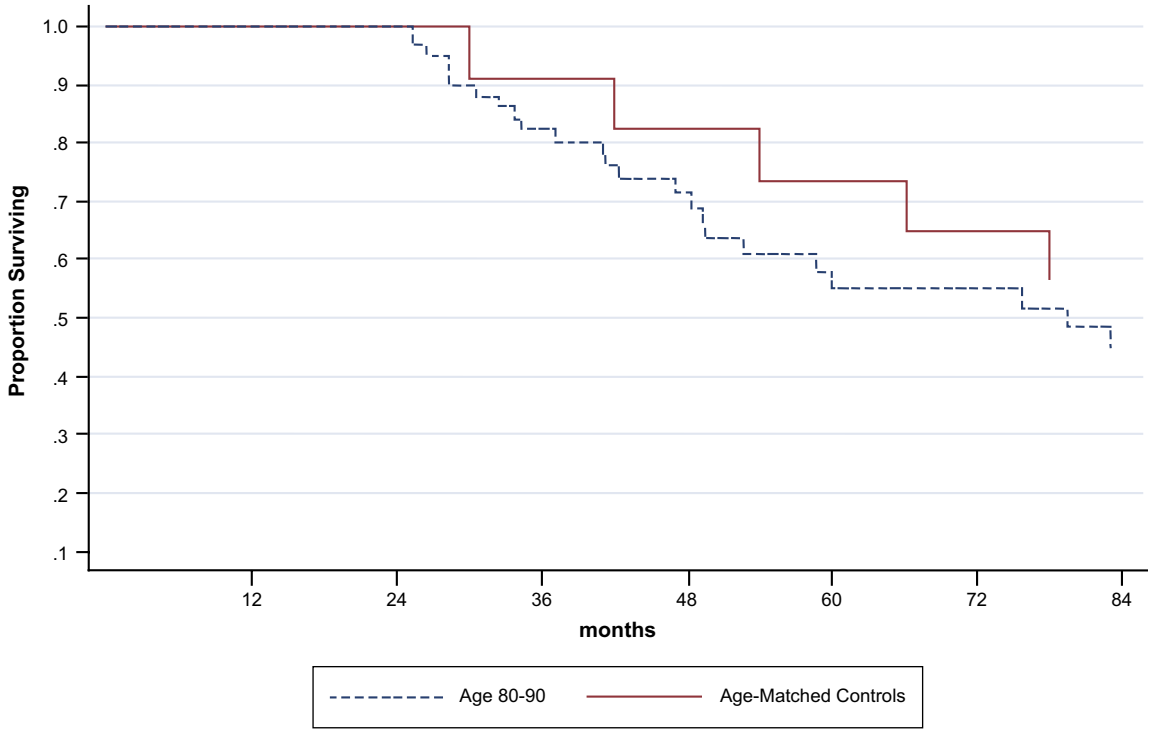

Fig. 5. Survival among 80- to 89-year-old 25+ month survivors following pancreaticoduodenectomy compared to age-matched controls in the general population. This plot only includes patients who have survived at least 25 months. Those individuals who were alive 25 months after surgery had a statistically indistinguishable survival curve (n = 60, median survival = 77 months, 5-year survival = 55%, $P = 0.08$) compared to 82-year-olds (the median age in our study population) in the general population (median survival = 88 months, 5-year survival = 69.0%).

survival curves of 25+ month survivors in very elderly patients undergoing PD, compared to the actuarial long-term survival of 82-year-olds in the general population. The median survival and 5-year survival for 25+ month PD survivors in the 80- to 89-year-old group were 77 months and 55%, respectively. These values for 82-year-olds in the general population are 88 months and 69%, respectively. Of note, one-third of the 25+ month survivors following PD had pancreatic cancer (ductal adenocarcinoma or IPMN with invasive cancer) and two-thirds of the patients had a malignancy. A power analysis of the data demonstrated that the number of 25+ month survivors between 80 and 89 years of age was large enough to demonstrate equivalency to age-matched controls at a resolution of ±25%. This confidence interval is considered acceptable resolution for demonstrating equivalency.[14]

DISCUSSION

The decision to recommend a PD for localized pancreatic cancer or other periampullary process in a very elderly patient is complicated by the frailty of the patient and the poor prognosis of the disease. The process of weighing the risks and indications for surgical resection is further made difficult by the lack of clinical data on major intra-abdominal surgery in the elderly. Many patients presenting for a second opinion at our referral center have reported to us that they previously have been denied an operation based on their advanced age. Our data indicate that currently (in 2005), approximately 9% of all patients who undergo a PD at Johns Hopkins are 80 years of age or older. Furthermore, there has been a clear increase in the number of PDs being performed on the very elderly in the last 10 years, consistent with the prediction of population epidemiologists that there will be a dramatic increase in elderly and very elderly patients presenting for surgery in the future.[4,5]

Based on our experience, there appears to be a slight increase in perioperative mortality in the very elderly (4.1% in the 80- to 89-year-old group compared to 1.7% in the <80 year group). Our results of operative mortality following PD are similar to our earlier reported experience with PD among

octogenarians[11] and a VA cooperative study reporting a 30-day mortality for colon cancer surgery of 2.8% for patients <65 years as compared to 5.6% for those >65 years.[15] Of interest, the observed 0% mortality among the 10 patients in the >90-year-old group exemplifies the feasibility of performing surgery successfully in very elderly patients, albeit at a low volume. Such safe results have been previously reported for patients with gastric cancer. Katai et al.[16] observed no "operation-associated" deaths among 141 patients over the age of 80 who underwent an elective gastrectomy.

We found that age is associated with an increase in the incidence of postoperative cardiac events and pneumonia. While this observation is consistent with other studies,[15,17] we found in our extensive subgroup analysis, that age was not associated with other postoperative complications, such as reoperation, delayed gastric emptying, pancreatic or biliary leak, sepsis, intra-abdominal abscess formation, or wound infection. In addition, hospital length of stay was not affected by patient age.

Predicting which elderly patients will do well following surgery has been the subject of much research.[18] Increasingly, nomograms are being developed to predict operative mortality based on interpolation from large databases.[19] Age is a factor entered into such nomograms; however, we have found that age alone does not significantly contribute to outcome and that such age-based nomograms may be inaccurate. Thus, with due consideration of cardiopulmonary risk factors, we maintain PD should not be withheld from appropriate patients based solely on age. Healthy patients 80 years of age and older should be considered for such potentially curative resection. Subgroup analysis of very elderly patients who survived over 2 years following PD demonstrates that nearly one-third of the patients (60 of 187) will achieve a long-term survival that is comparable to age-matched controls in the general population, even though the majority of these patients underwent PD for malignant disease (44 of 60).

Frailty is an entity that has recently been identified as a marker of physiologic reserves in elderly patients and is unique from comorbidity and disability.[20] The degree to which a person is frail (measured by a validated frailty score) correlates with activity level, strength, and functional capacity. Further study in a prospective fashion is needed to determine whether a measurement of frailty can accurately predict which elderly patients will do well following a major operation. Such information may help clinicians in surgical decision-making for elderly patients.

Based on our experience, we have found that the increase in the elderly population is beginning to be translated to increased volumes in the surgical setting. PD can be performed safely in the very elderly, and we conclude that age alone should not be a contraindication to pancreatic resection. The achievement of improved surgical outcomes in the context of an increasing elderly population likely will result in a significant increase in the number of PDs performed in the next few decades.

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Complement Depletion Enhances Pulmonary Inflammatory Response After Liver Injury

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Hepatic cryoablation can produce acute lung injury, with activation of nuclear factor (NF)-κB in the remnant liver and lungs, production of C-X-C chemokines, and neutrophil infiltration of the lungs. Activated complement stimulates NF-κB and cytokine secretion from Kupffer cells. The role of complement in the development of acute lung injury after cryoablation was examined using HLL transgenic mice (5′ *H*IV-*L*TR-*L*uciferase gene; 5′ HIV-LTR is an NF-κB–dependent promoter). Total complement depletion was achieved with preoperative administration of cobra venom factor (CVF). After hepatic cryoablation, bioluminescent NF-κB activity increased in the nonablated liver remnant by 4 hours in both control (119,093 ± 22,808 net RLU/mg protein) and CVF-treated mice (117,722 ± 14,932) from cumulative baseline (657 ± 90, $P < 0.0001$). In the lung, complement-depletion induced significantly greater increases in NF-κB activation at both early and later times. Likewise, chemokines were higher in complement-depleted mice relative to controls (KC: 493 ± 43 versus 269 ± 29 pg/mg protein, $P < 0.001$; MIP-2: 171 ± 29 versus 64 ± 13 pg/mg protein, $P < 0.0001$). Pulmonary myeloperoxidase activity was equivalent at 24 hours, but complement-depletion caused a significantly more rapid influx of neutrophils. Complement depletion results in increased pulmonary inflammation following liver cryo injury via relative upregulation of NF-κB activity. Activated complement is not the initiator of the systemic inflammatory response; in fact, downstream components of the complement cascade may diminish subsequent inflammation. (J GASTROINTEST SURG 2006;10:357–364)

KEY WORDS: Cryoablation, acute lung injury, complement, C3, CVF

Local ablative techniques for treating hepatic tumors, both primary and metastatic, are increasingly used as adjuncts to surgery, particularly in patients who are not candidates for standard oncologic resection. Cryoablation is one such method that has been used extensively to ablate liver masses.[1–3] This technique relies on the reduction of local temperatures to at least −35° C during a rapid freezing cycle, and it produces cell death through a variety of mechanisms, including (1) internal freezing with ice crystal disruption of cellular membranes, (2) solute/solvent shifts, and (3) hypoxia-induced programmed cell death from small vessel obliteration. [4–6] Initial clinical experience with hepatic cryoablation revealed the possibility of inducing a systemic inflammatory response, with the lungs seeming particularly susceptible to injury.[7] Acute lung injury tended to occur more frequently following larger ablations.[8] For unknown reasons, this acute inflammatory response is not observed as frequently following surgical resection of similar volumes of liver or when alternative methods of ablation are used.[4]

Prior research has demonstrated that the "cryoshock" phenomenon is mediated, at least in part, by activation of the transcription factor nuclear factor kappa-β (NF-κB) in the liver.[9–11] Binding of NF-κB to DNA leads to the production and elaboration of various cytokines (tumor necrosis factor α, interleukin [IL]-1β) and chemokines (IL-8, CINC), which then initiate a similar proinflammatory response in the lung, ultimately producing a mixed-cell pulmonary infiltrate and the resultant acute

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lung injury.[12] Presumably, the initial activation of NF-κB occurs in the hepatic Kupffer cells, which comprise over 80% of the body's tissue macrophages. However, why systemic inflammation occurs with large-volume cryoablation and not other hepatic ablative techniques is uncertain, and the initial stimulus of these NF-κB–dependent mechanisms remains unknown.

The complement cascade is a central component of innate immunity. The principal biological functions of the complement system include cell lysis, opsonization, potentiation of humoral responses, and activation of the inflammation cascade (via the anaphylotoxins C3a, C4a, and C5a).[13] Both C3a and C5a are known to stimulate NF-κB in cells of monocytic origin.[14] C3a modulates Kupffer cell prostaglandin synthesis and C5a induces secretion of C-X-C chemokines from alveolar macrophages.[15,16] Furthermore, upregulation of anaphylotoxin receptors in the liver and lung has been observed in other systemic proinflammatory states such as sepsis.[17]

The current study examined whether complement is the initial trigger of the NF-κB–mediated inflammation that follows large-volume hepatic cryoablation. An established experimental method of total complement depletion was used in combination with a model of cryoablation in HLL transgenic mice. Subsequently, we quantified the activation of NF-κB in both liver and lungs using bioluminescence, measured the generation of proinflammtory chemokines, and determined the degree of acute neutrophilic pulmonary infiltration. Our findings suggest that complement is not the initial proinflammatory stimulus within the liver and that downstream components of the complement cascade may actually diminish the systemic inflammatory response.

MATERIAL AND METHODS

Animal Model

All experiment were performed using transgenic mice expressing *photinus* luciferase cDNA under the control of the 5′ human immunodeficiency virus long terminal repeat promoter. The 5′-HIV-LTR is a known binding sequence for NF-κB, and the construct is termed HLL (5′-*H*IV-*L*TR-*L*uciferase gene). We have demonstrated successful quantification of NF-κB activation following hepatic cryoablation with this model using ex vivo measurement of luminescence.[10] Animals were housed under pathogen-free barrier conditions, acclimated to 12-hour light cycles, and provided access to food and water ad libitum throughout the experiments. All procedures were approved by the Washington University Animal Studies Committee.

Total complement depletion was achieved using serial doses of cobra venom factor (CVF) from the species *Naja kaouthai* as previously described.[18–20] This 149,000-kDa glycoprotein is a structural and functional C3 homolog that binds avidly to factor B. The CVF-Bb complex acts as a C3/C5 convertase, cleaving C3 and C5 to produce consumptive depletion of circulating complement through activation of both the classical and alternative pathways.[21] CVF was administered intraperitoneally in sterile phosphate-buffered physiologic saline (PBS, 200 μl) at 24 and 1 hour prior to hepatic cryoablation. Pilot studies were performed to determine the appropriate dose (15, 30, or 60 μg) necessary to achieve complete complement depletion (data not shown); subsequently, the 30-μg dose was used for all studies as this was the minimal dose that achieved near-total complement depletion. Mice receiving PBS only were used as controls.

Surgical anesthesia was established using ketamine (87 mg/kg) and xylazine 1% (13 mg/kg). Mice were then prepped and placed on a heating place to maintain systemic normothermia. Following midline laparotomy and limited hepatic mobilization, a commercial cryoablation device (Candela, Wayland, MA) that uses recirculating liquid N_2 through a 3-mm-diameter metallic probe was used to perform a 35% (by mass) ablation of the left lateral and median hepatic lobes. We have previously demonstrated a reproducible hepatic injury using this technique, and it consistently results in an acute, progressive systemic response and pulmonary inflammatory injury within 24 hours.[10,11,22] Following complete thawing and reperfusion of the injured liver, warmed PBS (2 ml) was instilled in the abdomen. The abdomen was then closed using a running 3-0 silk suture and metallic clips. Mice were killed with an overdose of anesthetic and rapid bilateral pneumothoraces at 4 or 24 hours postoperatively. The inferior vena cava was cannulated for phlebotomy. The liver (nonablated remnant) and lungs were collected sterilely, briefly rinsed in PBS, snap-frozen in liquid nitrogen, and stored in RNA/DNA-free containers at −80° C until further processing.

Complement Quantification

Serum intact C3 levels were quantified in experimental animals at the time of death using the radial immunodiffusion method of Mancini over 72 hours (National Jewish Hospital Labs, Denver, CO).

Results are expressed relative to a predetermined standard quantity of factor C3 derived from BALB/c mice.

Ex Vivo Bioluminescence

Luciferase activity (a marker for NF-κB–DNA binding activity) was measured in organ homogenates with slight modification from previously described techniques.[10,23] Briefly, 30-mg portions of frozen lung or liver tissue were homogenized in reporter lysis buffer 1 × (Promega Corp, Madison, WI), subjected to three freeze-thaw cycles, and centrifuged at 10,000 *g* to extract cytoplasmic protein. Protein extract (50 μl) was combined with 100 μl of reconstituted luciferase assay substrate (Promega), followed by measurement of relative light units (RLUs) using a standard luminometer (Berkhold Detection Systems, Oak Ridge, TN). Luciferase activity was normalized to protein concentration, as determined by the Bradford method with spectrophotometric analysis.[24]

Cytokine Detection

Enzyme-linked immunosorbent assays (ELISAs) (R&D Systems, Minneapolis, MN) for the murine C-X-C chemokines KC and MIP-2 were used according to the manufacturer's instructions. These proteins are homologs to human IL-8 and are believed to be the major proinflammatory alpha chemokines in mice. All samples were measured in duplicate. Total protein was extracted from snap-frozen mouse lung tissue by tissue homogenization in a 150 mM sodium chloride buffer containing HEPES (1 M), EDTA (0.2 M), PMSF in ethanol, and Nonidet P-40. Protein concentrations were measured using the Bradford assay. Cytokine levels in 30 μg of lung protein extracts were performed using an ELISA.

Myeloperoxidase Assay

The functional MPO assay has been demonstrated to be a reliable indicator of the degree of neutrophilic infiltration, particularly in the lung.[25,26] Frozen pulmonary tissue was homogenized using a tissue rotastator in a 1 M potassium phosphate buffer containing 10% hexadecyltrimethulammonium bromide (HTAB; Sigma Corp., St. Louis, MO), sonically disrupted, and centrifuged at 1700 *g* for 30 minutes. Supernatant (5 μl) was added to a 0.1 M potassium phosphate buffer solution supplemented with 10% bovine serum albumin, 7.5% sodium bicarbonate, 1 M HEPES, and 10 × HBSS. A solution of 0.05% H_2O_2 and o-dianisidine served to initiate the functional assay and resulting color shift, and this reaction was terminated by the addition of 1% sodium azide after 15 minutes. Spectrophotometric shift at 460 nm was determined at 5 and 20 minutes in duplicate. Results are expressed as the change in optical density per minute per mg of protein to yield a relative quantification of neutrophil content.

Statistical Analysis

Analysis of variance was used for comparisons between groups, with the Newman-Keuls post-hoc test for significance applied as appropriate. *P* values less than 0.05 were considered significant. Data are expressed as mean ± SEM.

RESULTS

Circulating factor C3 is enzymatically cleaved to produce the anaphylotoxin C3a, and factor C3b which further propagates the complement cascade. Serial dosing of CVF at two times prior to hepatic injury was highly effective at eliminating circulating intact factor C3 from experimental animals (Fig. 1). CVF treatment in unoperated mice resulted in complete depletion of circulating C3 relative to untreated control animals (41.7 ± 2.9% versus 0.0% of standard respectively; $P < 0.001$). In mice killed at 4 hours postcryoablation, C3 was also significantly decreased in the CVF-treated group. Cryoablation alone (without CVF pretreatment) produced a statistically significant decline in C3 levels of 43% relative to unoperated controls ($P < 0.001$).

Bioluminescent quantification of the DNA-binding activity of NF-κB in the lungs and in the nonablated liver remnant revealed different patterns of activation in C3-depleted and control mice. Basal NF-κB activity in the liver was unaltered by CVF treatment (control 760.6 ± 130.8 versus treated 490 ± 85.2 net RLU/mg protein; $P = 0.15$). In the nonablated liver remnant at 4 hours postcryoablation, NF-κB was markedly increased from baseline in both the CVF-treated and control groups (117,722 ± 14,932 versus 119,093 ± 22,808 net RLU/mg protein respectively; $P < 0.001$ versus baseline). However, CVF pretreatment did not change the degree of hepatic NF-κB activation following cryoablation. Conversely, while NF-κB binding activity in the lungs also increased in all mice posthepatic injury, there was a significantly greater increase from baseline in C3-depleted animals (Fig. 2). Basal pulmonary NF-κB activity was higher in the lungs than in the liver for all animals. At 4 hours after hepatic cryoablation, NF-κB activity in

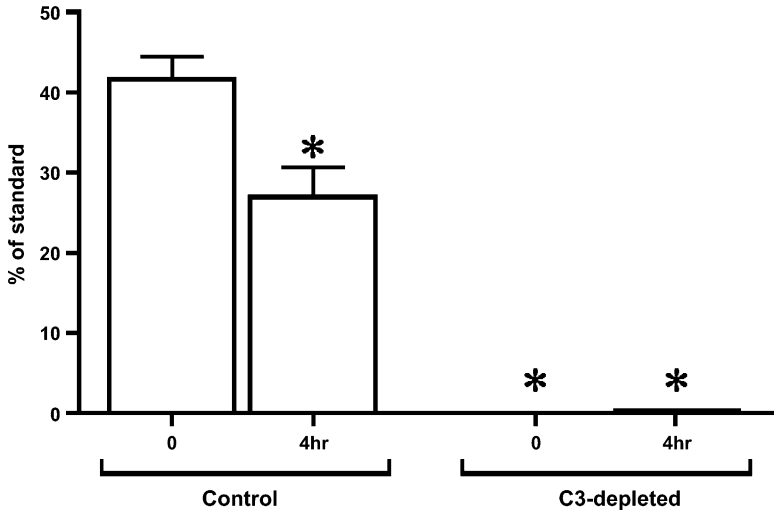

Fig. 1. Administration of CVF depletes circulating factor C3. Graph depicts quantitative serum C3 levels in mice treated with CVF and controls at baseline (t = 0) and 4 hours post–hepatic cryoablation. Data are expressed as a percentage of a BALB/c-derived standard. N = 6–8 per group. *$P < 0.001$ versus control.

controls was 1.9 times higher than baseline, while activity in the CVF-treated group had increased threefold ($P < 0.01$ versus baseline, $P = 0.14$ versus control at 4 hours). By 24 hours after liver injury, the induction of pulmonary NF-κB was significantly different between CVF-treated and control groups, with controls showing only a 3-fold induction of NF-κB in the lungs versus an approximate 5.5-fold increase in the C3-depleted group ($P < 0.001$ versus baseline, $P = 0.02$ versus control at 24 hours).

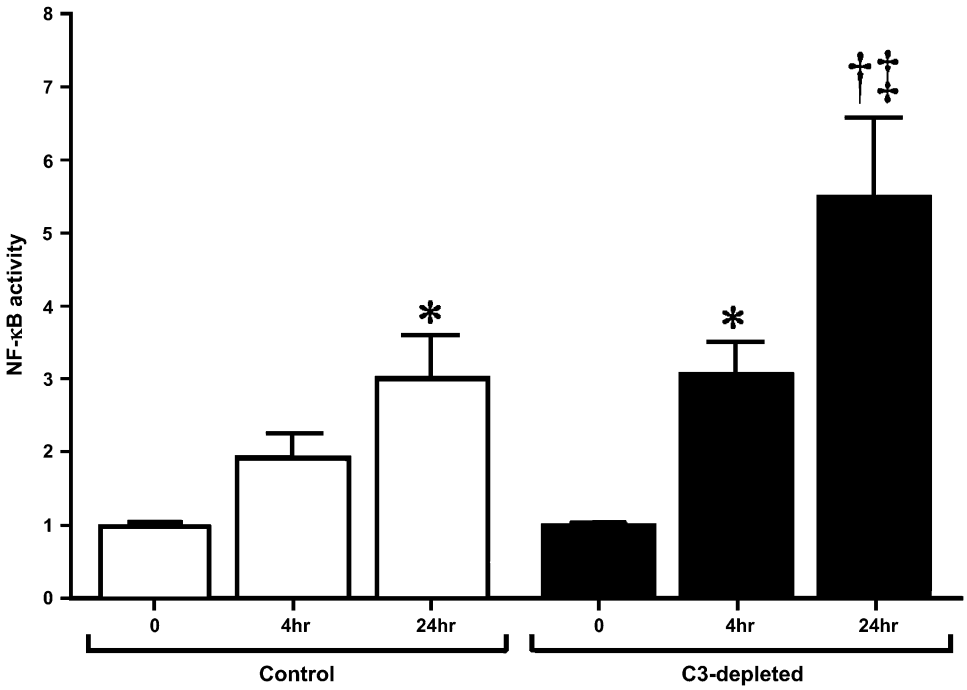

Fig. 2. Complement depletion leads to increased NF-κB activation within the lungs following hepatic injury. Graph depicts induction of pulmonary NF-κB activity at various times following hepatic cryoablation, relative to baseline. N = 6–8 per group. *$P < 0.01$ versus baseline, †$P < 0.001$ versus baseline, ‡$P < 0.05$ versus control.

The measured peak of production of C-X-C chemokines in the lung occurred at 4 hours after hepatic cryoablation, with a gradual return toward baseline by 24 hours post–liver injury (Fig. 3). However, both MIP-2 and KC were significantly overexpressed in lungs of C3-depleted mice relative to controls. MIP-2 in the CVF-treated mice peaked at 171.0 ± 28.8 pg/mg protein, with controls demonstrating a significantly smaller peak at 64.4 ± 12.7 ($P < 0.001$). By 24 hours post cryoablation, MIP-2 levels had returned to baseline in both groups. KC was similarly elevated in the CVF group relative to controls at 4 hours (493.2 ± 42.5 versus 268.7 ± 29.0 pg/mg protein; $P < 0.001$). Levels of this chemokine remained statistically significantly elevated in all mice at 24 hours.

MPO is a heme-containing compound found almost exclusively in the azurophilic granules of neutrophils.[27] Thus, the functional MPO assay provides a measure of neutrophilic infiltration of the lungs and quantifies the degree of acute inflammation. CVF treatment did not alter pulmonary

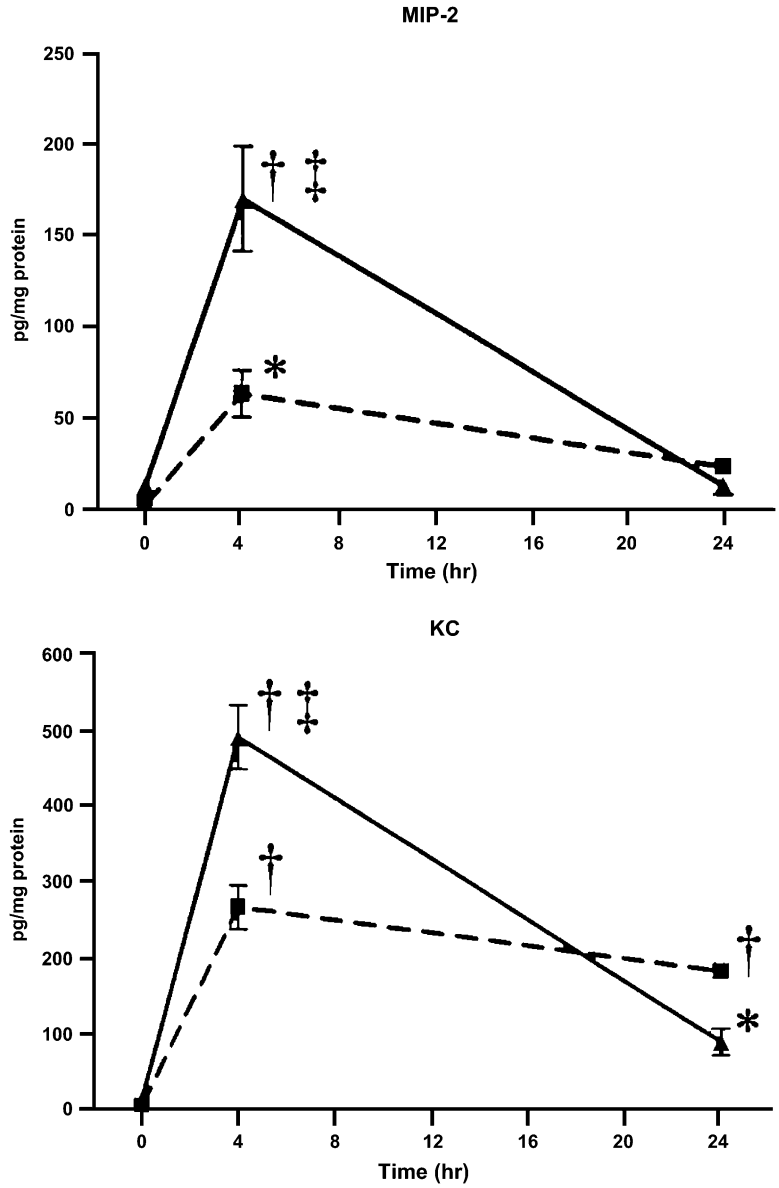

Fig. 3. Complement depletion results in augmented pulmonary chemokine production. Graphs depict time courses for the production of the proinflammatory chemokines MIP-2 and KC in the lungs following hepatic cryoablation. Dashed lines indicate control groups, and solid lines indicate C3-depleted groups. *$P < 0.05$ versus baseline, †$P < 0.001$ versus baseline, ‡$P < 0.001$ versus control.

MPO content at baseline (0.291 ± 0.04 versus 0.275 ± 0.03 ΔOD/min/mg protein, $P = 0.76$). As shown in Figure 4, both control and C3-depleted mice exhibited an almost twofold increase in MPO content in the lungs by 24 hours post cryoablation (0.587 ± 0.02 and 0.571 ± 0.03 ΔOD/min/mg protein respectively; $P < 0.001$ versus baseline). Notably, C3-depleted mice had a more rapid increase in pulmonary MPO (and thus neutrophils) than controls, with a significant elevation observed at 4 hours after liver injury (0.587 ± 0.02 ΔOD/min/mg protein; $P < 0.05$ versus baseline). This elevation in MPO also differed significantly from controls at 4 hours (0.296 ± 0.03 ΔOD/min/mg protein; $P < 0.05$), which remained statistically unchanged from baseline.

DISCUSSION

The current study has demonstrated that the early activation of NF-κB in the liver following cryoablation is unaltered by complement depletion, and thus it presumably occurs independent of this component of the innate immunity system. Complement activation does not appear to be the initial trigger within the liver initiating the subsequent inflammatory response. Hepatic cryoablation caused pulmonary NF-κB activation and a marked neutrophil invasion of the lungs in all animals. Interestingly, a significant relative increase in pulmonary NF-κB activation occurred after complement depletion with CVF. Likewise, proinflammatory chemokines were elevated in the lungs of C3-depleted mice, and a corresponding increase in early neutrophil migration was observed. These findings suggest that the acute lung injury following hepatic cryoablation is aggravated by the elimination of circulating complement and that components of the complement cascade may play a role in blunting the systemic proinflammatory response.

Total complement depletion by administering CVF is well described and accepted. The activation of factor C3 is common to all complement pathways, and elimination of C3 blocks the generation of C3a, C5a, and the membrane attack complex.[13] Consistent with previous studies, we were able to reproducibly deplete circulating C3 to undetectable levels using two preoperative doses of CVF.[18,20] Cryoablation alone (without CVF pretreatment) also depleted circulating C3. We have previously shown that cryoablation results in the destruction of lipid bilayers, including the plasma membrane; however, extensive protein denaturation and destruction of intracellular organelles do not occur.[4] C3 depletion after cryoablation in nontreated mice likely occurred through the activation of the complement cascade upon exposure to intracellular glycoproteins.

The finding that complement depletion did not alter hepatic NF-κB activation was somewhat unexpected. C5a initiates hepatic regeneration following resection, in part by mediating the induction of proinflammatory cytokines that stimulate hepatocyte entry into the cell cyle.[28] Similarly, C5a and C3a

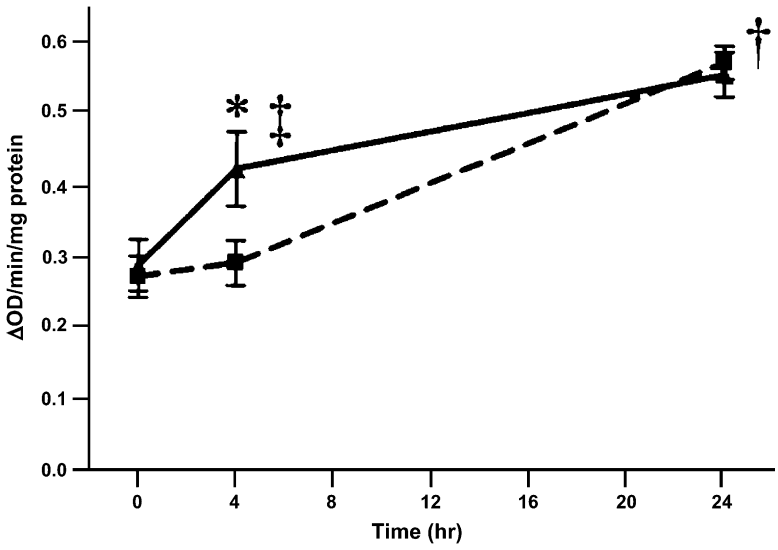

Fig. 4. Neutrophil influx is more rapid following hepatic injury in complement-depleted mice. Graph depicts pulmonary MPO content at various times after hepatic cryoablation. Dashed lines indicate control groups, and solid lines indicate C3-depleted groups. *$P < 0.05$ versus baseline, †$P < 0.001$ versus baseline, ‡$P < 0.05$ versus control at 4 hours.

seemed likely candidates to signal NF-κB activation in the Kupffer cells of the nonablated hepatic remnant. It is possible that differences in NF-κB activation occurred immediately after cryoablation but were not observed at the 4-hour timepoint used in the current study. We have demonstrated previously that transcription of NF-κB–dependent cytokine messenger RNA in the liver occurs within 30 minutes of cryoablation, suggesting a rapid signaling sequence transpires during hepatic injury.[11] Others have shown that the peak differential in NF-κB activation between C3-deficient and control animals occurred at 2 hours following hepatic injury.[28] Nonetheless, the same investigators demonstrated that NF-κB activity remained clearly diminished over several hours, making it unlikely that a significant difference in hepatic NF-κB activation was not detected in the current study.

Although the innate immunity system, and the anaphylotoxins C3a and C5a in particular, are most commonly described as creating a proinflammatory state, there are reports of the downstream effectors of the complement cascade acting as anti-inflammatory mediators. Bhatia and colleagues[29] described the apparent anti-inflammatory actions of C5a in a murine model of acute pancreatitis. They observed a more severe pancreatitis-induced acute lung injury in C5-deficient mice than in those with intact complement systems, with increases in pulmonary neutrophil influx and microvascular permeability. These findings concur with the current study, in which C3-depletion produced a greater abundance of C-X-C chemokines and increased pulmonary NF-κB activation, both of which lead to a more rapid neutrophil infiltrate in the lungs. Others have found that gradients of various chemoattractants (including C5a and IL-8) can cause preferential leukocyte migration against complex gradients of other chemoattractants, leading to a heterologous desensitization response.[30] Leukocytes desensitized in such a manner would be less responsive to subsequent chemokine exposure. It has been proposed that early generation of C5a in response to an inflammatory stimulus could limit subsequent cellular recruitment by chemokines and other secondary mediators of inflammation. Conversely, in complement-depleted systems, the acute inflammatory event generates an abundant chemokine response that is allowed to recruit cells which have not been partially desensitized by C5a, leading to a robust inflammatory response.[29] We hypothesize similar conditions occur in the C3-depleted mouse subjected to hepatic cryoablation. The lack of the products of C3 cleavage (e.g., the anaphylotoxins) prevents relative desensitization of Kupffer cells in the liver, which then release greater amounts of proinflammatory cytokines in response to hepatic injury. These molecules signal NF-κB activation remotely in the lungs, which in turn results in elaboration of chemoattractants and the rapid influx of neutrophils. The use of C3- and C3aR-deficient knockout animals will allow further validation of this hypothesis.

CONCLUSION

The complement system is not the initiator of the systemic inflammatory response following hepatic cryoablation. Treatment with CVF thoroughly depleted circulating factor C3, and thus abolished complement function. Despite abolishing complement activity, the activation of NF-κB in the liver remnant following cryoablation remained unchanged, suggesting that complement was not the initial stimulus of the inflammatory response observed during cryoshock. However, the progression of the acute lung injury was increased in conjunction with C3 depletion, as demonstrated by a greater chemokine response and more rapid influx of neutrophils. We hypothesize that C3 depletion prevents the relative desensitization of both resident hepatic macrophages (e.g., Kupffer cells) and remote leukocytes, thereby allowing secondary mediators of inflammation such as the proinflammatory C-X-C chemokines and possibly other cytokines to mount a more vigorous and brisk response. Further analysis is warranted to determine the initial proinflammatory signaling mechanism following hepatic injury.

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Chemotherapy Does Not Impair Hypertrophy of the Left Liver After Right Portal Vein Obstruction

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In patients with multiple colorectal liver metastases, the technical limits of curative surgery can be overcome by both reducing tumor volume with preoperative chemotherapy and by increasing the future remnant liver with portal vein embolization. Chemotherapy is generally discontinued before the embolization because it is alleged to impair hypertrophy of the future remnant liver. We have tested this assumption by comparing two groups of patients who had undergone right portal vein obstruction: 10 patients in whom chemotherapy was maintained until surgery and 10 patients in whom it was interrupted at least 1 month prior to portal obstruction. The two groups, with and without chemotherapy, were comparable for patient's age (60 ± 9 versus 61 ± 9 years), number of metastases (7.7 ± 3 versus 6.2 ± 3), and future remnant liver volume (25 ± 9% versus 23 ± 5% of the total liver). After right portal vein obstruction, the increase of the future remnant liver was comparable in the two groups (33 ± 26% versus 25 ± 7%). Liver resection was performed in 14 patients (7 in each group) with a similar morbidity rate (57% in each group). In conclusion, continuing chemotherapy while portal vein obstruction is performed did not impair the hypertrophy of the future remnant volume nor the postoperative course after liver resection. Therefore, chemotherapy can be safely continued until liver surgery, when portal vein obstruction is indicated. (J GASTROINTEST SURG 2006;10:365–370)

KEY WORDS: Portal vein embolization, portal vein ligation, chemotherapy, colorectal liver metastases, hepatectomy

Patients with multiple colorectal liver metastases have been shown, during the past 5 years, to benefit from curative liver resections,[1,2] even when their metastases were bilobar.[3] The main limitations to these resections are the small volume of the remnant liver[4–6] and the poor oncological prognosis of these advanced diseases.[7,8] The former increases the risk of postoperative liver failure, while the latter is associated with early recurrence. Recent studies have, however, shown that preoperatively increasing the future remnant liver volume through portal vein embolization (PVE) or ligation and administering effective neoadjuvant chemotherapies could overcome these limitations, at least in some patients.[4,9–11]

Patients with such advanced metastatic disease are usually referred to surgeons when a neoadjuvant chemotherapy has allowed downstaging of initially unresectable liver metastases[10] or when there is a documented chemosensitivity,[8,12] as in both situations, liver resection may further improve survival. Should a preoperative PVE be required, this chemotherapy is discontinued at least 1 month prior to the embolization and subsequently until surgery, performed at least 4 weeks thereafter,[9–11,13] because it is alleged to impair liver regeneration. This theoretical rationale has the real inherent drawback of allowing or favoring tumor progression during this 2-month period.[14–16]

To assess the rationale for discontinuing this chemotherapy, we have retrospectively compared the hypertrophy of the future remnant liver following right portal vein obstruction prior to a planed right or

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extended right hepatectomy on a group of 20 patients. In half of these patients, the chemotherapy was interrupted 1 month prior to right portal vein obstruction, while in the other half the chemotherapy was continued until surgery. We have compared the hypertrophy of the future remnant liver, the resectability rate, and the postoperative course in these two groups of patients with colorectal liver metastases.

PATIENTS AND METHODS

Patients

Between January 1999 and December 2003, 203 patients underwent resection of colorectal liver metastases, including 67 right or extended right hepatectomies. During the same period of time, 20 patients referred for the surgical treatment of multiple colorectal liver metastases underwent preoperative right portal vein obstruction. Seventeen patients had bilobar metastases and 15 had five metastases or more. These metastases were judged resectable by a right or an extended right hepatectomy, with or without tumorectomies of the left liver. A thoracoabdominal helicoidal computed tomography (CT) scan had ruled out extrahepatic deposits.

Obstruction was achieved by either embolization (n = 11) or ligation (n = 9). PVE was performed when the metastases were resectable in one stage but the future remnant liver volume was less than 30% of the total liver volume. Right portal vein ligation was performed, as part of a two-stage procedure, when the metastatic disease in the left liver was judged too extensive to be safely resected along with the right liver, especially when the resection of the primary tumor was also required (see later).

All patients were receiving neoadjuvant chemotherapy at the time of referral. According to the attending surgeon's choice, this chemotherapy was either discontinued, at least 1 month prior to the right portal vein obstruction and until surgery (n = 10), or maintained throughout the procedure (n = 10). When this was the case, chemotherapy was only transiently interrupted 1 week before and 1 week after the right PVE and maintained until 2 weeks before surgery. In case of ligation, chemotherapy was interrupted 2 weeks before surgery and was reintroduced 2 weeks after ligation and maintained until 3 weeks before the second stage of surgery. These latter 10 patients therefore received an additional 3.5 (median [range, 2–5]) courses of chemotherapy prior to surgery, consisting in the combined use of 5-fluorouracil and either oxaliplatin or irinotecan. Patients and tumor characteristics as well as technique of portal vein obstruction were otherwise comparable in these two groups (Table 1).

Table 1. Patients and tumor characteristics

	Chemotherapy continued (n = 10)	Chemotherapy interrupted (n = 10)
Age (y)	59.8 ± 9	60.8 ± 9
Male/female	5/5	5/5
No. liver metastases > 4	8	7
Bilobar metastases	9	8
Synchronous metastases	7	6
Right portal vein embolization	5	6
Right portal vein ligation	5	4

Right Portal Vein Obstruction

Right PVE was performed using the contralateral transhepatic approach as previously described.[17] In brief, a collateral vein of the left branch of the portal vein was punctured under light general anesthesia and ultrasound guidance. Following control venous portography, the right anterior and posterior portal branches were embolized with a mixture of cyanoacrylate (Histoacryle; Braun Lab, Hamburg, Germany) and lipiodol (Lipiodol Ultrafluide; Guerbert Lab, Paris, France). The branches to segment 4 were not embolized even in patients in whom this segment was to be resected. Surgery was scheduled 6 weeks after the embolization.

Ligation of the right branch of the portal vein was performed as part of a two-stage procedure.[18] During the first stage, the resection of the primary tumor was performed in six patients, and enucleation of the left-sided liver metastases, with at least a 5-mm margin, was achieved in all the patients except one who had unilobar metastases. Extraparenchymal ligation of the right portal branch was performed using a nonabsorbable suture. The second stage, scheduled at least 6 weeks later, consisted in a right or an extended right hepatectomy.

End Points

The primary end point of the analysis was the hypertrophy of the future remnant liver induced by the right portal vein obstruction. All patients underwent volumetric helicoidal CT scan estimation of their liver volumes before the obstruction and 4–6 weeks thereafter. Measurements were performed for the whole liver, as well as for the left and future remnant livers using the middle hepatic vein, gallbladder bed, and umbilical portion of the left portal vein as landmarks. The remnant liver volume was expressed as a percentage of the total liver volume. Its hypertrophy following portal vein obstruction was calculated as follows: Percent remnant liver volume 4 to 6 weeks

after portal vein obstruction – percent remnant liver volume before portal vein obstruction] × 100/percent remnant liver volume before portal vein obstruction.

The secondary end points of the analysis were the resectability rate and the postoperative course. *Operative mortality* was defined as death occurring within the same hospital stay or within 30 days of surgery. *Postoperative complications*, recorded prospectively, were defined as follow a) liver failure as a prothrombin time less than 50% and a serum bilirubin level greater than 50 μmol/L on the fifth postoperative day or thereafter, b) ascites as a fluid output from the abdominal drainage greater than 500 mL/day, c) biliary leak as the presence of bile in the abdominal drainage or abdominal collections greater than twice the serum level, d) symptomatic pleural effusions as those requiring drainage.

Statistical Analysis

These end points were compared between patients whose chemotherapy was continued and those in whom it was interrupted. Continuous variables were compared using the Fisher's exact *t* test, and categorical variables were compared using the Mann-Whitney test. A *P* value of less than 0.05 was considered as statistically significant. Data are expressed as mean (±SD) unless otherwise stated.

RESULTS

Liver Hypertrophy

Based on preoperative imaging, the future remnant liver volume accounted for 24.2 ± 7.6% for all the patients and was comparable between the two groups of patients: 25.1 ± 9.7% in the group with chemotherapy and 23.3 ± 5.3% in the group without chemotherapy. The mean time interval between portal vein obstruction and the CT scans used to assess the hypertrophy of the future remnant liver was comparable in the two groups with and without chemotherapy (39.0 ± 16 versus 39.3 ± 15 days, respectively). After right portal obstruction, the mean increase of the future remnant liver volume was not statistically different between patients in whom chemotherapy was continued and those in whom it was interrupted, respectively (33 ± 26% and 25 ± 7%; $P = 0.18$), as shown in Figure 1. The mean increase of the future remnant liver volume was not statistically different after embolization compared to ligation, respectively (35 ± 23% and 27 ± 7%; $P = 0.63$).

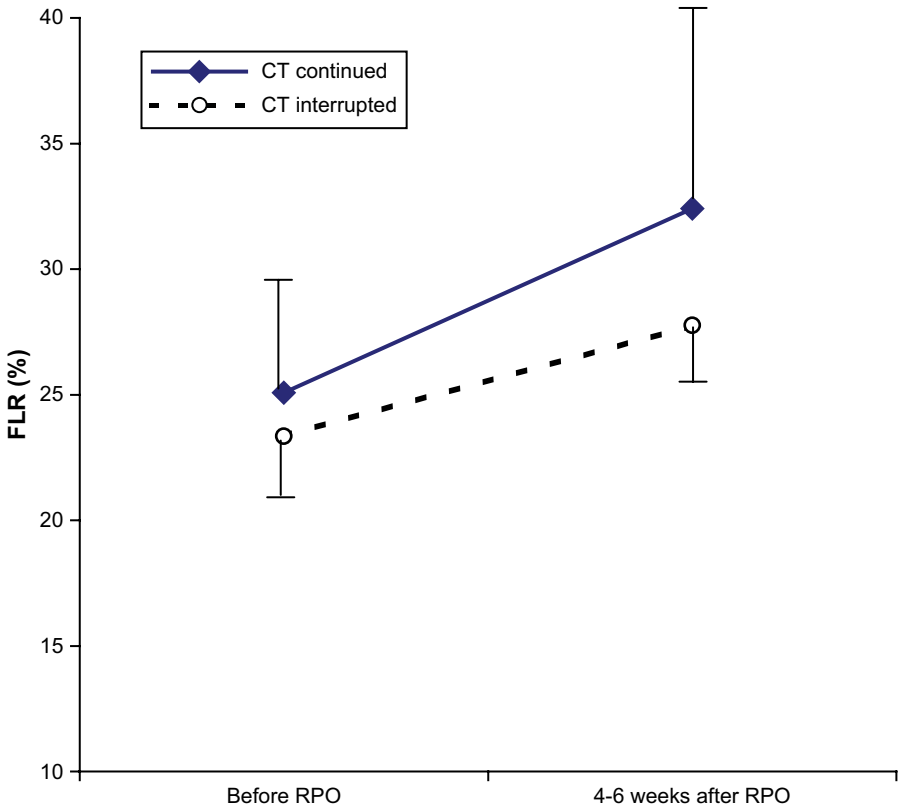

Fig. 1. Volume of the future remnant liver (FRL, expressed as a function of the total liver volume) before and 4–6 weeks after right portal obstruction, in patients whose chemotherapy was continued or interrupted.

Resectability and Postoperative Course

The resectability rate was the same in the two groups (seven patients in each group). Among patients in whom chemotherapy was interrupted, three did not undergo resection. The reason was the progression of their liver metastases. Among patients in whom chemotherapy was continued, three also did not undergo resection. Two had an incidentally discovered peritoneal carcinomatosis, 6 and 8 weeks respectively after a PVE. In the third patient, the liver proved to be too fibrotic and congestive intraoperatively to safely perform the planed resection.

Surgery consisted in right (n = 7) or extended right (n = 7) hepatectomies (Table 2) and associated procedures, performed in four patients, included the reconstruction of the portal vein and/or the inferior vena cava (n = 2), resection of the common bile duct (n = 1), and closure of an ileostomy (n = 1).

One patient, whose chemotherapy had been interrupted, died postoperatively of liver failure. She had undergone a right lobectomy with simultaneous resection of the invaded portal bifurcation, which required vascular reconstruction. None of the other patients developed liver failure. Morbidity rates (four of seven patients in each group) and numbers of complications (six in each group) were not increased in patients whose chemotherapy was not interrupted (Table 2).

DISCUSSION

The objective of the present study was to investigate the rationale for the usual practice that dictates to interrupt chemotherapy, when a preoperative portal vein obstruction is performed. Both techniques are increasingly used to improve the resectability rate of patients with multiple bilobar colorectal liver metastases.[4,9–11,13]

Table 2. Extent of resection and postoperative complications

	Chemotherapy continued (n = 7)	Chemotherapy interrupted (n = 7)
Extent of resection		
Right hepatectomy	4	3
Extended right hepatectomy	3	4
Associated procedures	2	2
Postoperative complications		
Ascites	3	1
Biliary leakage	1	1
Liver failure	0	1
Urinary sepsis	0	2
Wound sepsis	1	0
Symptomatic pleural effusion	1	0
Pulmonary embolism	0	1

Our patients had advanced metastatic liver disease and were receiving neoadjuvant chemotherapy at the time of referral. The choice to perform a PVE was based on the generally used criteria of a future remnant liver volume less than 30% of the total liver volume.[4–6] Portal vein ligation was used as an alternative way of increasing the volume of the future remnant liver, when a one-stage liver resection was considered impossible or unsafe.[18] Although the decision to continue or interrupt the chemotherapy during this preparation was not randomized, the demographics of the patients, number and spread of the metastases in the liver, left and future remnant volumes, and technique of portal vein obstruction were almost identical in the two groups.

PVE is anticipated to increase the future remnant liver volume by 20–42% in patients with liver metastases.[4,6,11,15,19] These results have been achieved in patients whose chemotherapy had been discontinued prior to the embolization. The rationale for this interruption is that various antimitotic agents have been shown, in experimental models, to interfere with liver resection–induced regeneration.[20,21] The hypertrophy of the future remnant liver following PVE was, however, the same in our patients whether chemotherapy had been continued or interrupted. The likely explanation for the discrepancy between this clinical and previous experimental studies is the timing of chemotherapy administration. In experimental models, antimitotic agents interfere with hepatocyte DNA synthesis when administered within 24 hours of the hepatectomy, whereas they have no impact when given at later time points.[22] In our patients, chemotherapy was reinitiated at least 1 week after the portal obstruction. Furthermore, the inhibition of liver regeneration by anticancer agents is of short duration,[23] whereas the hypertrophy was estimated in our patients 4–6 weeks after the obstruction.

The resectability rate in the present study was 70%. This result was expected considering that our patients had advanced metastatic disease. Only 63–75% of patients with colorectal metastases who require PVE are ultimately able to undergo an R0 resection.[4,9,11] As in previous studies, main reasons for not performing the planed resection were the progression of the intrahepatic metastases and the incidental discovery of peritoneal carcinomatosis, which is frequently misdiagnosed by preoperative imaging studies.[4,11] The former probably reflects an unfavorable natural history of the tumor, but some authors have suggested that it could also be promoted

by PVE itself.[14–16] One difference, though, was the reason for not performing surgery in each group. Contraindication for surgery in patients without chemotherapy was progression of intrahepatic metastases, while in patients with chemotherapy, incidental discovery of a peritoneal carcinomatosis was the main reason for not performing liver resection. Peritoneal carcinomatosis was probably already present at the time of PVE and is poorly responsive to systemic chemotherapy. However, the number of patients is obviously too small to draw definitive conclusions, but this difference may be relevant.

The final observation was that the postoperative course was not altered in patients whose chemotherapy was continued. The morbidity rates in the two groups were the same and the type of complications encountered was also comparable. Some previous studies failed to show higher morbidity after hepatectomy in patients receiving chemotherapy,[24–27] but, previous massive systemic or intra-arterial chemotherapy is generally considered as a risk factor for postoperative course of liver resection. Also, continuing chemotherapy could have worsen histological changes within the nontumorous liver, such as sinusoidal congestion or portal/sinusoidal fibrosis[28]; the small number of patients involved in this study, did not allow us to show histological changes due to neoadjuvant chemotherapy.

In conclusion, there is no rationale for interrupting an effective chemotherapy prior to or after a portal vein obstruction in patients with colorectal liver metastases. Continuing chemotherapy during this period does not impair hypertrophy of the future remnant liver and does not adversely impact the postoperative course.

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Surgical Treatment of Hepatocellular Carcinoma Originating From Caudate Lobe—A Report of 39 Cases

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The study objective was to study the therapeutic effect of surgical treatment for hepatocellular carcinoma (HCC) originating from the caudate lobe. From 1995 to 2003, caudate lobe resection was carried out for 97 cases; among them 39 were for HCC, who were divided into two groups. Group A consisted of 19 cases undergoing isolated caudatectomy, and group B consisted of 20 cases undergoing caudatectomy combined with other liver resections. The factors that might influence postoperative recovery were compared between the two groups. A special instrument, Peng's Multifunctional Operative Dissector, was used for surgical dissection. All tumors were resected successfully. One patient died of postoperative renal failure. Hydrothorax occurred in three patients, ascites occurred in four patients, and bile leakage occurred in one patient. Thirty cases received long-term follow-up with survival rates at 1, 3, and 5 years of 53%, 50%, and 39%, respectively. Caudate lobectomy is an effective therapeutic method for HCC originating in the caudate lobe. Isolated caudatectomy should be performed as the first choice whenever possible. Anterior transhepatic approach is appropriate in some cases. Peng's Multifunctional Operative Dissector is a very useful instrument for surgical dissection. (J GASTROINTEST SURG 2006;10:371–378)

KEY WORDS: Hepatocellular carcinoma, caudate lobectomy, porta hepatis, Peng's multifunctional operative dissector (PMOD), anterior transhepatic approach

Hepatocellular carcinoma (HCC) arising from the caudate lobe is not rare. In our hospital we have performed caudate lobe resection for 97 cases, among them 39 were for HCC. Resection of the caudate lobe with HCC is considered to be the most effective treatment, but which is the best choice between isolated caudate lobectomy and combined caudate lobectomy has not been well defined. We have elsewhere discussed different approaches to caudate lobectomy with "curettage and aspiration" dissection technique using a special instrument called Peng's Multifunctional Operative Dissector (PMOD) [FDA 510(K) No. k040780; Hangzhou Shuyou Medical Instrument Co Ltd., Hangzhou, Zhejiang, P. R. China].[1–4] In this study, we review our experiences in surgical management of HCC originating from the caudate lobe and analyze the impact of different surgical procedures on the outcomes.

MATERIAL AND METHODS

Patients

From 1995 to 2003, caudate lobecotomy was performed in 39 patients with HCC originating from the caudate lobe at the Surgical Department of the Second Affiliated Hospital of Medical School,

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Zhejiang University. They were divided into two groups (isolated resection as group A; combined resection as group B) for comparison of those factors influencing postoperative recovery: operating time, blood loss, amount of blood transfusion, and inflow occlusion time. Independent-samples *t* test and Kaplan-Meier survival curve were used as statistical method using SPSS 11.0 for Windows. Length of stay (LOS) in the hospital was also compared.

Surgical Procedures

In the majority of 39 cases, a reversed L-shaped skin incision, from the base of xiphoid to the tip of the twelfth right rib, was made, giving excellent exposure, which is of vital importance for caudate lobectomy.

After entering the patient, the whole abdominal cavity is explored to rule out intra-abdominal metastasis. The choice of approach is essential to the success for caudate lobectomy. Approaches are dependent largely on the size, the location of the lesion, and the severity of cirrhosis. In this series, four approaches were used for various types of caudate lobectomy: (1) left side approach, suitable for small tumors situated in the Spiegelian lobe or when caudate lobe is to be resected combined with the left liver; (2) right side approach, suitable for a tumor located in the caudate process or when the caudate lobe is resected together with the right liver, mostly right hemihepatectomy; (3) bilateral approach, a combination of the left side and right side approach—the caudate lobe may be approached mainly from the right or left side although dissection from both sides is necessary in many cases; and (4) anterior transhepatic approach, suitable for cases when isolated complete resection of the caudate lobe is indicated and non cancerous liver parenchyma should be preserved due to cirrhosis of the liver—the characteristics of this approach is that the liver is split through the mid-plane into two halves, so as to fully expose the caudate lobe. In addition, when the tumor is closely attached to the hepatic vein, the anterior approach is also the best indication (Fig. 1).

The anterior transhepatic approach usually includes seven steps.

1. Mobilization of the whole liver. The falciform ligament is divided up to the front of the suprahepatic inferior vena cava (IVC); then the incision is turned to the right and left, dividing the coronary ligaments, triangular ligaments, and the hepatorenal ligament. The right adrenal gland is detached from the liver, and the hepatogastric ligament is completely divided.
2. Dissecting and ligating the short hepatic veins caudal cranially; three to five thick short hepatic veins are divided in this process.
3. Tapes used to encircle the suprahepatic and infrahepatic IVCs.
4. Splitting the mid-plane, exposing the anterior surface of the paracaval portion and the hilar plate.
5. Ligating and dividing the ascending caudate portal triads (Fig. 2).
6. Separating the caudate lobe from the major hepatic veins (Figs. 3 and 4).
7. Detaching the caudate lobe from the neighboring liver parenchyma; usually there are no large branches that must be ligated. Some small vessels that are encountered can be cauterized with PMOD. Thus, isolated complete caudate lobe was resected, and the two halves of liver were sutured together (Fig. 5).

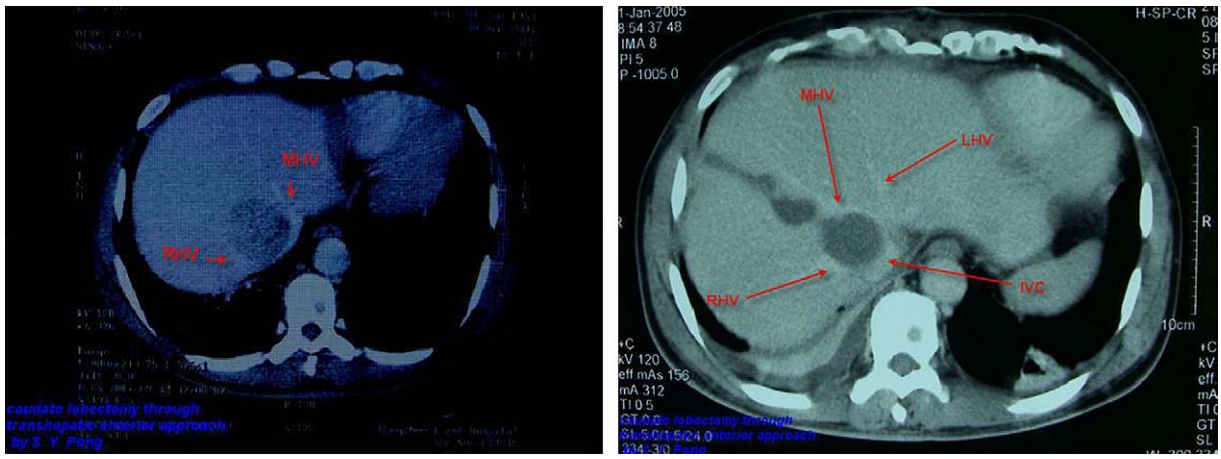

Fig. 1. (*Left*) CT scan: preoperative, tumor located in caudate lobe, compressing the inferior vena cava and sandwiched between middle and right hepatic veins. (*Right*) CT scan: 4 weeks after operation showing splitting line at mid-plane (*arrow*).

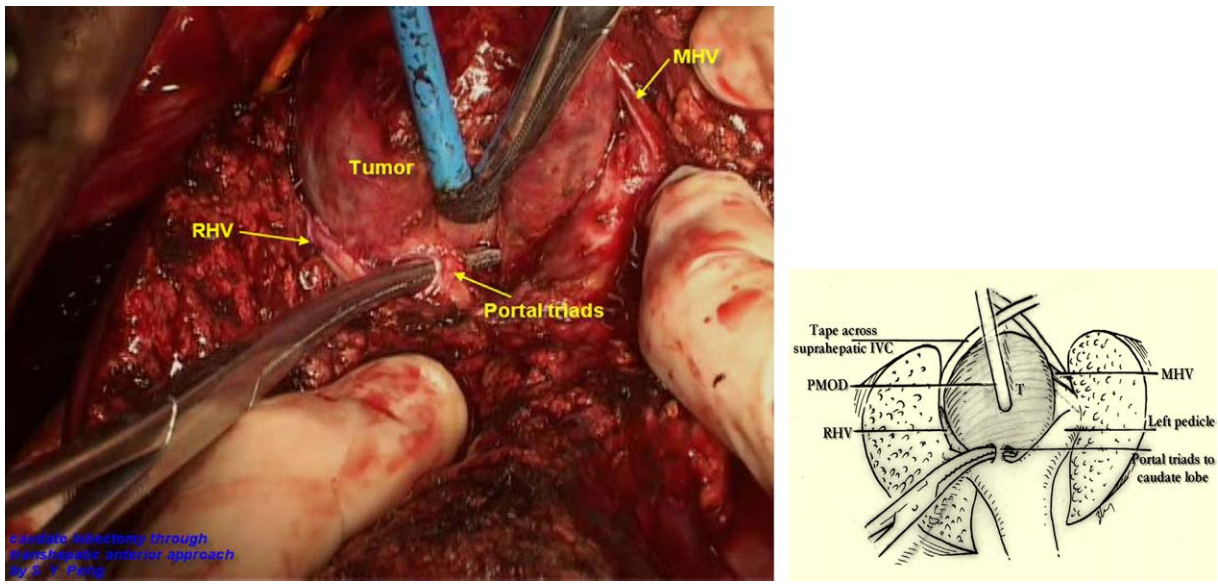

Fig. 2. Liver divided into two halves through mid-plane before portal triads to the caudate lobe were divided.

In this series, the mobilization of caudate lobe is first from left side in most of the cases. Bartlett et al.[5] reported dividing the ligamentous attachment and mobilizing the tip of caudate lobe before division of the caudate veins. It is the present authors' practice to dissect in the same way for some cases.

The liver parenchyma was transected by means of "curettage and aspiration" technique using PMOD under intermittent inflow occlusion at the hepatoduodenal ligament (Pringle's maneuver),[3] with the time limit being 10 minutes each time with a 2-minute interval for reperfusion. Total vascular exclusion was seldom necessary except when the tumor involves the IVC or major hepatic veins. PMOD is a specially designed instrument incorporating the functions of dissection, electrocoagulation, and aspiration, which can work separately or synchronously, so the operating field is kept clear and clean and the intrahepatic duct structures can be clearly identified, isolated, and dealt with individually.

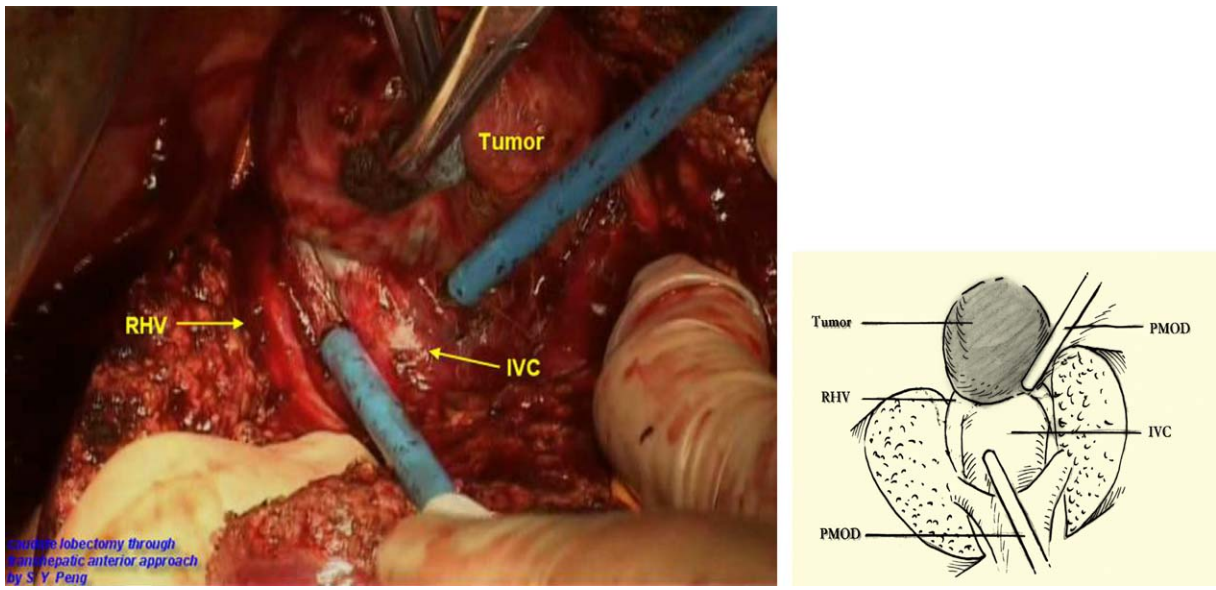

Fig. 3. Right hepatic vein (RHV) already free from tumor, which was being detached from the inferior vena cava.

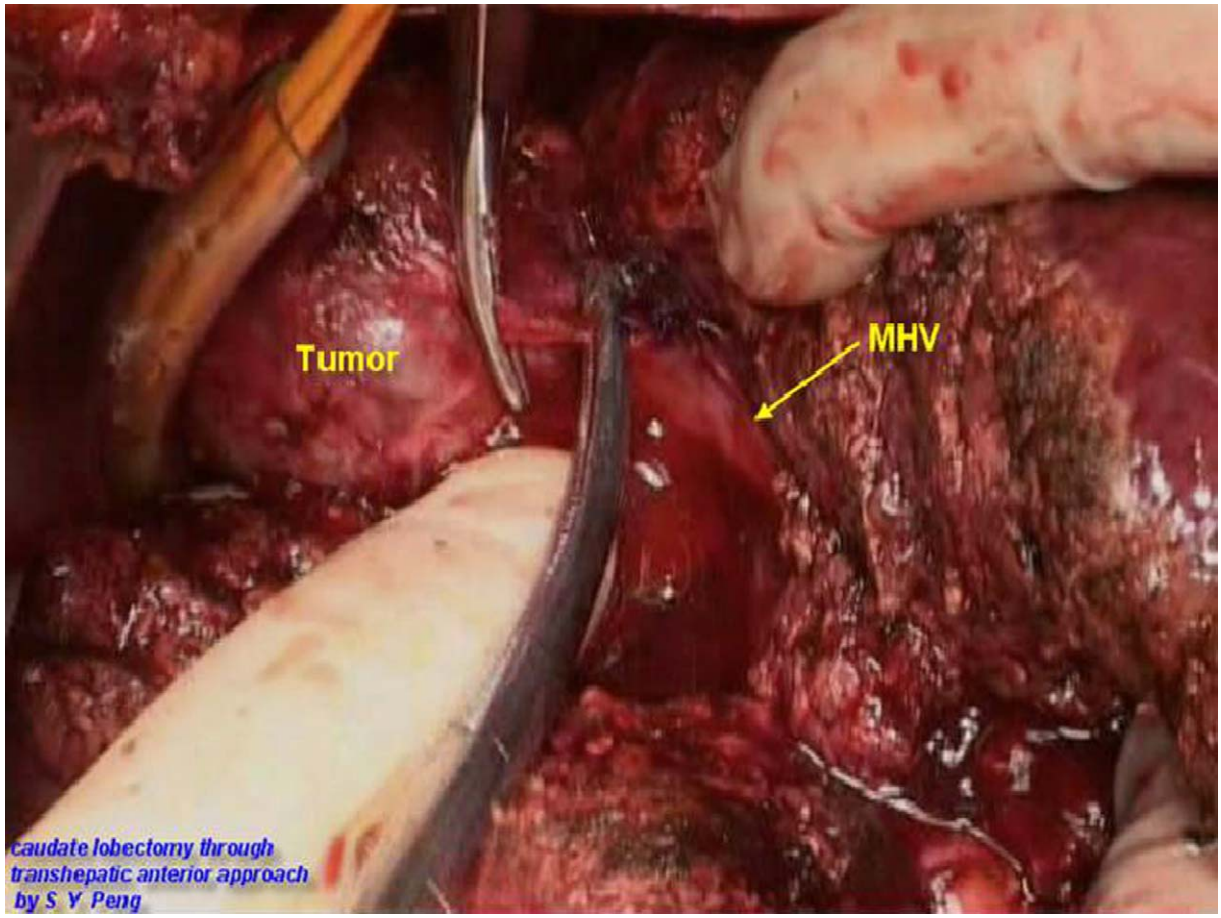

Fig. 4. Middle hepatic vein (MHV) branch to the tumor being divided.

RESULTS

There were 22 men and 17 women (age range, 20–68 years; mean age, 40.7 years). The tumor diameter ranged from 3.0 to 12.1 cm (mean, 6.0 cm) Assays for hepatitis B surface antigens were positive in 35 patients. Liver cirrhosis was confirmed by histologic examination of the nontumorous parts of the resected specimens and was noted in 35 patients. The serum α-fetoprotein value was positive (>20 ng/dl) in 31 cases (range, 20−3265.60 ng/dl; mean, 189.46 ± 14.36 ng/dl). Of the 39 patients, 19 underwent isolated caudatectomy and 20 underwent combined caudatectomy (Table 1).

Operating time, blood loss, amount of blood transfusion, and inflow occlusion time did not show a significant difference between the two groups ($P > 0.05$) (Table 2). However, LOS from the isolated group was shorter (16 versus 23 days, $P < 0.05$).

Three patients had hydrothorax, four patients had ascites, and one patient had bile leakage. All complications were cured by conservative treatment. One patient died of multisystem organ failure resulting from renal failure on postoperative day 30. Thirty patients received long-term follow-up. There was no significant difference in survival between the two groups ($P > 0.05$) (Fig. 6). The survival rates at 1, 3, and 5 years were 53%, 50%, and 39%, respectively.

DISCUSSION

The caudate lobe, segment 1 according to Couinaud, is divided into three subsegments: the Spiegel lobe, the paracaval portion, and the caudate process.[5] The Spiegel lobe is located behind the lesser omentum and to the left of the intrahepatic IVC. The paracaval portion is in front of the intrahepatic IVC, just to the right of the Spiegel lobe, and is closely attached to the right and middle hepatic veins. The caudate process is a tongue-like projection between the IVC and the adjacent portal vein, just to the right of the paracaval portion.

Shibata et al.[6] reported that percutaneous ethanol injection/transcatheter artery embolization was

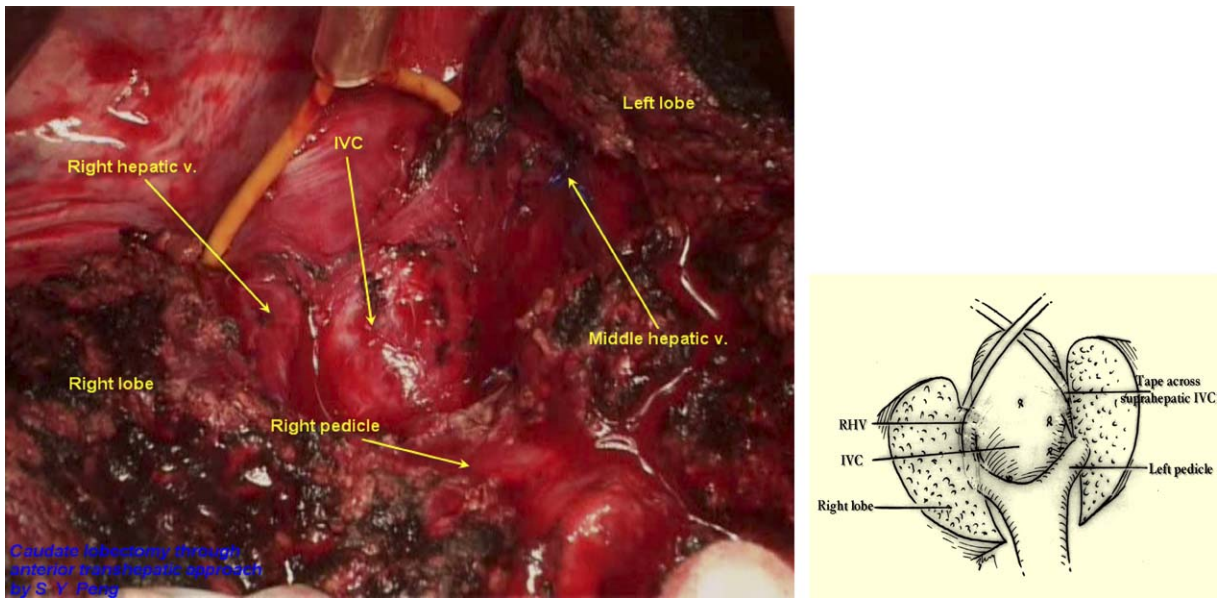

Fig. 5. Tumor already removed completely, leaving behind important structures.

effective for HCC originating in the caudate lobe if the caudate nodule was equal to or less than 3 cm in diameter. The effect was poor when the nodules were larger than 3 cm in diameter. Hepatectomy is considered to be the most effective therapy for HCC originating from the caudate lobe.[7,8]

In Chinese literature, *porta hepatis* denotes not only the hepatic hilum in general sense but also two other locations: one being the confluence of the major hepatic veins and the other being the segment of retrohepatic IVC with a series of short hepatic veins (F. Z. Qiu, personal communication regarding porta hepatis: first, second and third, 1957). These three different locations are named first, second, and third porta hepatis, respectively. In other words, first porta hepatic denotes the hilum in general sense, second portal hepatis denotes the confluence of major hepatic veins, and third porta hepatis denotes the segment of retrohepatic IVC with a series of short hepatic veins. Caudate lobe is thus surrounded by the three porta hepatis, which all consist of important and potentially dangerous structures in terms of performing operations. In view of the unique anatomical location, caudate lobe resection has been considered technically challenging, especially isolated caudectomy. For patients with fair to excellent liver function reserve, Yang et al.[9] advocate caudate lobectomy combined with other types of hepatic resection. Shimada et al.[10] consider Spiegel lobe resection should be combined with left lobe, and caudate process combined with right lobe. But for patients with marked liver cirrhosis and poor liver function reserve or a small HCC, they advocate simple partial caudate lobectomy (limited hepatic resection).

In this group, liver cirrhosis was confirmed in 32 patients (82.05%). Assays for hepatitis B surface antigens were positive in 35 patients (89.74%). Because excess liver resection would prolong postoperative liver function recovery, isolated caudate lobectomy was performed as much as possible unless the tumor involves the liver beyond caudate lobe. Five cases underwent isolated completed caudatectomy through anterior approach (Figs. 7–9).

Table 1. Resection procedures

Operation	No. of patients
Isolated caudate lobectomy (19 cases)	
Complete	15 (total)
Anterior tranhepatic approach	5
Other approach	10
Partial	4
Combined caudate lobectomy (20 cases)	
Complete	14 (total)
Right hepatectomy + S1 (C)	7
Left hepatectomy + S1 (C)	6
VI segmentectomy + S1 (C)	1
Partial	6 (total)
Left hepatectomy + S1 (P)	3
Right hepatectomy + S1 (P)	2
V + VI segmentectomy + S1 (P)	1
Total	39

S1 = caudate lobe; P = partial; C = complete.

Table 2. Clinical data

Group	Operating time (min)	Blood loss (ml)	Transfusion (ml)	Accumulated occlusion time (min)
Isolated	296 ± 99	1237 ± 893	1000 ± 789	52 ± 9
Combined	248 ± 96	1108 ± 970	840 ± 639	48 ± 7
P value	0.13	0.66	0.49	0.72

Several operative parameters were analyzed, and the results showed that there is no significant difference in terms of operating time, blood loss, amount of blood transfusion, and inflow occlusion time between the isolated resection group and the combined resection group. The LOS of patients undergoing isolated caudate lobectomy was shorter than that of patients undergoing combined caudate lobectomy. These results demonstrate that isolated resection should be used as the first choice whenever indicated.

Generally speaking, caudate lobectomy is classified by complete and partial resection; it is also classified by isolated and combined resection. Therefore, caudate lobectomy is generally composed of four types: isolate complete resection, combined complete resection, isolated partial resection, and combined partial resection. Partial or complete caudate lobectomy with major hepatectomy is often necessary for extirpation of the tumor. But in China, because most of the liver cancer occurs in cirrhotic liver, the poor liver function usually prevents the performance of combined resection for tumor situated only in the caudate lobe.

The selection of an appropriate surgical approach is essential for resection of caudate lobe. When the tumor is small, even isolated caudate lobectomy can be performed with a bilateral approach, where the liver is frequently rotated from side to side. However, when the tumor is large or the IVC and/or major hepatic vein is compressed by the tumor, yet the liver is cirrhotic, isolated complete caudate lobectomy without resection of innocent parenchyma is mandatory, The other approaches might not be appropriate due to the possibility of laceration of major hepatic veins. Under such circumstances, an anterior transhepatic approach is the best choice, in which the liver parenchyma is split through midplane to expose the front surface of the tumor. Both middle and right hepatic veins are now in front of the tumor and can be safely detached from the tumor under direct viewing (see Fig. 2).

The anterior transhepatic approach was first described by Yamamoto et al.[11] in 1992 for a patient with cirrhosis and a 3 × 3-cm HCC in the paracaval portion of the caudate lobe for whom they performed isolated caudate lobectomy by splitting the cirrhotic liver into two halves. The anterior

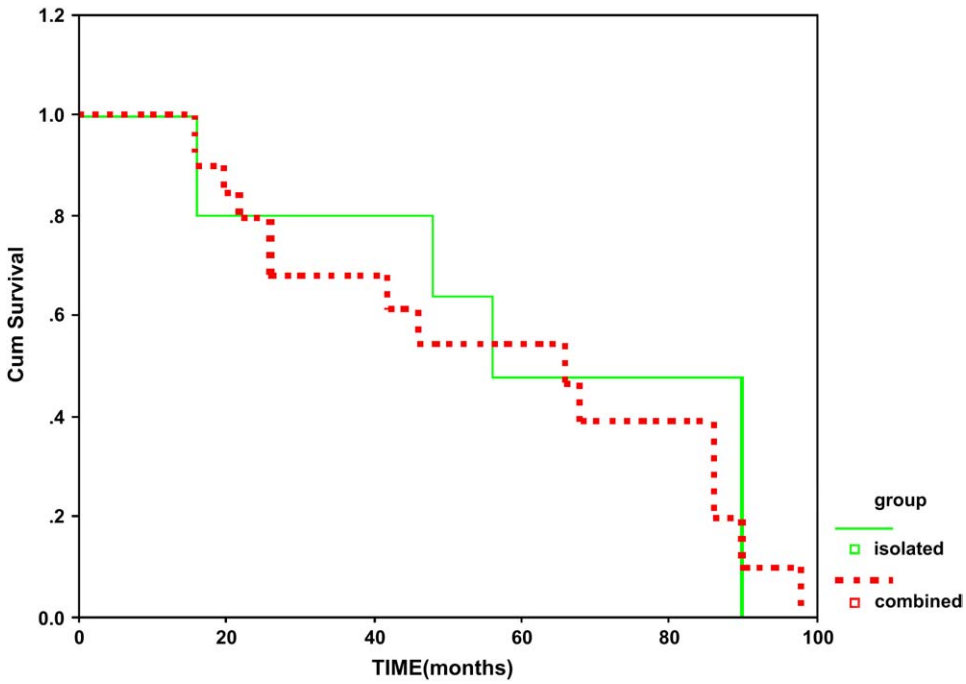

Fig. 6. Survival of the two groups (*$P < 0.05$).

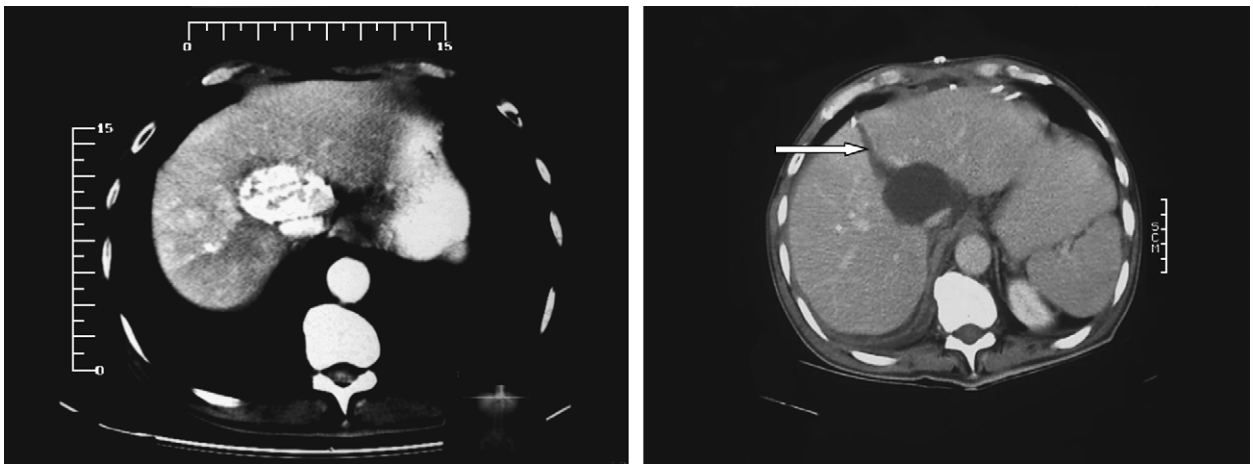

Fig. 7. Another case. (*Left*) Preoperative CT scan showing the tumor originated in caudate lobe after transarterial chemoembolization. (*Right*) Postoperative CT scan showing splitting line at mid-plane (*arrow*).

transhepatic approach provides a safe strategic alternative for isolated complete caudate lobectomy when the tumor is large and in close proximity with the major hepatic veins.

The separation of the hepatic parenchyma overlying the caudate lobe exposed the major hepatic veins and the hilar plate to direct view, facilitating control of venous bleeding and division of the ascending paracaval portal branches along the hilar plate. Sometimes the transection process would be associated with a significant amount of blood loss, if the middle hepatic vein was not carefully protected. In this series, we use PMOD to transect the liver parenchyma by means of "curettage and aspiration technique"; all of the branches from middle hepatic vein could be identified and isolated before they were divided and carefully ligated (Fig. 4). As a result, blood loss is decreased and operation time is shortened.

As a safety precaution, tapes were preplaced around both the suprahepatic IVC and infrahepatic IVC in case total vascular exclusion is needed. Such a maneuver is capable of limiting blood loss from the hepatic venous system and decreasing the risk of air

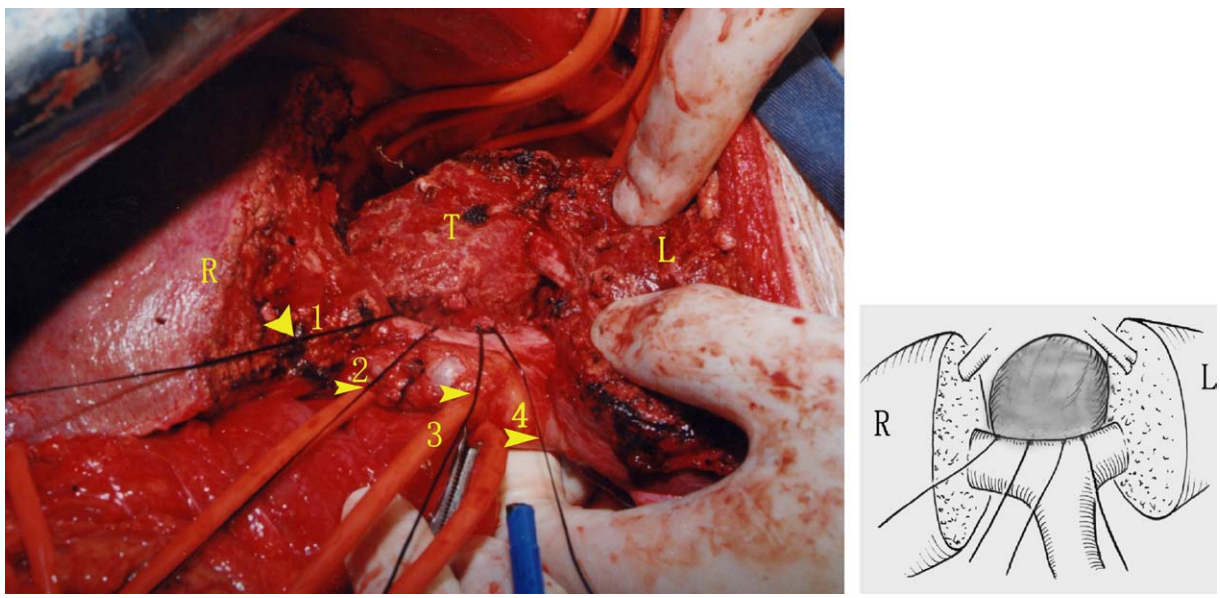

Fig. 8. Four groups of portal triad to the caudate lobe (*arrow*) already divided, detaching the tumor from hilum.

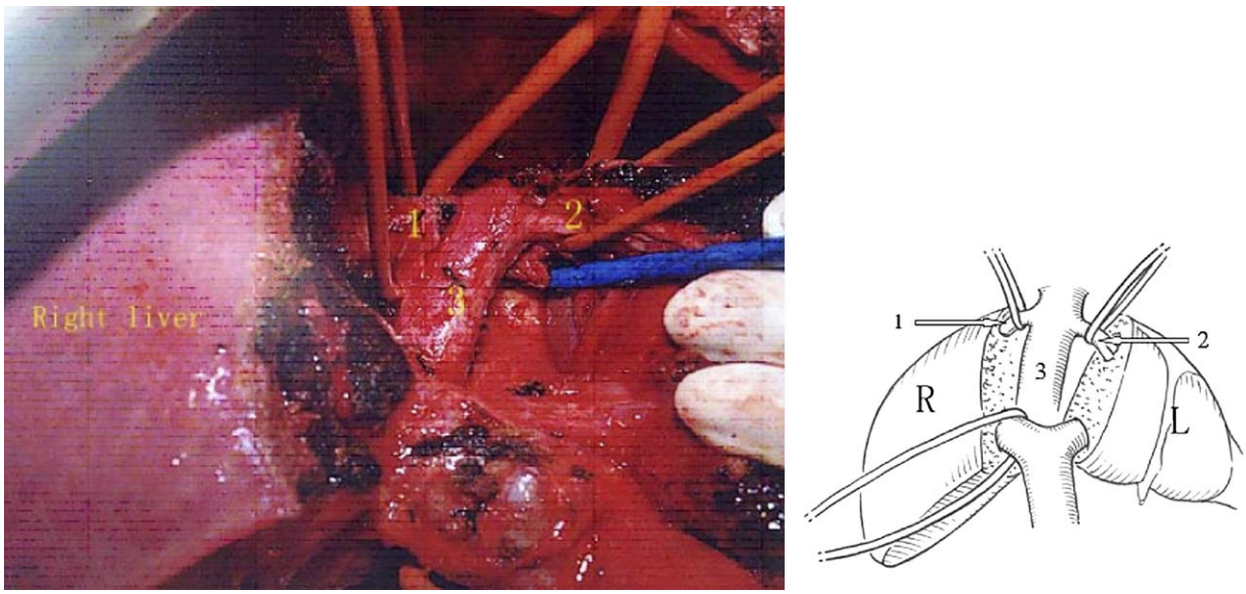

Fig. 9. Tumor was resected completely, leaving important structures behind (1, right hepatic vein; 2, common trunk of middle and left hepatic veins; 3, inferior vena cava).

embolism, although it results in hemodynamic instability in up to 40%.[12] In our series, whenever possible, we isolated the common trunk and the right hepatic vein to preplace the tape to control the three major hepatic veins. In case massive hemorrhage occurs from a hepatic vein, we can control the hepatic vein rather than the IVC,[2,13] so that the IVC is kept patent to avoid hemodynamic instability.

CONCLUSION

Caudate lobectomy is a curative procedure for HCC originating in the caudate lobe. Isolated resection is preferable whenever the tumor is confined to the caudate lobe, especially in the presence of cirrhosis. When the tumor is large, involving the IVC and/or the major hepatic vein, the anterior transhepatic approach is indicated. As PMOD and "curettage and aspiration" technique can clearly delineate intrahepatic and/or extrahepatic vessels, caudate lobe resection becomes easier and safer.

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Multidisciplinary Management of Ruptured Hepatocellular Carcinoma

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Spontaneous rupture of hepatocellular carcinoma (HCC) is a dramatic presentation of the disease. Most published studies are from Asian centers, and North American experience is limited. This study was undertaken to review the experience of ruptured HCC at a North American multidisciplinary unit. Thirty patients presenting with ruptured HCC at a tertiary care center from 1985 to 2004 were studied retrospectively and analyzed according to the demographics, clinical presentation, tumor characteristics, treatment, and outcome in four treatment groups: emergency resection, delayed resection (resection after angiographic embolization), transcatheter arterial embolization (TAE), and conservative management. Ten, 10, 7, and 3 patients underwent emergency resection, delayed resection, TAE, and conservative treatment, respectively. The mean age of all patients was 57 years, and the mean Child-Turcotte-Pugh score was 7 ± 2. Cirrhosis was present in 57% of the patients. Seventy percent of tumors were greater than 5 cm in diameter, and 68% of patients had multiple tumors. There was a trend toward higher 30-day mortality in the emergency resection group than in the delayed resection group. One-year survival was significantly better in the delayed resection group. In selected patients, the multidisciplinary approach of angiographic embolization and delayed resection affords better short-term survival than emergency resection. (J GASTROINTEST SURG 2006;10:379–386)

KEY WORDS: Hepatocellular carcinoma, rupture, transcatheter arterial embolization

Spontaneous rupture is a dramatic presentation of hepatocellular carcinoma (HCC). Its incidence is as high as 15% in Asia,[1–5] and as low as 3% in the United Kingdom.[6,7] In general, the outcome is poor without active treatment.[8]

The clinical presentation may be dramatic but nonspecific, which makes the diagnosis difficult based on history and physical examination alone. Imaging modalities such as ultrasound and CT are used to confirm the diagnosis. Paracentesis is able to detect the presence of bloody ascites but is not routinely used.[9]

Because of the high mortality rate of this condition, a number of studies have been conducted in attempts to establish a consensus on the optimal method of management. There is a general agreement on the principles of management and a trend toward incorporating transcatheter arterial embolization (TAE) in the management algorithm. The principles of management are threefold: resuscitation from hypovolemic shock, followed by hemostasis, and finally, the treatment of the underlying HCC.

Traditionally, various surgical techniques including emergency hepatic resection, hepatic artery ligation, suture plication, and packing have been used to secure hemostasis and to treat the tumor. However, owing to shock and hepatic decompensation in these patients, the mortality rate from emergency surgery has been high.[1,2,4,10–12] As an alternative, a multidisciplinary approach including TAE has led to decreased initial mortality, facilitating selection of the suitable patients for a delayed resection to address the pathology of HCC.[8,13–16]

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Most studies of the management of ruptured HCC have originated from Asia, where the prevalence of HCC is high. The North American experience on this subject has been limited to date. This study was conducted to investigate the management of ruptured HCC at a North American tertiary care center serving an ethnically diverse patient population.

MATERIAL AND METHODS

Study Design and Patient Population

The study was approved by the Institutional Ethics Board of the University of British Colombia and Vancouver Coastal Health Research Institute and conducted in a retrospective manner by review of patient charts. The management of patients with ruptured hepatic tumors at our institution is outlined in Fig. 1. Thirty-three patients who were admitted to the Hepato-Pancreato-Biliary Unit at the Vancouver Hospital and Health Sciences Center from 1985 to 2004 with a diagnosis of ruptured hepatic tumor were initially included in the study. The initial diagnosis was made clinically and radiologically. Three patients were excluded from the study. Two of these patients proved to have benign tumors and one patient had a hepatoblastoma. The underlying diagnosis of HCC was known at the time of clinical presentation in six patients. For 24 patients without the previous history of HCC, the diagnosis was confirmed by a biopsy in one patient, by histologic examination of surgical specimens in 20 patients, and by imaging and clinical course in three patients.

The patients were grouped according to the treatments they received. The emergency resection (ER) group was defined as patients who underwent emergency liver resection (n = 10). The TAE group was defined as patients who had only TAE as treatment (n = 7). The delayed resection (DR) group was defined as patients who underwent hemostasis by TAE or had spontaneous cessation of bleeding followed by delayed resection (n = 10). The mean delay, as defined by the number of days elapsed from clinical presentation to surgery, was 10 days (range, 1–16 days). The conservative management group consisted of patients who either declined surgical treatment or patients with ruptured HCCs that were deemed to be not amenable to surgical resection or embolization (n = 3).

At our institution, transcatheter arterial embolization was incorporated in the algorithm of treatment of ruptured HCC in 1995. This contributed to the rise in the number of patients who received TAE and delayed resection since 1995.

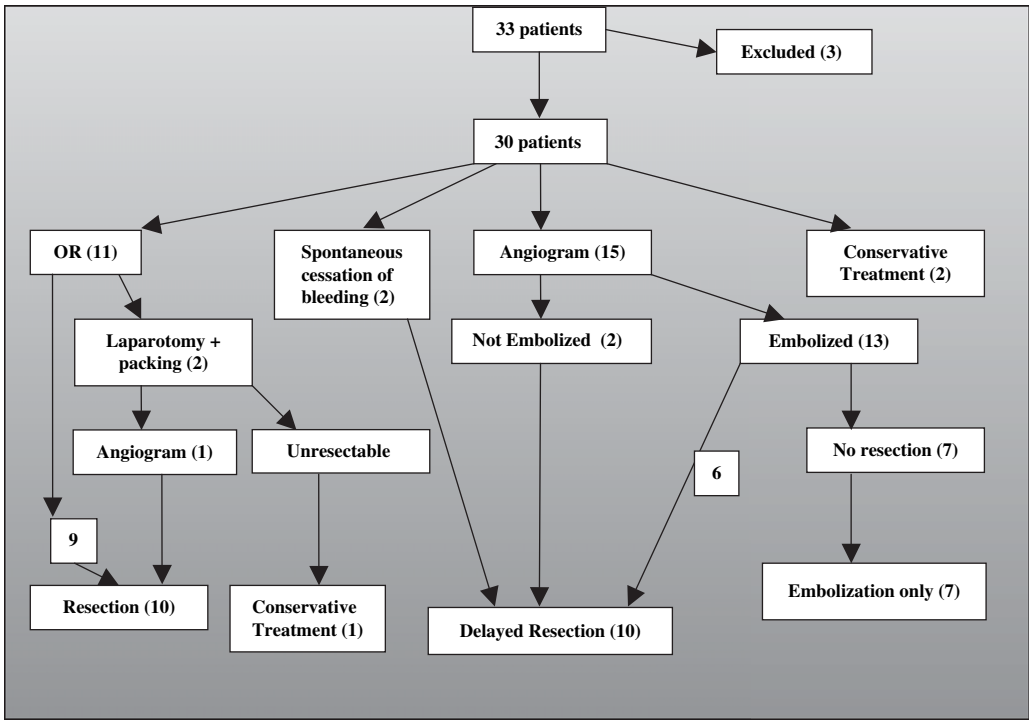

Fig. 1. An overview of the clinical course of the patients presenting with ruptured hepatocellular carcinoma.

Demographics

Each patient's age, sex, ethnic background, risk factors including hepatitis status, and alcohol history were obtained. The underlying liver function was determined by Child-Turcotte-Pugh score at the time of presentation.

Transcatheter Arterial Embolization

TAE was performed by an experienced interventional radiologist in an angiography suite. Standard Seldinger access of the right common femoral artery was performed with placement of a 5-French introducer sheath (Arrow International, Reading, PA). Digital subtraction flush aortography was performed with ioversol (Optiray 320, Mallinckrodt Inc., St. Louis, MO), a low osmolar, nonionic iodinated contrast to outline hepatic arterial anatomy and to define the site of bleeding. The hepatic artery was then selectively catheterized using standard visceral angiographic catheters, (AngioDynamics, Queensbury, NY and Cook Incorporated, Bloomington, IN). After selective catheterization, further subselective catheterization was achieved coaxially using a 3-French microcatheter (Boston Scientific, Natick, MA). Subselective catheterization was performed to minimize nontarget embolization. Once position of the microcatheter was confirmed with an additional injection of ioversol, embolic agents were injected under continuous fluoroscopy to achieve hemostasis. A variety of embolic agents were used, both permanent and nonpermanent, depending on location and degree of bleeding and operator preference. The types of agents used included Gelfoam pledgets, polyvinyl alcohol, or Embospheres (Biosphere Medical Inc., Rockland, MA).

Surgical Procedure

Anatomic liver resections were performed as described in the *Brisbane 2000 Terminology of Liver Anatomy and Resections*.[17] Inflow occlusion was performed at the surgeon's discretion in 11 (55%) patients, for mean occlusion time of 28 ± 25 minutes. Parenchymal resection was performed with a GIA-100 surgical stapler (Autosuture, Autosuture Surgical, Norwalk, CT) in seven patients, Cavitational Ultrasonic Surgical Aspirator (CUSA, Valleylab, Boulder, CO) in four patients, and with finger fracture technique in one patient. In eight patients, the parenchymal resection technique data were not available.

Postoperative Course

All patients were admitted to the Hepato-Pancreato-Biliary Unit at the Vancouver Hospital and Health Sciences Center, and selected patients were admitted into the intensive care unit. The postoperative course of the patients was analyzed according to early (less than or equal to 2 weeks after surgery) and late (greater than 2 weeks after surgery) complications. In-hospital mortality was defined as death in the first 30 days after surgery.

Follow-up

The follow-up was complete in 25 (83%) patients, and the median follow-up was 5 months (range, 0–33 months). The median follow-up for the respective groups were as follows: ER group, 4 months (range, 0–33 months); DR group, 13 months (range, 1–27 months); and TAE group, 3 months (range, 2–7 months). Patients who underwent conservative/palliative treatment were followed for less than 1 month.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL) program. Student's two-tailed independent *t* test, chi-square test, and the two-sided Fisher exact test were used in the analysis when appropriate. $P < 0.05$ was considered statistically significant. Survival for the delayed resection and emergency resection group was calculated and plotted with a Kaplan-Meier curve. Survival comparison was made with the log-rank test at 12 months, and the 24-month survival comparison was made by a separate log-rank test. Because two log-rank tests were performed, Bonferroni's correction was performed and $P < 0.025$ was considered to be significant for the second log-rank test.

RESULTS

Demographics

The demographics of the following four groups are outlined in Table 1: emergency liver resection (n = 10), delayed resection (n = 10), TAE (n = 7), and conservative management (n = 3). The groups were similar with regards to the age, sex distribution, liver disease risk factors, comorbidities, presence of cirrhosis, and Child-Turcotte-Pugh scores. Out of 30 patients, 17 (57%) patients had cirrhosis and the overall mean Child-Turcotte-Pugh score was 7 ± 2.

Clinical Presentation/Diagnosis

The most common presentation was abdominal pain, which was present in 25 (83%) patients. Seventeen (57%) patients presented with shock, defined as a history of syncope, presyncope, hemodynamic

Table 1. Demographics, risk factors, and comorbidities of patients who underwent emergency resection, delayed resection, TAE, or conservative treatment

	Emergency resection (n = 10)	Delayed resection (n = 10)	TAE (n = 7)	Conservative treatment (n = 3)	*P* value
Demographics					
Age	51 ± 19	58 ± 13	60 ± 17	62 ± 3	0.2
M:F	7:3 (70:30)	8:2 (80:20)	5:2 (71:29)	2:1 (67:23)	
Ethnicity					
Asian	4 (40%)	6 (60%)	4 (57%)	1 (33%)	0.2
White	6 (60%)	4 (40%)	1 (14%)	1 (33%)	0.2
East Indian	0	0	1 (14%)	1 (33%)	0.2
American Indian	0	0	1 (14%)	0	0.2
Risk Factors (Total)	9 (90%)	6 (60%)	6 (86%)	1 (33%)	0.2
Hep B	6 (60%)	3 (30%)	5 (71%)	1 (33%)	0.2
Hep C	2 (20%)	2 (20%)	1 (14%)	0	0.2
Ethanol	1 (10%)	3 (30%)	0	0	0.2
Cirrhosis	7 (70%)	5 (50%)	3 (43%)	2 (67%)	0.2

M:F = male-to-female ratio; Hep = hepatitis.

instability, and a need for blood transfusions. In seven (23%) patients, the bleeding stopped spontaneously. A CT scan was performed in 25 (83%) patients, and an abdominal ultrasound was performed in 12 (40%) patients.

Tumor Characteristics

Tumor size and distribution as determined from imaging and pathology resection specimens are outlined in Table 2. This information was available for 28 patients. Fifty percent of the tumors were in the right hemiliver, 33% of the tumors were in the left hemiliver, and 17% involved the entire liver. Nineteen (68%) patients had multiple tumors. Tumor size was recorded in 27 patients, and in 19 (70%) patients, the tumors were greater than or equal to 5 cm in diameter. The average size of the tumor was 7 ± 4 cm in diameter.

TAE

Out of 16 patients who underwent attempted TAE, 13 had a successful embolization. Of these 13 patients, 6 underwent a delayed tumor resection. No rebleeding was noted in any of the patients who underwent TAE.

Surgical Procedure

The type of operation performed for the emergency resection and delayed resection groups is outlined in Table 3. The intraoperative resuscitative parameters and the operating room time are outlined in Table 4. There was no statistically significant difference between the two groups (ER vs. DR) in terms of surgery time, estimated blood loss, resuscitative fluids received in the operating room, and intraoperative complication rates.

Table 2. Tumor characteristics according to the respective treatment groups

	Total (n = 30)	Emergency resection (n = 10)	Delayed resection (n = 10)	TAE (n = 7)	Conservative management (n = 3)	*P* value
Location						
Right hemiliver	15 (50%)	3 (30%)	5 (50%)	5 (71%)	2 (67%)	0.7
Left hemiliver	10 (33%)	5 (50%)	4 (40%)	1 (14%)	0	0.7
Entire liver	5 (17%)	2 (20%)	1 (10%)	1 (14%)	1 (33%)	0.7
Size* (total)	27	9	10	6	2	
0–5 cm	8 (30%)	3 (33%)	4 (40%)	1 (17%)	0	0.7
5–10 cm	13 (48%)	4 (44%)	5 (50%)	2 (33%)	2 (100%)	0.7
>10 cm	6 (22%)	2 (22%)	1 (10%)	3 (50%)	0	0.7
Mean size (cm)	7 ± 4	7 ± 4	7 ± 3	9 ± 4	7 ± 2	0.7

*Data available only in 27 patients; the percentage for each group is calculated according to the corrected total number of patients with available information.

Table 3. Operations performed in emergency and delayed resection groups for ruptured hepatocellular carcinoma

Surgery performed	Emergency resection (n = 10)	Delayed resection (n = 10)
Right (total)	4 (40%)	6 (60%)
Right hepatectomy	1 (10%)	1 (10%)
Right trisectionectomy (extended right hepatectomy)	1 (10%)	3 (30%)
Segmental resection	2 (20%)	2 (20%)
Left (total)	6 (60%)	4 (40%)
Left hepatectomy	2 (20%)	2 (20%)
Left trisectionectomy (extended left hepatectomy)	1 (10%)	0
Segmental resection*	3 (30%)	2 (20%)

*One patient had a partial gastrectomy; one patient had a splenectomy.

Postoperative Course

As outlined in Table 5, the rates of postoperative complications were not statistically different between the two groups. In-hospital (30 days) mortality occurred only in the emergency resection group (40%) and not in the delayed resection group. Although there was a trend toward decreased mortality in the delayed resection group, the difference was not statistically significant. Causes of death for these patients were cardiac arrest (n = 1), liver failure (n = 1), sepsis (n = 1), and multiorgan failure (n = 1). The difference in the total length of stay and the postoperative length of stay between the two groups did not reach statistical significance.

Follow-up/Survival/Recurrence

As illustrated in Fig. 2, the cumulative 1-year rate of survival was higher in the delayed resection group (76%) than in the emergency resection group (33%; $P = 0.02$). The cumulative 2-year survival rates were 33% and 38% for emergency resection and delayed resection, respectively. The average survival time for the emergency resection group was 12 months, and 19 months for the delayed resection group. The mean disease-free survival time was 9 months and 8 months for the emergency resection group and the delayed resection group, respectively ($P = 0.3$).

In the ER group, after 1 month, four patients were available for follow-up of recurrence (67% follow-up rate, excluding those with 30 day mortality). HCC recurred in all four of these patients. One patient had a recurrence and died within the first 30 days. In the DR group, after 1 month, nine patients were available for follow-up of recurrence (90% follow-up rate). Of these nine patients, the recurrence rate was 56%. The longest survival in the emergency resection group was 33 months, and 27 months in the delayed resection group.

Table 4. Resuscitative parameters from the surgeries performed in emergency and delayed resection groups

	Emergency resection	Delayed resection	*P* value
OR time (min)	190 ± 100	170 ± 100	0.6
Estimated blood loss (mL)	2000 ± 1500	970 ± 1200	0.12
Transfusion requirements			
Packed red blood cells (U)	4 ± 3	2.5 ± 3.6	0.4
Plasma (U)	2 ± 2	0.8 ± 2	0.2
Platelets (U)	1.8 ± 4.2	1.2 ± 2.4	0.8
Intraoperative complications	1 (10%)	1 (10%)	1

OR = operating room.

Table 5. Postoperative course for patients treated in emergency and delayed resection groups

Postoperative course	Emergency resection	Delayed resection	*P* value
Early complications (≤14 days)	5 (50%)	7 (70%)	0.7*
Late complications (>14 days)	3 (30%)	0	0.07*
In-hospital mortality (30 days)	4 (40%)	0	0.09*
Total length of stay (days)	20 ± 22	25 ± 6	0.5
Postoperative length of stay (days)	20 ± 22	15 ± 6	0.46
Delay to surgery† (days)	1 ± 1.3	10 ± 6	<0.0001

*By Fisher exact test (two-sided).
†Number of days elapsed from onset of symptoms to surgery.

DISCUSSION

Hepatocellular carcinoma is a relatively uncommon disease in Western countries, with 2.8 new cases per 100,000 persons annually in the United States, although the incidence and mortality related to HCC is rising in Western countries, in part due to the increasing incidence of hepatitis C infection.[18] It is more common in Asia and sub-Saharan Africa. This patient series demonstrates a high proportion of Asian patients (50%). This is likely due to migration of Chinese patients to North America from a region with high prevalence of HCC.

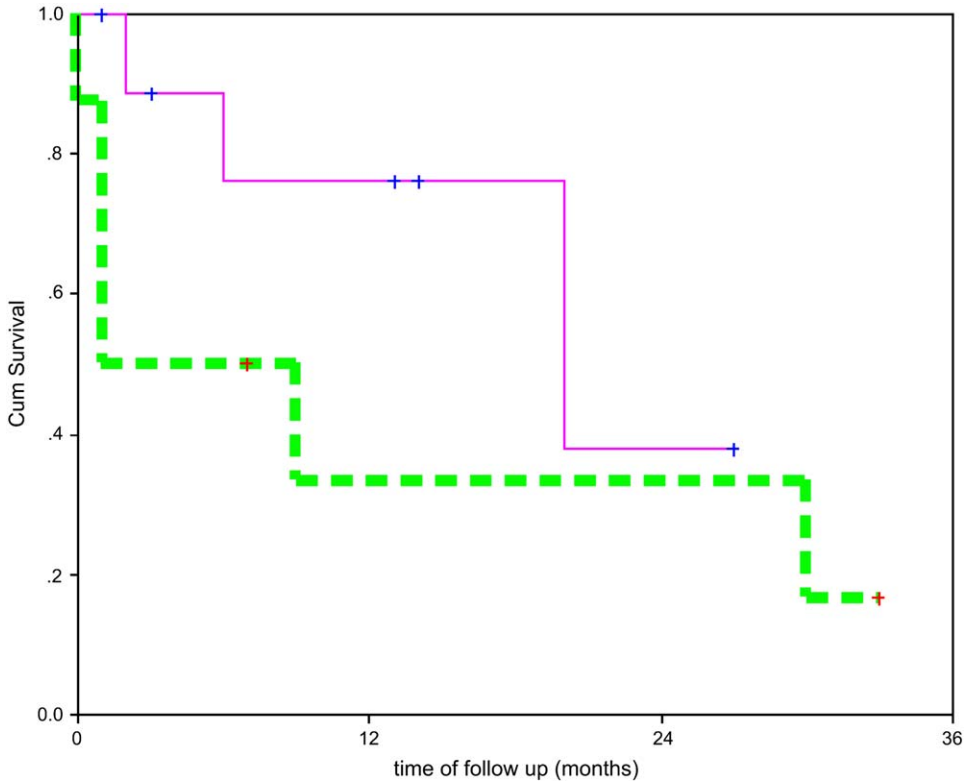

Fig. 2. Kaplan-Meier survival curve for patients who have undergone emergency resection (ER: dashed line) and delayed resection (DR: solid line) for the ruptured HCC. The 12-month survival was higher in the delayed resection group (76%) than in the emergency resection group (33%), ($P = 0.02$). The 24-month survival was not significantly different ($P = 0.2$). Survival comparison was performed by log-rank test for a 12-month time period. Another log-rank test was performed for 24-month time period. Bonferroni's correction was made for the P value, because two separate log-rank tests were performed. Statistical significance for the log-rank tests was assumed to be $P < 0.025$. Cum = cumulative.

According to the Liver Cancer Study Group of Japan,[19] spontaneous rupture was the cause of death in 10% of patients with HCC. Despite the popular belief that most of the patients with ruptured HCC have severe liver dysfunction, most of the patients in our study had moderate liver dysfunction as evidenced by the average Child-Turcotte-Pugh score of 7. The reported incidence of concomitant cirrhosis varies widely in the literature. The incidence reported is as low as 56% and as high as 97%.[3,10] In our series, the incidence of cirrhosis was 57%, reflecting the lower limit of what is reported in the literature.

The clinical presentation of the disease observed in this study was nonspecific. Not every patient was noted to have abdominal pain, because some patients presented with collapse and confusion and thus were unable to admit to having abdominal pain. Although shock was present initially in 56% of the patients, most patients (83%) could be resuscitated to hemodynamic stability, enabling them to undergo a CT scan to confirm the diagnosis. Because of the grave consequences of missed diagnosis or delayed treatment, a high clinical suspicion for ruptured HCC should be exercised in patients with known risk factors for HCC who present with abdominal pain and shock.

Most HCCs observed in our study were advanced tumors. They were large (greater than 5 cm) with an average size of 7 cm (range, 2.5–15 cm), and there was a high rate (68%) of multiple tumors. In the literature, ruptured HCCs tend to be large (greater than 5 cm); however, tumors as small as 2 cm have been reported to rupture.[20] The expanding growth behavior of HCC has been postulated to play a part in events leading to the rupture. The mechanism of rupture favored by Zhu et al.[21] is thought to be initiated by invasion and occlusion of the hepatic veins by tumor cells, resulting in increased pressure within the tumor mass. The venous congestion in combination with various factors such as central tumor necrosis, trauma, and coagulopathy, leads to hemorrhage within the HCC. This further increases the pressure in the HCC and results in splitting of

the overlying liver parenchyma and rupture of HCC at the surface. This hypothesis has some support and may apply to the large HCCs that are located deep within the liver parenchyma; however, it is difficult to explain how a small HCC located in the periphery would rupture by this mechanism. More recent studies suggest that underlying vascular dysfunction may play a role,[22] in that the vessels in the ruptured HCC tend to be more friable due to increased collagenase expression and increased collagen IV degradation.[23] This proposed mechanism may explain why some of the small tumors and the tumors that are located on the surface rupture.

The surgical management of ruptured HCC is a challenging task principally due to coexisting impaired hepatic reserve and cirrhosis resulting in high operative mortality. Therefore, a recent shift in trend in surgical management has been away from emergency surgical resection to TAE followed by a delayed resection.

At our institution, TAE was incorporated routinely in the management of ruptured HCC since the mid-1990s. Sixteen of 22 (73%) patients who presented after 1995 received attempted TAE, and of these patients, 13 (81%) underwent successful embolization. No rebleeding was noted. No patients before 1995 received TAE. The beneficial role of TAE is supported by the observation that no in-hospital mortality occurred in patients who underwent delayed resection after TAE, compared to 40% in-hospital mortality in patients who underwent emergency resection. In two case series of delayed resection for ruptured HCCs from Japan, no in-hospital mortality was observed, and 1- and 3-year survival rates of 71%–77% and 48%–54%, respectively, were achieved.[24,25] These studies attributed elimination of in-hospital mortality to the inclusion of TAE in the treatment algorithm, which allowed for early hemostasis and afforded the patients time to recover from the initial insult. In these two studies, the reported time interval to surgery ranged from as early as 12 days to 126 days. The surgeons involved in these studies used normalization of liver enzymes and bilirubin levels as surrogate markers for return of prerupture liver function to achieve zero operative mortality. In our study, the length of delay before the liver resection was determined at the discretion of the attending surgeon, with the contribution of the patient's clinical status and the laboratory data.

The resuscitative parameters observed in the operating room were not significantly different between the delayed resection group and the emergency resection group. However, there was a trend toward lower blood loss and less need for blood transfusions for the patients who underwent delayed resection. This is likely due to the fact that hemostasis was achieved before the resection by TAE, and surgery could be performed under stable conditions.

In our series, 1-year survival rate was higher in the delayed resection group than in the emergency resection group. These survival rates are comparable to reported rates in the literature. In the published studies, the 1-year survival rates ranged from 54% to 77%, and the 3-year survival rates ranged from 35% to 48% for patients who underwent delayed resection.[24–26] In another series, the 1-year and 3-year survival rates for patients who underwent emergency resection only were 60% and 42%, respectively.[27] The 1-year and 2-year survival rates observed in our study were 76% and 38%, respectively, for the patients with delayed resection.

Historically, because of multiple factors, the prognosis for ruptured HCC is thought to be worse than for nonruptured HCC, due to multiple factors. The patients with ruptured HCC harbor advanced disease at presentation, the incidence of coexisting cirrhosis is high, and peritoneal seeding may occur at the time of rupture. However, recent studies have challenged this concept, stating that the long-term survival for ruptured HCC may be equivalent to nonruptured HCC,[26] especially when the comparison was adjusted for tumor stage.[28] The current tumor lymph node metastasis staging system classifies ruptured HCC as T4 and as stage IV.[29]

One of the main limitations of this study is the small sample size of 30 patients. This reflects the low incidence of HCC in North America and even lower incidence of ruptured HCC. This small sample size has made it difficult to achieve significance in statistical analysis of the data. If the sample size had been greater, a statistically significant difference may have been observed in parameters such as the 30-day mortality.

CONCLUSIONS

Ruptured HCC is a life threatening condition not commonly seen in North America. However, with a rise in the incidence of HCC, rupture may become a more commonly encountered surgical emergency. The treatment has seen an evolution with the advent of TAE, from emergency operative management to delayed resection. In our experience, multidisciplinary management of this condition with the incorporation of TAE early in the treatment algorithm, the in-hospital mortality can be decreased and delayed resection of the tumor can be safely performed in selected patients. We observed that delayed resection

improves short-term survival (12 months), but the long-term survival may remain unaffected due to the advanced stage of the disease.

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Access to Pediatric Liver Transplantation: Does Regional Variation Play a Role?

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The purpose of this study was to assess regional variability in access to pediatric liver transplantation. The study population included all pediatric patients (age less than 18 years) listed for liver transplantation in the United Network for Organ Sharing (UNOS) database between 1988 and 2004. The effect of region on waiting list survival, the proportion of patients transplanted, and the proportion of patients remaining on the list was determined using Kaplan-Meier and Cox proportional hazard methods. The proportion of technical variant grafts used was compared between regions using chi-square analysis. Kaplan-Meier analyses showed significant effects of region on survival on the waiting list, transplantation, and remaining on the list (all log-rank $P < 0.001$). Cox proportional hazard models demonstrated that region, urgency status, and listing period exerted independent effects on survival on the waiting list, transplantation, and remaining on the list (all model $P < 0.01$). Regional variation existed with regard to donor type ($P < 0.001$). Similar to adults, pediatric survival on the waiting list, the proportion of patients transplanted, and the proportion of patients remaining on the waiting list vary considerably within the 11 U.S. regions. Organ procurement organization specific effects and regional differences in utilization of deceased donor split and living donor organs may contribute to this variability. (J GASTROINTEST SURG 2006;10:387–394)

KEY WORDS: Pediatric liver transplantation, access, regional variation, UNOS

In 1984, Congress established the Organ Procurement and Transplantation Network (OPTN) to collect and manage data about every transplant in the United States, facilitate organ matching and placement, and help develop organ transplantation policies. The United Network for Organ Sharing (UNOS) received its first federal contract to operate the OPTN in 1986. The UNOS mission is "to advance organ availability and transplantation by uniting our communities for the benefit of patients through education, technology and policy development." The national UNOS membership is divided into 11 regions to facilitate organ allocation and provide individuals with the opportunity to identify concerns regarding organ procurement, allocation, and transplantation that are unique to their particular geographic area.[1]

After the surgical technique of liver transplantation was refined and overall graft and patient survival rates dramatically improved by the early 1990s, the crisis in donor supply became increasingly more evident. Due to the increasing demand on a relatively small donor pool, significant debate has developed regarding organ allocation policies. The UNOS regions currently form the basis for organ allocation in the United States.

Recently, Ellison and colleagues[2] evaluated the geographic differences in access to solid organ transplantation for adults in the United States. For liver candidates, the overall national transplant rate at 4 months after listing was 22%, but the overall regional rate varied from 11.8% to 36.5%. In addition, the rate for each medical urgency status varied considerably across regions. For example, the 30-day transplant rate for status 1 liver candidates (i.e., those candidates deemed in need of emergent transplantation) varied from 37.2% to 66.1%. Regional variation also proved significant with respect to waiting

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list mortality regardless of blood group, sensitization level, and degree of medical urgency.

Adults currently outnumber children by 15 to 1 on the UNOS waiting list. Children less than 5 years old have the highest waiting list mortality compared with all other age ranges and compose 46% of all children listed. This disproportion affects a pediatric candidate's chance of being allocated an organ. However, children may have some advantage for receiving organs due to the pool of living donor grafts and deceased donor technical variants grafts.[3] Several centers have demonstrated decreased waiting list mortality for pediatric candidates due to the implementation of living donor and split donor programs.[4,5]

However, many centers do not perform pediatric liver transplants, including deceased donor split and living donor transplants. It is probable that this transplant center variability may contribute to significant regional disparity in liver allocation for pediatric transplant candidates. Therefore, regional differences in transplant allocation observed in adults may be even greater in the pediatric population. The purpose of this study was to assess regional variability in access to liver transplantation for pediatric patients with end-stage liver disease as determined by variances in survival on the waiting list, the proportion of pediatric candidates transplanted, and the proportion of patients that remain on the waiting list over time.

MATERIALS AND METHODS

Data Source, Study Period, and Study Population

All cases were obtained from the UNOS Standard Transplant Analysis and Research files, a registry maintained by UNOS that prospectively collects pretransplant, transplant, and follow-up data on all individuals listed for solid organ and intestinal transplantation in the United States. Registry data include demographic information, pretransplant clinical and laboratory information, patient status codes used in the allocation of donor organs, and comprehensive transplant and follow-up data. Data are collected at the time of listing, transplant, 6 months post-transplant, and thereafter on the transplant anniversary for every living organ recipient.

The study population included all listing events during the study period for pediatric liver transplant candidates. The study period started on January 1, 1988 and ended on July 30, 2004. Pediatric candidates and recipients were identified as having age at listing (or transplant) less than 18 years. All listings occurring after an initial liver transplantation (i.e., listing for retransplantation) were excluded. Reasons for multiple listings included initial refusal of an organ, improvement to the point of not requiring transplantation, transfer to another center, multiple simultaneous listings at more than one center, and removal in error. If multiple pretransplant listings occurred, the single listing associated with transplantation, death on the waiting list, or the most recent listing (last status = waiting or removed for other reasons) was analyzed.

The Vanderbilt University Medical Center Institutional Review Board was contacted before the study, and because the data were deidentified before release to our institution, no formal review or approval was required.

Database Preparation

The database included all listing events from January 1988 through July of 2004. Urgency status was dichotomized as urgent (status 1, old status 2A, or pediatric end-stage liver disease [PELD] score greater than 30) or not urgent (all others) on the basis of the following variable priorities: (1) ending status for registration, (2) if in the intensive care unit, or (3) if status 1 at listing. The year of listing was stratified as follows: period 1 = 1988 to 1989, period 2 = 1990 to 1994, period 3 = 1995 to 1999, and period 4 = 2000 to 2004. The primary variable used to identify patient status was "listing removal code", which was collapsed into one of four possible outcomes (death or too ill for transplantation, transplantation, removal for other reasons, or still waiting). Additionally, those patients for whom the listing removal code was blank (which is generally indicative of being still listed), but for whom "ending status for registration" was coded as temporarily inactive, were considered not to be actively listed for analyses of the proportion of candidates remaining on the waiting list.

Statistical Methods

Summary statistics are reported as the mean ± SD or percentages, and chi-square tests of proportions were employed to determine the effect—in organ recipients only—of regional variation on organ type (deceased donor whole, deceased donor split, and living donor organs).

The effect of region on three outcome events (survival on the waiting list, transplantation, and remaining on the waiting list) was analyzed via Kaplan-Meier survival methods. In an attempt to minimize selection bias, we treated patients removed from the waiting list due to death and those removed

because they were too sick to receive a transplant as a combined end point, because both represent a treatment failure of the allocation system. The log-rank statistic was used to test the overall effect of region on each outcome variable. These analyses were followed by Cox proportional hazards regression models that tested the effects of region, urgency, time period (if relevant), and whether the candidate had a single or multiple listing. Because the evaluation of patients remaining on the waiting list includes predominantly those patients with recent listings, the effect of listing period was not included in the multivariate model for the outcome event of remaining on the waiting list.

RESULTS

General Characteristics

Since 1988, a total of 10,299 pediatric liver transplant candidates have been listed for transplantation. As of July 2004, 6,996 (68%) patients received transplants, 1,074 (10%) died on the waiting list, 139 (1%) patients were removed due to the severity of their illness precluding transplantation, 1,229 (12%) were removed for other reasons, 391 (4%) are temporarily inactive, and 470 (5%) remain on the waiting list. The average number of registrants per year for each time period is as follows: period 1 had 391 registrants per year, period 2 had 556 registrants per year, period 3 had 700 registrants per year, and period 4 had 720 registrants per year. The mean age at listing for pediatric registrants was 4.79 ± 5.8 years.

Effect of Region on Waiting List Survival

Survival on the waiting list (time to death or removal due to being too ill) varied by region (log-rank $P < 0.001$). Specifically, regional variability in the percentage of patients surviving on the waiting list at 3, 6, and 12 months was 87% to 92%, 82% to 88%, and 72% to 85%, respectively. Figure 1 shows Kaplan-Meier survival curves for patients on the waiting list, stratified by region. A multivariate Cox proportional hazard regression model (model $P < 0.001$) also showed a significant impact of region as well as an independent effect of both urgency status and listing period on survival on the waiting list (all effects $P < 0.01$). Patients listed as urgent status showed significantly increased risk of death on the waiting list than patients listed as not urgent (odds ratio [OR] = 5.28, confidence interval [CI] = 4.6, 6.0, $P < 0.001$). A second Cox proportional hazards

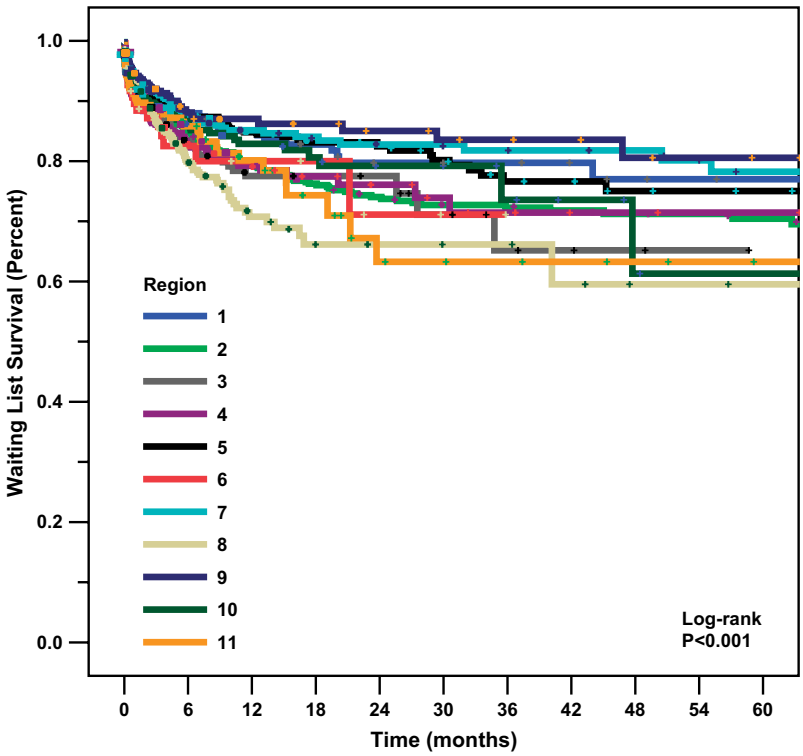

Fig. 1. Kaplan-Meier survival curves for patients on the waiting list, stratified by region. Survival on the waiting list varied by region (log-rank $P < 0.001$).

analysis was performed in which the effect of multiple listings was added to the model (model $P < 0.001$). Although multiple listing events had an effect on survival on the waiting list ($P = 0.002$), the independent effects of region, urgency status, and period of listing remained significant after controlling for whether the patient had multiple listing events.

Effect of Region on Transplantation

The cumulative proportion of patients transplanted also varied by region (log-rank $P < 0.001$). Specifically, regional variability in the percentage of patients transplanted at 3, 6, and 12 months on the waiting list was 27% to 49%, 38% to 71%, and 53% to 86%, respectively. Figure 2 shows the Kaplan-Meier curves for the cumulative proportion of patients who received transplants over time, stratified by region. A multivariate Cox proportional hazard regression model (model $P < 0.001$) also showed a significant impact of region on the proportion of patients transplanted as well as an independent effect of both urgency status and listing period (all effects $P < 0.01$). Patients listed as urgent status showed significantly increased odds of transplantation than patients listed as not urgent (OR = 2.64, CI = 2.50, 2.78, $P < 0.001$). A second Cox proportional hazards model analysis was performed in which the effect of multiple listings was added to the model. Although multiple listing events had an effect on the proportion of patients transplanted over time ($P < 0.001$), the independent effects of region, urgency status, and period of listing remained significant after controlling for multiple listing events in the model.

Effect of Region on Remaining on the List

The proportion of patients remaining on the waiting list varied by region (log-rank $P < 0.001$). Specifically, regional variability in the percentage of patients remaining on the waiting list at 3, 6, and 12 months was 0.4% to 1.8%, 0.9% to 7.9%, and 1.9% to 9.0%, respectively. Figure 3 shows the Kaplan-Meier curves for the cumulative proportion of patients remaining on the waiting list, stratified by region. A multivariate Cox proportional hazard regression model (model $P < 0.001$) also showed a significant effect of region on the proportion of patients remaining on the list, and again, independent effects of urgency status (all effects $P < 0.001$). Patients listed as urgent status were less likely to remain on the waiting list compared with patients listed as not urgent (OR = 0.60, CI = 0.43, 0.85,

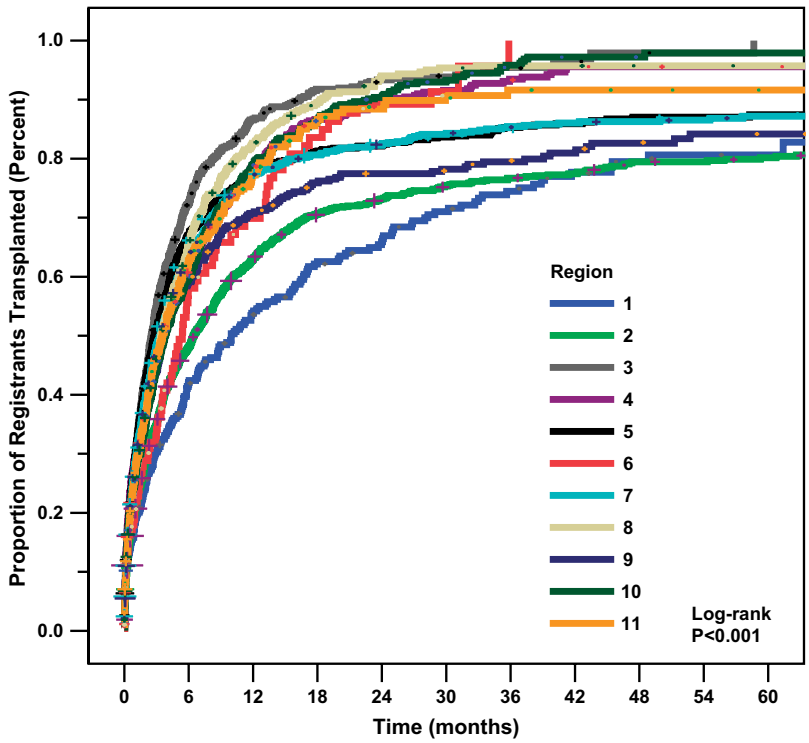

Fig. 2. Kaplan-Meier curves for the cumulative proportion of patients who received transplants over time, stratified by region. The cumulative proportion of patients transplanted also varied by region (log-rank $P < 0.001$).

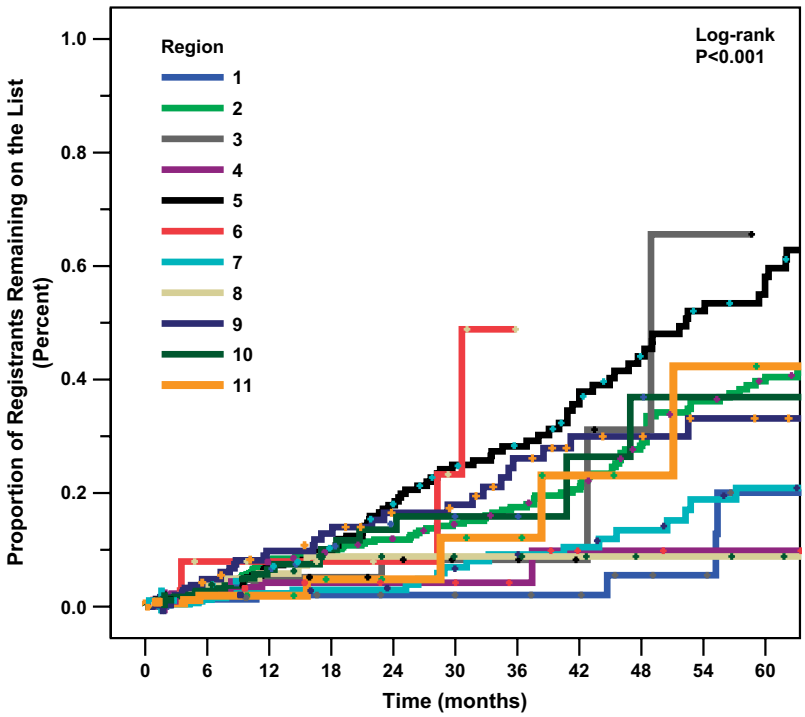

Fig. 3. Kaplan-Meier curves for the cumulative proportion of patients remaining on the waiting list, stratified by region. The proportion of patients remaining on the waiting list varied by region (log-rank $P < 0.001$).

$P = 0.003$). Again, the effects of region and urgency status persisted despite controlling for multiple listing events in a second Cox model.

Table 1 summarizes the results of the multivariate models for the independent effects of urgency status and period of listing on the three outcome measures: survival on the waiting list, transplantation, and remaining on the waiting list.

Effect of Region on Donor Type

For the pediatric patients who received transplants during the study period, regional variation also existed with regard to the proportion of deceased donor whole, deceased donor split, and living donor organs used (chi-square $P < 0.001$). Specifically, regional variability in the proportion of deceased donor whole, deceased donor split, and living donor organs was 58% to 83%, 11% to 30%, and 1% to 26%, respectively.

DISCUSSION

Similar to the data presented in the adult transplant literature,[2] this study provides evidence that regional variability in access to organs also exists in the pediatric population with end-stage liver disease. We found significant regional variability in several factors related to access to transplantation. Previously, the Institute of Medicine (IOM) deemed waiting list mortality, severity of illness, and rate of transplantation as good measures of access to liver transplantation.[6] In our study, we evaluated the impact of region on waiting list survival, the proportion of pediatric candidates who received transplants, and the proportion of candidates who remained on the waiting list. Region had a significant effect on all of these outcome measures in univariate as well as multivariate analyses, in which we controlled for severity of illness and listing period. Thus, significant regional variability exists with regard to these measures of access to transplantation in the pediatric population. Not surprisingly, we also found significant regional variation with regard to the utilization of alternative graft sources in the pediatric population.

Given the severe shortage of livers, coupled with the exponential increase in the number of patients with end-stage liver disease, both allocation procedure and policy are critically important, and several recent studies have focused on the regional disparities associated with various allocation systems in both the United States and abroad.[2,7-10] In 2003, Miranda and colleagues[9] evaluated disparities in access to transplantation in Spain and found that

Table 1. Results of the Cox proportional hazards models for waiting list mortality, transplantation, and remaining on the waiting list*

	OR	CI	*P*
Death on the waiting list			
Urgency (urgent vs. not urgent)	5.28	4.6, 6.0	<0.001
List Period			
Prior to 1990	Reference†	Reference†	—
1990–1994	2.52	1.67, 3.82	<0.001
1995–1999	2.40	1.79, 4.06	<0.001
After 1999	1.89	1.25, 2.85	0.002
Transplantation			
Urgency (urgent vs. not urgent)	2.64	2.50, 2.78	<0.001
List period			
Prior to 1990	Reference†	Reference†	—
1990–1994	1.62	1.40, 1.89	<0.001
1995–1999	1.23	1.06, 1.42	0.007
After 1999	1.07	0.92, 1.24	0.406
Remaining on the waiting list			
Urgency (urgent vs. not urgent)	0.60	0.43, 0.85	0.003

*The overall effects of region on the models for survival on the waiting list, transplantation, and remaining on the waiting list were significant with all models $P < 0.01$.
†Reference group used in the Cox proportional hazards models. OR = odds ratio; CI = confidence interval.

significant differences existed between regions with regard to indications for transplantation, which was associated with the presence and number of transplant teams within a region. Similarly, Mullen and colleagues described inconsistencies in the selection criteria based on social support and waiting time across Canadian transplant centers.[7]

In the United States, Tuttle-Newhall and colleagues[8] also showed that amongst other demographic variables, a patient's distance to the nearest transplant center is predictive of whether or not the patient will receive a liver transplant. In a recent editorial regarding United States organ allocation and distribution as it relates to the model for end-stage liver disease (MELD), Brown and Lake[10] described significant organ procurement organization (OPO)-to-OPO variability in the acuity of patients transplanted as determined by their listing MELD scores. For example, the transplantation rate for candidates with MELD scores less than 11 varies from 0% to 25%, depending on the OPO. A greater survival benefit could be ascertained by shifting these transplants to candidates with MELD scores greater than 15. They re-emphasize that the goal of liver transplantation is to decrease overall mortality for all individuals eligible for transplantation.[10]

Several studies have focused on the contributing factors to regional variability in access to liver transplantation in the United States.[1,6,11] In 1999, the OPTN and the Department of Health and Human Services evaluated factors that influenced waiting time for liver transplantation, which varied across different geographical regions. These factors included the number of potential organ donors, organ procurement rates, waiting list size, the number of transplant programs in a region, organ acceptance rates, and the number of highly sensitized patients within a region.[1,11] In 2003, Gibbons and colleagues[6] published the results of an analysis performed by the IOM, which evaluated the OPO-specific effects on regional variability in transplantation rates. For status 1 patients, less than 5% of the regional variability was attributable to OPO-specific effects; however, for status 2B and 3 patients, the OPO-specific effects on regional variability in transplantation rates were much greater (13% and 35%, respectively). Certainly, in our study, the regional variability noted in the access to pediatric liver transplantation may result from OPO-specific effects as described by Gibbons and colleagues,[6] but OPO-specific data was not readily available in our database for further analysis. Specifically, the variability is likely, in part, attributable to OPO variability with regard to the number and size of pediatric transplant centers.

From these reports as well as our own study, it is quite clear that regional variation exists with regard to access to liver transplantation in both the United States and abroad. In the report published by Gibbons and colleagues,[6] the IOM suggested that the allocation model should incorporate regional and statewide sharing amongst two or more OPOs

to increase the transplantation rate and decrease the waiting time and mortality for status 1 candidates, as well as to decrease the transplantation rate for less ill candidates.[6] The IOM recommended that at least 9 million people be included in an organ allocation region to maximize the chance of transplantation for the most severely ill patients. In response to the IOM's request, Freeman and colleagues[12] tested the redrawing of the organ allocation regions using hypothetical scenarios to include a minimum of 9 million people. Although the models decreased interregional variation, all plans led to a decrease in the number of transplantations performed and most resulted in an increased number of deaths and decreased number of life years gained. The study called into question whether or not it is appropriate to correct the regional variability that exists.

More recently, Stahl and colleagues[13] used an integer program designed to maximize a weighted combination of intraregional transplants and geographic parity. They found that reorganizing the regions and constraining their number to 11 resulted in up to 17 additional transplants per year, and if no constraints on the number of regions were maintained, reorganization of the regions resulted in up to 18 additional transplants per year. They found a benefit to clustering large metropolitan centers, which was associated with increased intraregional transplantation. However, they also demonstrated that incorporating geographic equity into the model decreased intraregional transplantation and vice versa. Therefore, the optimal allocation plan must establish a balance between the two results.

Significant debate has also focused on the development of a single national waiting list based on urgency status.[14] A single national waiting list would eliminate the disparity between regions as well as the incentive for multiple listings. Several state laws currently prohibit such a policy and require organs procured within the state to remain in the state for transplantation. A national waiting list may favor larger transplant centers with longer waiting lists over smaller centers and lead to a restructuring of transplant centers within the United States. In addition, individual organ procurement centers may lack incentive to procure organs that will most often be transported outside their region. Most importantly, the increased ischemic time as well as cost associated with long travel distances makes a single national waiting list impractical. Thus, this idea has not been readily adopted by the transplant community. With the recent change in organ allocation policy to MELD and PELD, it will be important to continue to evaluate disparities in access to liver transplantation for both the adult and pediatric populations and direct our attentions toward developing models for organ allocation that minimize these disparities.

We recognize both potential advantages and limitations to a retrospective study design that uses a large national database. Despite the immense breadth of the OPTN registry, some variables that may influence the outcome measures may not be captured in the database. In a retrospective design, confounders such as OPO shopping by patients and the distribution across OPOs of the use of technical variant grafts may exist that are not controlled for in the analyses. We attempted to control for multiple listings in our selection criteria for participants, as well as in a multivariate model that included multiple listing events as a covariate. Because UNOS relies upon individual transplant centers and organ procurement agencies to enter the data for each transplant candidate and recipient, missing and/or erroneous data may occur. However, no previous studies have focused on the regional disparity in the access to liver transplantation in the pediatric population with end-stage liver disease, likely due to the small number of outcome events in the pediatric population compared with the adult population with end-stage liver disease. The large sample size in this database provides sufficient power to detect meaningful associations between region and the outcome measures for this population of patients.

CONCLUSIONS

This study provides good evidence that regional variability plays a role in access to pediatric liver transplantation as measured by waiting list survival, the proportion of candidates who received transplants, and the proportion of candidates who remained on the waiting list over time. Significant regional variability also exists with regard to the utilization of alternative graft sources, including deceased donor split and living donor organs. This disparity in organ availability, as well as OPO-specific effects including OPO variability in number and size of pediatric transplant centers, likely contribute to the discrepancies in access to pediatric liver transplantation between regions.

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Clinical and Prognostic Aspects of Gastric Carcinoma in the Elderly

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The aim of the present study was to analyze the influence of various factors on the prognosis for elderly patients with gastric carcinoma. Forty-eight patients aged ⩾65 years admitted to Padova General Hospital were divided into two groups by age (<75 or >75 years). They all had a histologically confirmed diagnosis of gastric adenocarcinoma. Information on their clinicopathological characteristics was collected from the Padova Hospital medical records. On univariate analysis, significant prognostic factors in the two age groups were gender, stage, histotype (Lauren's intestinal type), Charlson index, and type of surgery (curative resection, palliative resection, and no surgery). On multivariate analysis, independent prognostic factors were the Charlson index, tumor stage, and age group. The 52-month survival rate was 72.7% for females and 12.5% for males for patients ⩾75 years ($P = 0.01$), while for the whole series of patients it was 67.5% for females and 29.9% for males ($P = 0.003$). The 17-month survival rate was 55.6% for surgically treated patients and 0% for the untreated cases in stage 4 ($P = 0.03$). Gastric cancer should be treated with conventional surgery even in the very elderly, since the survival rate for this age group does not differ significantly from the figures for younger patients. (J GASTROINTEST SURG 2006;10:395–401)

KEY WORDS: Gastric carcinoma, elderly, prognosis

The world population is aging.[1] Italy is one of the countries with the longest life expectancy (88 years for women and 83 for men) and the highest proportion of elderly people in the world (25%), followed by Japan, Germany, and Greece, all around 24%.[2–4]

The longer average life span has led to a greater incidence of neoplastic disease in old age, prompting much debate and research in the geriatric field, especially in view of the fact that, even in the older age brackets, the residual life expectancy is always longer than is likely to be granted by the natural evolution of the neoplasm.[5]

In people aged ⩾65 years, cancer represents the second cause of death and the first cause of morbidity.[6,7] For this age bracket, the risk of developing cancer is approximately 11 times higher than for those <65 years old and about two thirds of all deaths due to cancer occur after 64 years of age.[8,9] Surgery is the only potentially curative treatment for gastric carcinoma, regardless of the patient's age.[10–14] Previous studies[15–18] reported that gastric cancer in old people (>70 years) was characterized by advanced stage and a poor prognosis.

A rational approach to treating gastric cancer in the elderly should be to improve survival; there are several reports on the surgical treatment of patients over 70 years old and it seems that advanced stage is responsible for the poor prognosis. Few reports regarding prognostic factors deal with the patient's age.[13,19]

The aim of the present study was to analyze the influence of various factors on the prognosis for elderly patients with gastric carcinoma.

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MATERIAL AND METHODS

A retrospective study recruited 56 patients hospitalized for gastric adenocarcinoma aged ⩾65 years admitted to Padova General Hospital between January 1993 and May 2001. Information was collected from the Padova Hospital medical records. Eight patients were excluded because their files were incomplete. In all, therefore, we collected 48 patients, all with a histologically confirmed diagnosis of gastric adenocarcinoma. We considered the symptoms: there were seven common symptoms (pain, dysphagia, dyspepsia, heartburn and regurgitation, altered coenesthesia, vomiting, signs of anemia) and the lack of symptoms.

From the histological report on the surgical specimen, we recorded the stage (1 to 4), tumor site, and histotype (Lauren's intestinal or diffuse type).[20] We distinguished between curative and palliative operations; all operations were judged to be curative if all macroscopic disease was completely removed during surgery and the resection margins were disease free.[19]

For patients who did not have surgery, we consulted the medical records on their hospital stays after the diagnosis of carcinoma, evaluating all instrumental investigations (computed tomography scan, abdominal ultrasound, chest radiograph), the outcome of exploratory laparoscopy (if any), and the letter of discharge in order to establish the patients' clinical stage and physical conditions.

To quantify comorbidities, we used the Charlson comorbidity scale[21,22] (Table 1), a standardized tool based on the mortality risk at 1 year. This scale considers 19 different diseases weighted with a score from 1 to 6; it is valid for predicting mortality risk for periods ranging from a few weeks up to 10 years.

We also considered gender, age (>75 or < 75 years; as recommended by the World Health Organization[23]), and survival after diagnosis and/or after surgery in months. Survival rates were calculated dividing patients according to stage of disease, and a comparison was drawn between the survival curves obtained for operated patients with less than stage 4 disease, between gender and age ⩾75 years, and between genders.

Statistical Analysis

The statistical analysis was conducted using SPSS 11.5 and Microsoft Excel. Survival rates were calculated using the Kaplan-Meier method, and comparisons were drawn with the log-rank test. ANOVA was used for univariate analysis, and logistic regression for multivariate analysis. A P value of ⩽0.05 was considered statistically significant.

Table 1. Charlson comorbidity index

Comorbidity	Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes (uncomplicated)	1
Diabetes with end-organ damage	2
Ictus	2
Moderate or severe renal disease	2
Nonmetastatic second tumor	2
Leukemia	2
Lymphoma, multiple myeloma	2
Moderate or severe liver disease	3
Metastatic second tumor	6
AIDS	6
Total Score	

RESULTS

The study considered 48 patients aged ⩾65 years (range, 65−88 years; mean age, 74.33 years); 25 were between 65 and 74 years old (6 females and 19 males), and 23 were 75 or older (13 females and 10 males). Gender had a significant influence on survival in the two age groups ($P = 0.014$). No significant differences were observed between the two age groups as regarding symptoms.

Concerning tumor stage, among the patients ⩾75 years old, cancer was detected in stage 4 in 48% of cases (stages 0 and 2 in 17%, stage 1 in 13%, and stage 3 in 4%). In 36% of the patients aged between 65 and 74, the tumor was detected in stage 2 (stage 3 in 24%, stage 4 in 20%, stage 0 in 12%, and stage 1 in 8%). Stage significantly influenced survival in the two groups ($P < 0.001$) (Fig. 1).

As for histotype, Lauren's intestinal type was more common in both groups: it accounted for 65% of the patients ⩾75 years old and 68% of the <75-year-olds ($P = 0.04$). No statistically significant differences emerged between the two age groups vis-à-vis tumor site.

Regarding the type of surgery, 48% of the older patient group (⩾75 years) had curative resection, 22% had palliative resection, and 30% had no surgery, whereas 80% of the younger group (<75 years) had curative resection and 12% had palliative surgery ($P = 0.037$).

For each patient, we noted any diseases concomitant with the gastric carcinoma, performing

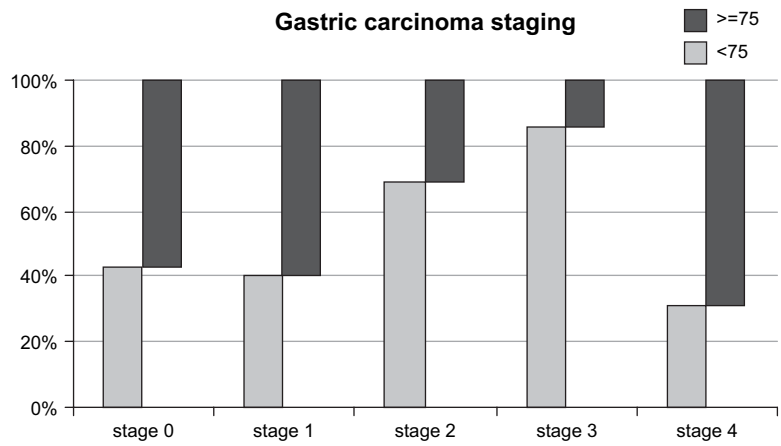

Fig. 1. Gastric carcinoma stage in relation to age.

a numerical conversion using the Charlson comorbidity scale (Table 1). The data analysis revealed that approximately 70% of the elderly patients had more than one pathology associated with their cancer. In particular, 26% of the patients aged ⩾75 had a Charlson index of 1, 17% scored 2 and 3, 13% scored 0, and the remainder scored more than 4. Among the under 75-year-olds, the Charlson index was 1 and 3 in 20% of cases, 0 in 8%, and 2 or higher than 3 in the remainder (Fig. 2). The Charlson index significantly influenced survival ($P = 0.024$).

The mean Charlson index in the operated patients between 65 and 75 years old (92%) was 3.78 ± 3.13 (SD); in the unoperated cases (8%), it was 7 ± 0. The mean Charlson index in the operated patients

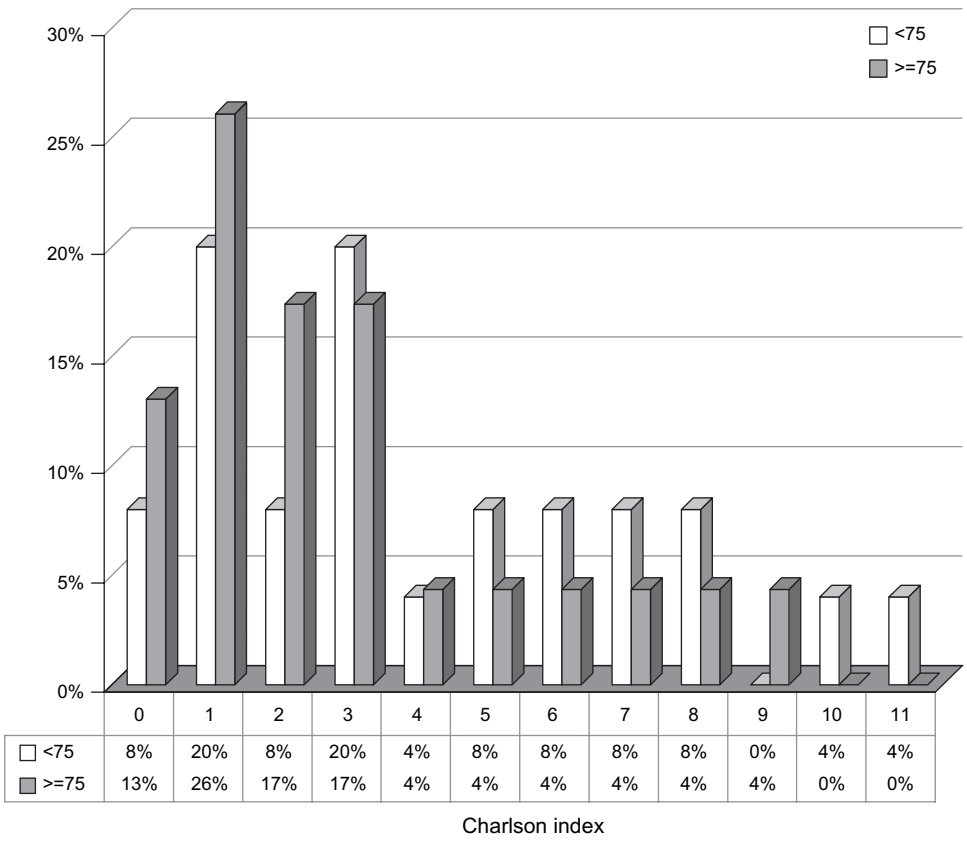

Fig. 2. Charlson index in relation to age bracket.

⩾75 years old (70%) was 3 ± 3.03 versus 2.43 ± 0.98 in the unoperated cases (30%). These differences were not significant, however. On multivariate analysis, the significant prognostic factors with a strong impact on survival were the Charlson index, tumor stage, and the two age groups. The importance of each prognostic factor is illustrated in Table 2.

Survival Analysis

The 52-month survival rate for the patients ⩾75 years was 72.7% for females and 12.5% for males ($P = 0.01$) (Fig. 3). Among the patients with stage 4 disease, the survival rate was significantly higher for the surgically-treated than for the untreated cases: the 14-month survival rate was 55.6% for those who had surgery and 14.3% for those who did not; and the 17-month survival rate was 55.6% for the former and 0 for the latter ($P = 0.03$) (Fig. 4). The survival rate was detected for males and females: at 52 months, it was 67.5% for females and 29.9% for males ($P = 0.003$) (Fig. 5).

A separate comparison was drawn between the two age groups with stage 4 disease, but no significant differences emerged. The same was true when the two age groups were compared in terms of surgical treatment and Charlson index (to assess the influence of any comorbidities on survival).

DISCUSSION

As life expectancy has risen in recent decades, there has also been a steady increase in the incidence of gastric cancer in the elderly, making it necessary to establish a rational approach to the treatment of elderly patients with gastric cancer.[19] Previous studies have evaluated prognostic factors and survival rates after gastric resection in the elderly but with inconsistent results.[12,15,24] This study evaluated the patient's entire clinical and outpatient course in order to gain a better idea of the variables that have the greatest impact on survival.

Table 2. Significant prognostic factors on survival, in multivariate analysis

	B	SE	Wald	*P*	Exp(B)
Index of Charlson	0.453	0.222	4.143	0.042	1.572
Stage	1.210	0.409	8.772	0.003	3.353
Age group (<75, ⩾75)	2.244	1.089	4.241	0.039	9.429
M/F	1.948	1.021	3.642	0.056	7.013

B and Wald = the B regression coefficient and the Wald coefficient are used to establish the relative weight or importance of one variable vis-à-vis others in predicting an event; SE = standard error, representing the expected variation in the dependent variable corresponding to a 1 scalar unit increase in the value of the independent variable; Exp(B) = the probability of the event given a variable.

A significant difference emerged between the two genders, both in subjects <75 and >75 years old, although the male-to-female ratio tends to level off with increasing age. This was the case in a recent study, where the relative odds of gastric cancer in men were higher than in women, in all age groups.[18] A previous study examined gastric cancer in two elderly groups (⩾65 years and >74 years), but the male-to-female ratio was 11:1, and this disproportion in gender reflected the type of patient population, which consisted of 60% veterans.[12] Other reports have investigated patients aged 69−80 or under 65, including very young patients.[15,19,25]

In the present study, the presenting symptoms in the two groups ("younger elderly" versus "older elderly") were similar to those reported in the literature and there was no significant difference between the two age brackets.[25] Certain symptoms and signs in elderly cancer patients are sometimes attributed "to age," however, thereby reducing the chances of a correct diagnosis ("cancer symptom confusion").[1,26]

Our study confirmed a correlation between stage and age. In 48% of patients aged ⩾75 years, gastric cancer was diagnosed in stage 4. This situation is confirmed by the literature: a greater incidence of advanced disease has been recorded in elderly patients and attributed to late diagnosis, whereas it is diagnosed in earlier stages among younger people. As for the Lauren histotype, in our series the intestinal type (which theoretically has a more favorable prognosis) dominated in both groups and significantly influenced survival, as in previous studies.[5,12,19] No statistically significant difference emerged concerning the location of the neoplasm, as reported elsewhere.[25]

The influence of surgery on survival was significant ($P = 0.037$). A possible explanation lies in the greater incidence of advanced disease among the more elderly patients. Less curative resection in these patients means a lower chance of survival.[5,27] Concern about the greater age-related risk, given the higher postoperative mortality rate after major surgery in the elderly, may prompt a more cautious assessment leading to elderly patients being neglected for surgery.[11,12] In addition, the frequent coexistence of several pathologies (as confirmed by the literature) further complicates the picture[1,28]: in our study, 70% of the elderly patients had more than one pathology associated with their cancer, although the perioperative mortality rate was nil. The Charlson

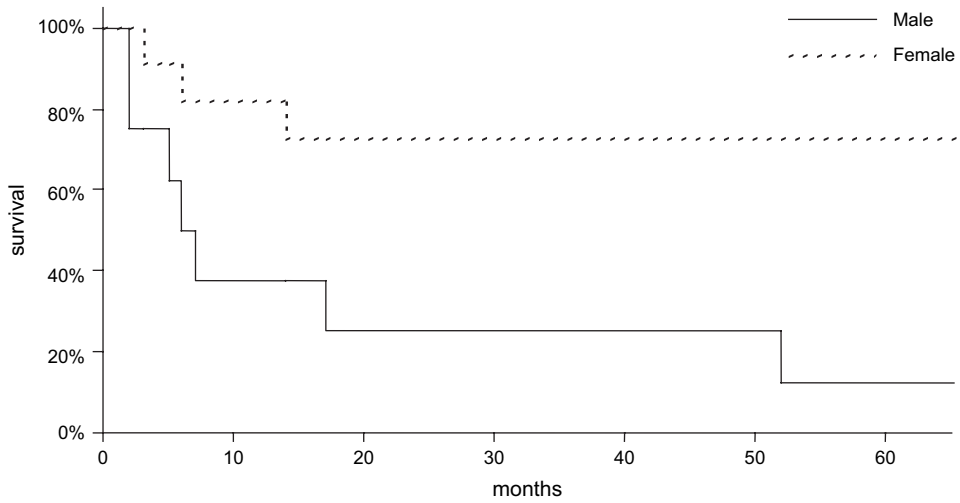

Fig. 3. Survival rate for patients ⩾75 years according to gender.

index significantly influenced the survival ($P = 0.024$). To our knowledge, no studies have used this indicator in assessing survival in elderly gastric carcinoma patients, although several works have considered quality of life and various associated pathologies—which also found some comorbidities significant.[12,13,29]

In our series, multivariate analysis suggested that the Charlson index, stage, and the two different age groups were independent significant prognostic factors ($P < 0.05$) affecting survival; data in the literature are inconclusive concerning age and the stage of neoplastic disease.[12,19,24,30] Advanced stage coincides with a poor prognosis at any age[19,25]: this was also confirmed by our data. Among the cases of advanced gastric cancer, the prognosis is worse in the unoperated patients than in the operated group, many patients cannot undergo surgery because of the dissemination of the tumor, whereas any comorbidity in these patients seems to be less influential, as emerged from our data. Our study showed that in stage 4, the survival rate was clearly higher in operated patients. Like other publications, these findings confirm that surgical therapy should be encouraged.[13,29,31] In the present series, the survival rate at 52 months was higher in females for both the younger elderly and the patients aged ⩾75 years . This can be explained by the higher incidence of carcinoma in men.[2,3,5,9,13,24]

In conclusion, age is not a perfect predictor of the competing risks faced by an individual and there is no age limit for gastric cancer surgery.[11,13] In the light of our findings, gastric cancer should be treated with traditional surgery even in the very elderly,

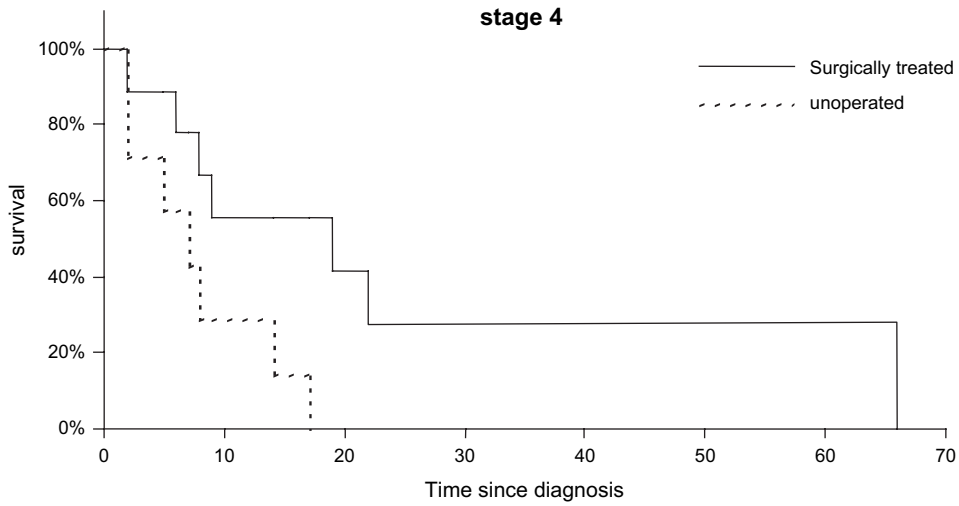

Fig. 4. Survival rate in surgically treated versus unoperated patients with stage 4 disease.

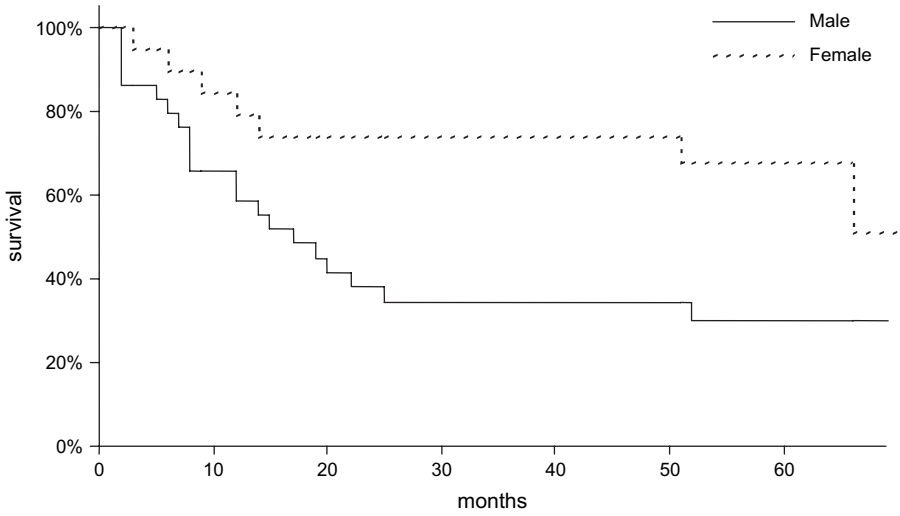

Fig. 5. Survival rate according to gender.

since the survival rate for this age group does not differ significantly from the figures for younger patients.

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Lymph Node Metastasis From Gastric Carcinoid Tumors Occurring Concomitantly With Gastric Adenocarcinomas and Atrophic Gastritis

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We describe a case of gastric carcinoids concomitant with gastric adenocarcinoma in a 50-year-old woman affected by atrophic gastritis. Number and size of the lesions, pathological examinations, and underlying gastric disease all indicated low-risk carcinoids. Nevertheless, when R1 gastrectomy was carried out, an unsuspected lymph node metastasis from carcinoid was found along the lesser curvature. The same occurrence is reported in several cases of the literature, which suggests that the association of gastric carcinoid to adenocarcinoma could point to the malignant nature of carcinoid, apart from underlying gastric disease and tumor characteristics. (J GASTROINTEST SURG 2006;10:402–406)

KEY WORDS: Carcinoid, concomitant tumors, lymph node metastasis, stomach

For a long time, gastric carcinoid tumors have been considered rare, accounting for no more than 0.3% of all gastric tumors and 1.9% of all gastrointestinal carcinoid tumors.[1,2] However, a more recent review reported that as many as 10−30% of all carcinoids may occur in the stomach,[3] and Japanese mass endoscopic screenings have led this rate up to 41%.[4]

As a general rule, it is commonly thought that the surgical management of gastric carcinoids depends mainly on dimensions, number, and type of the lesions. Tumor size greater than 1 cm, more than three to five tumors, and sporadic carcinoids (type III) require a major surgical procedure, due to usual malignant behavior. In contrast, gastric carcinoids associated with hypergastrinemia (types I and II), if fewer than five, and less than 1 cm in size might be managed by endoscopic excision.[5]

The occurrence of adenocarcinomas coexisting with carcinoids in the stomach is much less frequent, ranging from 7.8% to 14% of all carcinoids in a large series.[6] Since the earliest observations of such contemporary occurrence,[3] it appeared clear that carcinoids were not less malignant than adenocarcinomas. In fact, while adenocarcinomas behaved like well-differentiated tumors, all cases displayed an unfavorable prognosis due to carcinoids. This observation raises the question whether the biological behavior of carcinoids can no longer be related to their size, number, and underlying gastric disease when adenocarcinoma is associated.

We report a case of adenocarcinoma and carcinoid coexistence in the stomach, along with a brief review of the literature in the field.

REPORT OF A CASE

A 50-year-old female patient was referred to our Institution for the surgical treatment of a gastric adenocarcinoma. Her clinical history revealed she had been affected by asthma since the age of 16 years. The patient had had a cardiac arrest 13 years earlier, as a consequence of a severe attack of asthma. In addition, the patient had had Biermer's disease (pernicious anemia) for 12 years, and periodically, she underwent upper digestive endoscopy. At the last endoscopic follow-up, done because of well-known atrophic gastritis, a submucosal tumor (8 mm in diameter) had been found in the antrum. Following endoscopic removal and on pathological examination, the tumor was found to be a carcinoid, with intramucosal and submucosal growth, whose free-margin excision had been considered curative. In addition, a second tumor (1 cm in diameter) of the fundus underwent biopsy and was found to be a well-differentiated adenocarcinoma.

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Total gastrectomy was then carried out for the treatment of the adenocarcinoma. A Roux-en-Y reconstruction was chosen with a terminolateral esophagojejunal anastomosis and the ascending loop in antecolic position. Intraoperative liver ultrasonography excluded liver metastasis.

The histopathological examination of the gastric specimen revealed a new carcinoid tumor (1 cm in diameter) of the lesser curvature, caudal to that previously removed endoscopically, displaying hyperplasia and clustered dysplasia of enterochromaffin-like (ECL) cells (Fig.1). The fundal mass was confirmed to be a well-differentiated adenocarcinoma, but a second previously undetected early gastric cancer of the fundus was also found. A total of 24 lymph nodes were removed within the specimen (three pyloric, nine lesser curvature, eight cardiac, and four greater curvature). Each of them was cancer free except for one node along the lesser curvature that had a carcinoid metastasis (Fig. 2).

Postoperative outcome was uneventful. The patient was cancer free at the last follow-up, 3 months after operation.

DISCUSSION

Hypergastrinemia-associated gastric carcinoids (types I and II) are believed to have a good prognosis, because only 7.6−12% of patients have metastases.[6] Recent reports have confirmed that death rarely results from atrophic gastritis-related carcinoid tumors.[7,8] Usually, management of hypergastrinemia-associated carcinoids includes endoscopic excision sometimes followed by antrectomy when lesions are recurrent, larger than 1 cm, or more than 5 in number. Antrectomy, which reduces hypergastrinemia and its trophic effect on the carcinoid ECL cells, seems to be effective in patients with hypergastrinemia-related carcinoids in whom regression has been reported after removal of the antral mucosa.[5] Although hypergastrinemia-associated carcinoids are considered relatively nonaggressive, the risk of lymph nodes involvement cannot be ignored, even for type I carcinoids less than 1 cm in size, which has occurred in 2.4−8.2% of the patients.[3,7]

The major point of our case report is the finding of the lymph node metastasis from a carcinoid when metastases were unsuspected. The primary carcinoid tumor that was removed had no evident malignant features. Its size, around 1 cm, and the underlying atrophic gastritis all had convinced us that the endoscopic and surgical removal had likely been curative, at least as far as the carcinoid was concerned. In the end, it could be argued that nothing changed, because an R1 gastrectomy had to be carried out anyway due to the concomitant adenocarcinoma.

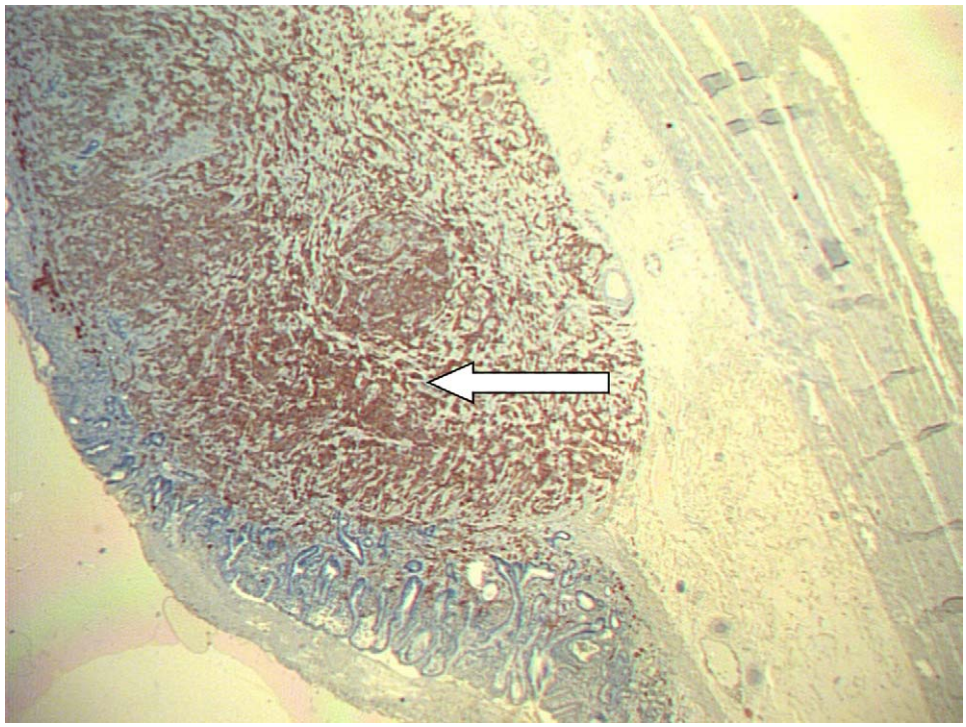

Fig. 1. Photomicrograph showing antral carcinoid (*arrow*) in the gastric wall (chromogranin A immunostaining, original magnification ×200) showing intense staining of enterochromaffin-like cells with moderate anisocariosis located within a fibrous stroma.

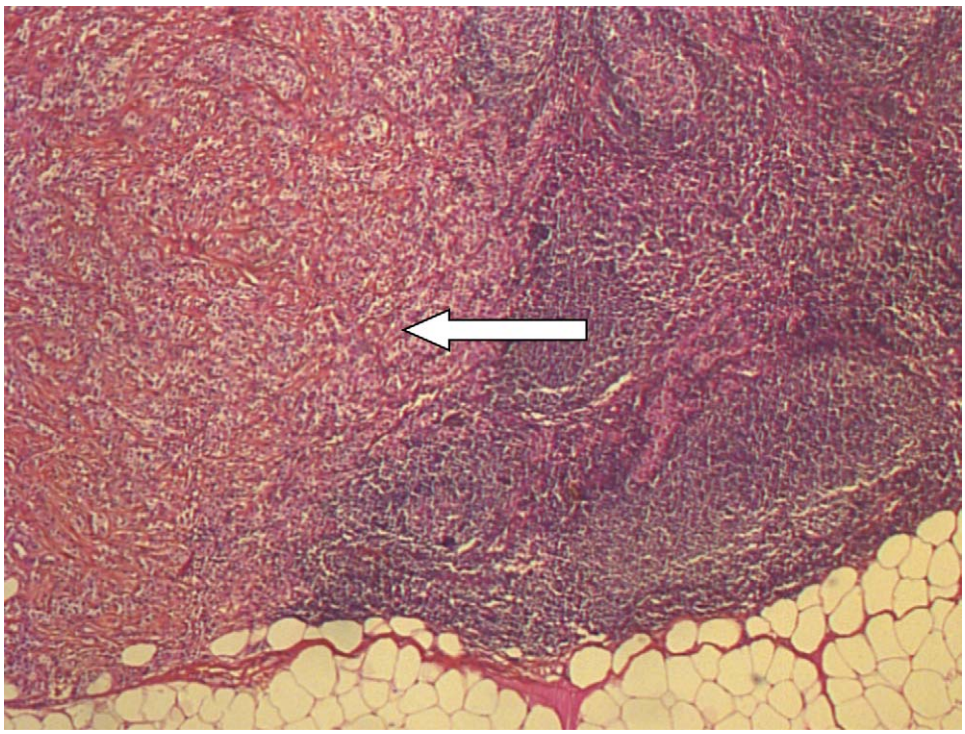

Fig. 2. Photomicrograph of a perigastric lymph node ((hematoxylin-eosin staiing, original magnification ×300), showing metastatic enterochromaffin-like cells (*arrow*).

Table 1. Case reports of gastric carcinoid-adenocarcinoma coexistence in which metastases from the carcinoid tumor were observed

Author (year)	n	Gender	Age (yr)	Gastric tumors	Microscopic pattern	Lymph node metastasis	Liver metastasis	Underlying gastric disease
Adhikari et al. (2002)	1	M	52	Malignant polyp (ADC + CRC) + Multiple nodules (CRC)	Composite/ concomitant	ADC + CRC	CRC	Atophic gastritis
Morishita et al. (1991)	1	M	49	Early gastric cancer (ADC) + adjacent nodule (CRC)	Collisional	Not found	CRC	Atrophic gastritis
Shinohara et al. (2003)	1	M	50	Early gastric cancer (ADC) + minute nodule (CRC)	Concomitant	CRC	Not found	Atrophic gastritis
Corsi and Bosman (1995)	1	M	72	Cardial gastric mass (ADC + CRC)	Collisional	ADC + CRC	Not found	Not reported
Bhatnagar and Borg-Grech (1995)	1	F	70	Malignant polyp (ADC) + multiple polyps (CRC)	Composite/ concomitant	CRC	Not found	Atrophic gastritis
Ulich et al. (1988)	1	M	60	Malignant polyp (ADC + CRC)	Composite	ADC + CRC	ADC + CRC	Not reported

ADC = adenocarcinoma; CRC = carcinoid; composite = mixed malignant cell; collisional = adjacent but not, or just a little, mixed, malignant cell; concomitant = two distinct tumoral masses.

However, it also must be noted that it was important to know whether a carcinoid instead of an adenocarcinoma spreads to the lymph nodes or, all the more, that no regional or distant metastasis occurred, because much changes in the postoperative adjuvant therapy and prognosis if metastases are present.

Literature on gastric carcinoid concomitant with adenocarcinoma is sparse and just a little informative from a surgical point of view, because it is focused mainly on the histopathological aspects of these tumors. However, when we had a careful look at all of the available reports,[9–23] our case was found to be consistent with six of them. When metastases are reported,[9,12,14–16,24] the carcinoid component is almost invariantly found spreading out, independent of the macroscopic and microscopic growth pattern (Table 1).

No clear clue exists that explains the malignant behavior of gastric carcinoids concomitant with adenocarcinomas. Some have noted that the bioactive agents secreted by carcinoids might function as growth factors, which in turn may promote phenotypic changes in susceptible cells and induce neoplastic transformation.[25,26] It is also possible that the higher the carcinoid propensity for the production of growth factors, the higher is the probability of its association with other noncarcinoid tumors. It is well known, in fact, that such an association is more frequent for carcinoids of jejunum and ileum, which show the highest propensity for the production of growth factors and also display the worst prognosis.[25,26] Whatever is the stimulus, it would be effective in the whole gastric mucosa, having the potential to cause multiple foci of malignant transformation, like in our patient, where a fundic adenocarcinoma in situ also was found.

In the end, our case report and literature review suggest that the association of carcinoid to adenocarcinoma points to a malignant nature of the carcinoid, apart from the underlying gastric disease and tumor characteristics. A major surgical procedure is obviously mandatory, but regional or distant metastasis must be expected from the carcinoid component, despite its initial classification as a possible low-risk tumor.

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Hepatic Atrophy-Hypertrophy Complex Due to *Echinococcus granulosus*

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Obstruction of a major hepatic vein, or major portal vein, or biliary tree branch causes atrophy of the related hepatic region, and frequently, hypertrophy in the remaining liver—the atrophy-hypertrophy complex (AHC). Whether hydatid cysts can cause AHC is controversial. The records of 370 patients who underwent surgery for hepatic hydatid disease between August 1993 and July 2002 were evaluated retrospectively. Excluding six patients with previous interventions on the liver, AHC had been recorded in the operative notes of 16 patients (4.4%); for all patients, a cyst located in the right hemiliver had caused atrophy of the right hemiliver and compensatory hypertrophy of the left hemiliver. The computed tomography images of seven patients were suitable for volumetric analysis. The median (range) right and left hemiliver volumes were 334 (0–686) ml and 1084 (663–1339) ml, respectively. The median (range) cyst volume was 392 (70–1363) ml. AHC due to *Echinococcus granulosus* was confirmed by objective volumetric analysis. The presence of AHC should alert the surgeon to two implications. First, pericystectomy may be hazardous due to association with major vascular and biliary structures. Second, in patients with AHC, the hepatoduodenal ligament rotates around its axis; this should be considered to avoid vascular injury if a common bile duct exploration is to be performed. (J GASTROINTEST SURG 2006;10:407–412)

KEY WORDS: Hydatid disease, *Echinococcus granulosus*, hepatic atrophy, hepatic hypertrophy, atrophy-hypertrophy complex

Obstruction of a major hepatic vein or major portal vein or biliary tree branch causes atrophy of the related hepatic region.[1–11] Because the liver has the capacity to regenerate, atrophy of a large hepatic parenchymal mass is usually associated with compensatory hypertrophy of the remaining liver—the atrophy-hypertrophy complex (AHC).[1–11] Adequate portal flow is a prerequisite for hypertrophy.[5]

In the few reports of hepatic atrophy associated with *Echinococcus granulosus*, frequencies ranging between 8.3% to 21% have been reported.[3,6] In contrast, neither atrophy nor hypertrophy was mentioned in large series of *E granulosus* patients.[12–19] The absence of uniform and practical criteria for atrophy and the AHC may account for these discrepancies.

This study was performed to investigate the AHC associated with *E granulosus* by objective volumetric measurements in computed tomography (CT) images.

PATIENTS AND METHODS

The records of 370 patients who underwent surgery for hepatic hydatid disease between August 1993 and July 2002 were evaluated retrospectively. Six patients who had undergone percutaneous (n = 2) or surgical intervention (n = 4) on the liver were excluded from analysis.

AHC had been recorded in the operative notes of 16 patients (4.4%) who had no history of intervention of the liver. The CT images of seven patients could be evaluated by image analysis (films were not available for six patients and were unsuitable for three patients). Five patients were women and two patients were men; mean age was 42 years

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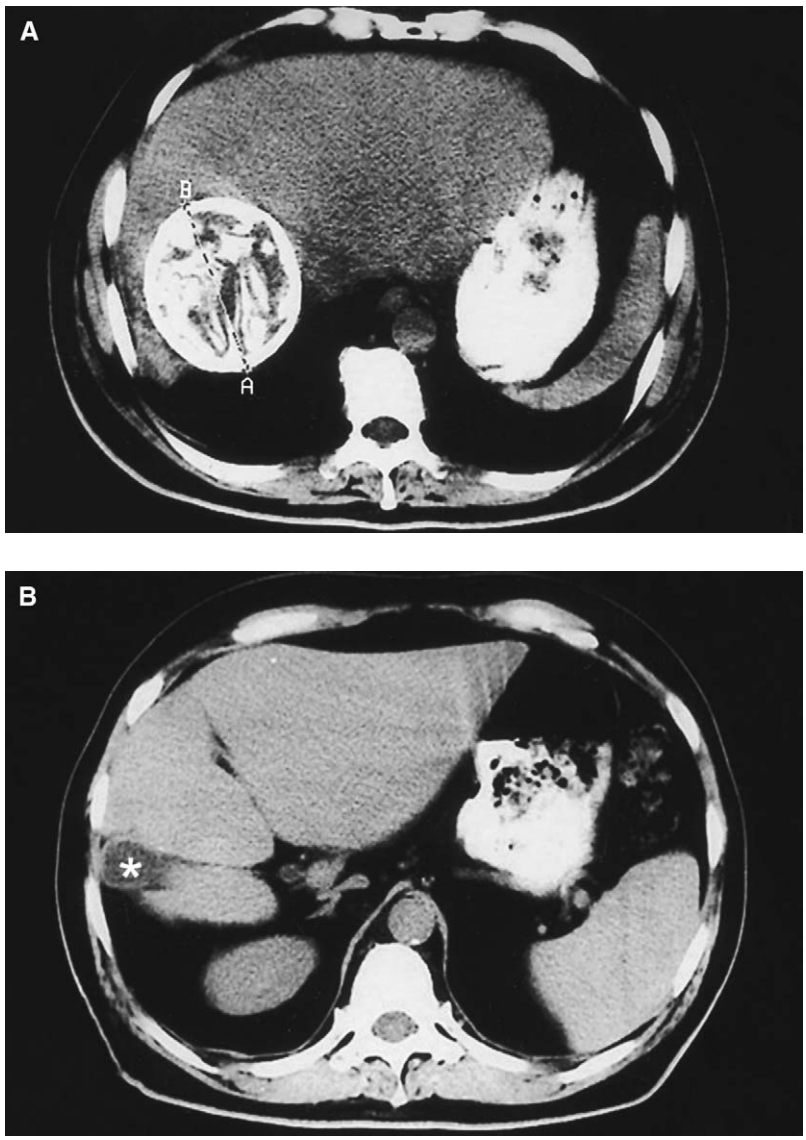

Fig. 1. (**A**) An 8.2 cm stage V cyst in segments 7 and 8. (**B**) Marked right hemiliver atrophy is evident in the lower sections of the same patient. The gallbladder (asterisk) is at the border of the liver.

(range, 26–61). For all patients, a cyst located in the right hemiliver[20] had caused atrophy of the right hemiliver and compensatory hypertrophy of the left hemiliver. The cysts were staged according to the criteria of Gharbi et al.[21]

The Scion image analysis program (Scion Image, version beta 4.0.2, Frederick, MD) available from the National Institutes of Health (NIH) Web site was used for volumetric analysis. The landmarks proposed by Mukai et al.[22] were adopted. The following lines and their projections were used in the upper and lower sections as appropriate: a line containing the main trunk of the middle hepatic vein and a line passing from the middle of the gallbladder bed and center of the inferior vena cava.

Volumetric studies on healthy liver donors revealed that the volume of the left hemiliver may approach that of the right hemiliver, but very rarely exceeds it.[23,24] Therefore, AHC was diagnosed when the left hemiliver volume was equal to or higher than that of the right hemiliver.

RESULTS

The results of volumetric analysis are presented in Table 1. In all seven patients with films suitable for evaluation, the operative observations were confirmed by objective volumetric analysis. The cyst was located in the right hemiliver. Right hemiliver atrophy and compensatory hypertrophy of the left

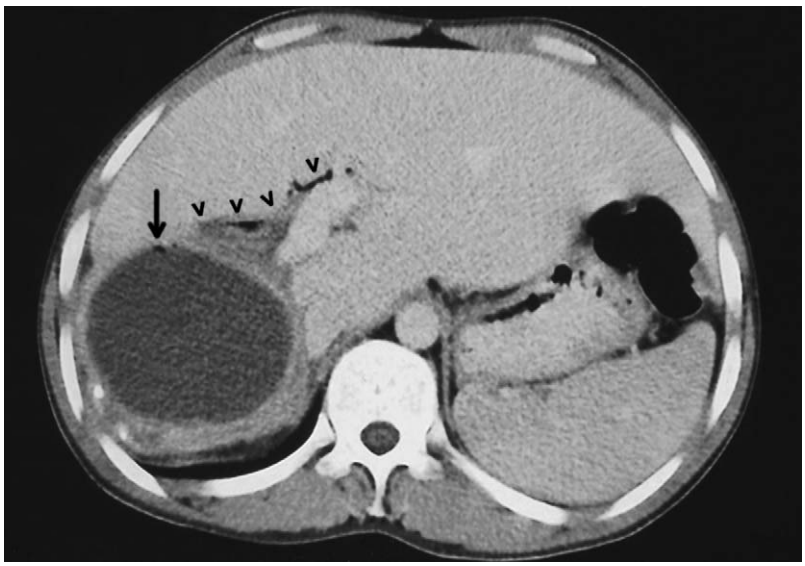

Fig. 2. A 7.5 × 8 cm cyst in the atrophic right hemiliver that ruptured into the biliary tree. An air bubble is anterior to the lesion (*arrow*), and the neighboring bile ducts (*arrowheads*) are dilated. The right branch of the portal vein is amputated by the cyst. Marked left hemiliver hypertrophy is evident.

hemiliver were observed. The converse situation was not recorded in any patient.

Interestingly, cyst volume showed a very wide range. A large cyst (e.g., 1363 ml) could cause AHC by simply replacing the hepatic parenchyma, whereas a small cyst (e.g., 70 ml) could effect the same result by vascular compression.

All patients were treated by drainage of the cavity. Unroofing was added in two patients and omentoplasty in one patient. One patient was lost to follow-up. Postoperative CT examinations were performed in six patients to detect possible recurrences at various intervals after the operation. No significant changes were detected in the volumes of the right and left hemilivers. This is probably because the liver had undergone "ultimate remodeling," that is, there was no stimulus for regrowth of the atrophied right hemiliver because the left hemiliver had already compensated for the loss of parenchymal mass.

DISCUSSION

To the best of our information, this is the first demonstration of AHC due to *E granulosus* by CT volumetric analysis. The previous reports on AHC due to hydatid disease are controversial.[3,6,7] Lobar atrophy due to *E granulosus* was first reported by Hueston in 1953.[1] Postmortem examination of four livers revealed segmental atrophy due to compression of the portal vein, hepatic artery, and bile duct by the cyst, and also hypertrophy in the remaining liver.[1] Ham,[3] in a study on patients with liver atrophy, listed hydatid disease along with hepatocellular carcinoma and cholangiocellular carcinoma as the most frequent causes of hepatic atrophy. Atrophy was noted in 13 of the 61 patients (21%) in that surgical series. On the other hand, this phenomenon has not been mentioned at all in larger series with 100 to 350 patients each.[12–19] In some studies,[1,8,25] compensatory hypertrophy was noted in all patients with atrophy, whereas Hann et al.[5] noted contralateral hypertrophy in only 30% of the cases. The discrepancies may be due to the limited number of patients in some studies, and more importantly, the lack of uniform and practical criteria for atrophy. A definition was not given at all by some authors,[1,6,7,8] whereas others used impractical definitions such as "50% volume reduction in the size of a recognized anatomical segment or lobe."[3–5,8] In the present study using criteria based on volumetric analysis, AHC was observed in 4.4% of the patients. That volumetric analysis could be performed in 7 of 16 cases is a shortcoming. However, it must be emphasized that operative observations were confirmed by objective measurements in analysis in all cases.

An important discrepancy with the literature[1,3,5,7,8] is the absence of left-sided atrophy in the present report. This probably stems from the original method of data acquisition. In the present study, the first step was to review the operative records that describe the size and the appearance of the liver. Because the size of a "normal" left hemiliver is extremely variable,[23,24] it may be difficult to

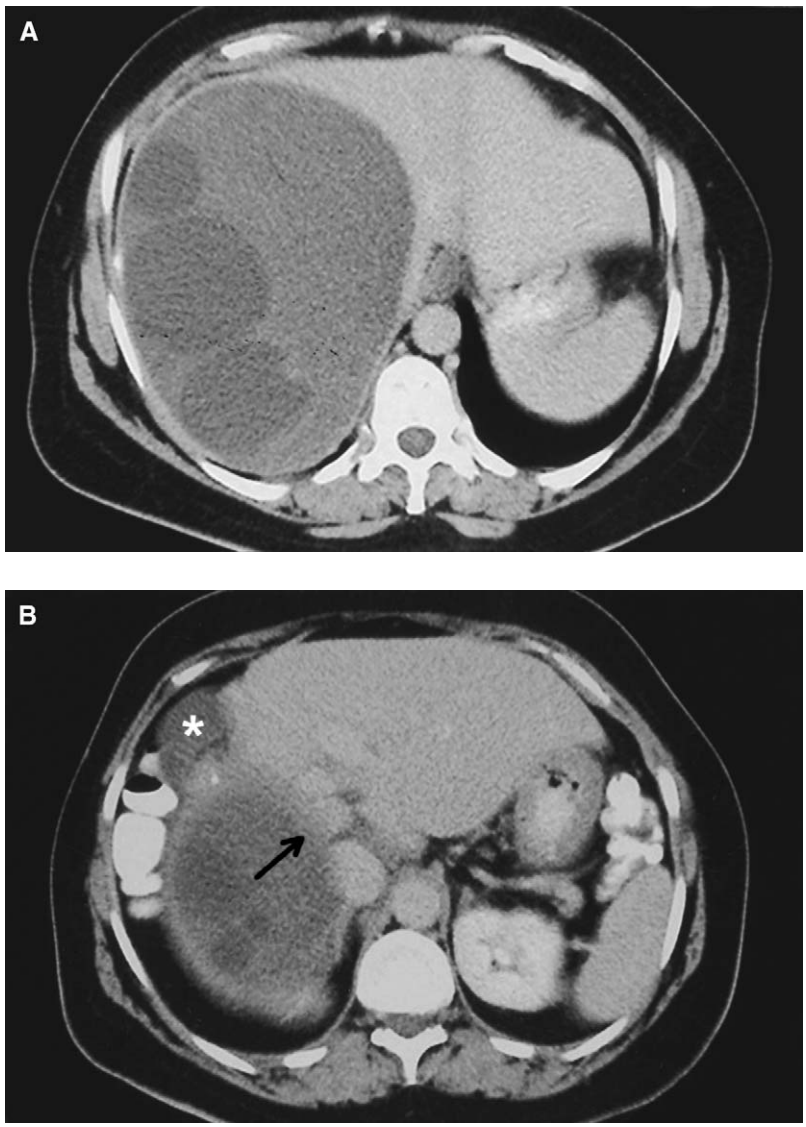

Fig. 3. (**A**) A stage 3 cyst filling the right hemiliver completely. (**B**) A more inferior section shows that the right branch of the portal vein (*arrow*) ends in the cyst. Displacement of the gallbladder (asterisk) and colonic interposition occurred due to right hemiliver atrophy. Marked hypertrophy of the left hemiliver is evident.

appreciate left hemiliver atrophy intraoperatively unless it is markedly shrunken and fibrotic. In contrast, in studies based primarily on CT images, important signs such as crowding of the intraparenchymal vasculature and bile ducts can be more readily detected.[3,5,8] In other words, some cases of left-sided atrophy may have been overlooked in the present study.

The detection of AHC has two surgical implications. First, AHC reflects that the cyst is tightly involved with one or more of the portal triad structures or a major hepatic vein. Pericystectomy is an effective radical operation in selected patients.[26] However, close association with major vascular and biliary structures is a relative contraindication for this operation.[26] As is the case in the present report, conservative surgical procedures (i.e., drainage combined with various cavity management methods) should be preferred to avoid injury in patients with AHC.

Table 1. The results of volumetric analysis

Median (range) right hemiliver vol*	334 (0–686) ml
Median (range) left hemiliver vol	1084 (663–1339) ml
Median (range) right hemiliver vol/left hemiliver vol ratio	47% (0%–54%)
Median (range) cyst vol	392 (70–1363) ml

*Excluding the cyst.

Second, AHC markedly alters the hepatic anatomy and causes rotation of the organ around the axis of the hepatoduodenal ligament.[4,27–30] Consequently, the hepatic artery, and even the portal vein, may move to a location anterior to the common bile duct. This anatomical pitfall should be taken into consideration to avoid vascular injury if common bile duct exploration is performed for intrabiliary rupture of the hydatid cyst.[31]

The diagnosis of atrophy and the associated hypertrophy depends heavily on consideration of this phenomenon.[3] The following points should be considered in the evaluation of imaging studies[3,5,8,28]: (a) volume reduction or expansion in a liver section or hemiliver—hepatic venous anatomy has been found most useful for this purpose,[8] (b) "crowding" of vasculobiliary structures in a part of the liver (the possibly atrophic area), (c) the presence of "splaying" and enlargement of vascular and biliary structures in a part of the liver (the hypertrophied area).

Preoperative diagnosis of atrophy and associated hypertrophy is important in choosing a safe surgical approach and avoiding vascular injury.

CONCLUSIONS

Hydatid disease should be considered as a cause of AHC in endemic regions. The diagnosis of atrophy depends heavily on consideration of this phenomenon.[3] This is important in choosing a safe surgical approach and avoiding vascular injury.

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Successful Embolization of Hepatocelluar Carcinoma With Yttrium-90 Glass Microspheres Prior to Liver Transplantation

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We report a case of a patient with end-stage liver disease secondary to hepatitis C, complicated by a large hepatocellular carcinoma. Because of the size of the tumor exceeded the Milan criteria, he was not a candidate for liver transplantation. However, after two treatments with yttrium-90 glass microsphere infusions, the tumor became smaller and the patient's α-fetoprotein level dropped to normal range. He was listed for transplantation and subsequently received a deceased donor liver transplant. Two years after his transplantation, he remains tumor free and has normal α-fetoprotein levels. This is the first reported case in the literature of using yttrium-90 microspheres as a bridge to liver transplantation in a patient with a large hepatocellular carcinoma. This therapy should be considered in patients with cirrhosis and large hepatocellular carcinomas exceeding current size criterion, who would otherwise be good candidates for transplantation. (J GASTROINTEST SURG 2006;10:413–416)

KEY WORDS: Transplantation, liver, carcinoma, hepatocellular, yttrium, brachytherapy

CASE REPORT

A 50-year-old white man developed end-stage liver disease as a consequence of hepatitis C (HCV). He was diagnosed with HCV in June 2000. In review of systems, the patient recalled an episode of spontaneously resolving acute hepatitis and jaundice in 1974 while using recreational intravenous drugs. Soon after diagnosis with HCV, the patient underwent treatment with pegylated interferon and ribavirin for 7 months in 2001. However, on follow-up examination, he was found to have a mass on liver ultrasound, which was confirmed by magnetic resonance imaging (MRI). Needle biopsy was performed under computed tomography guidance demonstrating poorly differentiated hepatocellular carcinoma (HCC).

When the patient presented to our hepatobiliary clinic, he had mildly abnormal liver function tests with an alanine amino transferase (ALT) of 75 IU/L, aspartate amino transferase (AST) of 141 IU/L, total bilirubin of 1.2 mg/dl, and alkaline phosphatase of 340 IU/L. He had an α-fetoprotein (AFP) level of 1272 ng/ml. Review of MRI from the outside institution confirmed a 7-cm mass with central necrosis located within the posterior aspect of the right lobe as well as a portion of the caudate lobe. In addition, the mass was suspected to invade the right portal vein and intrahepatic portal vein branches. There was also significant compression of the vena cava to almost complete occlusion.

Management options for HCC, including surgical resection, ablative therapies, and orthotopic liver transplantation (OLT), were discussed with the patient in detail. Given the size of the mass, its anatomic location, and vascular invasion, resection or ablative therapy such as radiofrequency ablation (RFA) was not a good option. Although OLT was an option, due to the poorly differentiated nature and size of the carcinoma, as well as the concern about vascular invasion, the patient failed to meet the current criteria for OLT. Thus, the patient agreed to undergo selective tumor embolization.

The patient underwent selective tumor arterial embolization and responded initially with a decrial

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in his AFP level from 1272 to 123.5 ng/ml 1 month after angioembolization. However, it rose to 144.4 ng/ml 3 months later. MRI 3 months after embolization revealed partial necrosis of the tumor, but a fair amount of tumor bulk remained. The tumor, measuring 7.5 cm at its largest diameter 3 months earlier, was now 6 cm × 6 cm. Because the patient's arterial anatomy was not favorable for further selective arterial embolizations and given his current tumor burden, he was enrolled in investigational embolizations using yttrium-90 glass microspheres (TheraSphere, MDS Nordion, Ottawa, Canada) after informed consent was obtained. After two TheraSphere treatments, for a total of 600 Gy administered to the tumor, his AFP dropped to 10.1 ng/ml. Follow-up MRI revealed the mass had not changed in size compared to previous study, but there was more necrosis and vascular invasion was not definitive. Because of the normal AFP level and stable mass size on MRI, he was reevaluated for OLT by our multidisciplinary committee, accepted for transplantation, and placed on the waiting list.

The patient underwent an OLT in November 2003, 3 months after the second TheraSphere treatment. After the abdominal cavity was entered, native hepatectomy was performed in the usual fashion and a sample was sent for pathology. There was no evidence of any lymph node involvement. Pathology revealed a 4.8-cm moderately differentiated, solitary tumor without vascular invasion (Fig. 1). Upon review of the permanent sections with the pathologist, there were several slides that demonstrated the glass microspheres in the vicinity of the necrotic tumor (Figs. 1–3).

Following OLT, the patient underwent systemic adjuvant chemotherapy because of the size of the tumor and its initial presentation (7.5 cm at its largest dimension, with vascular invasion). He tolerated the chemotherapy well. Follow-up MRI 1 year after OLT did not reveal any suspicious masses, and all follow-up AFP measurements have been less than 5 ng/ml, with the most recent being 4.2 ng/ml in March 2005.

DISCUSSION

HCC is a devastating primary cancer of the liver, with a 5-year survival rate of less than 5% if untreated.[1] The three highest risk factors associated with HCC in the United States are infection with HCV, infection with hepatitis B virus, and alcoholic cirrhosis. According to the National Institutes of Health annual consensus report, the annual probability of liver cancer among patients with HBV-related chronic hepatitis is 0.5% and that among patients with cirrhosis is 2.4 %. The incidence of HCC in the United States has increased by nearly 75% over the past decade.[2,3] In addition, the mortality from primary liver cancer has increased by 41%.[3]

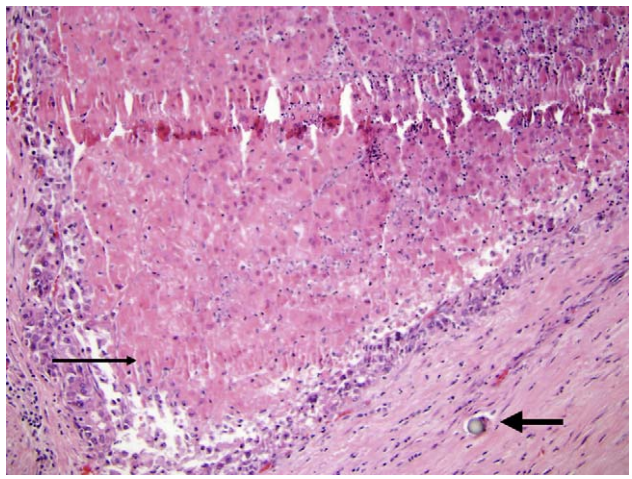

Fig. 1. Hematoxylin and eosin staining of the explanted liver, specifically sections of the hepatocellular carcinoma, showing the necrotic nature of the tumor. The *wide arrow* points to the necrotic tumor, and the *narrow arrow* demonstrates the microspheres in the vicinity surrounding the tumor.

The treatment of HCC depends on the degree of liver dysfunction, size and anatomic location, and number of masses. Mazzaferro et al[4] demonstrated that OLT for solitary liver nodules not exceeding 5 cm in maximum diameter or two or three tumors not exceeding 3 cm in diameter provides patients with good disease-free survival. With multiple studies producing similar results of disease-free survival using the aforementioned Milan criteria, OLT is

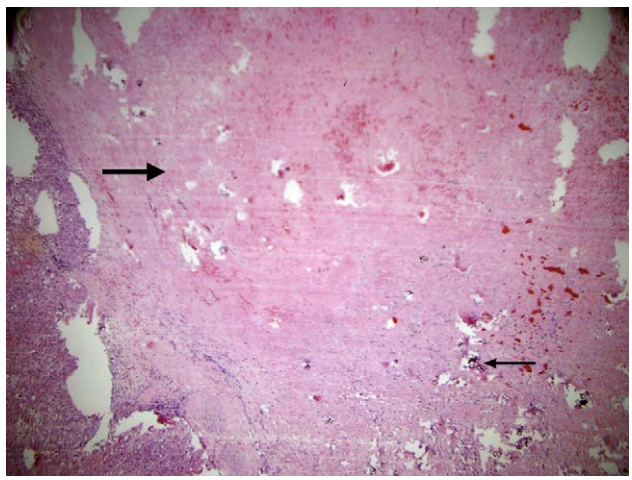

Fig. 2. A closer section stained with hematoxylin and eosin. Broad arrow shows a microsphere within the fibrotic parenchyma, while the thin arrow indicates the hepatocellular carcinoma.

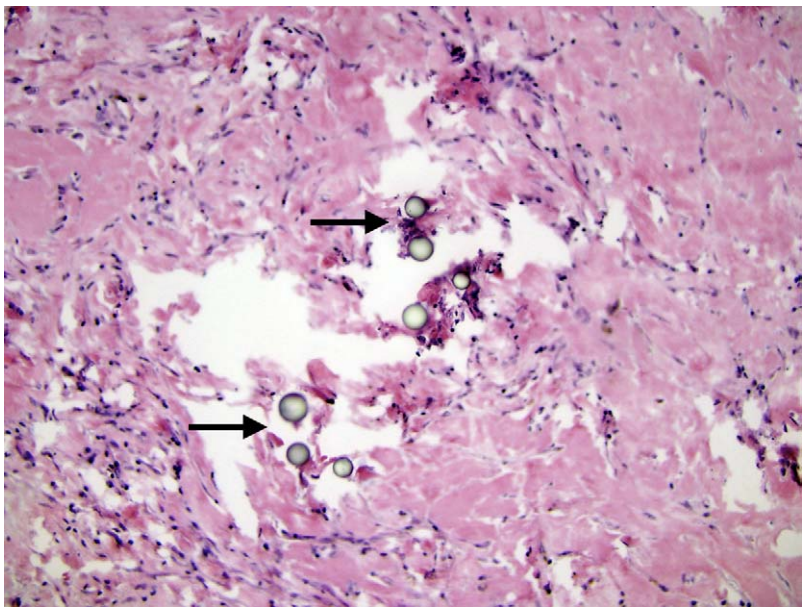

Fig. 3. A magnified view of the microspheres within the liver parenchyma. None of the microspheres have degraded or have been sheared despite the fact that they were infused over three months prior to explant.

now considered a treatment option for patients with cirrhosis and HCC.

However, there are a large number of patients who do not meet the Milan criteria and therefore are not presently candidates for OLT. Approximately 10–25% of these patients with surgically unresectable HCC will survive to 1 year postdiagnosis.[5,6] These patients have the option to undergo alternative modalities or bridge treatments such as tumor RFA, transarterial angioembolization, or liver resection in attempts to delay or halt tumor progression.[7–9] Because of the limited successes with these therapies, investigators have studied other novel methods of treating unresectable HCC.

Infusion of ^{90}Y glass microspheres (^{90}Y-μS; TheraSphere) is an FDA-approved brachytherapy for unresectable HCC that has shown survival benefit in patients with HCC.[10] The particles are 15- to 35-μm beta-irradiating glass microspheres that can be delivered directly to the tumors angiographically.[11] ^{90}Y has a physical half-life of 64.1 hours and decays to zirconium-90, which is biologically stable. Due to its size and glass nature, these microspheres do not traverse tumor vasculature, do not degrade, and, when embolized within a tumor, exert local radiation therapy and extensive cytotoxic effect against large tumors with little injury to normal tissue.[12] Because they are delivered via intra-arterial infusion and because HCC is a highly vascular tumor, the microspheres may be infused directly at the tumor, a segmental portion of the liver or whole liver depending on the areas affected, generally without significant damage to normal liver parenchyma.[13]

Currently approved in the United States for use in patients with unresectable HCC, the clinical uses for ^{90}Y microspheres are promising. ^{90}Y microspheres have a low toxicity profile and have been well tolerated by patients.[14–16] From 40% to 70% of patients had stabilization or reduction of unresectable HCC within 3 months of therapy, ultimately extending median survival times.[17] In some instances, complete tumor destruction has been confirmed histologically.[12]

However, this therapy is not without risks. Investigators have attempted to risk stratify patients who would most benefit from ^{90}Y glass microsphere therapy. Unfortunately, there have not been many patients treated with this therapy, so drawing conclusions from the data is difficult.[17] Aside from patient mortality after treatment, patients may also experience major complications that include hepatitis, hepatorenal syndrome, gastric ulcer, and pneumonitis.[17] The same investigators also attempted to define parameters associated with liver toxicities.[13] They noted pretreatment bilirubin and liver radiation dose were associated with liver toxicity, but most toxicities resolved. Those that did not were attributed to tumor progression or advanced cirrhosis. They concluded that a maximum dose for single administration was 150 Gy and 268 Gy for total dose administration. Other authors had similar observations.[11,18]

We report the adjuvant therapeutic benefit of ^{90}Y glass microspheres while awaiting OLT, which has not been described in the literature to date. While OLT is known to extend median survival time as far as 59 months,[19] it is limited by donor availability and increasing numbers of ineligible candidates who do not meet the Milan criteria. In the interim waiting period, patients often suffer progression of disease such that they can never benefit from OLT. In this instance, ^{90}Y glass microsphere infusion reduced tumor burden significantly to allow our patient to become a suitable candidate for OLT. In our experience, yttrium therapy arrested tumor progression and achieved significant control of HCC. It also served as a successful mode of therapy to make a select patient who exceeded the current size criterion an eligible candidate for OLT.

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Budd-Chiari Syndrome and Acute Portal Vein Thrombosis: Management by a Transjugular Intrahepatic Portosystemic Shunt (TIPS) and Portal Vein Interventions via a TIPS

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Acute portal vein thrombosis (PVT) is a devastating complication of Budd-Chiari syndrome (BCS). Conservative approach, anticoagulation, systemic or transarterial thrombolysis, and urgent liver transplantation were applied in this scenario but with poor results. We present and discuss an approach to treat BCS complicated by acute PVT. Two young female patients presented with acute liver failure, rapidly progressive tense ascites, renal- and respiratory failure. The diagnosis of chronic BCS complicated by acute PVT was confirmed with ultrasound Doppler. Initial treatment was supportive. Right portal vein localization was by transarterial portogram or by computed tomography–guided microcoil placement. Transjugular intrahepatic portosystemic shunt (TIPS) was performed and included Wallstents and a Jograft in one case and Viatorr stentgraft that was extended later with a Hemobahn stentgraft in another. Mechanical clot removal from the portal system was performed in the primary procedure and in a revision procedure in the following few days. Stents were placed precisely with no extension into the inferior vena cava or deeply into the main portal vein. Patients were fully anticoagulated and patency was assessed by ultrasound Doppler. The procedures were performed on days 5 and 10 following admission. In both cases, successful thrombectomies were reveised and maintained. Partial occlusion of the TIPS and reaccumulation of ascites were reversed with repeated procedure. Both patients were discharged without ascites and normal liver function. In conclusion, urgent TIPS and portal vein thrombectomy via TIPS are emerging therapeutic options that offer a safe and effective treatment to patients with BCS complicated by acute portal vein thrombosis. (J GASTROINTEST SURG 2006;10:417–421)

KEY WORDS: Budd-Chiari syndrome, portal vein thrombosis, hepatic failure, transjugular intrahepatic porto-systemic shunt, thrombectomy

Budd-Chiari syndrome (BCS) is a rare disease with a wide range of different clinical courses, depending upon the acuity and the extent of venous occlusion. More often than not, the clinical course of BCS in Western countries is acute, with rapid progression of liver disease and its sequelae over time periods ranging from weeks to months. Portal vein thrombosis (PVT) is the most common cause of presinusoidal portal hypertension. With the exception of systemic anticoagulation, the current treatment of a patient presenting with acute PVT is rather disappointing. A transjugular intrahepatic portosystemic shunt (TIPS) is the most commonly used treatment for the complications of portal hypertension caused by PVT,[1] but there are insufficient data on its ability to control acute cases of PVT. Both acute and chronic PVT may be found concomitantly with BCS in up to 25% of the patients.[2] This subgroup of patients (especially the majority, who have *chronic* PVT) has a much worse prognosis because neither liver transplantation nor shunt surgery are easily feasible any longer. The clinical

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appearance and the management of the two entities in a single patient have been published only in isolated case reports[3,4] so far. We describe two patients, both presenting with chronic/subacute BCS complicated by acute thrombosis of the portal venous system, and describe their management by the construction of a TIPS and mechanical evacuation of the portal thrombus via this route.

CASE REPORTS

Case 1

A 42-year-old woman was admitted to our department complaining of vague abdominal pain, abdominal distention, and worsening jaundice over the 2 weeks prior to her admission. She had been previously healthy and had not taken any medications. Physical examination revealed a fully alert and conscious patient with normal vital signs, icteric sclerae, distended abdomen with tense ascites, and mild pedal edema with neither respiratory distress nor other signs of chronic liver disease. Laboratory findings on admission were as follows: a normal complete blood count, activated partial thromboplastin time (APTT) of 32 seconds, international normalized ratio (INR) of 2.29, serum glucose of 110 mg/dl, sodium of 132 mEq/L, blood urea nitrogen of 44 mg/dl, and creatinine of 1.63 mg/dl. Levels of serum liver enzyme throughout the course of the disease are presented in Table 1. Serology for hepatitis A, B, and C viruses was negative. Serum levels of ceruloplasmin, ferritin, and transferrin as well as thyroid function tests were within the normal range. Doppler ultrasound study of the abdomen revealed chronic thrombosis of all the hepatic veins and acute thrombosis of the main portal vein extending into the right portal vein with slow hepatofugal flow in the left portal vein. Distally, a thrombus was seen extending into the splenic and superior mesenteric veins. Intravenous heparinization was promptly initiated, but a marked deterioration of the patient's status was observed during the next 48 hours. Disorientation, flapping tremor, oliguria, growing ascites, and respiratory failure ensued. The patient was intubated, and medical treatment for hepatic failure was initiated. An indwelling arterial catheter was placed in the superior mesenteric artery, and selective thrombolysis with urokinase was begun. During the following 48 hours, the patient lost consciousness and became anuric. She was then taken to the interventional radiology suite for a TIPS procedure. Before the TIPS insertion, the thrombosed right portal vein had been marked by a microcoil that was placed under computerized tomographic guidance. Left internal jugular access enabled easier entrance to the stump of the thrombosed right hepatic vein. Using the microcoil as a target, the portal system was accessed via the right portal vein. Venography revealed diffuse thrombosis of the splenic vein and the inferior mesenteric vein, occlusion of the upper superior mesenteric vein at the confluence and extensive non-occlusive thrombosis of the extrahepatic and intrahepatic portal tree. Pre-TIPS pressures were not measured. Mechanical declotting was carried out using the OASIS system (Boston Scientific, Natick, MA) with partial resolution of the thrombus (Fig. 1*A*). This was followed by the construction of a TIPS with a 10 × 80-mm Viatorr stent graft that was extended to the inferior vena cava with a 9 × 50 mm Hemobahn stent graft (both from Gore Medical, Flagstaff, AZ) (Fig. 1*B*). Dilatation of the shunt with an 8-mm balloon yielded a portosystemic gradient of 5 mm Hg.

Table 1. Liver function throughout the clinical course of patients 1 and 2

Patient	Time	AST (U/L)	ALT (U/L)	GGT (U/L)	Alk-P (U/L)	Total bilirubin (mg/dl)	Ammonia (μg/dl)
1	Admission	1468	1615	81	54	2.9	138
	Systemic heparinization	1392	2100	77	54	4.1	191
	Urokinase via SMA	880	1000	67	91	3.0	130
	TIPS and thromectomy	85	55	140	80	1.7	79
	Before revision of TIPS	192	322	108	110	2.5	112
	After revision of TIPS	68	49	112	90	1.3	67
2	Admission	880	910	130	110	2.7	99
	Systemic heparinization	990	844	130	122	4.2	131
	TIPS and thrombectomy	310	212	122	100	1.7	90
	Before revision of TIPS	166	196	100	269	2.8	100
	After revision of TIPS	84	69	100	133	1.7	87

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-glutamyl transferase; Alk-P = alkaline phosphatase; SMA = superior mesenteric artery; TIPS = transhepatic portosystemic shunt.

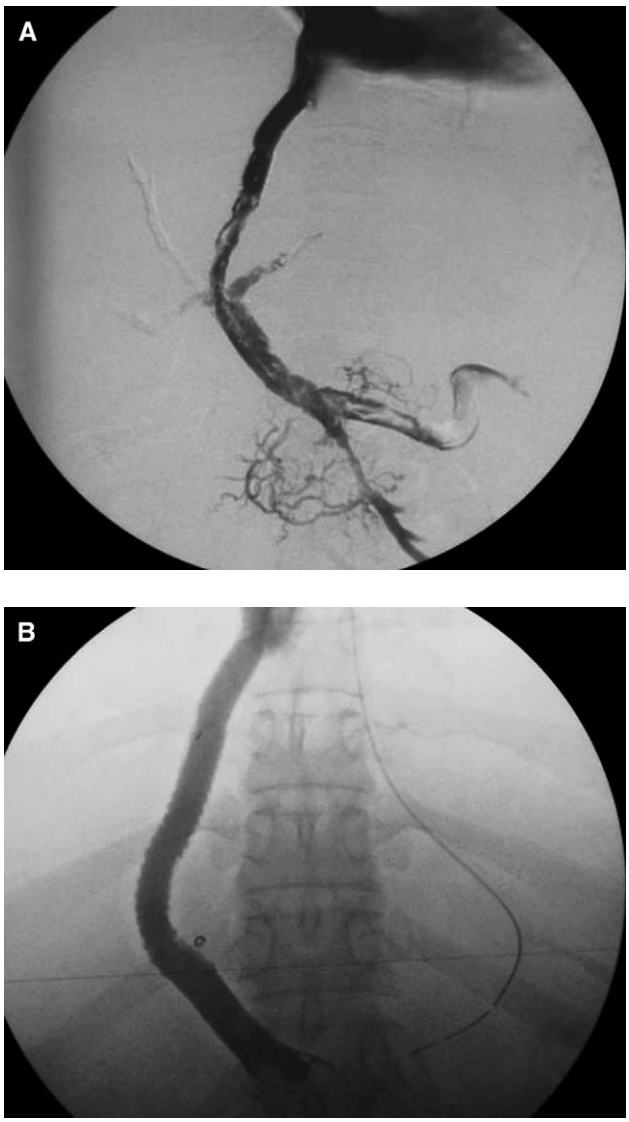

Fig. 1. Creation of TIPS before (**A**) and after (**B**) portal declotting in patient 1.

After the procedure, the patient was anticoagulated with intravenous heparin. She regained consciousness and was safely weaned from ventilatory support. Urinary output recovered to normal values, and there was no need for repeated tapping of the ascites.

Anticoagulation was switched to low-molecular-weight heparin 1 week after the procedure, but growing ascites and deterioration in liver enzymes were detected 2 days later. Although a Doppler ultrasound showed a notably improved flow in the portal vein and its tributaries with some residual thrombus, the flow at mid-TIPS was measured as being only 10 cm/sec. Because of this finding, consistent with a failing TIPS, she was referred to TIPS revision, which revealed a portosystemic gradient of 18 mm Hg with residual thrombi in the portal tributaries. After further declotting of the splenic and superior mesenteric veins, the shunt was further dilated to 10 mm with a final portosystemic gradient of 8 mm Hg. Evaluation of hypercoagulability was negative for activated protein C resistance, proteins C and S and antithrombin III deficiencies, factor V Leiden, and *MTHFR* gene mutations. No evidence of a myeloproliferative disorder was disclosed. The patient was then discharged in good medical condition and treated with warfarin 5 mg daily. Three months after discharge, liver function tests are normal, the ascites is mild, and there is adequate flow through the TIPS.

Case 2

A 49-year-old woman was admitted complaining of gradually worsening abdominal distention for 2 months prior to her admission. The patient denied fever, jaundice, or other gastrointestinal symptoms. Prior to her admission, she had been healthy and had not been treated medically. Past medical history was negative for evidence of hypercoagulability as well. On admission, all vital signs were normal and she was fully alert and conscious, with no encephalopathy or other signs of chronic liver disease other than moderate ascites and icteric sclerae. Laboratory findings were as follows: a normal complete blood count, APTT of 35 seconds, INR of 1.9, serum glucose of 141 mg/dl, Na of 128 mEq/L, blood urea nitrogen of 59 mg/dl, and creatinine of 1.8 mg/dl. Levels of serum liver enzymes throughout the course of the disease are presented in Table 1.

Abdominal sonography demonstrated ascites and an enlarged liver with a hypertrophied caudate lobe. Left and middle hepatic veins were not demonstrated, and flow was absent in the right hepatic vein. The flow in the right portal vein was reversed. Given these findings, which were consistent with BCS, she was started on intravenous heparinization. However, under maximal diuretic therapy there was a further deterioration of the ascites, and a repeat sonogram revealed a nonocclusive thrombus in the main portal vein extending and occluding the right portal vein. Liver function tests worsened. A transarterial portogram delineated the thrombosed portal system, and a tract was created between the stump of the right hepatic vein (which was accessed via the left internal jugular vein) and the thrombosed right portal vein. A TIPS was created using three 12 $\times$ 60 mm Wallstents (Boston Scientific) that were aligned from the main portal vein all the way to the inferior vena cava. Dilatation with a 12-mm balloon yielded a portosystemic gradient of 19 mm Hg. Angiography was discontinued in order to limit the amount of

contrast medium, and 5 days later, the patient was referred for a revision. A mid-TIPS stenosis was dilated with a 6-12 mm (diameter range)/38 Jograft (Jomed, Rangendingen, Germany) that was delivered on a 10-mm balloon, resulting in a portosystemic gradient of 13 mm Hg. The ascites almost disappeared after 2 weeks, and liver enzymes normalized. The patient continued treatment with enoxaparin 40 mg twice daily. A Doppler study performed 9 months after the TIPS procedure showed normal velocities within the stent with no evidence of ascites.

DISCUSSION

Both of the patients described above developed acute thrombosis of the portal vein and its tributaries following subacute/chronic BCS and probably secondary to an undefined hypercoagulable disorder. With the rapid deterioration of their liver function, it became apparent that either prompt restoration of the portal flow or decompression of the portal system was needed.

Acute PVT can often go undetected because of nonspecific symptoms. If it is left untreated and the symptoms resolve, collateral vessels become established, ending up with cavernous transformation of the portal vein and the development of portal hypertension. Therefore, all appropriate measures should be taken in order to prevent such a scenario.[1] Previous studies demonstrated resolution of thrombosis by using several techniques, among them intravenous heparinization followed by long-term oral anticoagulation,[5,6] selective venography with infusion of thrombolytic agents,[1] and angiographic/surgical thrombectomy. Thrombolytic therapy can be administered either systemically or, as has been the case in recent years, selectively via either the superior mesenteric artery (SMA) or the portal vein (transhepatically or through construction of a TIPS).[7] Only the first option has proved to be effective in reducing the risk of thrombotic events after acute PVT by recanalization of the vessel, thus preventing portal hypertension and its complications.[5] There have been reports of using thrombolytic agents through transjugular or percutaneous transhepatic approaches in patients with acute PVT,[8] but as with surgical thrombectomy, no confirmed data regarding the yield of these procedures have yet been published. The risk of penetrating a failing liver must also be taken into account. The role of a TIPS in patients with PVT remains inconclusive because of procedure-related complications, technical difficulties due to a thrombus, and recurrent shunt occlusion. In a patient presenting with acute variceal bleeding due to PVT, however, the option of systemic anticoagulation is less appealing, and so a TIPS procedure is preferred in many such cases.

In two other reported cases of BCS associated with PVT that were managed percutaneously by means of a TIPS placement and thrombolysis, the thrombosis of the portal vein was acute but incomplete (i.e., there was residual portal flow).[9,10] This was essentially the situation in both of our presented cases. To date, Pfammatter and colleagues[7] published the only report describing a similar management of PVT complicating BCS that involved using interventional radiology methods. They restored portal and hepatic venous flow by combining transhepatic recanalization (using a self-expanding stent) of the mesenteric and portal veins with a TIPS procedure. Indeed, the rapid deterioration of our two patients was a result of the development of portal vein thrombosis on top of their chronic BCS. Intravenous heparinization was either not feasible or gave unsatisfactory results in both of them. Because selective thrombolytic therapy had also failed, the main goal in our therapeutic strategy was to remove the newly formed thrombus from the portal system in conjunction with restoration of outflow. This was achieved by the insertion of a TIPS and thrombectomy of the portal tributaries and branches via this route. The role of the TIPS procedure itself was not only to decompress the portal system but also to create adequate hepatic outflow tract, so that thrombosis of the portal system would not recur due to low blood flow and stasis. Declotting the portal vein served to provide inflow to the shunt and improve shunt patency. In the presence of acute portal vein thrombosis, where antithrombotic and thrombolytic therapies are exhausted, thrombectomy via a TIPS procedure seems promising for reversing the rapid deterioration towards fulminant hepatic failure and obviating the need for urgent transplantation, which may not always be practical.

To conclude, in the setting of complicated BCS unresponsive to medical therapy, we suggest early intervention by means of a TIPS procedure because of the advantages described above. Because the exact timing of such a complicated procedure remains to be clarified, a multidisciplinary approach with close cooperation of all the professionals involved in the care of these patients is mandatory.

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Laparoscopic Hepatic Resection Using Saline-Enhanced Electrocautery Permits Short Hospital Stays

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Laparoscopic hepatic resection has been reported to yield lower morbidity and shorter hospital stays than open resection. However, few studies have evaluated patient and technical factors associated with short hospital stays. We conducted a retrospective review of patients undergoing laparoscopic hepatic resection at our institution from May 2002 to February 2004. Patient and operative factors were analyzed with respect to time to discharge. Seventeen patients underwent 10 wedge resections and seven segmentectomies or bisegmentectomies. There were no mortalities, conversions to open procedure, clinically evident bile leaks, or transfusion requirements. Eleven patients were discharged within 24 hours. When compared with those discharged later than 24 hours, there were fewer patients with advanced ASA classification (0 versus 3 in ASA class 3, $p < 0.05$). With appropriate patient selection, laparoscopic hepatic resections may be safely performed, result in short hospital stays, and are facilitated by technologies such as saline-enhanced electrocautery and endoscopic ultrasound. Information reflected in advanced ASA class may predict patients unlikely to be discharged within 24 hours. (J GASTROINTEST SURG 2006;10:422–427)

KEY WORDS: Hepatectomy, laparoscopy, electrocautery

Laparoscopic hepatic resection has been reported to yield equivalent or lower morbidity and shorter hospital stays than equivalent open resections,[1–4] and the role of laparoscopy in procedures of increasing scope, including major hepatectomies, continues to be explored.[5] In nearly all reports of series, careful selection of patients is emphasized, and authors reinforce the point of not changing the surgical indications simply because a minimally invasive technique is possible.

In the development of this approach, legitimate concerns remain over the ability to control hemorrhage, prevent bile leaks, obtain oncologically appropriate margins, and avoid gas embolism.[6] The threat of hemorrhage encompasses not only intraoperative bleeding obscuring the operative field but also severe postoperative bleeding. Fortunately, application of currently available equipment and the evolution of laparoscopic techniques in hepatic surgery are addressing these issues. In addition, long-term outcomes following laparoscopic hepatectomies for malignancy remain to be explored in well-designed trials, although initial experience with malignant tumors has been positive.[7]

As the technique matures, early discharge following laparoscopic hepatic surgery is reported within some series,[2,8] but few studies have directly addressed the factors influencing the length of stay following laparoscopic hepatic resections. In this report, we review our experience with laparoscopic hepatic resections using saline-enhanced electrocautery and detail our approach to overcoming persisting safety and oncologic concerns. We also evaluated factors that might influence the likelihood of achieving shorter hospital stays.

METHODS

We performed a retrospective review of 17 consecutive patients undergoing laparoscopic hepatic resections at our institution between May 2002 and

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February 2004. Their mean ± SD age was 55 ± 16 years (range, 24–74 years). One surgeon was primarily involved in all cases (K.T.W.) and evaluated all patients for candidacy for laparoscopic resection. In general, patients were offered a laparoscopic approach if they had no medical contraindications to laparoscopy and the tumor appeared laparoscopically accessible. Patient and operative factors expected to potentially impact postoperative recovery were analyzed with respect to time to discharge. Permission to perform this study was obtained from the institutional review board.

We considered discharge within 24 hours of the operation to be a short stay and divided patients into short-stay and long-stay groups based on this categorization. These groups were then compared for statistically significant differences with respect to defined characteristics. Statistical comparisons were performed with Fisher's exact test and the Mann-Whitney test using SPSS (SPSS Inc., Chicago, IL).

Table 1. Characteristics of 17 patients undergoing resection of hepatic masses

Patient characteristics	No. of patients
Female gender	7
ASA Class	
1	3
2	11
3	3
Couinaud segment involvement	
II	2
III	4
IV	4
V	4
VI	3
VII	2
VIII	1
Operative indication	
Suspicion of primary malignancy	13
Benign mass with associated symptoms	4
Rule out metastasis	2

ASA = American Society of Anesthesiologists.

Operative Technique

Pneumoperitoneum was achieved using the Veress needle technique. A 12-mm camera port was placed 12 cm from the costal margin and biased toward the lobe containing the mass to be resected. Most cases were performed with the patient in the supine position, although some cases required lateral decubitus positioning. A camera with a deflecting tip (Olympus, Melville, NY) was used in nearly all cases. Two or three additional 5- and 12-mm ports were placed as required.

Laparoscopic ultrasound was performed in all cases to identify the target lesion, survey the liver for additional lesions, and locate portal pedicles. Parenchymal dissection was performed primarily with the use of saline-enhanced electrocautery (TissueLink Medical, Inc., Dover, NH) and less frequently with an ultrasonic dissector. Larger vascular structures were isolated and then divided using an endoscopic six-row GIA stapler (Ethicon Endo-Surgery, Inc., Cincinnati, OH). Specimens were placed in a retrieval bag and removed through an extended port site or through a Pfannensteil incision if deemed too large for port site extension. Hypovolemic anesthetic techniques and hepatic inflow occlusion were not used.

RESULTS

Seventeen patients underwent laparoscopic hepatic resections during the study period (Table 1). Fourteen patients presented with additional medical comorbidities and were classified as American Society of Anesthesiologists (ASA) class 2 or 3. Lesions were removed for the following indications: benign symptomatic mass, radiographic findings worrisome for malignancy, and lesions associated with the gallbladder fossa in a patient undergoing cholecystectomy for symptomatic biliary disease. Pathologic diagnoses of the resected lesions by order of frequency were hemangioma (n = 6), including three sclerosed hemangiomas, focal nodular hyperplasia (n = 4), cysts (n = 2), adenoma (n = 1), neuroendocrine metastasis (n = 1), gallbladder adenomyosis (n = 1), focal fatty infiltration (n = 1), and hepatocellular carcinoma (n = 1). The two cystic lesions were proteinaceous cysts demonstrating highly irregular radiographic characteristics, with one in a patient undergoing evaluation for liver transplant. The sclerosed hemangiomas were an interesting subgroup of lesions, all with suspicious radiographic findings at time of presentation. The mean ± SD size of the lesions was 3.5 ± 2.0 cm (range, 1.6–10 cm).

Operative details are outlined in Table 2. Resections were performed in primarily the anterior and medial segments of the liver, although some lesions were located in traditionally difficult to access segments (segments VI–VIII). Seven patients required at least a segmentectomy, and seven patients underwent coincident laparoscopic procedures, including five who underwent a cholecystectomy, one who underwent an abdominoperineal resection, and one who underwent distal pancreatectomy and splenectomy.

Table 2. Postoperative outcomes in 17 patients

Outcome	Mean ± SD (range)
Total postoperative inpatient narcotic requirement, mg intravenous morphine equivalents	13 ± 15 (0–52)
Mean time to discharge (hr)	29 ± 35 (7–151)
Excluding other major procedures (n = 15 patients)	18 ± 10 (7–40)
Postoperative follow-up (days)	52 ± 77 (6–253)

In these latter two patients, the hepatic resections were performed to remove lesions suspicious for metastasis. All operations were completed without conversion to an open procedure. Hand access was used in the patient undergoing distal pancreatectomy and splenectomy with resection of neuroendocrine hepatic metastases. The operative time for all 17 cases was 206 ± 120 minutes (range, 61–453 minutes). Postoperatively, only one patient had a complication, a port-site hernia that was later primarily repaired without incident. Estimated blood loss for the entire group was 165 ± 177 ml (range, 10–500 ml). No bile leaks were identified, and no patients required intraoperative or postoperative transfusions.

The length of stay for all 17 patients was 29 ± 35 hours (range, 7–151 hours). When evaluating variables associated with short stays following the procedures, the two patients who underwent major associated procedures (one abdominoperineal resection and one distal pancreatectomy and splenectomy) were excluded because the nature of the other procedure mandated hospitalization for longer than 24 hours. With exclusion of these two patients, the length of stay for the group became 18 ± 10 hours (range, 7–40 hours) (Table 2).

The remaining 15 patients were analyzed as a subgroup and compared by multiple variables that were considered likely to affect discharge times, including duration of procedure, location of lesion, extent of resection, age, inpatient narcotic requirements, and ASA classification (Table 3). Because inpatient narcotic pain requirements would be expected to covary with length of stay, we compared the hourly narcotic pain requirement for each patient by dividing total morphine equivalents by length of stay in hours. The 11 patients included from the short-stay group were discharged at an average of 14 hours, while the four patients in the long-stay group were discharged at an average of 31 hours following surgery ($P < 0.005$), verifying a meaningful difference in discharge times between these groups. When comparing the groups, the only other statistically significant variable identified was the ASA classification. Patients in the long-stay group had a more advanced ASA classification than the short-stay group ($P < 0.05$). No associations were found with respect to age, location or size of the mass, length of procedure, operative blood loss, or inpatient narcotic requirements.

DISCUSSION

We performed 17 laparoscopic hepatic resections using SEE as the primary means of performing the parenchymal transaction. Eleven of these were

Table 3. Comparing patients discharged within 24 hours or greater than 24 hours

Outcome or Characteristic	Group A	Group B	*P* value
Mean time to discharge (hr)*	14 ± 7 (7–23)	31 ± 6 (27–40)	<0.005†
Age (yrs)*	51 ± 16 (41–65)	61 ± 6 (52–66)	NS
ASA classification (no. of patients)			
1	3	0	
2	8	1	<0.05†
3	0	3	
Tumor size (cm)*	3.8 ± 2.5 (1.6–10)	2.8 ± 1.0 (1.8–4)	NS
Segmentectomy or greater (no. of patients)	5	1	NS
Operative time (min)*	174 ± 68 (69–296)	171 ± 128 (61–356)	NS
Operative EBL (ml)*	168 ± 186 (10–500)	165 ± 226 (10–500)	NS
Postoperative inpatient narcotic requirement per hour length of stay (mg intravenous morphine equivalents/hr)*	0.7 ± 0.9 (0–2.8)	0.7 ± 0.9 (0–1.9)	NS

Group A = discharge <24 hours; group B = discharge >24 hours; ASA = American Society of Anesthesiologists; EBL = estimated blood loss.
*Mean ± SD (range).
†By Mann-Whitney test.
NS = not significant.

accomplished with short hospital stays, influenced strongly by careful patient selection and confidence in the technique. No operations were converted to open, and there were no intraoperative complications. We identified only one significant postoperative complication. Literature has generally endorsed the safety of laparoscopic hepatic resections in appropriately selected patients,[6,8–12] and our results support these conclusions.

In addition to appropriate patient selection, we attribute our success and low complication rate partially to our operative approach. Among the tools we find critical in these operations is intraoperative laparoscopic ultrasound, considered invaluable for several reasons. Anatomically, ultrasound permits rapid identification of the primary lesion and associated vascular pedicles. Ultrasound also facilitates identification of synchronous lesions, providing information that can dramatically alter operative plans. Toward this end, laparoscopic ultrasound has been demonstrated to yield increased sensitivity for detection of liver tumors over triple-phase computed tomography scans obtained 1 week prior to operation.[13] Finally, the use of ultrasound increases the ability to obtain appropriate margins for suspected or known malignancies (Fig. 1) when tactile feedback is by definition unavailable. For these reasons, we use routine intraoperative ultrasound.

Hemorrhage remains the most common perioperative complication of laparoscopic hepatic resection,[6] and we use various approaches to minimize this problem. Our approach includes ultrasonic identification and stapling of large vascular pedicles. We have also found good results with the use of saline-enhanced electrocautery, a technology that has been applied to surgery of various organs with promising results.[14–17] Continuous saline flow permits conduction of the radiofrequency energy without direct contact of the tip to the tissue, reducing the likelihood of peeling away the eschar with the electrode. Furthermore, the alteration in the distribution of the energy results in greater collagen shrinkage, which may be instrumental in sealing small bile ducts and vascular sinusoids. Minimizing the likelihood of bile leaks and hemorrhage is critical to comfort in performing this operation, especially in the context of short stays, and we have found saline-enhanced electrocautery to be a facilitating technology.

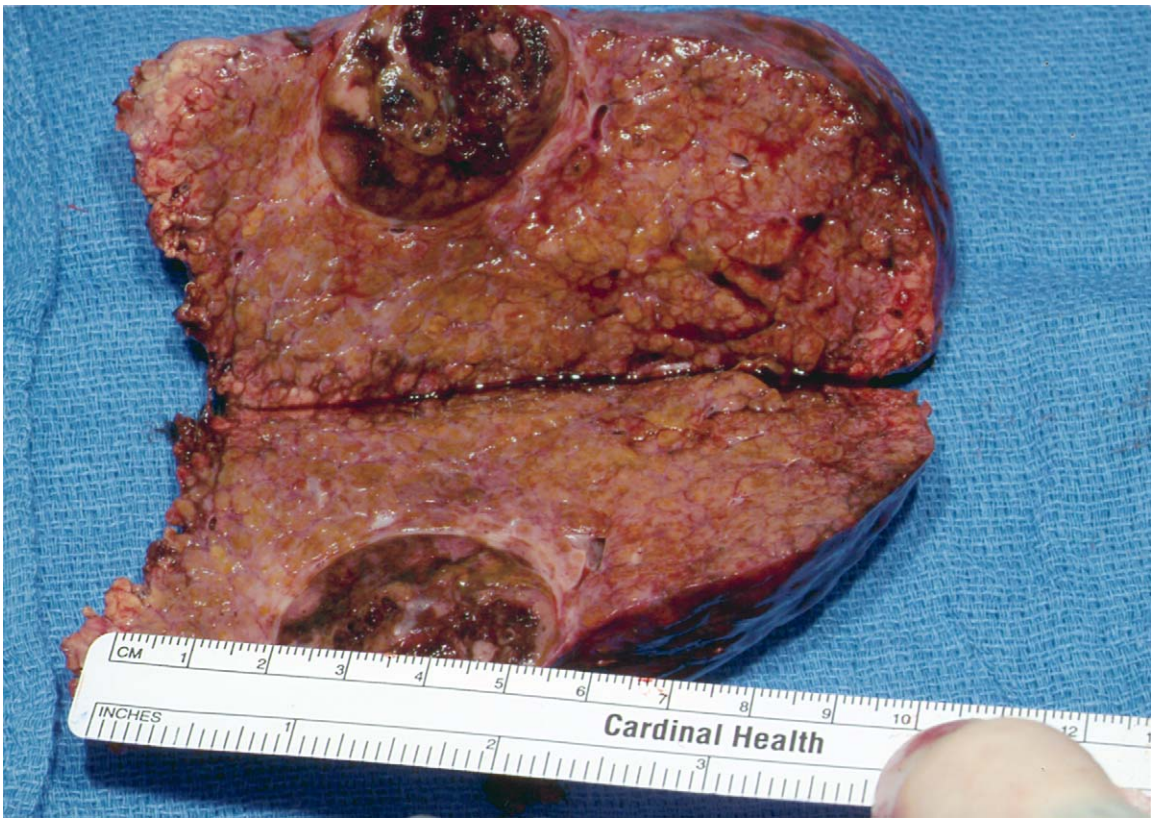

Fig. 1. Resected specimen containing 3 cm hepatocellular carcinoma with demonstration of oncologically appropriate margins. The margins were defined prior to resection with the use of laparoscopic ultrasound.

CO_2 embolism is a frequently cited concern in laparoscopic hepatic surgery, and driven by these concerns, some groups have reported the feasibility of gasless laparoscopy.[18–20] In animal studies, one investigation using transesophageal echocardiography suggested a high rate of incidence with associated arrhythmias in four of seven animals.[21] However, another porcine study did not observe significant evidence of gas embolism,[22] and in human studies, it has been rarely reported as a clinically significant problem. One review of 186 laparoscopic liver resections identified two cases of possible gas embolism, one resulting in cardiac arrest, although both were observed with the use of argon cautery.[23] Despite our routine use of CO_2 pneumoperitoneum, we have not seen clinical manifestations of CO_2 embolism and attribute this to a practice of maintaining appropriately low insufflation pressures and use of saline-enhanced electrocautery. Although poor visibility often triggers an inclination to increase insufflation pressures, in the case of laparoscopic hepatic surgery, it should probably be considered a reason for conversion.

Recognizing that safe and early discharge is feasible in our experience with laparoscopic hepatic resections, we compared patients based on discharge within 24 hours. The designation of short stay is somewhat arbitrary, and our typical convention is to consider patients discharged within 24 hours of the operation as a short stay. We consider this designation a rough surrogate for rapid recovery and minimizing exposure to nosocomial complications. In our study, most short-stay patients were discharged well before 24 hours, and the designation was further validated by the statistical difference in discharge times between the two groups.

Based on this designation, we have identified advanced ASA classification as a factor associated with postoperative stays longer than 1 day in patients undergoing hepatic resection as the primary procedure. Nevertheless, even patients with advanced ASA classification were discharged within 48 hours of operation, including two patients with cirrhosis. While ASA classification is prone to observer bias, it is a widely applicable estimate of the patient's general health, and it provides some quantification of what most surgeons instinctively recognize when assessing a patient's operative risk. Carefully interpreted, two conclusions may be derived from this result. First, as a part of patient selection, advanced ASA classification does not necessarily preclude a patient from consideration for a laparoscopic approach, although clearly the assessment of ability to tolerate a laparoscopic procedure will screen out many patients in the higher classes. Second, ASA classification, as a rough surrogate of the surgeon's assessment of the patient, may be useful when predicting a patient's postoperative recovery course. Last, surgeons are likely more reluctant to rapidly discharge patients with more comorbidities even though there may be no apparent clinical benefit to slightly longer lengths of stay.

Limitations of this study include its retrospective design with its attendant biases. Our study is also small, and our findings require validation in larger series. In addition, we have not compared the laparoscopic group with a matched control group, to establish a direct comparison. However, our primary goal was not to compare the laparoscopic and open approaches but to describe our approach and identify factors influencing the ability to perform resections on a short-stay basis. Previous studies have already reported that the laparoscopic approach offers decreased pain and wound-related morbidity compared with the open approach.[2–4,6] We have elaborated upon these findings with the demonstration that laparoscopic hepatic resections may be safely performed with a short hospital stay.

As the laparoscopic approach becomes more popular, increasing notice will need to be given to its judicious application. Our resections were performed either in conjunction with a planned procedure or based on symptoms or risks thought to be directly related to the tumor itself. Although malignancy was a potential concern in most of our patients, final pathology revealed all but two of the resected masses to be benign. In many of our cases, preoperative radiographic studies and even attempts at percutaneous biopsy were unable to yield reasonably certain diagnoses regarding the nature of the tumor. Interestingly, in a large, European, multicenter study of laparoscopic hepatic resections for benign disease, Descottes et al.[9] found that tumor biopsy had an accuracy rate of only 44% with false-negative or inconclusive findings in 25% of attempted biopsies. While laparoscopic resection offered a minimally invasive and definitive answer in our cases with inconclusive biopsies, we would still advocate exhausting all available diagnostic modalities prior to undertaking laparoscopic resection. However, as seen in the European study, biopsy results may not be helpful when negative.

CONCLUSION

Based on our experience, laparoscopic hepatic resection can be safely performed with short hospital stays with appropriate patient selection. ASA classification may offer guidance regarding the

postoperative course of patients but does not preclude patients from undergoing this approach outright. To our knowledge, this represents the first discussion of the factors influencing laparoscopic hepatic resection with saline-enhanced electrocautery and time to discharge. Further investigation into the comparability of surgical result in laparoscopic and open hepatic resections is needed.

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Transduodenal Excision of Bleeding Periampullary Endocrine Tumor as a Bridge to Pancreaticoduodenectomy in a Jehovah's Witness Patient

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We discuss the case of a Jehovah's Witness patient who presented with a bleeding endocrine periampullary mass. Transduodenal excision of the ampullary mass was successfully performed as a bridge to pancreaticoduodenectomy in this critically ill patient. The roles of pancreaticoduodenectomy and alternatives to pancreaticoduodenectomy in the emergency setting are reviewed, in particular, for patients who decline transfusion of blood products. The surgical approach to surgery and perioperative anemia in Jehovah's Witness patients is described. Finally, we reviewed the role of transduodenal excision in the management of ampullary tumors and describe its use as a bridge to pancreaticoduodenectomy in a patient with a malignant neoplasm of the ampulla. (J GASTROINTEST SURG 2006;10:428–433)

KEY WORDS: Endocrine periampullary tumor, Jehovah's Witness, pancreaticoduodenectomy, transduodenal excision

There are about 1 million Jehovah's Witnesses (JW) in the United States and about 6 million worldwide. Because of their religious beliefs, JW decline to receive whole blood or packed cell transfusions. They also decline the use of stored autologous blood. However, patients may consent to the use of intraoperative blood salvage provided that a closed circuit is established with the patient's circulation.

The influence of preoperative and postoperative hemoglobin (Hb) on mortality in surgery without transfusion has been assessed. In a study of 113 operations in 107 consecutive JW patients who underwent major elective surgery, mortality for preoperative Hb higher than 10 g/dl was 3.2%, and that for levels between 6 and 10 g/dl was 5%. Mortality was significantly increased with estimated blood loss (EBL) of greater than 500 ml, regardless of preoperative Hb. The authors concluded that mortality in elective surgery appears to depend more on EBL than on preoperative Hb level and that elective surgery can be done safely in patients with a preoperative Hb level as low as 6 g/dl if EBL is kept below 500 ml.[1]

Carson et al.[2] studied 1958 patients who declined blood transfusions and underwent surgery. This series included not only elective but also emergency cases. The 30-day mortality rate for patients with preoperative Hb levels of 12 g/dl was 1.3% compared with 33.3% for patients with preoperative levels of less than 6 g/dl. Viele and Weiskopf[3] performed a MEDLINE search of all cases of untransfused JW patients with Hb levels of <8 g/dl. Although these data have limitations, the authors concluded that nearly all deaths due to anemia occurred in patients with Hb levels of less than 5 g/dl.

The effect of postoperative Hb levels in surgical morbidity and mortality has also been studied. A retrospective cohort study of patients who declined RBC transfusions for religious reasons demonstrated that for patients with a postoperative Hb level of 7.1 to 8.0, 0 of 300 died and 9.4% had a morbid event. In patients with postoperative Hb level of 4.1 to

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5.0, 34.4% died and 57.7% had a morbid event or died. The odds of death in patients with postoperative Hb of less or equal to 8 g/dl increased 2.5 times for each gram decrease in Hb level.[4]

REPORT OF A CASE

The patient was a 45-year-old black JW who presented to the emergency department with the chief complaint of passing blood per rectum. The patient had no prior history of gastrointestinal bleeding or peptic ulcer disease. He was admitted to the intensive care unit under the medical team. Because of his religious beliefs, the patient refused any blood products. He was tachycardic and his Hb on admission was 7.5 g/dl. He was started on erythropoietin, parenteral iron, and octreotide. The patient underwent colonoscopy, demonstrating dark blood and no obvious site for bleeding. Upper endoscopy demonstrated a 3- to 4-cm submucosal mass in the second portion of the duodenum, likely ampullary, with active bleeding from an ulcerated area (Fig. 1). Attempts at endoscopic control of the bleeding were not deemed possible by our endoscopist. This was due, at least in part, to the depth of the ulceration within the mass, which did not permit injection or electrocoagulation. A biopsy sample was taken and demonstrated normal mucosa. Computed tomography scanning of the abdomen and pelvis was performed, demonstrating a soft tissue, filling defect in the second portion of the duodenum (Fig. 2). No evidence of metastatic disease was identified. Angiography was performed, demonstrating abnormal vessels in the region of the duodenum suggesting neoplasia; however, no overt hemorrhage was identified and embolization was not attempted.

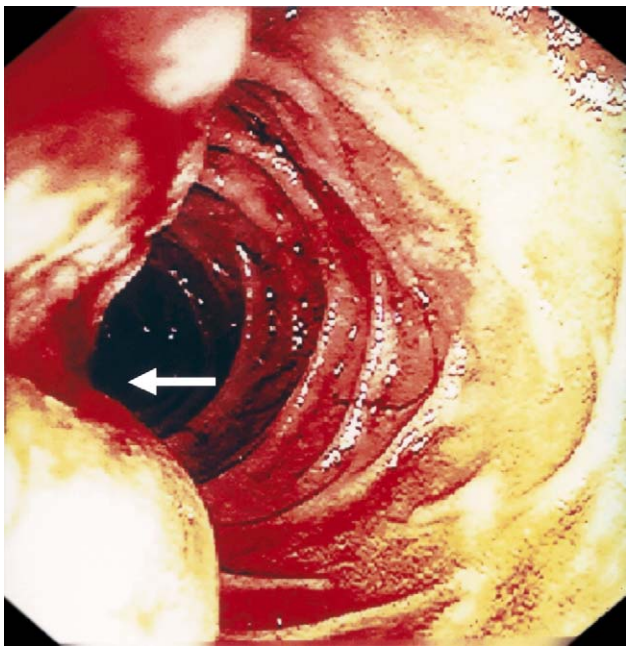

Fig. 1. Upper endoscopy demonstrating a submucosal ampullary mass with a deep area of ulceration and bleeding. The *arrow* demonstrates the depressed and ulcerated area centrally located within the mass.

The patient continued to decline transfusion of blood products. He consented for exploratory laparotomy, possible pancreaticoduodenectomy (PD), and possible transduodenal excision of tumor. He also consented to the use of intraoperative blood salvage. His preoperative Hb was 5.8 g/dl. Upon transfer from the holding area to the operating room, the patient complained of chest pain and chest pressure; no obvious ischemic changes were seen on subsequent monitoring. Laparotomy revealed some degree of tissue edema. No metastatic disease was observed. Wide Kocher maneuver was performed, demonstrating a palpable, very discrete 3-cm mass in the second portion of the duodenum, medially. Due to extreme anemia, potential cardiac ischemic event, and tissue edema, it was decided to proceed with transduodenal excision of the ampullary mass (TDE) as opposed to PD. This option was considered possible due to the discrete nature and small size of the lesion.

A longitudinal duodenotomy was performed. The mass appeared to be submucosal with a central area of ulceration and bleeding and was located in the ampulla, immediately inferior to the common bile duct (Fig. 3). A cholecystectomy was performed, and a biliary ballon catheter was advanced though the cystic duct into the common bile duct and ampulla. This allowed adequate identification of the intrapancreatic portion of the biliary duct and its relationship to the mass. At this point, the mucosa was circumferentially incised around the ulcerated mucosa over the tumor. The submucosal tumor was excised off the muscular layer of the duodenum. This resulted in exposure of two separate openings, the common bile duct and pancreatic duct, as the mass was abutting into the inferior wall of a short common channel and distal pancreatic duct causing pancreatic duct dilatation and, to a lesser extent, bile duct dilatation. The balloon catheter was removed and the cystic duct was ligated. The duodenal mucosal defect was closed, and interrupted monofilament absorbable sutures were applied to approximate both ducts to the mucosa of the duodenum circumferentially. Because of the large size of the ducts, the reconstruction of the pancreatico-biliary-duodenal junction was performed without sphincteroplasty and pancreatic duct septoplasty. The duodenotomy was closed, and a round 19

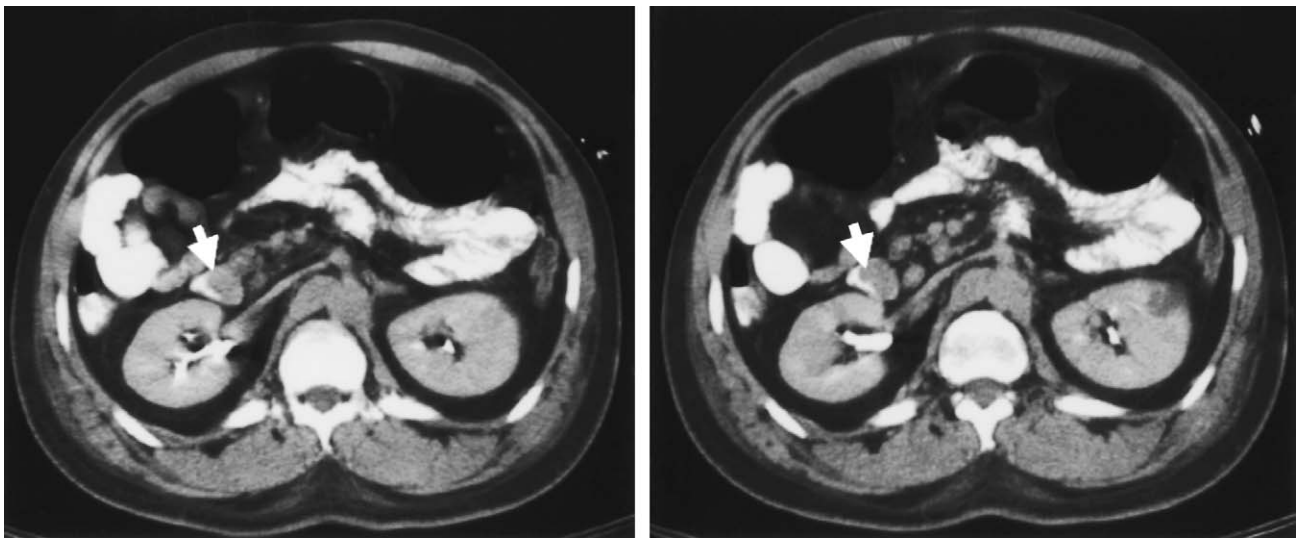

Fig. 2. Thin-section CT scan of the abdomen demonstrating a soft tissue, filling defect (*arrow*) in the second portion of the duodenum.

French drain was placed in proximity. Jejunostomy and gastrostomy tube was placed; in retrospect, a nasogastric tube would have sufficed to decompress the stomach. Blood loss was minimal, and intraoperative blood salvage was not used.

Postoperativelly, the patient was continued on erythropoietin and parenteral iron. Blood draws were limited and pediatric tubes were used. His Hb remained stable on days 1 and 2 and later checked on day 7 and found to be 7.8 g/dl. He had bowel function on day 5 and did well upon clamping of gastric tube. On day 8, diet was advanced. Tube feeds had been started on day 3 and continued throughout his stay and at home during nights. Drains were removed after demonstrating low serous output and normal amylase content. He did have evidence of subclinical pancreatitis with mildly elevated serum amylase. He was discharged on day 13 after home health care for tube feeding had been arranged.

Pathology demonstrated a 2.2-cm pancreatic endocrine neoplasm. Pancreatic polypeptide and neuron-specific enolase were strongly reactive, and chromogranin and somatostatin were both reactive. The tumor diffusely infiltrated the muscular structure of the ampulla and partially obliterated the ducts, with a positive deep margin.

In preparation for PD, the patient continued to receive nutritional support at home through his jejunostomy tube at night while improving his tolerance to a regular diet. He continued oral iron replacement at home. His preoperative Hb was 13 g/dl. Six weeks after surgery we performed non–pylorus-preserving PD. Pathology report revealed no residual tumor in the primary site, but metastatic disease to three of five peripancreatic lymph nodes was identified. Given the presence of metastatic disease to regional lymph nodes, this tumor was classified as a malignant endocrine tumor. The patient was referred to Medical Oncology and adjuvant chemotherapy was recommended. Importantly, although anecdotal case reports of neuroendocrine tumors of the periampullary region, in particular, small cell tumors, treated with adjuvant therapy have been reported,[5,6] there are no data demonstrating a survival benefit of adjuvant chemotherapy for neuroendocrine tumors.[7,8] The patient completed adjuvant therapy and has no evidence of disease at 31 months of follow-up after his PD.

DISCUSSION

Alternatives to PD have been described in the literature for patients in the emergency setting. Emergency PD with delayed reconstruction was performed for an acute episode of chronic pancreatitis-induced massive bleeding.[9] Second-stage pancreaticojejunostomy following PD in high-risk patients involving tube pancreatostomy for complete external pancreatic juice drainage has been described,[10] as well as ligation of the pancreatic duct during difficult operative circumstances and the need for expedient termination of the operation.[11] These surgical approaches are not without morbidity, including pancreatic fistula, pancreatitis, pseudocyst, and abscess formation.[11]

Several single-institution, high-volume experiences indicate that PD can be performed safely for a variety of malignant and benign disorders of the

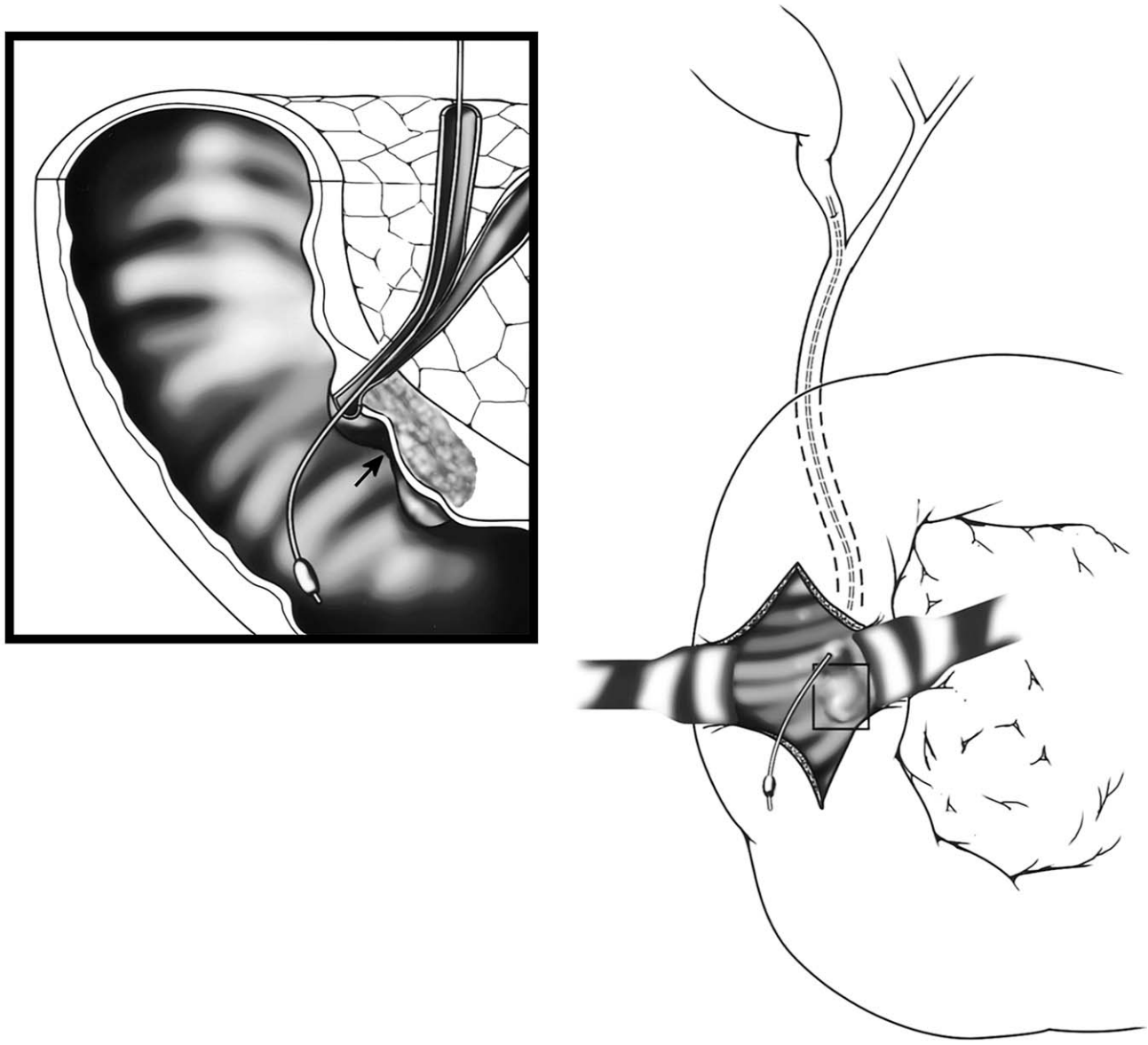

Fig. 3. Identification of the common bile duct with a balloon catheter advanced through the cystic duct. *Inset*, Submucosal ampullary mass in relation to the pancreatic and common bile duct. The *arrow* points to the depressed and ulcerated area within the mass.

pancreas and periampullary region. Reported operative 30-day mortalities for PD have decreased to less than 4%.[12,13] However, operative mortality has been found to correlate with hospital volume, with high-volume institutions having the lowest operative mortality rates.[14] Nontrauma emergency PD has been described as successful for the treatment of endoscopic perforation.[15] Other described indications have been uncontrollable bleeding after failed resection of an abdominal leiomyoma, recurrent endoscopically uncontrollable upper gastrointestinal bleeding from a large duodenal ulceration, and continuous bleeding from an ampullary tumor.[16] In the latter series four patients underwent emergent PD without local complications but with high morbidity, with one patient dying after surgery.

PD has been successfully performed in JW patients. Shiozawa et al.[17] describe a case of successful PD without homologous blood transfusion in a 60-year-old JW with pancreatic cancer. The patient consented to human recombinant erythropoietin, saccharated ferric oxide, and 25% human serum albumin to be administered for 7 consecutive days prior to the operation. An increase in the Hb level by 1.6 g/dl was observed during that week, to a Hb level of 13.6 g/dl. Pylorus-preserving PD was

performed using transfusion of diluted autologous blood, hypervolemic hemodilution, with a closed circuit cell-saver autologous transfusion, as well as controlled hypotension. PD was also reported in an anemic JW; A 42-year-old woman presented with a bleeding ampullary carcinoma and preoperative Hb level of 5.5 g/dl. With evidence that the bleeding had stopped, the patient was treated for 2 weeks with erythropoietin and oral ferrous sulphate with an increase in Hb to 7.6 g/dl. Two weeks later she presented with recurrent bleeding to Hb of 5.1 g/dl. She underwent PD with EBL of 800 mL and autotransfusion of 400 mL of red blood cells. During surgery she received 1600 mL of Fluosol and her postoperative Hb level was 3.8 g/dl. Her successful recovery was attributed to careful surgical technique, intraoperative autotransfusion, avoidance of postoperative complications, minimizing perioperative phlebotomies, and use of recombinant erythropoietin. Consideration to the use of Fluosol was advocated.[18]

The modern surgical approach to surgery and perioperative anemia in JW patients includes several methods and principles. Atabek et al.[18] summarized these approaches, which are based in their extensive surgical experience with JW patients. These surgical and anesthetic principles of blood conservation and bloodless management have also been reviewed by Loubser et al.[19] in a report of three cases of JW undergoing complex aortic surgery and by Moskowitz et al.[20] as they describe in detail the multidisciplinary management of a JW patient for the removal of a renal cell carcinoma extending into the right atrium. Briefly, proposed methods include the following. If possible, perform preoperative management of anemia with exogenous erythropoietin to increase red cell mass[21] and oral or parenteral iron to improve iron stores; operate early for active bleeding; and use careful technique to prevent sepsis, as demonstrated in a randomized controlled study of 47 patients with severe anemia, where active bleeding and sepsis were the strongest predictors of outcome.[22] Minimize blood loss by limiting blood draws and using pediatric tubes, as well as through intraoperative blood conservation by meticulous hemostasis (perform sharp dissection, tie before cutting, stop all bleeding right away even if minor), use of normovolemic hemodilution, autotransfusion with closed circuit if patient has consented, pharmaceutical enhancement of hemostasis, and maintenance of normotermia. Postoperatively, it is important to maintain adequate fluid resuscitation to keep normovolemia, restrict the use of phlebotomy, and use exogenous erythropoietin and iron, while maintaining good oxygenation.

Local excision has been proposed for the management of some ampullary tumors.[23–27] Transduodenal local excision (TDE) and endoscopic snare resection (ESE) have been described as alternatives to PD for selected cases in these cited studies. The use of TDE and ESE has been limited by the low frequency of ampullary tumors, the difficulties in establishing accurate preoperative histologic diagnosis excluding malignancy,[28–33] and the improvements in PD morbidity. PD should be performed for invasive carcinoma and lesions suspicious for malignancy. TDE has been advocated for benign tumors less than 3 to 4 cm.[24,34,35] ESE has been advocated for small, less than 2 cm, benign lesions of the papilla. The indications for each of these procedures have not been completely defined but were discussed by Paramythiotis et al.[27] The technique of TDE has been described in detail by Sakorafas and Sarr,[23] Beger et al.,[34] and Branum et al.[26] Hospital mortality for TDE has been described to be less than 0.4%, with morbidity below 10%, mainly pancreatitis, leak from the duodenotomy site, cholestasis, and delayed gastric emptying.[23,24,36]

In summary, we present a case where TDE of an ampullary malignancy was used as a bridge to PD in a critically ill patient. The patient was treated, while preoperative evaluation was performed, with erythropoietin and parenteral iron. The patient was taken to the operating room as soon as it became evident that less invasive procedures, like endoscopic and angiographic techniques, could not be successfully used. This approach prevents further blood loss. We will never know if our patient would have tolerated PD upfront. Clinical judgment led us to do a less morbid procedure in an attempt to prevent further blood loss and decrease the possibility of sepsis. Although the patient required two surgical procedures, he was able to recover and complete his treatment including PD. We performed meticulous hemostasis and had intraoperative blood salvage available in the operating room. Postoperative care included continuation of erythropoietin and parenteral iron, use of limited blood draws and use of pediatric tubes, and adequate fluid resuscitation. The same approach was used when we performed definitive PD in this patient.

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Dorsal Pancreatectomy: An Embryology-Based Resection

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In a 45-year-old man with acute pancreatitis and recent onset of diabetes mellitus, intraductal papillary mucinous neoplasm (IPMN) associated with pancreas divisum was found. There were no arguments for an invasive component in the IPMN lesions, which seemed to involve nearly all the dorsal pancreas. Resection of only the dorsal pancreas was performed with division of the pancreas at the internal side of the duodenum and at the anterior edge of the common bile duct. The gastroduodenal artery was preserved resulting in good vascularization of both common bile duct and proximal duodenum. Postoperative course was marked by a transient pancreatic fistula. Definitive pathological examination revealed noninvasive IPMN involving several branch ducts and partially the cephalic dorsal duct, with an 8 mm tumor-free segment from the transection level. Twelve months after resection, the patient had normal gastrointestinal function with neither clinical exocrine insufficiency nor uncontrolled diabetes. Postoperative magnetic resonance imaging revealed no signs of recurrence in the ventral pancreas. In patients with pancreas divisum, dorsal pancreatectomy can be proposed for noninvasive IPMN involving only the dorsal pancreas to avoid drawbacks of total duodenopancreatic resection. (J GASTROINTEST SURG 2006;10:434–438)

KEY WORDS: Pancreas, intraductal papillary mucinous neoplasm, pancreas divisum, pancreatectomy

Absence of fusion between the dorsal and ventral primordia at the end of the sixth week during embryologic development, also called pancreas divisum (PD), is a theoretically favorable anatomical entity that could allow surgical segmental resection of the pancreas.[1] In case of benign disease confined to the dorsal or ventral part of the pancreas, an "embryology-based resection" should be evaluated, particularly if total pancreatectomy is the only alternative. In fact, total pancreatectomy systematically leads to diabetes with a significant risk of severe hypoglycemia.[2] One of the technical keys of this procedure remains the ability to preserve viability of both duodenum and common bile duct (CBD).[1] Moreover, a dorsal pancreatectomy was recently reported, but in this case, ischemic damage of the first part of the duodenum led to its removal.[3] Intraductal papillary mucinous neoplasm (IPMN) is a rare pancreatic disease often needing major pancreatic resection and is rarely associated with PD.[3,4] Herein, we report a case of dorsal pancreatectomy, with successful preservation of both duodenum and CBD, performed for noninvasive IPMN involving nearly all the dorsal part of a pancreas divisum.

CASE REPORT

A 45-year-old man, with a medical history of one attack of acute pancreatitis 5 months ago and recent onset of diabetes requiring insulin therapy, was found to have marked dilatation of pancreatic ducts, maximal in the body and tail. These dilatations involved both main duct and secondary branches. Magnetic resonance imaging (MRI), computed tomography (CT), and endoscopic ultrasound (EUS) revealed a PD anatomy and showed that ductal dilatations were present only in its dorsal portion. In the left part of the pancreas, dilatation of both main duct and branch ducts was seen, with some mural nodules in branch ducts (Fig. 1, *B*); neither parenchymal infiltration nor adenopathy were observed. In the

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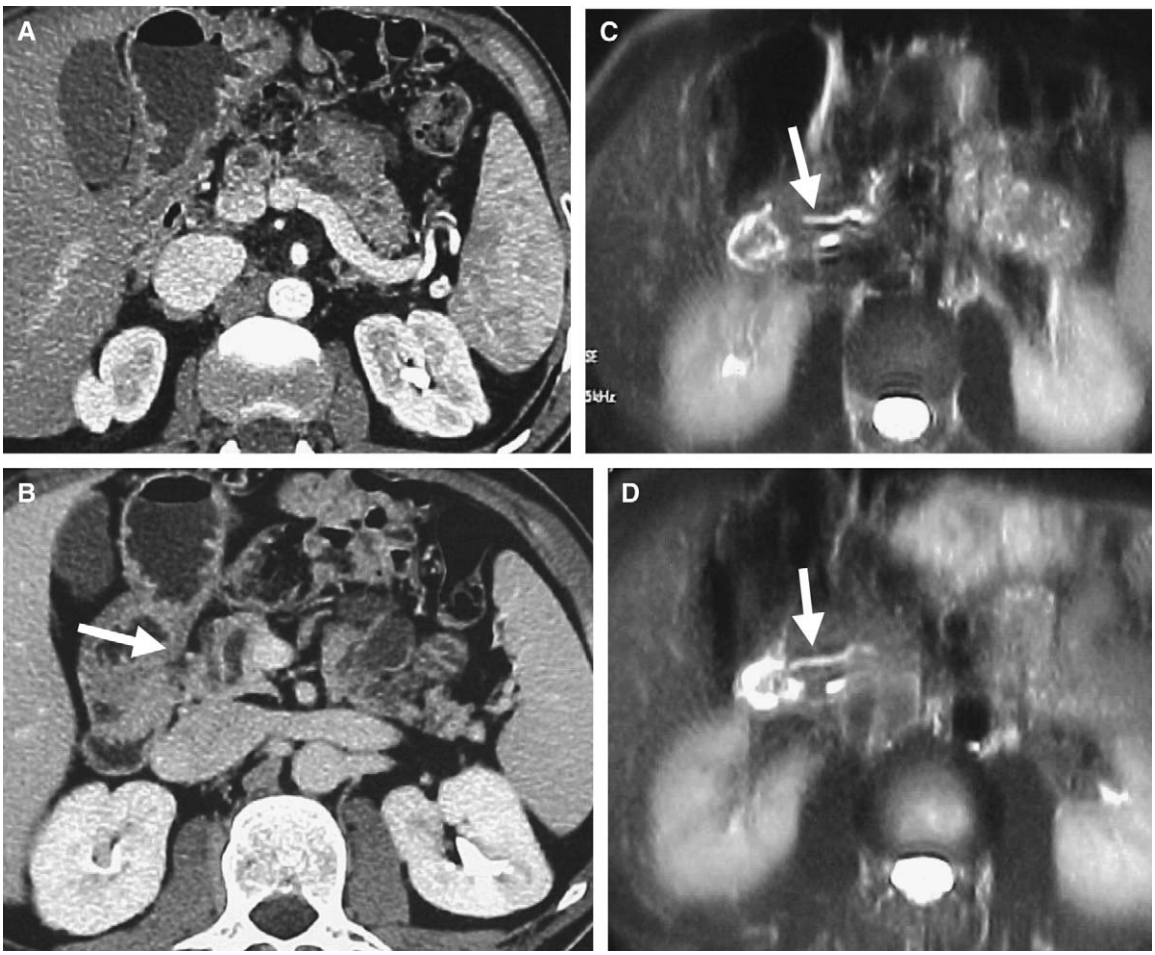

Fig. 1. Preoperative imaging. (**A**) and (**B**) Computed tomogram demonstrating marked dilatation of pancreatic ducts, from the tail to the head at the level of the gastroduodenal artery (*arrow*). (**C**) and (**D**) Magnetic resonance images demonstrating dilatation of the dorsal pancreatic duct (*arrow*) on the left of the common bile duct; this latter is posterior to the former due to disposition in pancreas divisum.

dorsal part of the pancreatic head, the dorsal duct was dilated except in its last 15 millimeters (Fig. 1, *B–D*). Ducts in the ventral part were normal. Diagnosis of IPMN was suggested by clinical history, imaging findings, and gelatinous material extruding from the dilated minor papilla at EUS. Absence of an infiltrative mass and mural nodules in the right part of the pancreas, normality of serum tumor markers (carcinoembryonic antigen and carbohydrate 19-9 antigen) suggesting absence of invasive malignancy, and an "encouraging" anatomy led us to plan resection of only the dorsal pancreas, with frozen section of the transection margin. The patient was informed that involvement of the transection margin or presence of invasive malignancy could lead to a total pancreatectomy.

At operation, a catheter was inserted, after cholecystectomy, via the cystic duct into the CBD to facilitate its location during pancreatic transection and to check its integrity at the end of the procedure. Palpation and intraoperative ultrasound confirmed the integrity of the ventral pancreas. The pancreatic neck was fully mobilized and taped. To minimize the risk of duodenal ischemia, no Köcher maneuver was performed, and both the gastroduodenal artery and the posterior pancreaticoduodenal arterial arcade were preserved. All small collateral branches of the gastroduodenal artery in front of the pancreatic neck were ligated, allowing mobilization of this artery to the right. This latter maneuver allowed exposure of the anterior side of CBD at the upper edge of the pancreas. At this level, pancreatic lateral transection was begun at 2–3 millimeters from the internal edge of the duodenum and was continued caudally. Posteriorly, the transection plane was located along the anterior side of CBD. This plane was sometimes difficult to identify, but preservation of the CBD was facilitated by using an ultrasonic

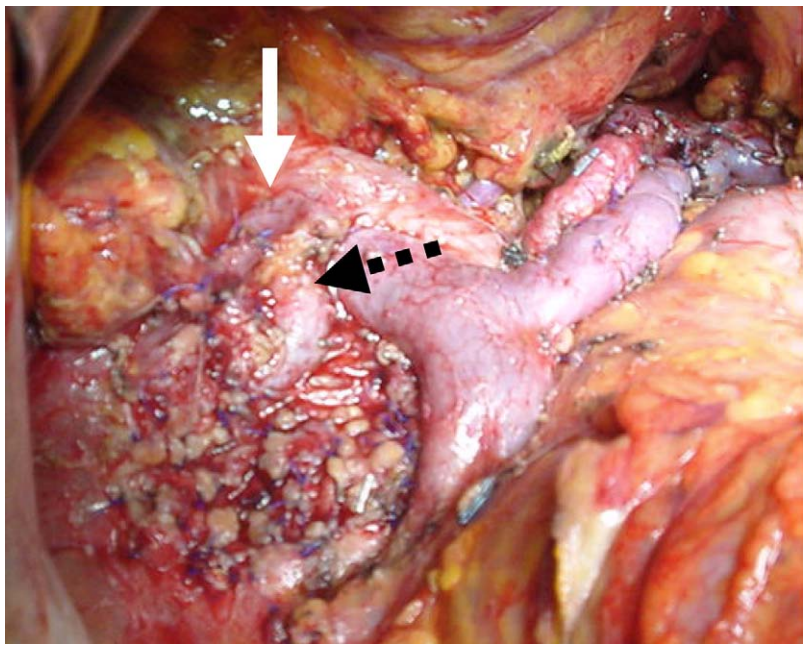

Fig. 2. Intraoperative photogram showing anterior view of pancreatic cut surface after dorsal pancreatectomy. The gastroduodenal artery (*white arrow*) has been preserved, and the anterior side of the common bile duct (*black dotted arrow*) is exposed.

dissector. Complete excision of the dorsal pancreas required segmental interruption of the anterior pancreatic arterial arcade, as well as the ligation of the anterior-inferior pancreaticoduodenal vein at its confluence with the superior mesenteric vein. The dorsal pancreatic duct was divided and ligated 3 millimeters away from the duodenal lumen and was free of neoplasia on frozen section examination. Transection was then continued to expose completely the CBD, except its last centimeter, to avoid interruption of its confluence with the ventral duct (Fig. 2). Anteriorly, the transection plane joined the head-uncus junction. Then, the left pancreas was removed with skeletonization of the splenic vessels (Fig. 2). Intraoperative cholangiography showed no stenosis or leakage from CBD. The duodenum was not cyanotic. An open drainage was left close to the pancreatic cut surface. Total blood loss was 500 ml and the patient was not transfused. The postoperative course was marked by a low output (less than 20 ml a day) pancreatic fistula that started on postoperative day 5 and ceased within 1 month. Oral intake was begun at day 10.

Definitive pathologic examination revealed noninvasive IMPN with some foci of severe dysplasia involving several branch ducts and partially the cephalic dorsal duct. An 8 mm segment of dorsal duct from the transection level was free of tumor. The remaining parenchymal transection margin was free of tumor.

At 18-month follow-up, the patient has regained his preoperative weight, had normal gastrointestinal function, and had no clinical signs of exocrine insufficiency. Endocrine function was impaired as compared to the preoperative period. The patient required more exogenous insulin than before the operation. No clinically significant hypoglycemic episode occurred. Periodical follow-up imaging was planned. MRI performed 18 months after surgery revealed no signs of IPMN recurrence in the ventral pancreatic ducts, which still had a normal diameter (Fig. 3).

DISCUSSION

In pancreas divisum, theoretical disconnection between the ventral and dorsal pancreas seems to be a favorable situation for segmental resection. Our previous experience of segmental resection, such as medial pancreatectomy,[5] led us to propose "an embryology-based resection" in the present case of noninvasive IPMN developing in PD and involving nearly all the dorsal pancreas.

Dorsal pancreatectomy poses two technical problems. The first one is the ability to preserve adequate vascularization of the duodenum and the CBD. In autopsy specimens, arterial preservation seems necessary to assume a good blood supply to the ventral pancreatic segment, CBD, and duodenum, as

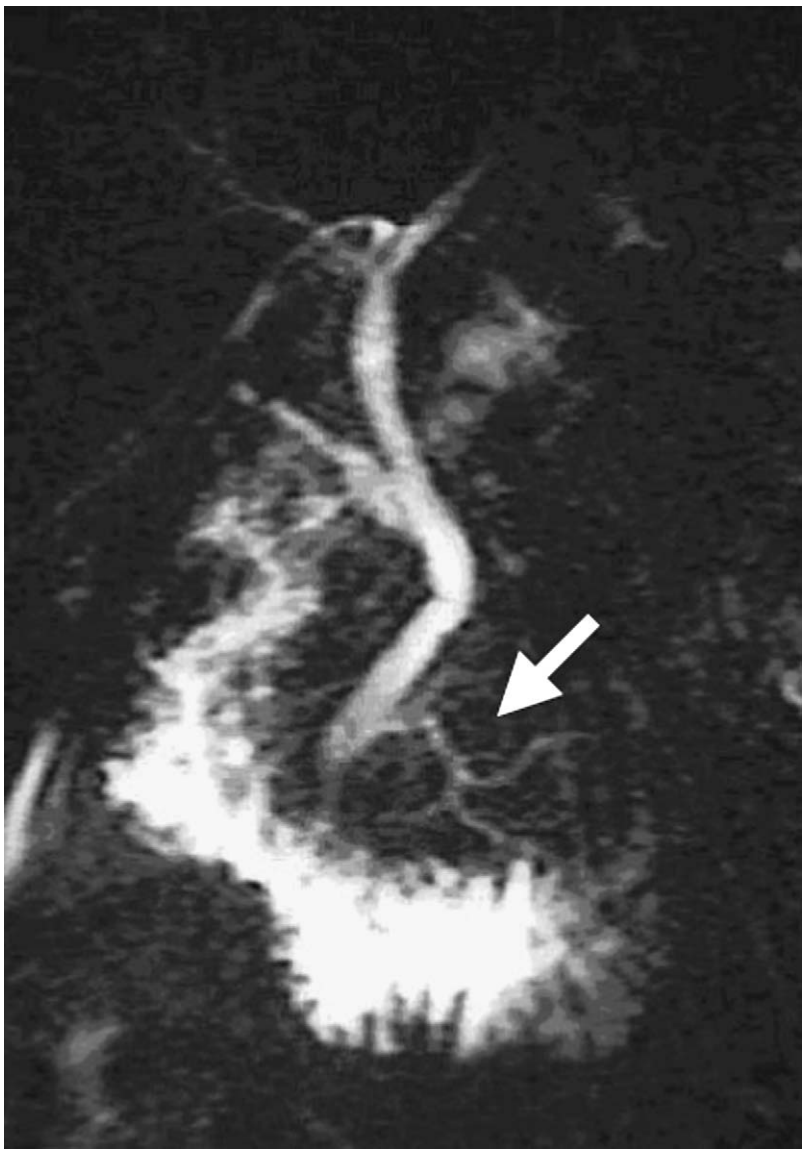

Fig. 3. Postoperative magnetic resonance image demonstrating complete resection of the dorsal pancreatic duct. The duct of the ventral pancreas (*white arrow*) is not dilated and joins the common bile duct.

suggested by Sakamoto et al.[1] and Kimura and Nagai[6] As a matter of fact, duodenum-preserving resection of the head of the pancreas can result in CBD necrosis.[7] In a previously reported case of dorsal pancreatectomy, the first part of the duodenum was resected because of ischemic damage. However, in that procedure, the gastroduodenal artery has been ligated.[3] In our patient, we meticulously preserved both the gastroduodenal artery and the posterior pancreaticoduodenal arterial arcade, although we resected only a segmental part of the anterior inferior arcade. Furthermore, the no Köcher maneuver was performed[8] and the posterior wall of the pancreatic parenchyma was preserved along with the CBD to maintain sufficient vascularization of the latter.

A second technical problem was to locate the fusion plane between the dorsal and the ventral pancreas. Described by Thayer et al.[3] as a fibrous septum allowing relatively simple separation of the two segments, this plane was sometimes difficult for us to identify. However, some autopsy studies mentioned the presence of few pancreatic ducts and vascular communications into this plane,[1] suggesting that fusion between both primordia does not result in strict delimitation. In our patient, this plane was sometimes fibrous, perhaps related to a previous attack of acute pancreatitis. Although no pancreatic duct was identified, a pancreatic fistula developed postoperatively and lasted for 1 month, suggesting that the ventral pancreas has been

wounded. A pancreatic fistula also complicated the previously reported dorsal pancreatectomy.[3] Practically, following the anterior side of the CBD allows resection of the whole dorsal pancreas and is simpler than finding the true embryological plane.

Dorsal pancreatectomy can not be considered a radical procedure for invasive malignancy, due to lack of lymphatic clearance. Although preoperative assessment (including CT, MRI, EUS, and assay of serum tumor markers) concluded that both ventral pancreas and a short segment of the proximal dorsal duct were free of disease, we used intraoperative frozen sectioning to minimize the risk of doing an inadequate resection.[9] In fact, ductal dilatation is not a reliable criterion to determine the extent of resection, and frozen sectioning of pancreatic margin in IPMN is reliable with an accuracy up to 92%.[9] Furthermore, no invasive tumor on definitive pathologic examination was present in our patient. However, we preoperatively informed the patient that a complete pancreatectomy would be done if moderate to severe dysplasia was found on the pancreatic margin or invasive carcinoma was present in the resected specimen at definitive pathologic examination.

In our patient, an alternative was total pancreatectomy with duodenal resection. An extended left pancreatectomy would not have been able to ensure free margins, because the length of disease-free dorsal duct on the specimen was only 8 mm. Duodenum-preserving subtotal head resection was not feasible because this latter procedure needs preservation of dorsal parenchyma all around the CBD to avoid duodenal devascularization.[6] Total pancreatectomy results in both exocrine and endocrine pancreatic insufficiency, including the risk of severe hypoglycemia.[2] In the previous reported case of dorsal pancreatectomy[3] and in our patient, no clinically significant exocrine insufficiency occurred despite the low amount of preserved parenchyma, and postoperative diabetes was easily controlled by exogenous insulin. Persisting secretion of both hormones and enzymes from the ventral pancreas with physiological drainage likely explains the functional result observed after dorsal pancreatectomy. After partial pancreatectomy for IPMN, follow-up of the pancreatic remnant is recommended to detect tumor recurrence, even though it rarely occurs when a negative margin for tumor is present.[10] None the less, the functional advantages of a partial pancreatectomy for IMPN are balanced against the risk of recurrent disease in the remaining pancreas and the drawbacks of prolonged periodical follow-up.

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Long-term Outcome of Laparoscopic Antireflux Surgery in the Elderly

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The aim of this retrospective study was to compare results and five-year surgical outcome of laparoscopic antireflux surgery (LARS) in patients younger than 65 years and elderly patients aged 65 years or older. From January 1992 to December 1998, 2684 patients underwent LARS in 31 surgical units; 369 elderly patients (group 1) were compared with 2315 younger patients (group 2). Elderly patients have a higher American Society of Anesthesiologists score (mean, 2.38 versus 1.98). The conversion rate was higher in group 1 (10.2%, n = 38 versus 6.1%, n = 142), as was the morbidity rate (7.6% in group 1 versus 4.5% in group 2). Mean hospital stay was longer for group 1 (7.6 ± 5.6 days *versus* 5.9 ± 2.8 days). Functional evaluation was excellent in both groups (91–93%) at 3 months and 2 and 5 years. LARS in the elderly is a safe and efficient procedure. Good results appear to be sustainable in the long term. (J GASTROINTEST SURG 2006;10:439–444)

KEY WORDS: Elderly, gastroesophageal reflux disease, laparoscopic antireflux surgery, Visick classification

Gastroesophageal reflux disease (GERD) is one of the most common disorders affecting the upper gastrointestinal tract,[1] with approximately 10% of the population experiencing daily heartburn.[2] For most patients, their disease can be managed with lifestyle modifications and medication, in particular, proton pump inhibitors. However, a subset of patients will require long-term treatment to relieve symptoms and prevent peptic esophagitis and other complications such as Barrett's esophagus and upper gastrointestinal bleeding. Many procedures that are performed to treat GERD can be accomplished by laparoscopy. Several studies have shown excellent results with laparoscopic antireflux surgery (LARS), with success rates between 93% and 97% and a low incidence of complications.[3–5]

Currently, life expectancy in our country is increasing and more patients over 65 years of age are admitted for surgical intervention. Three studies have compared the results of LARS in young and elderly patients, often older than 65 years.[6–8] One previous study has evaluated LARS in patients in their 80s and older.[9] With the increasing age of the population, a good long-term outcome without complication is needed. The aim of this study was to evaluate the safety, efficacy, and long-term results of LARS in the elderly and to compare these results with those achieved in a younger group.

MATERIAL AND METHODS

Patients

From January 1992 to December 1998, a total of 2684 patients underwent LARS for symptomatic GERD in 31 hospital centers. Sixty-one surgeons contributed to this study and each surgeon performed more than 20 procedures. There were 1036 women (38.6%) and 1648 men (61.4%) ranging in age from 18 to 94 years with a mean age of 48.9 ± 13.8 years. Only patients undergoing their first LARS were included in this study. All patients with a second LARS for a relapse of GERD and patients with an initial open laparotomy antireflux surgery were excluded from this study.

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Patients were divided into two groups. Group 1 consisted of 369 elderly patients older than 65 years: 223 women (60.5%) and 146 men (39.5%) with a mean age of 70.4 ± 4.9 years (range, 65–94). Group 2 consisted of 2315 patients younger than 65 years: 813 women (35.1%) and 1502 men (64.9%) with a mean age of 45.4 ± 11.3 years (range, 18–64).

Preoperative Evaluation

The indications for surgery were intractable or recurrent symptoms resulting from GERD after an adequate trial (3 months' minimum) of conservative treatment consisting of omeprazole; complications of reflux esophagitis, stricture, and Barrett's esophagus; or complications of large sliding or paraesophageal hiatal hernia.

Preoperative evaluation included complete history and physical examination for all patients and esophagogastroduodenoscopy in 2541 patients (94.7%) showing peptic esophagitis in 2032 cases (75.7%), peptic stenosis in 44 cases (1.6%), and healthy mucosa in 419 cases (15.6%). There were 275 patients with Barrett's esophagus (10.2%) without dysplasia. Results were unknown for 6 patients.

Twenty-four-hour pH monitoring was performed in 1547 cases (57.6%). This was normal in 145 patients (5.4%) and pathologic in 1397 patients (52.2%). Results were unknown for 5 patients.

Esophageal manometry was performed in 1849 patients (68.9%). The manometry was normal in 355 patients (13.2%), showing an inferior esophagus sphincter hypotony in 1277 patients (47,6%) and an inferior esophagus sphincter hypertony in 212 patients (7.9%). There was no difference between group 1 and group 2. There was no more motor dysfunction in the elderly.

Barium swallow was performed in 1016 patients (37.8%).

Operative Technique

Three operations were performed: complete 360-degree fundoplication in 1363 patients (50.8%) including Nissen fundoplication with division of the short gastric vessels in 752 patients (28%) and without division of the short gastric vessels in 611 patients (22.8%); partial posterior fundoplication in 1175 patients (44.8%); and partial anterior fundoplication in 146 patients (5.4%).

In 937 patients (34.9%) the fundoplication was constructed around a 42 to 50 French Faucher bougie within the lumen of the esophagus. The fundic wrap was fixed to the esophagus in 1726 patients (64.3%) and to the right crus of the diaphragm in 1510 patients (56.2%). The wrap was less than 3 cm in 98 patients (3.6%), between 3 and 5 cm in 2071 patients (77.2%), and greater than 5 cm in 504 patients (18.8%). The wrap length was unknown in 11 patients (0.4%).

Postoperative Evaluation

Postoperative results were evaluated immediately and at 3 months, 2 years, and 5 years. The decision of discharge was not depended on strict criteria but on discretion of surgeons. Patients unable to return for a hospital visit were contacted by telephone for assessment of symptoms and response to treatment. Postoperative clinical follow-up was obtained through a standardized questionnaire. The presence or absence of heartburn and liquid- and solid-food dysphagia, as well as patient satisfaction with the procedure, was graded as a product of severity (none, moderate, or severe symptoms). The presence or absence of gaseous bloating, the ability to belch, the ability to relieve abdominal distention, the ability to eat a normal diet, and patients' opinions on whether they would undergo the same procedure again under similar circumstances were also determined. Details of adverse outcomes such as hospital readmission, complications, or surgical revision were recorded. Patients ranked the outcome of surgery using Visick classification (grade 1 = no symptoms, grade 2 = minimal symptoms, no lifestyle changes, no need to see a physician; grade 3 = significant symptoms requiring lifestyle changes with a physician's help; grade 4 = symptoms as bad or worse than preoperatively).

Statistical Analysis

Data were expressed as mean ± SD (with range). Statistical analysis was made calculating χ^2 test and Fisher's exact test or Student's *t* test. Data were analyzed using StatView 5.0 (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$.

RESULTS

Gender distribution was statistically different between the two groups ($P < 0.001$). In group 1, there was more women (60.5%) than men (39.5%) (Table 1).

Elderly patients have a significantly higher American Society of Anesthesiologists (ASA) score than the nonelderly patients (2.48 versus 1.98; $P < 0.001$).

There was no difference between the elderly (93.8%, n = 346) and the nonelderly patients (99.1%, n = 2296) concerning the main symptoms of GERD. Heartburn and retrosternal pain were

Table 1. Patient details

	Group 1 (n = 369)	Group 2 (n = 2315)	*P* value
Gender (n)			
Men	146 (39.5%)	1502 (64.9%)	<0.001
Women	223 (60.5%)	813 (35.1%)	<0.001
ASA Class (n)			
1 or 2	201	1934	<0.001
3 or 4	168	381	<0.001
Duration of symptoms (yr)	6.8	7.3	NS
Preoperative symptoms (n)			
Heartburn	348 (94.3%)	2190 (94.6%)	NS
Retrosternal pain	39 (10.6%)	236 (10.2%)	NS
Dysphagia	46 (12.5%)	85 (3.7%)	<0.0001
Chronic cough	20 (5.4%)	122 (5.3%)	NS
Asthma	9 (2.4%)	60 (2.6%)	NS
Anemia	25 (6.8%)	32 (1.4%)	<0.0001
Paraesophageal hernia	107 (29%)	222 (9.6%)	<0.0001
Esophagitis class (n)	247	1785	
I or II	87 (23.6%)	992 (42.9%)	<0.001
III or IV	160 (43.3%)	793 (34.3%)	<0.001
Barrett's esophagus (n)	56 (15.2%)	219 (9.5%)	<0.001
Operative technique (n)			
Complete fundoplication	185 (50.1%)	1178 (50.9%)	NS
Partial fundoplication	166 (44.9%)	1009 (43.6%)	NS
Anterior fundoplication	18 (5.0%)	128 (5.5%)	NS

NS = no statistical difference.

the predominant symptoms of GERD (2536 patients, 94.5%), and associated symptoms were classic: dyspepsia, regurgitation, dysphagia, chronic cough, and respiratory complications with exacerbation of asthma. Patients in group 1 presented more frequently with the symptoms of dysphagia (12.5%, n = 46) or anemia (6.8%, n = 25), more esophagitis grade 3 and 4 (43.3%, n = 160), and more Barrett's esophagus (15.2%, n = 56), compared to group 2 patients (Table 1). Paraesophageal hernia was diagnosed in 29% (n = 107) of group 1 patients. The mean duration of symptomatic GERD was 7.2 years (range, 3 months to 50 years). All patients had undergone medical therapy for a mean of 2.3 years (range, 3 months to 15 years).

Operative Results

Global conversion rate was 6.7% (n = 180). This rate was significantly higher in group 1 (10.2%, n = 38) than in group 2 (6.1%, n = 142) ($P = 0.003$). Fifty percent of the conversions were made because of dissection difficulties or adherences.

The global mortality rate was 0.1% (n = 3). There was no mortality in group 1. Two patients had a gas embolism and one patient had an acute coronary syndrome.

The morbidity rate was significantly higher in group 1 (7.6%; n = 28) than in group 2 (4.5%; n = 96) ($P = 0.003$) essentially due to pulmonary complications (Table 2). Results did not differ regardless of the operative technique (Table 3).

The mean postoperative hospital stay was significantly longer (5.9 ± 4.3 days) in group 1 than in group 2 (4.6 ± 2.6 days) ($P < 0.0001$).

Early Postoperative Results (0–3 Months)

After 3 months, 2619 patients were evaluated (97.6%): 360 elderly patients and 2,259 nonelderly patients. No difference was found between group 1 and group 2 concerning feeding, dysphagia, and recurrence (Table 3). Functional results were satisfactory (Visick 1 + Visick 2) in 87.1% of the 2684 patients and not satisfactory (Visick 3 + Visick 4) in 7.5% of the patients. There was no significant difference between both groups. Elderly patients had good results (Visick 1 + Visick 2) in 91.6% (n = 330), as did the patients younger than 65 years (92.3%; n = 2085) (NS) (Table 4).

Two-Year Results

After 2 years, 2141 patients were evaluated: 292 elderly patients and 1849 nonelderly patients. GERD global recurrence rate was 7.7% (n = 165). There was no significant difference between group 1 (7.2%; n = 21) and group 2 (7.8%; n = 144). Residual dysphagia was present in 137 patients (6.4%). There was no significant difference between group 1 (6.2%; n = 18) and group 2 (6.4%; n = 119). Results were similar regardless of the operative technique. Severe dysphagia was noted in 40 patients (1.8%). Moderate dysphagia was noted in 97 patients (4.5%). Results were satisfactory (Visick 1 + Visick 2) in 1993 patients (93.1%) and not satisfactory (Visick 3 + Visick 4) in 148 patients (6.9%). No difference was noted between group 1 and group 2 (Table 4). Satisfaction was noted in 92.8% (n = 271) of elderly patients and 93.1% (n = 1722) of younger patients.

Five-Year Results

After 5 years, 1340 patients were evaluated: 156 elderly patients and 1,184 nonelderly patients. No significant difference was found between both groups concerning dysphagia, recurrence, and

Table 2. Postoperative complications

Complication (n)	Group 1 (n = 369)	Group 2 (n = 2315)	*P* value
Pulmonary infection	9 (2.4%)	16 (0.7%)	0.005
Wound infection	2 (0.5%)	12 (0.5%)	NS
Pleural effusion	5 (1.4%)	7 (0.3%)	0.04
Pneumothorax	0	6 (0.2%)	0.05
Esophagus injury	3 (0.8%)	7 (0.3%)	NS
Arterial hypertension	1 (0.3%)	5 (0.2%)	NS
Acute coronary syndrome	1 (0.3%)	4 (0.2%)	NS
Bleeding	2 (0.5%)	8 (0.3%)	NS
Postoperative ileus	0	7 (0.3%)	NS
Acute pancreatitis	0	1 (0.04%)	NS
Subcutaneous emphysema	1 (0.3%)	2 (0.1%)	NS
Pulmonary embolism	1 (0.3%)	6 (0.2%)	NS
Pyrexia	0	7 (0.3%)	NS
Others	3 (0.8%)	8 (0.3%)	NS

NS = no statistical difference.

functional evaluation. The 5-year outcome was that 9 patients of group 1 (5.8%) and 59 patients of group 2 (5.0%) had dysphagia. Recurrence concerned 15 patients of group 1 (9.6%) and 121 patients of group 2 (10.2%). Functional evaluation showed good results (Visick 1 + Visick 2) for 146 patients older than 65 years (93.6%) and 1102 patients younger than 65 years (93.1%) (NS). Poor results were noted in only 10 elderly patients (6.4%) and 82 nonelderly patients (6.9%) (NS) (Table 4).

Results in Patients Older Than 75 Years

Seventy patients older than 75 years were included in this study. Results were similar to those of group 1. Among these 70 patients, there were 26 men (37.1%) and 44 women (62.9%). Mean age was 78.5 ± 3.7 years (range, 75–94). The ASA score was higher for patients older than 75 years. No difference was found concerning GERD symptoms, preoperative evaluation, indication for surgery, or operative techniques. There was no significant difference in the conversion rate (6.6% for young patients versus 11.4% for >75-year-old patients, $P = 0.1$). There were no deaths in this group. The morbidity was higher in this group of patients (10%, n = 7) compared with patients younger than 75 years (4.5%, n = 117) ($P = 0.02$). The elderly patient mean hospital stay was 8.8 ± 5.9 days. It was longer than the mean hospital stay of younger patients (6.0 ± 3.2) ($P < 0.0001$). Functional results are satisfactory (Visick 1 + Visick 2) for 98.6% (n = 69). Results are similar at 3 months and 2 years.

Table 3. Immediate and 3-month results

	Group 1 (n = 369)	Group 2 (n = 2315)	*P* value
Conversion (n)	38 (10.2%)	142 (6.1%)	0.0030
Mortality (n)	0	3 (0.1%)	NS
Morbidity (n)	28 (7.6%)	96 (4.1%)	0.0034
Complete fundoplication	13 (7.0%)	45 (3.8%)	NS
Partial fundoplication	12 (7.2%)	38 (3.8%)	NS
Anterior fundoplication	3 (16.6%)	13 (10.1%)	NS
Hospital stay (days)	5.9 ± 4.3	4.6 ± 2.6	<0.0001
Dysphagia (n)	137 (37.1%)	1013 (43.8%)	0.0168
Recurrence (n)	9 (2.4%)	31 (1.3%)	NS

NS = no statistical difference.

Table 4. Functional results

	Group 1 (N = 369)	Group 2 (N = 2315)	*P* value
3-month results	(n = 360)	(n = 2259)	
Visick 1 + 2	330 (91.7%)	2085 (92.3%)	NS
Visick 3 + 4	30 (8.3%)	174 (7.7%)	NS
2-year results	(n = 292)	(n = 1849)	
Visick 1 + 2	271 (92.8%)	1722 (93.1%)	NS
Visick 3 + 4	21 (7.2%)	127 (6.9%)	NS
5-year results	(n = 156)	(n = 1184)	
Visick 1 + 2	146 (93.6%)	1102 (93.1%)	NS
Visick 3 + 4	10 (6.4%)	82 (6.9%)	NS

NS = no statistical difference.

DISCUSSION

GERD is one of the most common disorders affecting the upper gastrointestinal tract,[1] with approximately 10% of the population experiencing daily symptoms. In Western countries, life expectancy is increasing, and more patients are 65 years or older. The elderly are increasingly fit and healthy. However, the physiologic effects of aging, including changes in esophageal motility, gastric emptying, lower esophageal sphincter, and reduced salivary flow, explain the high prevalence of GERD in the elderly population.[10] Lifestyle issues and quality of life are thus important considerations when decisions are made regarding management of medical problems in this population. The goal in treatment of the elderly is to restore the best possible quality of life with the lowest physiologic cost.

Medical treatment of GERD results in relief of symptoms in the majority of patients, but symptom relapse is common after cessation of medical therapy[11] in patients with severe GERD and hiatal

hernias.[12] Patients on medical therapy may have progression of disease and develop complications. Treatment options for elderly are becoming more important, and some of these patients will demand alternative therapy if medical treatment fails. Laparoscopic fundoplication has been shown to be an excellent therapy for young patients with GERD. LARS reduces the potential of long term complications of the disease such as Barrett's esophagus and stricture. The medical therapy based on lifestyle modifications and proton pump inhibitors is increasingly necessary. Antireflux surgery is entering a new era with the advent of minimally invasive techniques.[13,14] Several studies have shown the safety and excellent results of LARS in GERD patients between 60 and 80 years of age.[6–9] In our study, 13.7% of patients were older than 65 years. There appears to be an increased incidence in women, as reflected in our study. Currently in our country, life expectancy is increasing with women living longer than men. Age and medical history of patients explain the higher ASA score in the elderly. This classification is commonly used for preoperative evaluation; the first description was in 1941.[15]

Elderly patients who have GERD are more likely to present with atypical symptoms, including chest pain, anemia, or aspiration, than are their younger counterparts. Approximately 7% of the elderly were anemic in this study. GERD accounts for a greater percentage of cases of upper gastrointestinal bleeding in patients over age 80 than in younger patients.[16] Several studies[10,17,18] have suggested that elderly patients with GERD are likely to have more severe esophageal mucosal disease than are younger groups. Collen et al.[18] found that elderly patients with symptomatic GERD who required upper endoscopy for evaluation had a higher incidence of severe grade 3 or 4 esophagitis and Barrett's esophagitis. Collen et al.[18] showed a continuous increase of Barrett's with age (6% $<$30 years, 9% in fourth decade, 17% in the fifth and sixth decades, 36% in the seventh decade, and 32% $>$70 years). Similar findings were reported by Allen et al.,[17] although reflux symptoms were more severe in the non elderly. Mixed paraesophageal hiatal hernias (type III) develop from sliding hiatal hernias (type I) and are more frequent in the elderly.[19] Patients with these hernias represent an entirely different population. Repair of these hernias is often urgent, and the morbidity and mortality rates are higher.[20]

The conversion rate is higher in the elderly. This association may be due to the higher probability of previous abdominal surgery with subsequent adherences. Similar findings are not found in other reports. In this study, hospital stay is longer in the elderly; generally, this is because of medical complications and social considerations and not surgical complications. In the previous studies, hospital stay was similar[7,8] or longer.[6] The hospital stay remains long. There were two reasons: the converted patients were included in the analysis, and there was a period of waiting for a nursing home. Nevertheless, another finding from this study was the reduced need for inpatient rehabilitation for these compromised patients. This finding suggests that the reduced surgical stimulus and rapid postoperative mobilization are important factors in lowering the need for prolonged rehabilitation to regain the confidence required for independent mobilization and activities of daily living.

Elderly patients were satisfied with their functional results, as were younger patients. These studies illustrate that LARS is well tolerated in elderly patients. Functional evaluation shows that LARS is promising in the treatment of GERD. Long-term follow-up confirms this because of the high rate of patient satisfaction.

In summary, LARS in the elderly is a safe and efficient procedure. Elderly patients undergoing surgery for severe GERD or large symptomatic paraesophageal hernias reported substantial relief from symptoms for several years after surgery.

Study Participants

Surgeons who participated in this study include the following: J. F. Ain (Macon), Al Naasan (Chambery), J. P. Arnaud (Angers), J. M. Atah (Amiens), D. Balenbois (Aubagne), J. Baulieux (Lyon), J. P. Bazin (Elbeuf), P. Berard (Lyon), P. Bouchet (Chambery), O. Brehant (Angers), L. Bresler (Nancy), C. Bunea (Amiens), J. L. Cardin (Laval), M. Carretier (Poitiers), B. Castel (Lille), Y. Chen (Grenoble), D. Collet (Bordeaux), J. M. Cucchi (Bordeaux), A. Dabrowski (Seclin), N. De Manzini (Strasbourg), J. F. Delattre (Reims), C. Delteil (Chateauroux), A. Dhahri (Lyon), J. Domergue (Montpellier), N. El Zeenni (Altkirch), Y. Fouques (Caen), G. Fourtanier (Toulouse), A. Gainant (Limoges), F. Gayral (Bicêtre), J. F. Gillion (Thiais), C. Gouillat (Lyon), L. Grimaud (Lyon), A. Hamy (Nantes), P. Herbiere (Albi), J. Lagoutte (Arnas), J. M. Leloup (Ermont), C. Letoublon (Grenoble), B. Masson (Bordeaux), M. Mathonnet (Limoges), C. Meyer (Strasbourg), C. Mondésert (Feurs), J. Paineau (Nantes), D. Paterne (Bicêtre), P. Pessaux (Angers), D. Pezet (Clermont-Ferrand), J. P. Porta (Desertines), S. Rohr (Strasbourg), P. Segol (Caen), J. F. Sledzianowski (Toulouse), O. Touchard (Nancy), G. Trébuchet (Rennes), J. P. Triboulet (Lille), J. R. Tubiana (Elbeuf), P. Verhaeghe (Amiens).

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Abdominal Wall Abscesses in Patients With Crohn's Disease: Clinical Outcome

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Abdominal wall abscess due to Crohn's Disease used to be one of the definitive indications for operative treatment. The advent of interventional radiology, the accessibility to percutaneous drainage, and the availability of new medications raised the possibility of nonoperative treatment of this condition. The clinical presentation, treatment, and follow-up of 13 patients with abdominal wall abscesses secondary to Crohn's Disease were retrospectively reviewed. During a 10-year period (1993–2003), 13 patients with abdominal wall abscess were treated. Five patients had an anterolateral abdominal wall abscess and eight had a posterior abscess (psoas). In 11 patients, 17 drainage procedures were performed: 12 percutaneous and 5 operative. Despite initial adequate drainage and resolution of the abscess, all 13 patients eventually needed resection of the offending bowel segment, which was undertaken in 12 patients. The mean time between abscess presentation and definitive operation was 2 months. Percutaneous drainage is an attractive option in most cases of abdominal abscesses. However, in Crohn's Disease patients with an abdominal wall abscess, we found a high failure rate despite initial adequate drainage. We suggest that surgical resection of the diseased bowel segment should be the definitive therapy. (J GASTROINTEST SURG 2006;10:445–449)

KEY WORDS: Crohn's Disease, psoas abscess, percutaneous drainage, fistula

Crohn's disease is a chronic, transmural, inflammatory disease of the gastrointestinal tract, most frequently affecting the terminal ileum and colon. Diarrhea, abdominal pain, anorexia, nausea, and weight loss are the most common clinical symptoms. Abdominal wall abscesses, that is, ileopsoas and rectus sheath abscesses with or without concomitant enterocutaneous fistulae, are uncommon complications of Crohn's Disease, with an incidence of 0.4%–4%.[1,2] However, in the postoperative patient, fistulae may occur in up to 21% of cases.[3] They can cause significant morbidity and even mortality. The conventional therapy in Crohn's Disease complicated by an abscess has been initial surgical drainage followed by resection of the diseased bowel. Nowadays, percutaneous drainage under imaging guidance (when accessible) has become the main method of abscess drainage. There are reports suggesting drainage followed by medical treatment as the sole management of abscesses of Crohn's Disease.[4]

We retrospectively reviewed 13 patients with Crohn's Disease who presented with abdominal wall abscesses. We describe the mode of therapy in each case and the outcome. We wish to report our experience with emphasis on the recommended management.

MATERIALS AND METHODS

The clinical data of 13 patients with Crohn's Disease and an abdominal wall abscess diagnosed by CT scan were retrospectively reviewed. These patients were diagnosed over a period of 10 years (1993–2003). The study group included nine men and four women, with ages ranging from 17 to 63 years (mean age, 32.8 years). The median length of Crohn's Disease from its onset to the presentation of the abscess was 9 years (range, 1 month to 33 years). In two patients, the abdominal wall abscess was the initial presentation of their disease. In all

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patients, the clinical picture, radiologic and endoscopic findings, and/or histological examination of the endoscopic biopsy or surgical specimen established the diagnosis. Five patients were maintained on immunosuppressive treatment by a combination of steroids and azathioprine or 6-mercaptopurine, four patients were treated with steroids with or without 5-ASA, two patients were treated by 5-ASA alone, and the last two patients had no medical treatment (Table 1).

In 10 patients, the presentation of the abscess was nonspecific and associated at the time of admission with some degree of disease activity manifested by diarrhea, weight loss, and fever. In three remaining patients, the onset was acute with a sudden fever associated with flank or abdominal pains. One of these patients had a chronic draining from a sinus opening in the flank region that had recently stopped draining, and in another patient, inguinal lymphadenopathy was the first presentation of the disease. Five of the 13 patients had a palpable abdominal mass in the iliac fossa or an anterior abdominal wall mass.

The CT scans were obtained on a nonhelical scanner (Elscint 2400 Elite, Elscint, Haifa, Israel) or on a helical scanner (Elscint CT Twin flash), with 10 mm collimation and 1.0 cm interval from the diaphragm to the pelvis. All patients received orally diluted water-soluble contrast material, 1000 ml administered over 2 hours before the examination and an additional 250 ml just before the study. Intravenous contrast (80–100 ml) of Urografin (sodium-diatrizoate) or Telebrix (meglumine-ioxitalamic) was manually injected in all patients. The clinical course was meticulously reviewed using the hospital and the outpatient charts.

RESULTS

Six patients had colonic Crohn's Disease, five patients had ileocecal involvement, and two patients had the disease in the small bowel. Four patients had a previous bowel resection, and three of them had two resections. Five patients had an anterior abdominal wall abscess, and eight had a posterior abdominal wall abscess within the psoas or the ileopsoas muscles (Table 1).

CT findings of the involved muscle showed a significant enlargement in comparison to the unaffected contralateral side, with the presence of low density in all patients (Fig. 1). Gas bubbles or an air/fluid level were seen in eight abscesses (Fig. 2). The affected bowel loop was clearly seen adjacent to the abscess (Fig. 3). In two patients, the orally ingested contrast material was seen within the abscess cavity, indicating a fistulous communication (Figs. 1 and 3).

All 13 patients received antibiotic therapy. In 11 patients, 17 drainages were performed as well: 12 patients had percutaneous CT-guided drainage and five patients had operative drainages (Table 1). In the latter, the operative route was undertaken after recurrence of the abscess after percutaneous drainage in four patients, and as the primary treatment in one patient. Four patients underwent two drainages each, and one patient was drained three times.

Twelve of the 13 patients (92%) had definitive bowel resection surgery as dictated by either

Table 1. Characteristics, treatment, and outcome of the patients with abdominal wall abscesses

Patient	Prior therapy	Disease/abscess location	Number of drainages (percutaneous/oper)	Definitive operation	Delay to definitive operation (mo)
1	Aza,S	Rt colon/lt psoas	2 (1/1)	Subtotal colectomy	17
2	Aza,S	Ileocecal/rt psoas	0	Segmental resection	1.5
3	Aza,S	Term ileum/rt psoas	1 (1/0)	Ileocecectomy	1
4	S	Ileum, sigmoid/lt psoas	1 (1/0)	Subtotal colectomy	1
5	S	Ileocecal/rt rectus	2 (2/0)	Ileocecetomy	1
6	Aza, R	Ileocecal/rt psoas	1 (0/1)	Subtotal colectomy	5
7	5-ASA	Rt colon/rt psoas	1 (1/0)	Segmental resection	5
8	6-MP, S	Ileocecal/rt rectus	2 (1/1)	Rt colectomy	1.5
9	—	Ileocecal/rt rectus	2 (1/1)	Segmental resection	4
10	S,5-ASA	Ileocecal/rt rectus	1 (1/0)	Ileocecectomy	2
11	S	Ileum/rt rectus	3 (2/1)	—*	—*
12	—	Ileocecal/rt psoas	1 (1/0)	Rt colectomy	1
13	S	Ileocecal/rt psoas	0	Ileocecectomy	0.66

Aza = azathioprine; 5-ASA = 5-acethylsalicylic acid analogs; R = remicade (monoclonal anti-TNF antibodies); S = steroids; 6-MP = 6-mercaptopurine.
*Still suffers from fistula.

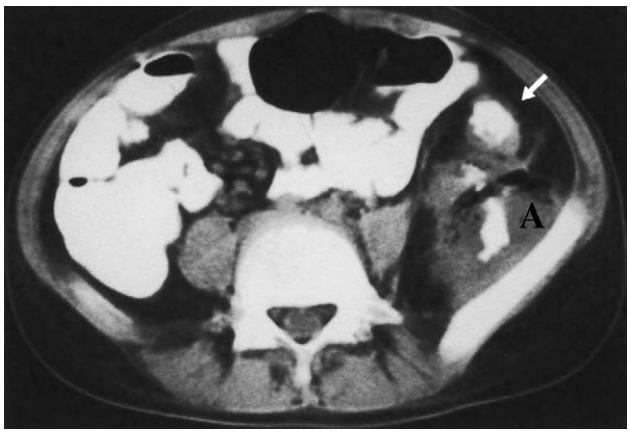

Fig. 1. A 17-year-old man with Crohn's Disease for 5 years presented with fever and left lower quadrant pain. Contrast-enhanced CT at the pelvis shows low density within an enlarged left iliacus muscle with numerous gas bubbles and the orally ingested contrast material (**A**), apparently filled through a fistulous tract from the thickened wall, adjacent descending colon abutting the muscle (*arrow*). Note the surrounding reactive fat infiltration. (From Zissin R, Gayer G, Kots E, Werner M, Shapiro-Feinberg M, Hertz M. Iliopsoas abscess: a report of 24 patients diagnosed on CT. Abdom Imaging 2001:26:533–539. Reprinted with permission from Springer-Verlag.).

intractability of their disease to medical treatment in four patients, or the recurrence or persistence of the abscess in eight patients. Of the eight patients with a recurrent abscess, five had a second drainage and were operated shortly thereafter. In three patients, the operation was undertaken after the initial control of the sepsis with antibiotic treatment. The last (13th) patient suffered from three recurrences of

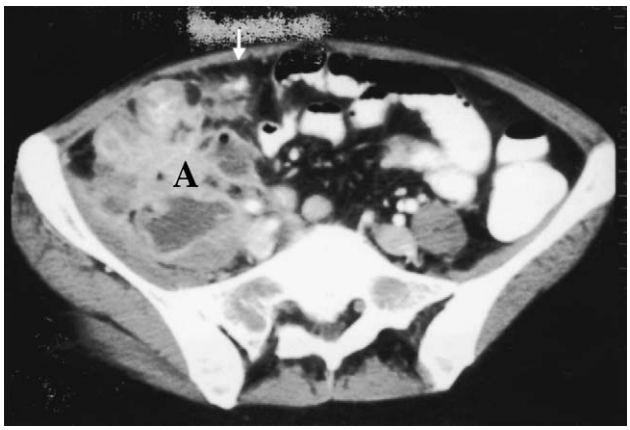

Fig. 2. Contrast-enhanced CT of a 26-year-old woman with known Crohn's Disease. Right-sided femoral neuropathy shows a multiloculated collection within the right iliopsoas muscle with indistinct margins and minute gas bubble (**A**). Note the adjacent thickened-wall small bowel loops, entrapped toward the collection (*arrow*).

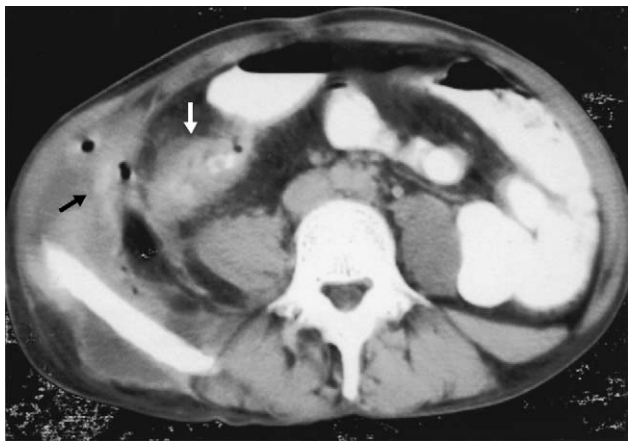

Fig. 3. A 36-year-old man with Crohn's Disease presented with fever and tender, right-sided abdominal wall mass. Contrast-enhanced CT shows the thickened-wall intestinal loop with surrounding mesenteric changes (*white arrow*) as well as the hypodense, right-sided, enlarged abdominal-wall muscles containing gas bubbles, and the orally ingested contrast material (*black arrow*).

a rectus sheath abscess, and after repeatedly refusing surgical resection, was drained three times and still suffers from a persistent enterocutaneous fistula with intermittent rectus sheath abscesses. On all operations, resection of the macroscopically diseased bowel segment that was the source of the fistula was performed.

The mean time between the abscess presentation and the definitive operation was 2 months. Eleven of the 12 patients had the resection within 5 months of the abscess presentation (six patients had resection within 1 month of the diagnosis; Table 1). In only one patient was the resection performed 17 months after the presentation, due to procrastinations related to prolonged attempts of treatment with newer anti-inflammatory drugs. That patient was then operated with a persistent abscess and continuous drainage in a very depleted and catabolic state.

DISCUSSION

Because the pathological process in Crohn's Disease involves all the layers of the bowel wall, it frequently penetrates into the adjacent tissues and into other organs situated in the vicinity of the diseased bowel. It may involve any organ, and thus explains the fistula formation. It may extend to potential cavities, resulting in an abscess. This explains the relatively high incidence of 10%–30% of intra-abdominal abscesses in this ailment.[1,2] A review by Michelassi et al.[4] of 639 cases of Crohn's Disease that underwent surgery revealed that 222 (34.7%) patients were found to have 290 intra-abdominal

fistulae. Forty-two percent of the patients that had an abdominal inflammatory mass actually had an abscess or a fistula. In this series, all patients underwent resection of the diseased portion of the small bowel. Forty-six of 222 patients (21%) had a fistulous tract to the abdominal wall. These patients had resection of the diseased bowel together with debridement of the fistulous tract.

A rectus sheath abscess is an abscess that develops when the disease process extends to the rectus muscle. It will manifest itself as a lower quadrant mass with fever and leukocytosis and may mimic a rectus sheath hematoma.[5] A psoas muscle abscess is usually an extension of a mesenteric abscess through the mesentery into the potential retroperitoneal space overlying the psoas muscle.

Ricci and Meyer,[6] in a review of psoas abscesses, point out that, classically, this condition was a manifestation of TB spondylitis. Nowadays, it is more frequently a complication of an intra-abdominal process, Crohn's Disease being among the most prevalent.[7] It manifests with fever, weight loss, and sometimes with flexion contracture of the hip, and these may even be the first signs of the disease, with the absence of gastrointestinal symptoms. A psoas abscess was the first manifestation of Crohn's Disease in 13 of 46 patients with this condition in the series of Ricci and Meyer,[6] and in 2 of the 13 patients in our series. Besides the usual septic complications inherent to any abscess, the dreaded consequence of this type of an abscess is the development of septic arthritis of the hip, which could lead to a long-term handicap.[8]

The conventional therapy in Crohn's Disease, which is complicated by an abscess, has been initial surgical drainage followed later by resection of the diseased bowel. When incision and drainage was combined with resection,[6] 14 of 18 patients (77.8%) were cured. Only 7 of 26 patients (27%) were cured with incision and drainage alone. Effective therapy therefore included appropriate antibiotics, drainage of the abscess, and resection of the fistulous tract together with the portion of intestine feeding the tract.

With the advent of percutaneous imaging-guided drainage techniques, this became the main way of abscess drainage when the site is accessible, and it obviated the need for a surgical drainage in certain cases such as postoperative abscesses, and even in abscesses of Crohn's Disease. However, this has been reported as the definitive therapy without further bowel resection.[1,9,10] Lambiase et al.[11] even assumed that abscesses in patients with Crohn's Disease without enteric communication may be treated by percutaneous drainage alone, as any other intra-abdominal abscess. We question this belief regarding the special subgroup of patients suffering from an abdominal wall abscess secondary to Crohn's Disease.

Most of the series do not differentiate between intra-abdominal abscesses and retroperitoneal abscesses. The reported series usually comprises small groups of patients, followed-up for relatively short periods of time. In a series[1] of 15 patients with abscesses associated with Crohn's Disease, there were only four patients suffering from an iliopsoas abscess. All these patients were treated successfully by percutaneous drainage alone, but the length of follow-up was not stated.

In contrast, other authors state that the definitive therapy of a psoas abscess should include resection of the offending bowel segment. In the study by Van Dongen and Lubbers,[12] 7 of 161 patients who were treated surgically for Crohn's Disease had a psoas abscess. Drainage as the sole treatment was insufficient therapy, and subsequent resection of the involved portion of bowel was necessary for cure. Burul et al.[13] described eight patients with a long history of disease who underwent drainage of psoas abscesses. Five of them (62.5%) required redrainage. The diseased portion of the bowel was then resected in all patients, with complete remission in seven patients and an additional bowel resection in one patient. In a review by Durning and Schofield[14] of four patients with a psoas abscess, all underwent resection of the diseased portion of the bowel, together with appropriate drainage of the abscess cavity.

In our series of 13 patients with an abdominal wall abscess, early or late resection of the diseased bowel that fed the abscess cavity was necessary in all patients, despite successful drainage of the abscess. Retrospectively, we can state that the drainage of an abdominal wall abscess was only a temporizing measure in contrast to intra-abdominal abscesses that may occur with this ailment and can be successfully treated with percutaneous drainage alone. Nonoperative treatment of an abdominal wall abscess secondary to Crohn's Disease leads to a 100% failure rate. Our findings support the recommendations of the previous authors that the diseased segment of the bowel should be resected.[6,12–14]

A preoperative percutaneous drainage of an abscess may, however, be beneficial by decreasing the patient's catabolism and by allowing improvement of the nutritional status. The operative field can then be converted to a noninfected area, thus raising the odds of safe healing after a single operation for resection of a diseased bowel with immediate anastomosis, rather than resorting to the standard two-stage procedure (i.e., initial surgical abscess drainage followed by a second operation for bowel resection).

It is our assertion that an abdominal wall abscess is the harbinger of complicated Crohn's Disease that justifies drainage in preparation for definitive surgery, rather than the drainage alone being the definitive treatment.

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Thoracolaparoscopic Modification of the Ivor Lewis Esophagogastrectomy

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Ivor Lewis esophagogastrectomy, first described in 1946, consists of a laparotomy and a right thoracotomy with an esophagogastric anastomosis performed transthoracically.[1] Minimally invasive surgical approaches to esophagectomy were developed in the early 1990s in an attempt to reduce the morbidity associated with combined thoracic and abdominal incisions. The initial minimally invasive approach for esophagectomy was to replace the thoracotomy with thoracoscopy for esophageal mobilization.[2–4] Then in 1995, DePaula and colleagues[5] reported a small series of total laparoscopic transhiatal esophagectomies. Their approach was similar to that of the blunt transhiatal esophagectomy but used laparoscopy to mobilize the mediastinal esophagus rather than blunt dissection of the cervical and middle third of the esophagus. Subsequently, Luketich et al.[6] reported the combined thoracoscopic and laparoscopic approach to esophagectomy. Their technique consists of thoracoscopic esophageal mobilization followed by fashioning the gastric conduit laparoscopically and construction of an anastomosis in the cervical esophagus. There have been few reports, however, on the minimally invasive Ivor Lewis resection using an intrathoracic anastomosis.[7,8] The major limiting step in the development of minimally invasive Ivor Lewis esophagogastrectomy is creation of a safe thoracoscopic esophagogastrostomy. In this article, we describe our technique of thoracolaparoscopic Ivor Lewis esophagectomy emphasizing a unique thoracoscopic method for construction of an intrathoracic anastomosis.

INDICATIONS

Minimally invasive Ivor Lewis resection is indicated primarily for cancer of the distal third of the esophagus and gastric cardia. In patients with gastric cardia involvement, a wider resection of the proximal stomach is required to obtain a negative distal margin. The shortened length of the gastric conduit precludes construction of a neck anastomosis, and an intrathoracic anastomosis is mandated to create a tension-free esophagogastric anastomosis. Thoracolaparoscopic Ivor Lewis resection should not be performed for upper-third esophageal cancer. Essentially resectable tumors located endoscopically proximal to 33 cm from the incisors should undergo total esophagectomy with a neck anastomosis to ensure adequate margin of resection.

SURGICAL TECHNIQUE

Thoracolaparoscopic Ivor Lewis resection is performed in two stages. In the first stage, the patient is positioned in the supine position for laparoscopic construction of the gastric conduit and transhiatal mediastinal dissection of the distal-third esophagus under direct visualization. In the second stage, the patient is repositioned to a left lateral decubitus position for mobilization of the thoracic esophagus, removal of the surgical specimen, and creation of an intrathoracic esophagogastric anastomosis.

Stage 1: Laparoscopic Construction of the Gastric Conduit

The patient is positioned in a supine position. The surgeon stands on the patient's right side and the assistant stands on the left. Abdominal insufflation is achieved using the Veress needle, and pneumoperitoneum is maintained at 15 mm Hg. Five abdominal

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trocars are placed. The first trocar (11 mm), placed at the left midclavicular line at the level of the umbilicus, is used for the camera. A 5-mm trocar is placed at the left anterior axillary line below the costal margin to be used by the assistant surgeon. A 5-mm trocar is placed at the right anterior axillary line below the costal margin to be used for retraction of the left lobe of the liver. Another 5-mm trocar is placed at the right midclavicular line below the costal margin to be used by the surgeon. The fifth trocar (12 mm) is placed close to the midline above the umbilicus and used by the surgeon as the main operative port. Laparoscopic survey of the peritoneal and liver surface is performed immediately to detect the presence of any distant disease. A needle-catheter jejunostomy is placed in the jejunum approximately 20 cm distal to the ligament of Treitz. The patient is placed in a reverse Trendelenburg position to help with exposure by displacing the colon caudally. The greater curvature of the stomach is mobilized carefully to avoid injury to the right gastroepiploic vessels. Adhesions in the posterior aspect of the stomach are divided. The gastric fundus is mobilized by dividing the short gastric vessels. The hepatogastric ligament is divided to enter the lesser sac. The left gastric vessels are isolated and divided with a linear stapler (vascular load). Currently, we perform neither pyloroplasty nor pyloromyotomy. Linear staplers are used to create the gastric conduit, starting at the junction of the antrum and body of the stomach and advanced toward the angle of His. A relatively small gastric conduit (3−4 cm in diameter) is created based on the greater curvature of the stomach and separated from the surgical specimen near the angle of His. The gastric conduit is sutured to the surgical specimen with interrupted sutures. The last portion of the abdominal dissection is mobilization of the distal-third esophagus through the hiatus. If needed, a portion of the crus of the diaphragm is divided to enlarge the esophageal hiatus to facilitate delivery of the surgical specimen and gastric conduit.

Stage 2: Thoracoscopic Construction of an Intrathoracic Anastomosis

The patient is now turned to a left lateral decubitus position on a beanbag cushion. The surgeon stands facing the patient's back. Single-lung ventilation using a double-lumen endotracheal tube is initiated by occluding ventilation to the right lung. Four thoracic trocars are introduced in the right chest. The first trocar (11 mm) is placed at the eighth intercostal space below the tip of the scapula and used for the camera. A 5-mm port is placed immediately posterior to the scapula to be used by the surgeon. A 3-cm incision is performed at the ninth intercostal space and 2 cm behind the posterior axillary line. A wound protector sleeve is placed to retract the incision. The last trocar (5 mm) is placed at the sixth intercostal space at the anterior axillary line to be used by the surgical assistant. Carbon dioxide insufflation is not required during thoracoscopy. The 30°-angled scope is used to inspect the mediastinum, pleural cavity, and the surface of the lung for the presence of metastatic disease. The lung lobes are retracted laterally to expose the mediastinal esophagus. The inferior pulmonary ligament is divided with the ultrasonic dissector. The mediastinal pleura, overlying the esophagus, is divided to expose the intrathoracic esophagus. The azygous vein is isolated and divided with the linear stapler (Fig. 1). The esophagus is circumferentially mobilized just below the azygous vein, and a Penrose drain is placed around the esophagus to facilitate esophageal retraction. The esophagus is circumferentially mobilized from the esophageal hiatus up to a level above the azygous vein (Fig. 2). The mediastinal lymph nodes are removed en bloc with the surgical specimen. The esophagus is divided above the azygous vein. The surgical specimen is advanced into the chest, pulling along with it the tethered gastric conduit. The surgical specimen is detached from the gastric conduit and removed through the thoracic incision using the wound protector (Fig. 3). A 25-mm anvil is placed transthoracically into the esophageal stump (Fig. 4). A purse-string suture is placed at the esophageal stump to secure the anvil. A gastrotomy is made at the staple line of the gastric conduit. The 25-mm circular stapler is inserted transthoracically (Fig. 5), placed through the gastrotomy of the gastric conduit, with its tip exiting through the apex of the gastric conduit (Fig. 6). The

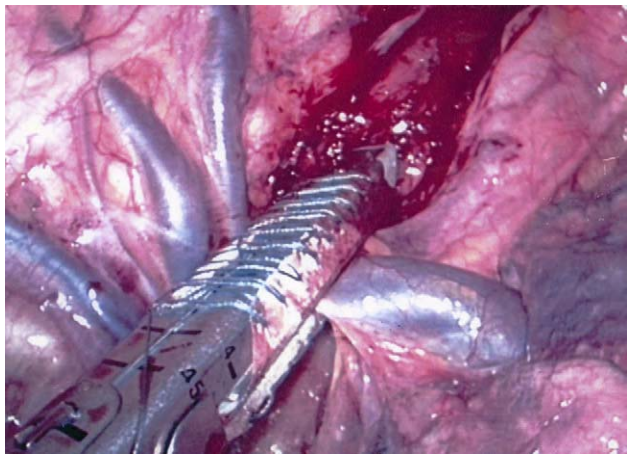

Fig. 1. Thoracoscopic division of the azygous vein with the linear stapler.

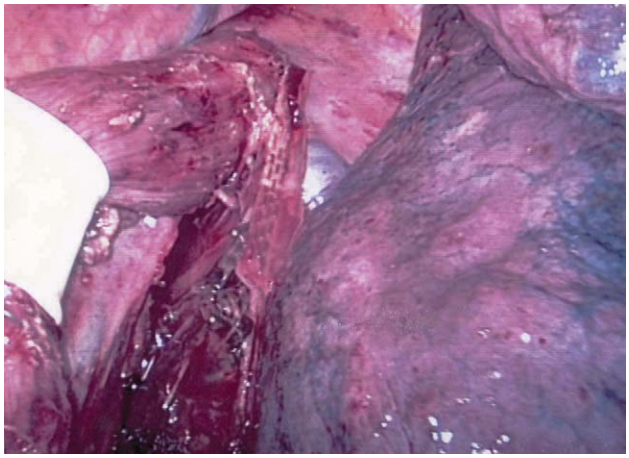

Fig. 2. Thoracoscopic mobilization of the middle-third esophagus above the level of the azygous vein.

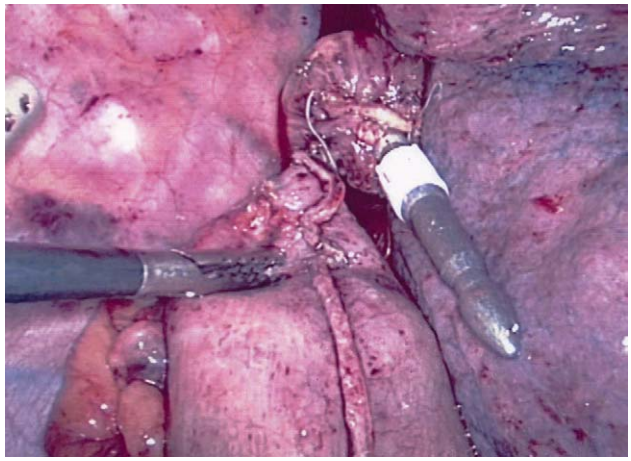

Fig. 4. Thoracoscopic view of gastric conduit and the esophageal stump (an anvil has been placed within the esophageal stump).

cartridge of the circular stapler is attached to the anvil placed within the esophageal stump, and a circular esophagogastric anastomosis is created. A nasogastric tube is positioned through the esophagogastric anastomosis into the gastric conduit using the gastrotomy for direct visualization (Fig. 7). The gastrotomy is closed with a running suture (Fig. 8). The anastomosis is oversewn with interrupted sutures. Fibrin sealant is placed over the anastomosis. A 28-F chest tube is inserted through the camera port for postoperative chest drainage.

DISCUSSION

The Ivor Lewis technique for esophagogastrectomy is a common approach for the treatment for cancer of the distal third of the esophagus and gastric cardia. Minimally invasive Ivor Lewis resection uses both thoracoscopy and laparoscopy rather than a thoracotomy and laparotomy and therefore reduces the operative trauma to the host. The laparoscopic portion of this procedure has been well described by many investigators; however, there have been few reports on the technique of thoracoscopic performance of an esophagogastric anastomosis.[6,7] There are three methods for thoracoscopic construction of the esophagogastric anastomosis: the hand-sewn technique, the linear stapler technique, and the circular stapler technique. Having obtained experience in all three thoracoscopic techniques for creation of an intrathoracic anastomosis, we currently favor the circular stapler technique because of its ease of use and reproducibility.

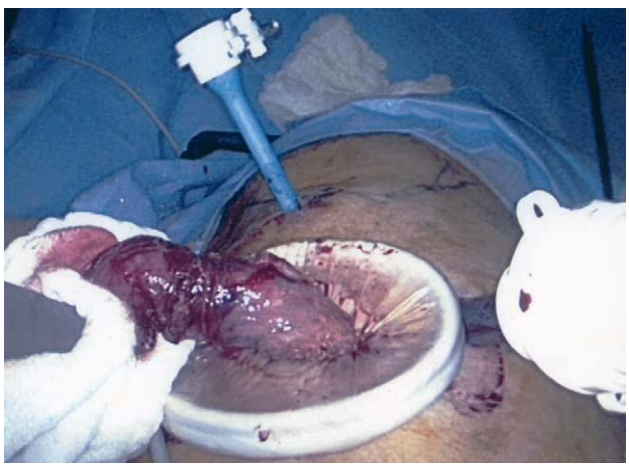

Fig. 3. Removal of the esophageal surgical specimen through the thoracic port, which is protected by a wound protector.

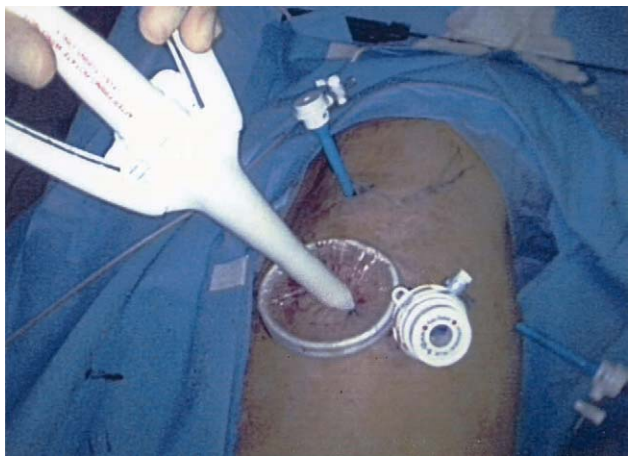

Fig. 5. A circular stapler is inserted transthoracically for creation of the esophagogastric anastomosis.

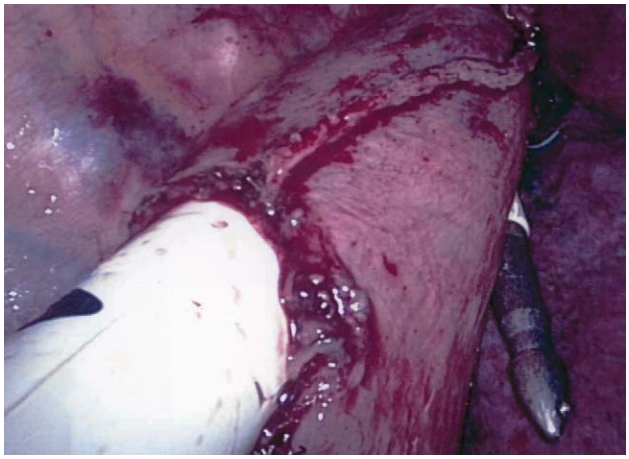

Fig. 6. The circular stapler is inserted through the gastrotomy of the gastric conduit for creation of the esophagogastric anastomosis.

The hand-sewn method is technically challenging and can be time consuming. The linear stapler technique requires a longer gastric conduit, which is not available in all cases. The circular staple technique requires a minimal length of gastric conduit. The most challenging aspect of this technique is placement of the anvil through the esophageal stump and securing it with a purse-string suture. An alternative method is to divide the esophagus with a linear stapler and place the anvil transorally using a nasogastric tube. The transoral method for placement of the anvil has been well described in the laparoscopic gastric bypass literature.[9] This method is facilitated by using an anvil that can be tilted to ease its introduction through the oral pharynx.[10] The 25-mm circular stapler can be placed transthoracically, without the need for resection of a rib, into the gastric conduit. It is important to emphasize that the gastrotomy on the gastric conduit is performed at the staple line. A gastrotomy at any other site on the gastric conduit can compromise the blood flow to the apex of the conduit. The gastrotomy should be closed with sutures rather than with the linear stapler as staple closure can lead to narrowing of the conduit. In addition, tension-relieving sutures should be placed circumferentially at the esophagogastric anastomosis.

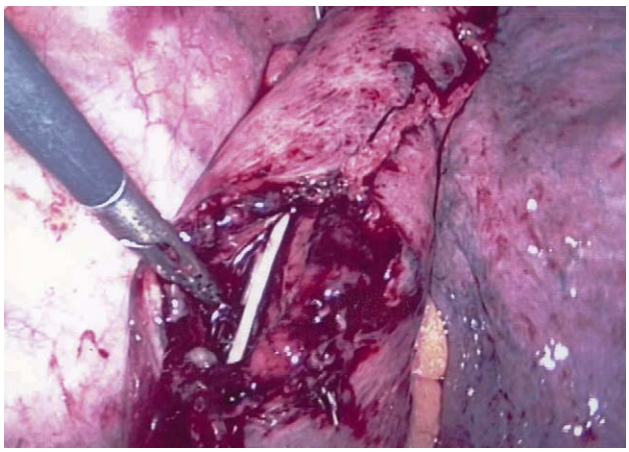

Fig. 7. Thoracoscopic view of the nasogastric tube being positioned through the esophagogastric anastomosis into the gastric conduit.

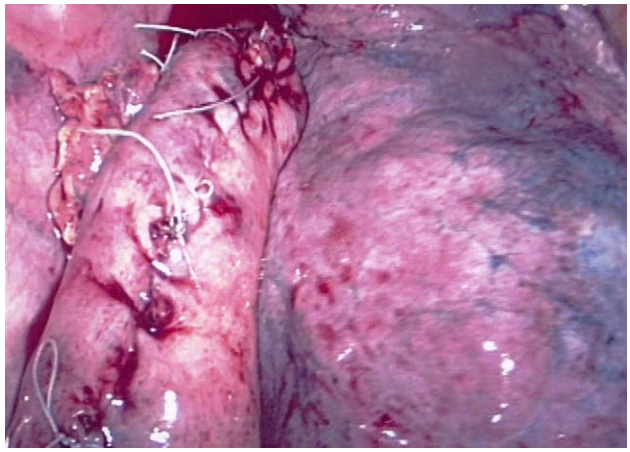

Fig. 8. Two-layer closure of the gastrotomy on the gastric conduit.

In summary, we have described a new and technically feasible thoracoscopic technique for construction of an esophagogastric anastomosis using a circular stapler. This method is applicable for patients requiring resection of the distal esophagus with an intrathoracic anastomosis. As with any new technique, the "learning curve" consists of mastering important steps in performing the procedure and developing the prerequisite technical skills. Surgeons interested in performing thoracolaparoscopic Ivor Lewis resection are encouraged to use the steps described in this article as the basis of performing this complex minimally invasive operation.

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Review Article

Current Management of Enterocutaneous Fistula

Amy R. Evenson, M.D., Josef E. Fischer, M.D., F.A.C.S.

Enterocutaneous fistulas, defined as abnormal communications between bowel and skin, are among the most challenging conditions managed by the general surgeon. In an era when the mortality from pancreaticoduodenectomy is less than 3%, the mortality of enterocutaneous fistulas remains 10 to 30% due to the often-present complications of sepsis, malnutrition, and electrolyte abnormalities. Taking advantage of recent advances in techniques of pre- and post-surgical management and support, employing a multidisciplinary team approach, and executing a well-delineated management plan provide the patient and surgeon with the best possibility of success in treating this potentially devastating condition. (J GASTROINTEST SURG 2006;10:455–464)

KEY WORDS: Enterocutaneous fistula, sepsis, nutrition

CLASSIFICATION, ETIOLOGY, AND PREVENTION

Enterocutaneous fistulas may be categorized by anatomic, physiologic, or etiologic criteria, all of which may influence the patient's course and the likelihood of spontaneous closure of the fistula (Table 1). Anatomic classifications divide fistulas into internal and external fistulas, identify the organs involved, and provide characteristics of the fistula tract. Internal fistulas are connections between two hollow viscera that, if symptomatic or dangerous, should be treated by resection and reanastomosis. The focus of this review will be external fistulas that adjoin hollow viscera to the skin. Favorable external fistula types include esophageal, duodenal stump, pancreaticobiliary, and jejunal fistulas with small enteric defects (<1 cm) and long tracts (>2 cm). Gastric, lateral duodenal, ligament of Treitz, and ileal fistulas are less likely to close spontaneously, as are fistulas associated with complete disruption of intestinal continuity, adjacent abscess, strictured or diseased bowel, foreign bodies, or distal obstruction.[1] Anatomic information is often the first data available and may allow the surgeon to predict the patient's ultimate need for surgical closure.

The external loss of intestinal fluids rich in electrolytes, minerals, and protein contribute to the physiologic complications of electrolyte imbalance and malnutrition in patients with enterocutaneous fistulas. Fistulas may be high-output (>500 ml per day), moderate-output (200–500 ml per day), or low-output (<200 ml per day).[2] Accurate measurement of fistula output allows physiologic classification that assists in anticipating and providing appropriate metabolic support for these patients. Fistula output can also be used to predict mortality as noted in the classic series by Edmunds et al.[3] in which patients with high-output fistulas had a mortality rate of 54%, whereas patients with low-output fistulas died in 16% of cases. In more recent series, Levy et al.[4] report a mortality of 50% and 26% in high- and low-output fistulas, respectively.

The association between fistula output and closure rate is not as clear as that between output and mortality. However, a recent multivariate analysis of 188 patients by Campos et al.[5] revealed that patients with low-output fistulas (defined as <500 ml/day) were three times more likely to undergo spontaneous closure than those with high-output fistulas. This was not the case, however, in the largest series (404 patients)

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Table 1. Predictive factors for spontaneous closure and/or mortality

Factor	Favorable	Unfavorable
Organ of origin	Esophageal	Gastric
	Duodenal stump	Lateral duodenal
	Pancreatic, biliary	Ligament of Treitz
	Jejunal	Ileal
	Colonic	
Etiology	Postoperative (anastomotic leakage)	Malignancy
	Appendicitis	Inflammatory bowel disease
	Diverticulitis	
Output	Low (<200–500 ml/day)	High (>500 ml/day)
Nutritional status	Well nourished	Malnourished
	Transferrin >200 mg/dL	Transferrin <200 mg/dL
Sepsis	Absent	Present
State of bowel	Intestinal continuity	Diseased adjacent bowel
	Absence of obstruction	Distal obstruction
		Large abscess
		Bowel discontinuity
		Previous irradiation
Fistula characteristics	Tract >2 cm	Tract <1 cm
	Defect <1 cm	Defect >1 cm
Miscellaneous	Original operation performed at same institution	Referred from outside institution

published to date.[6] Quantification of fistula output allows more accurate management of the patient, and it may also provide prognostic information regarding mortality and likelihood of eventual surgical therapy.

Determination of the etiologic factors involved in fistula formation also allows prediction of the course of the patient and likelihood of spontaneous closure. Fistulas may first be classified as spontaneous or postoperative, and typically reflect either diseased bowel extending to surrounding structures, normal bowel involved in extraintestinal disease, trauma to the bowel, or anastomotic breakdown. Spontaneous fistulas account for 15%–25% of all enterocutaneous fistulas and are likely to occur in the presence of cancer or radiation, inflammatory conditions including inflammatory bowel disease, diverticular disease, appendicitis, and perforated ulcer disease or ischemic bowel.[1] Of these conditions, cancer and inflammatory bowel disease are most common. Fistulas resulting from malignancy or radiated bowel are unlikely to close spontaneously, whereas those resulting from inflammatory bowel disease may close only to reopen upon resumption of enteral feeding.[6,7] Knowledge of the etiology of spontaneous fistulas, therefore, may lead to earlier surgical therapy.

The majority of enterocutaneous fistulas (75%–85%) are postoperative. Procedures performed for malignancy, inflammatory bowel disease, or adhesiolysis are the most common operations antecedent to the development of enterocutaneous fistulas.[2] Factors contributing to the development of postoperative enterocutaneous fistulas may be classified as patient-specific or technique-specific. Specific risk factors for patients include operation for the previously listed conditions, previous radiation therapy, malnutrition, infection or sepsis, and operations in an emergency setting with possible concomitant hypotension, anemia, hypothermia, or poor oxygen delivery. For elective operations, control of infection and improvement of nutrition may be possible, but for emergency operations, one can only hope to optimize resuscitation and perfusion and perform a technically meticulous procedure.

Specific techniques to decrease the incidence of postoperative enterocutaneous fistulas are those of sound surgical practice. Preoperatively, the nutritional status of the patient should be assessed. Patients with a recent 10%–15% weight loss, an albumin of less than 3.0 grams per deciliter, or low transferrin or total lymphocyte levels (although this is less well proven) are at increased risk for poor healing and possible anastomotic dehiscence. Patients should be normovolemic and not anemic to optimize oxygen delivery. Preoperative skin preparation, mechanical and antibiotic bowel preparation, and systemic antibiotics decrease the risk of infection, abscess, and therefore, fistula formation. During the procedure, the surgeon's emphasis should be on avoiding tension, ensuring adequate blood supply, and using nondistended, nondiseased bowel for anastomosis.[1] Additionally, meticulous hemostasis must be achieved, and inadvertent enterotomies and serosal injuries should be identified and repaired. If possible, the anastomosis should be shielded from the incision by an omental flap. Finally, a secure abdominal wall closure should be performed, taking care to not injure underlying bowel.[7] In the postoperative period, adequate oxygen-carrying capacity should be maintained and nutritional support provided as necessary. In cases of significant contamination, antibiotics—as therapeutic agents—should be continued briefly in the postoperative period (24–48 hours). Given the complex physiologic and management challenges created by

postoperative enterocutaneous fistulas, use of sound surgical technique in preventing this catastrophic complication is paramount.

COMPLICATIONS

Edmunds et al.[3] identified the classic triad of complications of enterocutaneous fistula as sepsis, malnutrition, and electrolyte and fluid abnormalities. The presence of bowel contents outside the lumen may lead to localized abscess, soft tissue infection, generalized peritonitis, or frank sepsis, depending on whether the bowel leak communicates with the peritoneal cavity or soft tissues. Early control of fistula output, drainage of localized collections, and appropriate antibiotic therapy are keys in the early management of these patients. In a recent large series, Campos et al.[5] reported that the presence of infectious complications increased the odds ratio of death by 22-fold. Most recent series suggest that sepsis, with its concomitant malnutrition, is the leading cause of death in patients with enterocutaneous fistulas.[5,6,8]

Postoperative ileus, the loss of bowel integrity and absorptive surface area, and the external loss of protein-rich enteric contents all contribute to the malnutrition and fluid and electrolyte abnormalities seen in patients with enterocutaneous fistulas. Even in an era when rapid, accurate determination of serum electrolytes is available, disorders of electrolytes are frequently present for greater than 24 hours, perhaps reflecting the difficulty in "keeping up" with fistula losses. Identifying the source of the fistula will allow a rough estimate of the composition of the fluid lost. In complex situations, analysis of fistula-output electrolyte composition may aid in maintaining normal levels of important electrolytes, including sodium, magnesium, potassium, phosphate, bicarbonate, and calcium.

Further complicating the scenario, septic patients are extremely hypercatabolic and are unable to achieve positive nitrogen balance, regardless of the provision of artificial nutrition. In the series of Hill et al.,[9] patients with uncontrolled sepsis lost 2% of body protein stores per day, even though they were receiving parenteral nutrition. Over the course of two weeks, these patients lost 1.4 kg of body protein (24% of total) despite the gain of 1.9 kg of fat.[9] Developing a plan to control sepsis and provide adequate nutrition through a combination of enteral and/or parenteral nutrition is a key element to management of these patients.

The provision of total parenteral nutrition has been associated with an increased rate of spontaneous closure of fistulas in several series.[6,9–12] In patients requiring surgical closure of their fistulas, any improvement in the nutritional status will aid in maintaining bowel continuity by promoting wound healing, enhancing the immune system, and preserving lean cell mass. Nutritional status is an important predictor of mortality in patients with enterocutaneous fistulas. Fazio et al.[8] reported no mortality in patients with serum albumin levels greater than 3.5 g/dL, whereas those with albumin levels less than 2.5 g/dL experienced a mortality rate of 42%. Similarly, serum transferrin level was recently reported to predict both mortality and the rate of spontaneous closure of enterocutaneous fistulas, whereas retinol-binding protein and thyroxin-binding prealbumin predicted only mortality.[13] Interestingly, in this group of patients, serum albumin predicted neither mortality nor spontaneous closure.

MANAGEMENT

When approaching any complex situation, the use of a detailed, multidisciplinary plan aids in management. The following five steps represent a progression from identification and stabilization of the patient, investigation into the type and character of the fistula, decision making regarding the need for surgery, definitive surgical repair, and promotion of healing. The ultimate goal is to restore the integrity of the patient's gastrointestinal tract and allow enteral nutrition while minimizing morbidity and mortality (Table 2).

Stabilization

Identification. Typically, the patient with an enterocutaneous fistula has had a poor early postoperative course complicated by fevers and a prolonged ileus. Toward the end of the first postoperative week, wound erythema has developed. The wound has been opened and drained purulent fluid, followed shortly by enteric contents. At this point, the patient has suffered multiple stresses, including the disease process leading to operation, a preoperative bowel preparation, the surgical stress of the procedure, and a prolonged postoperative course now complicated by sepsis and the metabolic consequences of the fistula. The patient has typically lost lean body mass due to this prolonged period of no or limited nutritional support. The patient is likely to be dehydrated, anemic, and have low levels of the major serum oncotic proteins including albumin.

Resuscitation. Restoration of circulating volume is the first goal. Crystalloid resuscitation may require several liters to correct for losses into the bowel

Table 2. Management phases

Phase	Goal	Time course
Recognition/stabilization	Resuscitation Crystalloid, colloid, blood	24–48 hours
	Control of sepsis CT-guided or open drainage, antibiotics	
	Electrolyte repletion	
	Provision of nutrition	
	Control of fistula drainage	
	Commencement of local skin care/protection	
Investigation	Fistulogram to define anatomy and characteristics of fistula	7–10 days
Decision	Evaluate likelihood of spontaneous closure Etiology, anatomy, drainage output	
	Decide duration of trial of nonoperative management	10 days to 6 weeks
Definitive therapy	Plan operative approach	When closure unlikely or after 4–6 weeks
	Refunctionalization of entire bowel	
	Resection of fistula with end-to-end anastomosis	
	Secure abdominal closure	
	Gastrostomy/jejunostomy	
Healing	Continue nutrition support until full oral nutrition is achieved by patient	Starting 5–10 days after closure until full oral nutrition
	Zinc supplementation	

wall and third spaces. Transfusion of red blood cells will improve oxygen-carrying capacity, whereas infusion of albumin will help restore plasma oncotic pressure. Caution should be exercised in patients with sepsis-induced capillary leak, as albumin may wors respiratory parameters due to accumulation in the pulmonary interstitium. In patients at risk of pulmonary or cardiac embarrassment, placement of a central venous pressure monitor or pulmonary artery catheter may aid in resuscitation.

Control of sepsis. Concurrent with resuscitation, evaluation for treatable foci of sepsis should be a primary goal during this phase of management. Computed tomography may assist in revealing intraperitoneal abscesses that may then be percutaneously or operatively drained. Proximal diversion may be considered if operative drainage is required, but definitive resection and repair of the fistula should be deferred due to the high probability of recurrence in the setting of emergency surgery in a septic patient. In draining abscesses, the surgeon should consider injection of water-soluble contrast into the abscess cavity as a means of identifying the fistulous tract and its communication with the bowel. Understanding that any manipulation of septic foci may lead to bacteremia, central venous catheters should not be placed for 24 hours following drainage. Material from the abscess should be sent for microbiologic culture.

Septic patients should be treated initially with empiric antibiotics that are then tailored to the specific pathogens identified. The presence of an enterocutaneous fistula without evidence of sepsis (high fever, rigors, and hypotension) or a localized infection (cellulitis, pneumonia, etc.) does not warrant antibiotic therapy. Indiscriminate use of prophylactic antibiotics in patients with enterocutaneous fistulas will lead to the emergence of highly resistant bacteria. Special consideration should be given to the treatment of fungal infections in patients with enterocutaneous fistulas. In patients with yeast cultured from two or more sites, a low threshold for use of amphotericin B should be maintained.

Nutritional support. The provision of nutritional support is a key component of the stabilization phase. As previously discussed, patients with enterocutaneous fistulas are often malnourished due to the lack of food intake, the hypercatabolism of sepsis, and the loss of protein-rich enteral contents. After sepsis has been controlled, the metabolic needs of the patient are considered. The patient's current nutritional status should be assessed using such tools as the bedside subjective global assessment,[14] baseline laboratory values, anthropometric analysis, and potentially new techniques such as multiple-frequency bioelectric impedance analysis.[15,16] Once baseline assessment has occurred, the patient's estimated metabolic needs should be calculated. Traditionally,

the Harris-Benedict equations and use of the appropriate stress factor have provided a meaningful starting point for nutritional support. More recent use of metabolic cart analysis (indirect calorimetry) allows for assessment of the respiratory quotient and appropriateness of the macronutrient balance. In our experience, patients with enterocutaneous fistulas generally require 25 to 32 kcal/kg per day in total calories with a calorie-to-nitrogen ratio of 150:1 to 200:1 and a protein intake of at least 1.5 g/kg per day. As many authors have noted, formulas provide a convenient starting point for estimating the nutritional requirements of patients with enterocutaneous fistulas, but ongoing clinical assessment with adjustment according to the patient's course is essential in managing these complex situations.

Parenteral nutrition has long been recognized to be an integral part of the management of enterocutaneous fistulas.[6,11,12] Our own experience and several recent series report the use of enteral nutrition either in combination with parenteral nutrition or as a primary means of nutritional support.[4,17] Whereas 85% of Levy's patients with high-output small bowel fistulas were able to be sustained on enteral nutrition alone, the provision of only 20% of calories fed enterally may protect the integrity of the mucosal barrier as well as the immunologic and hormonal function of the gut. Enteral feeding also improves hepatic protein synthesis. As patients often do not reach caloric support goals via the enteral route for several days after starting the feedings, it is prudent to commence both parenteral and enteral support early in these patients, with the plan to cease parenteral support if enteral feeding goals are met. In cases of proximal fistulas, feedings may be infused into the fistula if there is sufficient distal small bowel length (approximately 4 feet) and no distal obstruction. Newer enteral formulations containing supplements, including glutamine, arginine, omega-3 fatty acids, and nucleotides, may provide immune-enhancing effects in critically ill patients, but studies in this population have not yet been reported.

Except for extremely high-output fistulas, the provision of electrolytes via parenteral or enteral nutrition is adequate. Although knowledge of the source of fistula output may allow estimation of the composition of the losses, the effluent may be a combination of secretions from sites proximal and distal to the fistula.[18] Vitamins and trace minerals are often deficient in malnourished patients with enterocutaneous fistulas. We often provide twice the recommended daily allowance of vitamins and trace minerals, and up to 10 times the recommended daily allowance for vitamin C and zinc. For long-standing small bowel fistulas, supplemental copper, folic acid, and vitamin B12 may be necessary.

Control of fistula drainage. Many authors have recommended the use of long-term nasogastric drainage as a means to decrease fistula output. In the absence of obstruction or prolonged ileus, however, there is little evidence that nasogastric drainage is beneficial. Nasogastric tubes may instead contribute to sinusitis, gastroesophageal reflux, pulmonary aspiration, and patient discomfort. Use over a prolonged course may also place patients at risk of late esophageal strictures.

Acid suppression with H_2-receptor antagonists or proton-pump inhibitors may decrease the volume and acidity of gastric secretion. Although these interventions have not been shown to increase the rate of fistula closure, acid suppression may aid in the prevention of gastritis and stress ulceration, whereas decreasing fistula output will allow easier control of electrolyte and acid-base imbalances. Another method for decreasing gastric acidity is the use of sucralfate; this agent also has the ability to constipate, thereby decreasing fistula output as well.

Somatostatin and its analog, octreotide, inhibit the endocrine and exocrine secretion of many gastrointestinal hormones, including gastrin, cholecystokinin, secretin, insulin, glucagon, and vasoactive intestinal peptides.[19] Additionally, somatostatin and its analogues inhibit gastric acid secretion, pancreatic exocrine secretion, and intestinal and gallbladder motility and contractility. The potential role of somatostatin and octreotide in the treatment of enterocutaneous fistulas is obvious; unfortunately, the use of these substances in management of patients has not significantly improved outcome.[20,21] Randomized controlled trials comparing the use of somatostatin—in combination with conservative measures including total parenteral nutrition (TPN) to conservative measures alone—demonstrated an inconsistent decrease in fistula output and time to closure but did not increase the rate of nonoperative closure.[22] Randomized controlled trials comparing the use of octreotide with nonoperative therapy similarly failed to demonstrate a consistent decrease in fistula output, time to closure, or closure rate.[23–25] Additional problems related to somatostatin use include the need for a continuous intravenous infusion, the frequent incidence of hyperglycemia, and significant rebound effect when discontinued.[20] The use of octreotide allows subcutaneous dosing on a two or three times per day schedule and does not seem to be associated with hyperglycemia. Both hormones are associated with an increased incidence of cholelithiasis. In summary, although these hormones may decrease fistula output and therefore simplify the

management of enterocutaneous fistulas, evidence from randomized controlled trials does not indicate their use in the routine care of fistula patients.

Recent success in the treatment of perianal fistulizing Crohn's disease has lead to interest in the use of infliximab, a chimeric monoclonal antibody to tumor necrosis factor α, in patients with enterocutaneous fistulas. Present et al.[26] reported a randomized controlled trial enrolling 94 patients with abdominal (10%) and perianal (90%) fistulas secondary to Crohn's disease, which had been present for at least 3 months. In this population, a significantly larger proportion of patients receiving infliximab had a reduction in the number of draining fistulas at follow-up than control patients. As 90% of these patients had perianal fistulas, and all fistulas had been present greater than 3 months, the applicability of these results to the patients with typical enterocutaneous fistulas described throughout this review is limited. A smaller study of seven patients with enterocutaneous fistulas in the setting of refractory pouchitis following ileal pouch-anal anastomosis for ulcerative colitis revealed encouraging preliminary results.[27] In this series, six of the seven patients had a complete symptomatic response, whereas five had complete fistula closure after 10 weeks of follow-up.[27] Although encouraging, this is a small, nonrandomized study in a highly selected population. Side effects reported in these studies included headache, abscess, upper respiratory tract infection, and fatigue. Of concern in typical enterocutaneous fistula patients, infliximab should not be used in the setting of clinically important, acute infections. The role of infliximab in the management of enterocutaneous fistulas remains to be resolved.

Protecting the integrity of the skin surrounding a fistula will decrease local irritation and infection. Further, an intact abdominal wall will aid in secure closure of the abdomen should operation be required. There have been many methods reported for the management of fistula drainage, including simple gauze dressings, skin barriers, pouches, and suction catheters. If the fistula output is low, simple absorbent dressings may suffice. However, in more complicated cases, karaya powder or seal, Stomahesive (ConvaTec, Victoria, Australia), glycerin, or ion exchange resins may be needed to protect the skin from maceration and breakdown. A sump drain constructed from a Robinson nephrostomy catheter vented using a 14-gauge Angiocath provides effective drainage for most fistulas (Fig. 1). A skilled enterostomal therapist can significantly contribute to the care of patients with enterocutaneous fistulas.

Several authors have reported the use of vacuum-assisted closure (VAC) systems in managing enterocutaneous fistulas. Erdmann et al.[28] reported the successful use of a VAC dressing in treating a small bowel fistula draining 200–500 ml per day. After 4 weeks of every-other-day dressing changes, the fistula output had decreased to less than 30 ml per day, and the fistula was completely closed by 8 weeks of treatment. Alvarez et al.[29] reported a patient who developed an enterocutaneous fistula during chemotherapy for ovarian cancer. A VAC dressing was applied with daily dressing changes, resulting in closure of the fistula by 2 months of treatment. Cro et al.[30] reported a series of three patients with high-output small bowel fistulas (300 ml/day to over 1000 ml/day). After treatment of the fistulas with a VAC dressing system, all three patients experienced significant decreases in fistula output within 4 weeks of treatment, and two of the three fistulas resolved without surgical intervention. When a fistula is large and difficult to dress, a VAC system may make skin care easier (Fig. 2). Although these cases are encouraging, it must be noted that the use of the VAC system on enterocutaneous fistulas is considered experimental and should be used with caution.

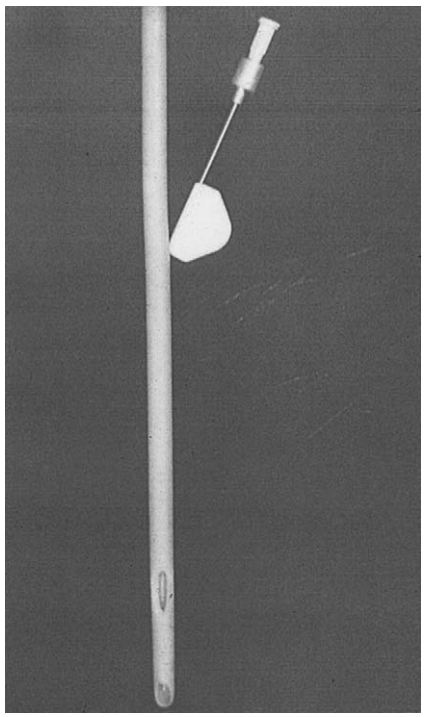

Fig. 1. Construction of a wound sump. A Robinson nephrostomy catheter is placed in the wound near the fistula opening. The catheter is vented with a 14-gauge Angiocath and connected to wall suction. The catheter is sutured to the wound edges and covered with gauze or a VAC dressing.

Investigation

Once the patient has been resuscitated and stabilized, investigation into the course and nature of the

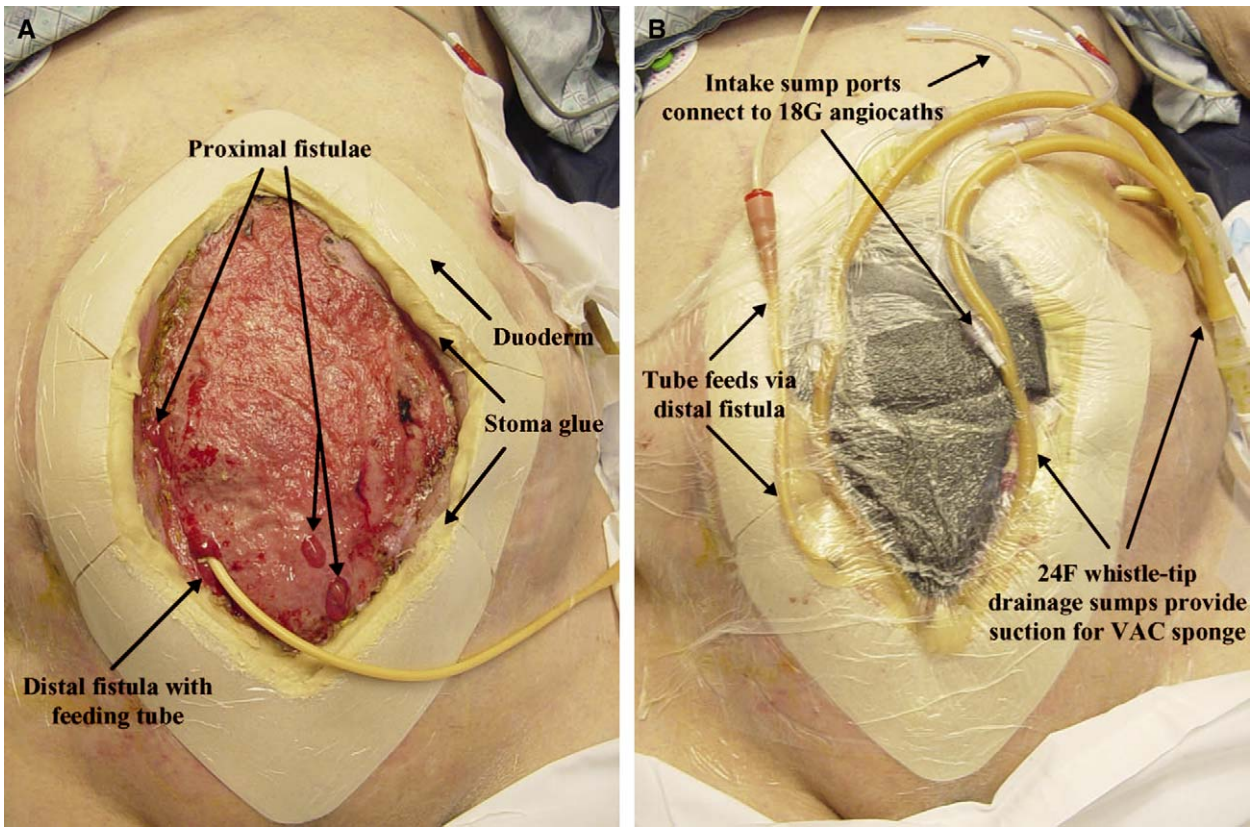

Fig. 2. Use of VAC dressing in the management of an enterocutaneous fistula. In this patient, we used a VAC dressing to manage wound drainage. Additionally, tube feeding into the distal fistula provided nutrition during this stage of management of the fistula. The dressing change initially took two to two and one half hours and was performed every 3 to 5 days. Operative closure of the fistula was successful and was combined with a flap abdominal wall closure. (**A**) Demonstrates the multiple fistula openings, a distally placed feeding tube, and surrounding DuoDerm and stoma glue. (**B**) Demonstrates the VAC dressing in place with suction applied.

fistula should be undertaken. Some authors recommend enteral use of methylene blue as a "rough and ready" test to confirm the presence of an enterocutaneous fistula and to determine whether the leak is from a segment of bowel in continuity with the rest of the digestive tract versus a leak from a segment not in continuity.[31] The methylene blue test does not provide significant anatomic information and is not often used in our practice.

After 7 to 10 days, the patient has generally stabilized, and the fistula has matured to the point of supporting intubation of thin catheters in all orifices. At this point, the patient should undergo fluoroscopic fistulography with water-soluble contrast under the direct supervision of a senior radiologist and the senior surgeon responsible for the patient's care. The information gained by such a study includes (1) the source of the fistula; (2) the nature (length, course, and relationships) of the fistula tract; (3) the absence or presence of bowel continuity (end vs. side fistula); (4) the absence or presence of distal obstruction; (5) the nature of the bowel adjacent to the fistula (inflammation, stricture); and (6) the absence or presence of an abscess cavity in communication with the fistula.[32]

The fistulogram provides information not obtainable through any other study, and early films can be particularly useful in defining anatomy and relationships. As previously discussed, water-soluble contrast may also be injected into abscesses at the time of drainage as a type of early fistulogram.

As discussed previously, in a septic patient CT can identify abscesses and may guide percutaneous drainage. Fistulas are not often seen distinctly on axial CT. However, data derived from the use of saggital or three-dimensional reconstructions may be helpful. Upper gastrointestinal studies and barium contrast enemas rarely provide information not obtained via fistulography. When considering the use of multiple contrast studies, the order of the tests

needs to be considered, as retained contrast may limit the utility of subsequent studies.

Decision

Ideally, the provision for adequate nutrition in patients free of sepsis will result in closure of enterocutaneous fistulas within 4 to 6 weeks. Unfortunately, spontaneous closure occurs only in about 30% of patients. It is possible to identify anatomic, etiologic, and functional characteristics of fistulas that are unlikely to close spontaneously (Table 1). Fistulas of the stomach, ileum, and ligament of Treitz are less likely to close spontaneously, as are fistulas associated with large abscesses, short fistula tracts, large openings in the bowel, damaged or strictured intestine, intestinal discontinuity, or distal obstruction. In these cases, if closure or signs of imminent closure (decrease in output) do not occur after 4 weeks, plans for operative resection should be made. Fistulas associated with cancer, radiation, or inflammatory bowel diseases are also unlikely to close or remain closed without surgical intervention. In the case of inflammatory bowel disease, should the fistula close spontaneously, definitive resection and reanastomosis should be performed to avoid recurrence. Similarly, fistulas occurring in the setting of cancer should be resected with consideration of intraoperative radiation, if appropriate. One etiology of fistulas that has become more common is erosion of previously placed Marlex mesh. In a recent case of fistulization involving Marlex mesh, resection of the mesh allowed spontaneous fistula closure.

In planning for operative management of enterocutaneous fistulas, the surgeon must balance the adequacy of nutritional support, the likelihood of spontaneous closure, and the likelihood of the technical feasibility of the procedure. Fazio et al.[8] described the "obliterative peritonitis" that occurs during the period from approximately 10 days to 6 weeks following laparotomy in patients with enterocutaneous fistulas associated with sepsis. Although selection bias was clearly involved, patients who were operated on within 10 days of their original surgery and those whose operations were delayed at least 6 weeks had mortality rates of 13% and 11%, respectively.[8] In contrast, patients requiring relaparotomy during the period between 10 days and 6 weeks of their initial surgery suffered a mortality rate of 21%.[8] Soeters et al.[6] similarly recommended providing nutritional support during this period to allow the "future operative field to become quiescent." Ninety to 95% of fistulas that will spontaneously resolve do so postoperatively within the first 4 to 5 weeks. Delaying an operation this long will both allow those fistulas that are likely to close an opportunity to do so, while at the same time decreasing the risks of multiple enterotomies and difficult dissection in the immediate postoperative period.[12] Our own practice generally tries to wait at least 4 months from the previous operation. This does not prolong the wait, as most of the patients in this practice are transferred from other facilities and require weeks of preparation for nutritional parameters to improve so that operation can be carried out safely. Our own operative mortality for an elective operation in patients with fistulas is less than 2%, despite the length of operation—often 8 hours.

Definitive Therapy

The decision to operate on a patient for resolution of an enterocutaneous fistula represents a significant commitment of time, energy, and resources. The surgical team should be well rested and have a 6 to 8 hour block of time to dedicate to the case. The patient should have achieved optimal nutritional status and should be free of all sources of sepsis. A healed abdominal wall with minimal inflammation will afford the most secure closure. Enteral tube feedings should be decreased in the days preceding operation to allow luminal antibiotic preparation. Microbiologic data should be reviewed and appropriate antibiotic prophylaxis administered.

At operation, the abdomen should be entered through a new incision far from any areas of potential sepsis. A transverse incision often offers the best opportunity of entering the abdomen in an area free of dense adhesions. If use of the prior midline incision is required, the abdomen should be entered either above or below the extent of the previous incision. Either approach minimizes the risk of creating enterotomies while attempting to gain access to the peritoneum. Once the peritoneum has been entered, either wound towels or wound protectors should be employed to protect the tissues of the abdominal wall from contamination.

The goal of the next and main stage of the operation is to free the entire bowel from the ligament of Treitz to the rectum. Exploration of the bowel in this manner ensures that all abscesses and sources of obstruction are identified and resolved to avoid failure of the present anastomosis. Some authors advocate commencing dissection at the ileum and working proximally. In general, the pattern of adhesions may guide the operation with effort concentrated on the "easiest" sections first. Application of antibiotic-soaked laparotomy pads to areas of dense adhesions creates edema that facilitates further dissection. Dissection of adhesions should be

performed sharply using a combination of scalpel and scissor dissection. Placing the operating surgeon's left hand behind the adhesions and cutting them from the side provides a controlled environment to further protect the bowel from inadvertent enterotomy.

Upon isolation of the segment of bowel containing the fistula, optimal management requires resection of the diseased segment. If multiple loops of bowel are involved in the fistula, they are most often adjacent, facilitating management. Exteriorization, bypass, Roux-en-Y drainages, and serosal patches, typically using jejunum, are options for difficult cases but do not provide optimal results. The creation of a two-layer, interrupted, end-to-end anastomosis using healthy bowel and nonabsorbable sutures maximizes the likelihood of a secure anastomosis. Upon completion of the resection and anastomosis, the entire bowel surface is inspected to identify serosal tears or enterotomies. Serosal tears are repaired using nonabsorbable Lembert sutures, usually a monofilament 4.0 or 5.0 suture. Closure of full-thickness enterotomies is in the manner of Heineke-Mikulicz. Meticulous attention to detail in reoperative surgery increases the odds of a good outcome.

Prior to closure of the abdominal wall, extensive peritoneal irrigation with antibiotic solution is performed. If available, the omentum may be placed between the fresh anastomosis and the peritoneal closure. Placement of a decompressive gastrostomy and a feeding jejunostomy will aid in the postoperative management of most patients undergoing procedures of this magnitude. Closed suction drainage may be considered in particularly difficult cases. Seprafilm is a useful adjunct to minimize future adhesions.

Secure abdominal wall closure is paramount to prevent recurrence of fistulization. Maintenance of an infection- and inflammation-free abdominal wound during the preoperative period may allow for primary closure of the incision. If a difficult closure is anticipated, the involvement of the plastic and reconstructive surgical service in the planning of such a procedure is advised. The undertaking of a complicated myocutaneous flap procedure is best left to a fresh team after a difficult abdominal dissection.

Healing

Whether closure occurs spontaneously or by operative means, continued nutritional support is essential for maintenance of intestinal continuity and abdominal wall closure. Healing requires positive nitrogen balance, and the cessation of adequate caloric and protein support in the early postoperative period often results in the degradation of newly synthesized protein. The provision of supplementary nutrition is advised until the patient is able to consistently consume 1500 kilocalories by mouth. Passage through the traditional steps of dietary advancement (clear liquids, full liquids, soft diet, and full diet) is unlikely to be tolerated by these patients. Instead, starting a soft diet approximately 1 week postoperatively and inviting family members to bring in the patient's favorite foods may increase the patient's desire to eat. Similarly, cycling tube feedings to run overnight may increase the patient's appetite during the day. Finally, the provision of zinc supplementation with 220 mg per day may improve or restore the patient's sense of taste and increase food intake.

CONCLUSIONS

Knowledge of the pathophysiology and risk factors for the development of enterocutaneous fistulas may optimize the ability to avoid their creation in the first place. Once this catastrophic complication occurs, the best outcomes result from a rational, well-defined management protocol. Early diagnosis of the fistula and resuscitation of the patient, the control of sepsis, and the provision of nutritional support may limit the morbidity and mortality associated with this complication. After adequate stabilization, investigation and an attempt at nonoperative management may allow for spontaneous closure of the fistula, thus avoiding the risks of a major reoperative procedure. Should operative intervention be required, careful planning and meticulous execution of the resection, reanastomosis, and reconstruction of the abdominal wall maximize the patient's chances of successful resolution. Attention to postoperative maintenance of adequate nutrition during the transition back to oral feedings ensures the durability of the repair. Solid, evidence-based surgical and perioperative management may allow restoration of the patient to a functional and productive role in society.

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Giant Peritoneal Loose Bodies

Kazuaki Takabe, M.D., Ph.D., Joshua I. Greenberg, M.D., Sarah L. Blair, M.D., F.A.C.S.

Peritoneal loose bodies are usually small, white or pale gray, pea-shaped objects with a smooth glistening surface, which lie free in the peritoneal cavity. They rarely cause symptoms and are usually found incidentally during laparotomy or autopsy. We herein report a patient with two giant peritoneal loose bodies that were found during laparotomy for partial small bowel obstruction. (J GASTROINTEST SURG 2006;10:465–468)

KEY WORDS: Peritoneal loose body, small bowel obstruction, appendices epiploicae, calcified body, incidental finding

Peritoneal loose bodies are usually small, white or pale gray, pea-shaped objects with a smooth glistening surface, occasionally found incidentally during laparotomy or autopsy.[1] They usually lie free in the peritoneal cavity, are 5–25 mm in diameter, and rarely cause symptoms. Herein, we report a patient who presented with partial small bowel obstruction and had two giant peritoneal loose bodies at operation.

CASE REPORT

A 68-year-old Caucasian male was admitted to the hospital with a 4-day history of nausea, vomiting, cramping abdominal pain, and diarrhea. He had repeated bouts of emesis after every meal. He had had an appendectomy for ruptured appendicitis complicated by abscess formation and a protracted hospital course of 6 weeks at the age of 18 years, and a small bowel obstruction at the age of 58 years, which resolved with conservative management. Upon admission the patient was afebrile, with mild abdominal distension, mild tenderness to palpation diffusely, guarding, no rebound, no masses felt, and tympanic high-pitched bowel sounds. Laboratory tests were all within normal limits. An abdominal radiograph revealed multiple dilated loops of small bowel with air-fluid levels consistent with partial small bowel obstruction. After 5 days of conservative management, which did not improve his symptoms, an abdominal computed tomographic (CT) scan revealed mild dilation of the proximal small bowel, two large, oval-shaped stones (4.2 × 3.3 cm and 3.2 × 2.2 cm; Fig. 1) with lamellar-like calcifications, and decompressed small bowel distal to the stones.

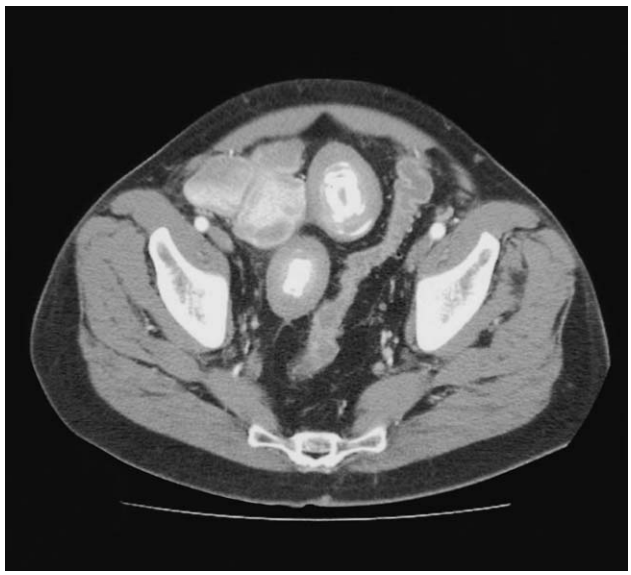

Fig. 1. Computed tomographic scan of the pelvis. Two large oval shaped objects with concentric, lamellar-like calcifications were visualized, sizing 4.2 × 3.3 cm and 3.2 × 2.2 cm, respectively. The small bowel appeared mildly dilated proximal and decompressed distal to the objects.

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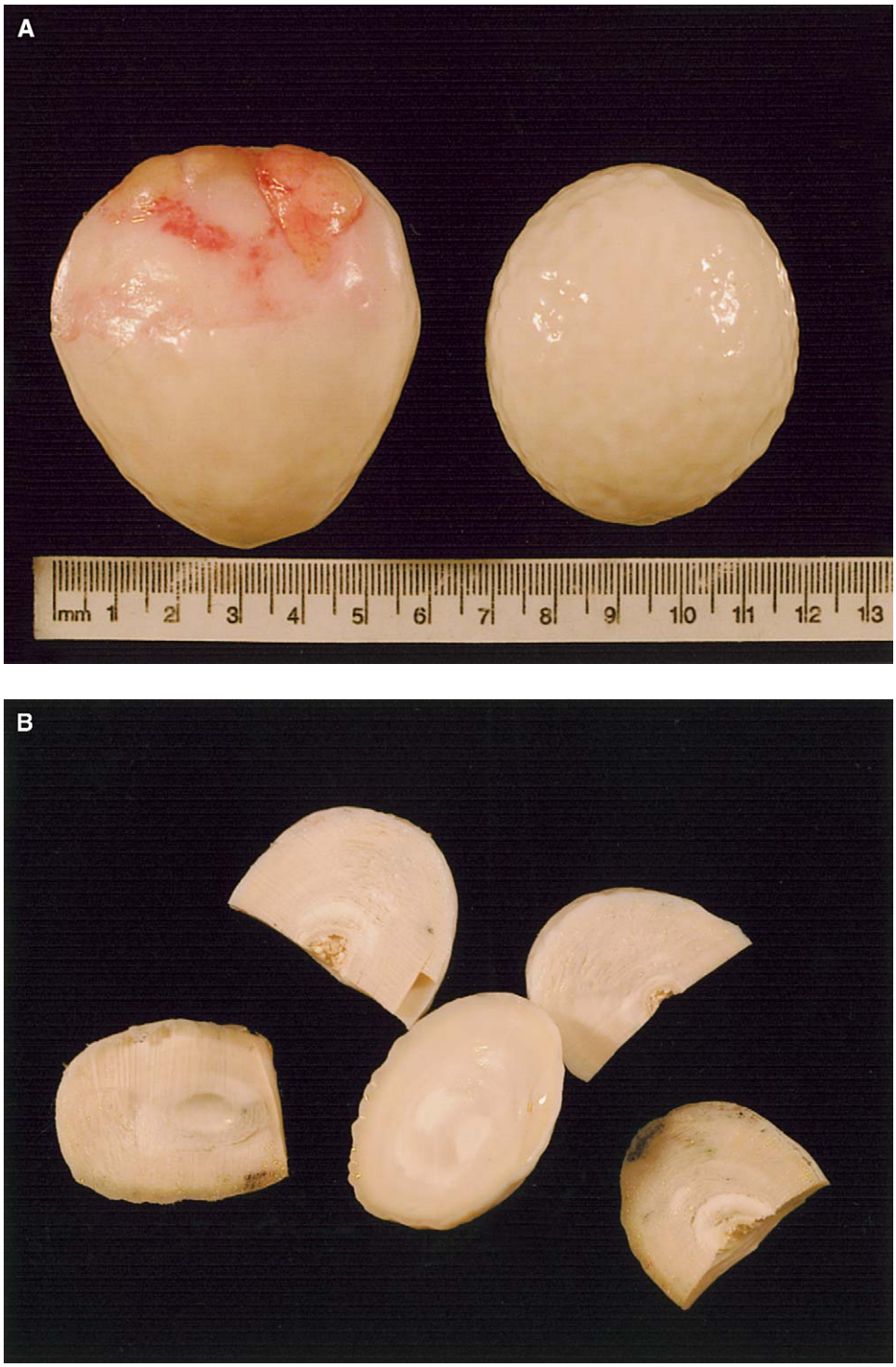

Fig. 2. (**A**) Macroscopic appearance of the giant peritoneal loose bodies. Spherical, egg-shaped, white firm tissue measuring 5.8 × 5.6 × 3.8 cm with small foci of adherent adipose tissue (left), and 5.2 × 4.5 × 3.7 cm (right), respectively. (**B**) Sections of the loose bodies revealed concentric, calcific, ringlike structures surrounding a 1.3 cm diameter central portion of white/yellow, cheesy/mushy material.

Together with the fact that several small stones were in the gallbladder, gallstone ileus was suspected, although there was no evidence of gallbladder fistula, gallbladder wall thickening, intrabiliary gas, or pericholecystic fluid.

Because the patient failed to improve, exploratory laparotomy was performed. Two giant peritoneal loose bodies were found, one free-floating in the right lower quadrant and another attached to the peritoneal surface of the bladder and sigmoid colon. The latter was easily removed from both organs (Fig. 2, *A*, *B*). Intraoperative cystogram with indigo carmine did not reveal extravasation. Histology of the loose bodies showed dense, focally laminated, eosinophilic material without associated inflammatory or foreign body reaction (Fig. 3). No evidence of tumor, parasite, or polarizable substance was present. Trichrome stain showed intensely staining collagen at the periphery of the object. The center showed what appeared to be a combination of fat and fibrinous material. Therefore, the loose bodies were diagnosed to be lesions with central fat necrosis surrounded by a dense fibrosis, findings consistent with large infarcted appendix epiploica. Postoperatively, the patient had slow return of his bowel function and was discharged on postoperative day seven tolerating a regular diet. The patient was followed up at our clinic 2 weeks after his discharge and had no signs or symptoms of bowel obstruction. He has never returned to our clinic.

DISCUSSION

Small bowel obstruction is one of the most common problems encountered by gastrointestinal surgeons in daily practice. The major cause by far of small bowel obstruction is postoperative adhesions (more than 60%), followed by malignant tumors (approximately 20%), hernias (approximately 10%), and Crohn's disease (approximately 5%). Miscellaneous causes of bowel obstruction account for 2–3% of all cases, including intra-abdominal abscess, intussusception, gallstone, enteroliths, foreign bodies, and phytobezoars.[2] To our knowledge, small bowel obstruction associated with giant peritoneal loose bodies has not been described previously. One of the loose bodies in our patient was free-floating in the right lower quadrant, whereas the other one was found attached to the peritoneal surface of the bladder and partially to the sigmoid colon. Neither of them was attached to the small bowel. Because the patient recovered from his symptoms of small bowel obstruction after removal of the loose bodies, we wondered whether the loose bodies might have been the cause of his obstruction, perhaps by compressing the bowel extraluminally. However, the evidence for this at operation was weak.

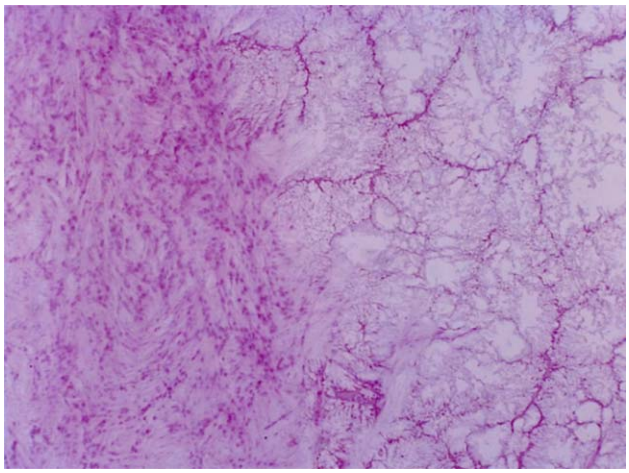

Fig. 3. Microscopic findings showed dense, focally laminated, eosinophilic material without associated inflammatory or foreign body giant cell reaction.

It has been generally believed that peritoneal loose bodies originate from appendices epiploicae.[3] Vesalius first described appendices epiploicae in 1543 as fingerlike projections of peritoneum that contain pericolic fat attached to antimesenteric tenia of the large intestine, most common in the sigmoid colon and cecum. They may be attached by a thin pedicle that undergoes torsion, leading to infarction or aseptic fat necrosis, which may cause a condition that mimics diverticulitis or appendicitis, known as primary epiploic appendagitis.[4] In 1703, Littre suggested that necrosis of these appendices gives rise to fibrous or calcified peritoneal loose bodies.[5] Our case presented with a long history of obstruction that made us suspect that the peritoneal loose body may have grown large by long-term existence in the peritoneal cavity. However, the precise mechanism of the formation of peritoneal loose bodies remains unclear. Microscopically, peritoneal loose bodies consist of many layers of laminated fibrous tissue with a paucity of cellular elements.

Differential diagnosis of bodies loose in the peritoneal cavity includes leiomyoma, desmoid tumors, teratoma/ovarian tumors, urinary stones, gallstones, and mesenteric calcifications. Leiomyomas are especially hard to distinguish from peritoneal loose bodies because they can be calcified as well, and both lesions appear alike on CT and magnetic resonance imaging (MRI).[1] However, leiomyoma has a contrast-enhancing effect, whereas peritoneal loose bodies do not.

Peritoneal loose bodies are usually small and found incidentally during laparotomy or autopsy.

They rarely grow to the size found in our patient and seldom become symptomatic.[1] In retrospect, considering the nature of the disease, it might have been better to treat our patient laparoscopically. With more popularity of CT and MRI, detection of this entity may increase. Therefore, one should consider the possibility of this entity when a tumor with calcification is detected in the peritoneal cavity.

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Pancreas: What Is in a Name?

To the Editor:

The pancreatic duct begins in the tail and traverses through the body to end in the head; thus, the pancreatic duct in the tail is proximal and that in the head is distal. Resection of the body and tail of pancreas is erroneously called a distal pancreatectomy, whereas it is actually a proximal pancreatectomy; "left hemipancreatectomy"[1] is a more diplomatic term. The lower end of the common bile duct unites with the main pancreatic duct to form the ampulla, which opens on the medial wall of second part of duodenum at the papilla. Thus, the tumor seen on side-viewing endoscopy is a papillary (and not ampullary) cancer. The therapeutic endoscopic procedure dividing the papilla should be called endoscopic papillotomy and not endoscopic sphincterotomy, as the sphincter can be divided by a transduodenal sphincteroplasty only.

Pancreas divisum results from failure of fusion of the ductal systems of the dorsal and ventral pancreatic buds, so that the upper part of the head, body, and tail of pancreas continue to drain into the dorsal duct, whereas the ventral duct drains only the lower part of the head and uncinate process. Dominant dorsal duct syndrome[2] is a more appropriate name.

The best (or worst) example of confusion in pancreatic nomenclature is "periampullary" cancer. A plethora of terms, such as "peripancreatic cancer," "pancreatic cancer," "periampullary cancer," and others, have been used by various authors to describe different pancreatic cancers.[1] Some authors differentiate between pancreatic (head, body, and tail) and periampullary (ampulla, papilla, duodenum, and distal bile duct) cancers, while others use "pancreatic cancer" as an all-inclusive term to include the cancers of pancreas and periampullary cancers as well. Some reports use the term "periampullary cancer" to include pancreatic head cancers in addition to cancers of the ampulla, papilla, duodenum, and distal bile duct, while others differentiate between periampullary and pancreatic head cancers. Some standard textbooks of surgery[3,4] do not even mention the term "periampullary cancer." Periampullary cancers need to be differentiated from pancreatic cancers as they differ in management and prognosis[5]—while almost all periampullary cancers are resectable, resection of pancreatic cancers is possible in only about 25% of cases; 5-year survival for periampullary cancers is about 50% as opposed to about 25% for pancreatic cancers.[1] The term "periampullary cancer" should be used to include a small pancreatic head cancer (which does not produce a mass lesion on imaging or at surgery) and cancers of the ampulla, papilla, duodenum, and distal bile duct—all within 1 cm of the ampulla, to differentiate it from a pancreatic head cancer, which produces a mass lesion.

A host of terms, such as "pancreatic resection," "pancreatectomy," "pancreaticoduodenal resection," "pancreaticoduodenectomy," and others, been used by various authors to describe different pancreatic resection.[1] Codivilla was the first to perform a pancreaticoduodenectomy in 1898, and Kausch performed the first successful pancreaticoduodenectomy in 1909, yet the procedure is named after Whipple, who reported it in 1935.[6] Traverso and Longmire described a modification of the classic Whipple's pancreaticoduodenectomy and called it pylorus-preserving pancreaticoduodenectomy (PPPD).[6] Pylorus is, however, a part of the stomach (and not duodenum); the conventional (Whipple's) operation should, therefore, be appropriately called

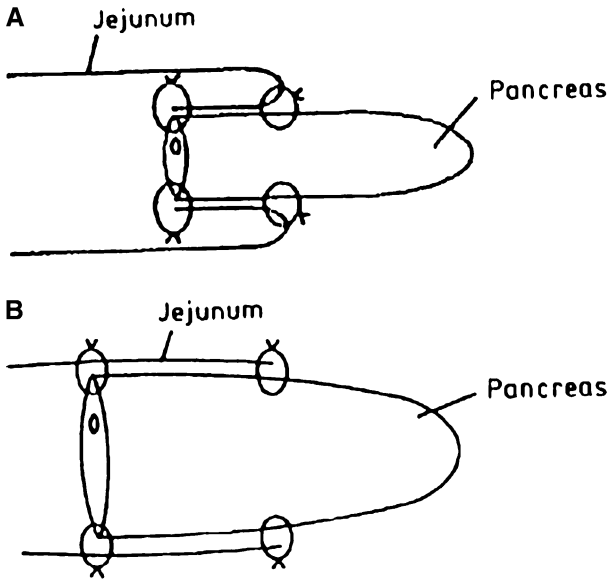

Fig. 1. Diagrammatic representation of (**A**) intususception and (**B**) invagination (telescoping).

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"pancreaticoantroduodenectomy,"[7] and the so-called PPPD is the "pancreaticoduodenectomy." Fortner[6] described extensive retroperitoneal lymph node dissection and segmental resection of adjacent vessels along with pancreaticoduodenectomy and (erroneously) called the procedure regional pancreatectomy; it should appropriately be called extended pancreaticoduodenectomy.

If the gland is firm and the duct is dilated, a duct-to-mucosa end-to-side pancreaticojejunostomy is the best option. A soft gland with an undilated duct is a difficult situation to manage. The end of pancreatic stump may then be intussuscepted into the end of the jejunum with two layers of sutures. Trede[8] wrongly describes this as telescoping; telescoping, however, is simple invagination of the pancreatic stump into the end of the jejunum. Many texts use the terms "invagination" and "intussusception" interchangeably, and the term "dunking" has been used as their synonym,[9] but these are technically different procedures (Fig. 1).

The beginning of wisdom is to call things by their right names.—Chinese proverb

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