Laparoscopic Total Abdominal Colectomy in the Acute Setting

Michael R. Marohn, D.O., Eric J. Hanly, M.D., Kevin J. McKenna, M.D., Carmen R. Varin, M.D.

We report results from a single surgeon's 10-year team experience with laparoscopic total abdominal colectomy. We review our series, which includes a large subgroup of ill, high-risk patients with acute colitis requiring urgent surgery. From 1993 to 2003, we performed 65 laparoscopic total abdominal colectomies. All patients referred for total abdominal colectomy were offered the laparoscopic approach. We prospectively collected the following data on all patients: demographics, surgical indications, preoperative status, duration of surgery, intraoperative blood loss, operative complications, length of stay, subsequent operations, patient satisfaction, and lessons learned from our team experience. Preoperative diagnoses included ulcerative colitis (n = 55), Crohn's colitis (n = 3), colonic inertia (n = 4), and familial adenomatous polyposis (n = 3). Among the patients with inflammatory bowel disease, 70% of cases were performed on ill patients, refractory to medical management, requiring urgent surgery. This subgroup was managed with laparoscopic total abdominal colectomy and Brooke ileostomy, with ileoanal pouch anastomosis deferred. Operative times were long, ranging from 6 to 11 hours. Mean intraoperative blood loss was 200 ml. Mean length of stay was 4.3 days and ranged from 2 to 13 days. There were no conversions to open surgery and there were no deaths. Complications occurred in 12% of patients and included intra-abdominal abscess (n = 2), wound infection (n = 3), stoma stenosis (n = 1), and incisional hernia (n = 2). Postoperative patient satisfaction was high. Subsequent operations, including restorative proctectomy, were also performed laparoscopically. Laparoscopic total abdominal colectomy is technically challenging and requires a team approach but offers patients significant benefit in length of stay and surgical recovery. This operation can be effectively used with minimal morbidity in difficult, ill patients requiring urgent surgery. (J GASTROINTEST SURG 2005;9:881–887)

KEY WORDS: Laparoscopic colon surgery, total abdominal colectomy, ulcerative colitis, colectomy, laparoscopy

Reports of laparoscopic total abdominal colectomy as early as 1992 were mixed, concluding that although the laparoscopic approach is technically feasible, it did not appear to offer recognizable benefits to patients compared with standard laparotomy.[1] By the late 1990s, reports examined laparoscopic abdominal colectomy for quiescent pancolonic diseases, such as familial adenomatous polyposis and inactive inflammatory bowel disease, with promising outcomes. This suggested that as techniques and instrumentation

Presented at the Forty-Fifth Annual Meeting of The Society for Surgery of the Alimentary Tract, New Orleans, Louisiana, May 15–19, 2004 (oral presentation).

From the Department of Surgery, Uniformed Services University (M.R.M., E.J.H., K.J.M., C.R.V.), Bethesda, Maryland; Malcolm Grow USAF Medical Center, (M.R.M., E.J.H., K.J.M., C.R.V.) Andrews Air Force Base, Maryland; and The Johns Hopkins University School of Medicine (M.R.M., E.J.H.), Baltimore, Maryland.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Uniformed Services University, the Department of the Air Force, or the Department of Defense.

Reprint requests: Michael R. Marohn, D.O., The Johns Hopkins Hospital, Department of Surgery, 600 North Wolfe St., Halsted 608, Baltimore, MD 21287. e-mail: mmarohn1@jhmi.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.017

were perfected, laparoscopic abdominal colectomy would become an appealing option.[2,3]

More recently, a few reports of laparoscopic total abdominal colectomy for acute colitis have been published. In 2000, Dunker et al.[4] retrospectively reported 42 inflammatory bowel disease patients requiring emergency colectomy with end-ileostomy, of which 32 patients had open colectomy and 10 patients had laparoscopic assisted colectomy. Operative times were longer in the laparoscopic group (271 versus 150 minutes; $P < 0.001$), but hospital stay was shorter (14.6 versus 18.0 days; $P = 0.05$). Complications were similar. They concluded that laparoscopic assisted colectomy in inflammatory bowel disease patients with acute colitis is feasible and as safe as open colectomy. In 2001, Marcello et al.[5] reported a case-control study investigating laparoscopic total colectomy for acute colitis. All patients underwent a total colectomy with creation of an end-ileostomy and buried mucous fistula. Patients with fulminant disease (tachycardia, fever, marked leukocytosis, peritonitis) were excluded, but all patients for whom medical treatment was failing were included. Reporting on 19 laparoscopic and 29 matched conventional patients, operative times were longer in the laparoscopic group (mean, 210 minutes; range, 150–270 minutes versus mean, 120 minutes; range, 60–180 minutes for conventional; $P < 0.001$), return of bowel function was shorter in the laparoscopic group (mean, 1 day; range, 1–3 days versus mean, 2 days; range, 1–4 days for conventional; $P = 0.003$). There were no inadvertent colostomies or conversions in the laparoscopic group. Complications occurred in three (16%) laparoscopic patients and in seven (24%) conventional patients. The authors concluded that laparoscopic total colectomy is feasible and safe in patients with acute nonfulminant colitis and may lead to faster recovery than conventional resection.

We reviewed results from a single surgeon's team 10-year experience with laparoscopic total abdominal colectomy, including a large subgroup of patients with acute colitis requiring urgent surgery. Our objective was to assess the feasibility and safety of laparoscopic total abdominal colectomy in the acute setting. Furthermore, we examined our experience for lessons learned in an effort to delineate why adoption of laparoscopy for colonic disease has been so slow compared with other minimally invasive surgery procedures. While greater than 95% of the 700,000 cholecystectomies performed in the United States are performed with a laparoscope, less than 10% of the 250,000 colon resections are performed laparoscopically.

MATERIAL AND METHODS

Surgery Team

Our report retrospectively describes laparoscopic total abdominal colectomies performed by a single surgeon's team in a U.S. military medical treatment facility between 1993 and 2003. Our group recognized early in our laparoscopic colon surgery experience, dating from 1991, that laparoscopic colon surgery was demanding, time consuming, and controversial for the most common colon surgery indication: cancer. We also recognized, however, potential patient benefits from laparoscopic colon surgery, particularly for total abdominal colectomy. We established prospective guidelines for our laparoscopic total abdominal colon surgery program. We recognized laparoscopic colon surgery as requiring advanced laparoscopic surgery skills—laparoscopic colon surgery is multiquadrant; requires extensive dissection, control of major blood vessels, and specimen removal; and can require either ostomy or anastomosis. Recognizing the importance of a core laparoscopic team, we dedicated two surgeons with advanced laparoscopic skills for all laparoscopic total abdominal colectomies. Our lead surgeon was a pioneer in laparoscopic surgery for the U.S. military and provided continuity for the team throughout the 10-year period. During the 10-year period, the second team member included several general surgery attendings who were intermittently involved and colorectal surgeons from sister facilities, but the majority of the cases involved one of two sequentially assigned colorectal attending surgeons. The significant impact of surgeon experience on the outcome of advanced laparoscopic cases has been demonstrated in numerous studies. Therefore, all surgeons involved in this series had completed hands-on courses in basic and advanced laparoscopic surgery and had completed at least 30 laparoscopic cholecystectomies prior to participating in the laparoscopic colectomy cases. We established regular access to a laparoscopic skills lab with at least quarterly laboratory sessions to sharpen surgeon skill sets.

In addition, because we worked in a federal facility, we were able to minimize concerns regarding time constraints, being aware that laparoscopic colon surgery required longer operating times than conventional procedures.

Patients

Patients referred for total abdominal colectomy for benign disease during the 10-year period between 1993 and 2003 were offered a laparoscopic total abdominal colectomy. Because of the lack of data 10 years ago from a prospective randomized trial examining the efficacy, safety, and equivalency of laparoscopy for colon cancer, we excluded colon cancer from

our laparoscopic total abdominal colectomy procedures. However, we did not exclude patients on the basis of prior abdominal surgery, and we did not exclude patients with acute colitis, although we did exclude patients with peritonitis.

Procedures

Patients with nonacute disease underwent laparoscopic total abdominal colectomy, proctectomy if indicated, and then ileoanal pouch anastomosis with diverting loop ileostomy, or ileorectal anastomosis, depending on the extent of their disease process. All patients with acute colitis underwent total abdominal colectomy, end-ileostomy, and creation of Hartmann's pouch.

Careful attention was given to patient positioning. For the nonacute group where restoration of gastrointestinal continuity was planned, we used low lithotomy, with the thighs projecting horizontally from the torso. For the acute group, patients were placed supine with a footboard. Both arms were tucked to maximize physician access to work from any location. A beanbag was used in most cases to stabilize the patient with bed movements during surgery.

We used four or five laparoscopic ports, all 10–11 mm to allow use of any instrument through any port, given the multiquadrant nature of the required dissection. We did not use hand-assist devices. Commercially available small wound protectors became readily available in the late 1990s, and we began using these devices at the extraction incision during the externalized portion of the procedures (colon transection and anvil placement). If the colon has been divided at the top of the rectum, completely mobilized, and mesentery divided, the entire colon can be delivered through a wound protector at an ileostomy site.

We used a 30- or 45-degree angled 10-mm laparoscope for all procedures. One challenge of laparoscopic colon surgery is retraction. The first assistant often works opposite the camera, making spatial orientation challenging. In addition, laparoscopic bowel graspers remain potentially traumatic. We endeavored to manipulate the bowel as little as possible, favoring retraction of the pericolic fat or mesentery.

Colon mesentery management can be tedious and challenging. Technology has advanced significantly in 10 years. Individual vessel dissection and ligation with endoloops or endoclips were required early in our experience. Later, we used sequential firings of the endo-GIA stapling device to divide the colon mesentery, with resultant exorbitant expense. The advent of the Harmonic Scalpel (Ethicon, Cincinnati, OH) facilitated mesenteric dissection. Introduction of the Ligasure (Valley Lab, Boulder, CO) device dramatically accelerated the time required for mesentery division.

Tactically, surgeons have debated the best approach to the colon mesentery: lateral to medial, or medial to lateral. Because we were dealing with benign disease, our initial experience favored the lateral-to-medial approach, particularly because the blood supply of the colon, once mobilized, is in the midline. In some cases, we were able to mobilize the entire colon and then divide the mesentery extracorporeally using traditional ligatures. More recently, particularly as we apply oncologic principles to laparoscopic colon surgery, we have adopted the medial-to-lateral approach, dividing the named vessels at the root of the mesentery, identifying ureters early, and leaving lateral attachments as suspensory aides during mesentery dissection.

Restoration of gastrointestinal continuity was not an issue for our acute colitis patients, who all underwent laparoscopic total abdominal colectomy, creation of a Hartmann's pouch, and end-ileostomy. For the nonacute patients, we used standard reconstruction techniques, including both double-stapled and hand-sewn anastomoses. As will be discussed, later in our experience, we expanded laparoscopic applications to ileostomy takedown, pouch creation, and completion proctectomy.

Database

We prospectively maintained a laparoscopic total abdominal colectomy database including patient demographics, surgical indications, preoperative status, operative times, operative blood loss, complications, length of stay, subsequent surgeries, patient satisfaction, and lessons learned from our experience.

RESULTS

Patients

Between 1993 and 2003, our group performed 65 laparoscopic total abdominal colectomies. The median age was 47 years (range, 21–68 years). There were 39 women and 26 men.

Diagnoses

Of the 65 patients, preoperative diagnoses included 55 (84.6%) patients with ulcerative colitis, 4 (6.2%) patients with colonic inertia, 3 (4.6%) patients with Crohn's colitis, and 3 (4.6%) patients with familial adenomatous polyposis (FAP).

Acute Colitis

Within the large subgroup of 58 (89% of the total) patients with inflammatory bowel disease (IBD), including the ulcerative colitis and Crohn's colitis patients, 40 (70% of the IBD group, 62% of the total) had acute colitis, with varying degrees of severity. One patient with Crohn's colitis had intramural abscesses of his left colon. Most of these patients were receiving intravenous steroids and antibiotics; many were receiving total parenteral nutrition. All of these patients were failing to respond to medical management.

Procedures

All of the 40 (62%) patients in this subgroup with acute colitis were managed with laparoscopic total abdominal colectomy, creation of a Hartmann's pouch, and end-ileostomy. Of the 40 IBD patients from the acute colitis group left with an end-ileostomy and Hartmann's pouch, 39 had ulcerative colitis and 1 had Crohn's colitis. The Crohn's patient eventually underwent elective ileostomy takedown and ileoproctostomy. Of the 39 ulcerative colitis patients, 37 eventually underwent elective ileostomy takedown, completion proctectomy, and ileoanal pouch anastomosis with diverting loop ileostomy; two patients declined proctectomy and retain their end-ileostomies.

As our laparoscopic team skills evolved, the last 10 of these patients underwent elective laparoscopic ileostomy takedown, completion proctectomy, and ileoanal pouch anastomosis with diverting loop ileostomy. For three of these patients, the only incisions were their ileostomy site and three laparoscopic port sites. At their urgent operation, their colon was removed through their eventual ileostomy site. At their elective surgery, after laparoscopic completion proctectomy and mobilization of the terminal ileal blood supply to the superior mesenteric artery, their ileostomy was taken down and exteriorized, their pouch was created and reintroduced into the abdomen, and then ileoanal anastomosis was performed, followed by diverting loop ileostomy. When their loop ileostomy was closed 6 weeks later, they had completed the three-stage total abdominal proctocolectomy with ileoanal pouch anastomosis with only an ileostomy and three port site scars.

Of the remaining 25 (38%) patients, 18 patients were nonacute IBD patients. Of these 18 patients, two were Crohn's colitis patients managed with laparoscopic total abdominal colectomy with ileoproctostomy. Of the 16 nonacute IBD patients with ulcerative colitis, 13 patients underwent laparoscopic total abdominal colectomy and "open" proctocolectomy with ileoanal pouch anastomosis with diverting loop ileostomy; and 3 patients, who were over 65 years old, underwent laparoscopic total abdominal colectomy with ileoproctostomy. Of the remaining 7 (11%) non-IBD patients, the four patients with colonic inertia underwent laparoscopic total colectomy with ileoproctostomy, whereas the three patients with FAP underwent laparoscopic total abdominal colectomy and "open" mucosal proctectomy with ileoanal pouch anastomosis and diverting loop ileostomy.

Operative Data

Operative times were long, averaging 7.4 hours and ranging from 6 to 11 hours. Blood loss averaged 200 ml, ranging from 100 to 700 ml. There were no conversions to "open" surgery, although early on, proctectomy and ileoanal pouches were performed through lower midline or pfannenstiel incisions. Two patients in the acute colitis group sustained inadvertent colotomies.

Complications

There were no deaths (mortality = 0%). Complications occurred in 8 (12%) of patients, including 2 (3%) intra-abdominal abscesses, 3 (5%) wound infections, 1 (2%) stomal stenosis, and 2 (3%) incisional hernias. The two intra-abdominal abscesses were percutaneously drained under computed tomography guidance. One of these two intra-abdominal abscesses occurred in the acute Crohn's colitis patient with left colon intramural abscesses; the other occurred in one of the acute patients who sustained an inadvertent colotomy. The single patient who developed stomal stenosis required operative revision. Of the two incisional hernias, one was repaired primarily at "open" surgery, and the other was repaired laparoscopically with mesh.

Length of Stay and Patient Satisfaction

Bowel function returned by day 1.5 (range, 1–4 days). Length of stay averaged 4.3 days, ranging from 2 to 13 days. Patient satisfaction was only informally surveyed but was subjectively high. We were particularly impressed by patients' reports of rapid at-home recovery to normal activities of daily living.

DISCUSSION

Adoption of laparoscopy for colonic disease has been slow compared with other minimally invasive surgical procedures. The timing of our report coincides with the publication of the Clinical Outcomes of

Surgical Therapy (COST) Study Group, comparing laparoscopically assisted with "open" surgery for colon cancer.[6] This trial involved 863 patients, 66 surgeons, and 48 hospitals, and reports rates of cancer recurrence, operative complications, and survival at 4.4 years to be similar between the two groups. This landmark study is, as the accompanying editorial described, "the end of the beginning."[7] We agree with their prediction that resistance to laparoscopic colon surgery will diminish. Cancer remains the number two leading cause of death in the United States, and colon cancer remains the leading gastrointestinal cancer, with 146,940 new colorectal cancers, and 56,730 deaths, projected for 2004.[8]

However, compared with the swift domination of laparoscopic cholecystectomy, rapid expansion of laparoscopic colon surgery may prove more challenging. Why has the progress of laparoscopic colon surgery been so divergent from laparoscopic cholecystectomy? The first laparoscopic cholecystectomy, performed by Philippe Mouret on March 17, 1987, in Lyons, France, triggered what many described as the "Nintendo surgery revolution." By 1992, use of laparoscopy to treat gallbladder disease was embraced as "standard of care."[9,10] More than 90% of the 700,000 cholecystectomies performed annually in the United States were performed with a laparoscope. By 1994, laparoscopy had been tried for surgeries ranging from solid organ removal (e.g., nephrectomy, adrenalectomy) to pancreatic resection to total colectomy. By the late 1990s, laparoscopy became the preferred approach for obesity and gastroesophageal reflux surgery.

The story for laparoscopic colon surgery is different. Use of laparoscopy for colorectal disease dates as early as 1990, when Jacobs reported laparoscopic right colectomy. The minimally invasive surgery promises of smaller incisions, reduced pain, shorter hospitalization, and shorter recovery, even if the cost is greater, have been reported for laparoscopic colon procedures by numerous surgeons, but many reports were equivocal. In 2004, most colon operations are still performed by "open," conventional techniques described before Halsted. Laparoscopic colon surgery accounts for less than 10% of the 250,000 colon resections performed in the United States. How does laparoscopic colon surgery differ from other laparoscopic procedures?

First, and most obvious, laparoscopic colon surgery is difficult. Basic laparoscopic surgery skills are one-handed skills and the surgeon can accomplish simple organ removal with limited vascular control and no reconstruction. Fortunately for the explosive growth of laparoscopic cholecystectomy, basic laparoscopic skills can be achieved by any surgeon.[11,12] Advanced laparoscopic surgery requires two-handed skills for bimanual manipulation, complex dissection, suturing, and knot tying. Laparoscopic colon surgery is technically demanding. In 1996, Steve Wexner detailed technical factors unique to laparoscopic colorectal surgery.[13] These difficulty factors can be expanded to include the following: multiquadrant surgery, requires two-handed "advanced" laparoscopic skills, labor intensive and may require two advanced laparoscopic surgeons, time consuming, requires control of named vascular structures, requires solutions for retrieval of specimens that may be large and/or contaminated with infections or cancerous tissue, usually requires bowel anastomosis, and often performed for malignancy.

Second, concerns about adequacy of laparoscopy for colon cancer have slowed the adoption of laparoscopy for colon disease. Colon cancer is the most common gastrointestinal cancer and is the most common indication for colon resection. Early reports of cancer at port sites following laparoscopy raised concerns about the role of laparoscopy for cancer.[14–17] Even though Beart published a reflective review finding that wound recurrence rates appear to be low, concerns about port site recurrences persisted.[18] Basic science data favor the impact of laparoscopy versus open surgery on the immune system, with implications for colon cancer surgery.[19] Still, controversy about the safety, efficacy, and equivalency of laparoscopy to "open," conventional colon surgery with respect to adequacy of staging, resection, lymphadenectomy, and specimen handling has led many surgeons and cancer centers to call for a moratorium on laparoscopy for colon cancer until a prospective double-blinded clinical trial has directly examined the safety, efficacy, and equivalency of the two approaches.[20–23] The moratorium was embraced by many practicing surgeons, relieved to delay adopting what was already recognized as a challenging arena for laparoscopic surgery.

Third, laparoscopic colon surgery exposes the limitations of current minimally invasive surgery technology, skills, and training. Although basic laparoscopic skills are achievable by any surgeon, as proved with laparoscopic cholecystectomy,[8,9] not only are advanced laparoscopic surgery skills more difficult, but their acquisition is more challenging. The average general surgery resident finishing training in the United States has performed fewer than one laparoscopic colon procedure. Currently, 90% of advanced complex laparoscopic surgeries are performed by less than 20% of surgeons. What is the future of surgery? A few laparoscopic wizards? Better training? Better technology?

The use of plastic wound protectors remains controversial. Kercher's group recently reported no significant reduction in wound infection using wound protectors for laparoscopic assisted colon surgery.[24] Wound infection rates are higher for inflammatory versus noninflammatory resections.

Watershed events, such as the publication of the COST trial, amplify needs in general surgery and colon and rectal surgery training to expand emphasis on minimally invasive surgery and enable educational technologies. Overcoming learning curves will remain challenging, but we can leverage skills acquisition in nonpatient venues to accelerate use of new skills in patient care.

CONCLUSIONS

Laparoscopic total abdominal colectomy is technically challenging and requires a team approach, but offers patients benefits in length of stay and surgical recovery and can be effectively used with minimal morbidity and no mortality, not only for elective pancolonic disease, but also for patients with acute colitis requiring urgent surgery.

Lessons learned from our 10-year experience with laparoscopic total abdominal colectomy are coincident with the recent publication of the COST Study Group data. There will be increased interest in expanding use of the laparoscope for colonic disease, particularly for colon cancer. Our 10-year experience with laparoscopic total abdominal colectomy has taught us that, unlike laparoscopic cholecystectomy, laparoscopic colon surgery is difficult and team based and requires advanced skill sets that are not easily acquired. Pressures to expand laparoscopic colon surgery will be challenging. Solutions lie in expanded simulator-based skills training, increased videoendoscopic surgery training, and collaboration among general and colorectal surgeons. Technology is needed to move laparoscopy from a transition technology to true computer-assisted surgery for better patient imaging, simulation, and enhanced surgeon education and performance.

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Discussion

Dr. B. Schirmer (Charlottesville, VA): I want to thank Dr. Marohn for providing a copy of the manuscript, and I want to congratulate him on a very nice paper. This is an important study that shows that it doesn't matter if you take a long time in the operating room; if you do good surgery, your patients can still have good outcomes. It is noteworthy also that removing the colon seems to eliminate postoperative ileus in these patients, whereas when we do partial colectomies, we still see an ileus.

My real question for you, Mike, is perhaps taking a lesson from bariatric surgery. I personally found in bariatric surgery that even though I was a skilled surgeon, I needed a single dedicated team that didn't change to be able to decrease operating times and have a better experience. You did 65 cases over 10 years, six-and-a-half cases per year. Do you think it was the limitation of volume that led to persistently long OR times? It took me about 100 to 200 cases to be able to do a gastric bypass laparoscopically with an unskilled assistant. What volume would it take to get you to that point, or how many of these cases did you do with a varying first assistant, and how much was the variability in the team responsible for the long OR times?

Dr. Marohn: Thank you for an insightful question. The transient nature of our operating room team was a major limiting step. My continuity for well over ten years at one institution in the US Military was atypical, but my teammates were transient, which contributed to our lengthy OR times. Three other factors are worth comment regarding OR times. First, I share your view that laparoscopic colon surgery benefits with a two-surgeon approach, at least, for laparoscopic total colectomies. Second, our reported operative times included set-up times, because set-up times, particularly with a variable team, are increased in an equipment-intensive advanced laparoscopic setting. Third, technology advances have impacted laparoscopic surgery. In ten years, we have moved from electrocautery and laparoscopic clips or pre-tied suture loops to the ultrasonic coagulating shears or high-current bipolar vessel sealers; each accelerating operative management for advanced laparoscopy, particularly mesenteric division.

Brain Preservation During Orthotopic Liver Transplantation in a Patient With Acute Liver Failure and Severe Elevation of Intracranial Pressure

Alexandru Gottlieb, M.D., Kathrine R. DeBoer

Acute liver failure (ALF) is a rare condition characterized by the development of encephalopathy and cerebral edema. The grades of the encephalopathy and coagulopathy are the most important predictors of outcome in ALF.[1] An uncontrolled increased intracranial pressure (ICP) is the cause of early death in 50–80% of patients with ALF. In patients with increased ICP, the greatest challenge for the anesthesiologist is to administer anesthesia without causing any further increase in ICP and to decrease the preexisting critical elevation in ICP. We describe here the perioperative management of liver transplantation in a patient with an extremely elevated ICP.

REPORT OF A CASE

A 39-year-old, 85-kg man presented with the symptoms of fatigue, nausea, jaundice, weight loss, abdominal pain, chills, and decreased mental alertness that started a month before his indexed surgery. He was diagnosed with ALF of unclear etiology and was referred to us 3 weeks later with progressive worsening of his symptoms. He was admitted to the medical intensive care unit and became deeply comatose (stage IV). A Camino intraparenchymal bolt ICP monitor was inserted; the first ICP was 50 mm Hg. He was sedated with propofol and treated with mannitol and furosemide.

On the day of surgery, the patient's ICP increased to 70 mm Hg and his pupils dilated. Neurology speculated imminent brain herniation would occur with ensuing brain death in the next 24–48 hours. The patient was taken to the operating room for orthotopic liver transplantation (OLT) with veno-venous bypass 2 hours later.

The patient was monitored with an arterial line and a pulmonary artery catheter. Hemodynamic and laboratory parameters included: arterial blood pressure 170/80 mmHg, pulmonary artery pressure (PA) 30/13 mmHg, cardiac output (CO) 12.4 L/min., ICP 60 mmHG, international normalized ration (INR) 5.26, prothrombin time (PT) 57.9 sec., activated partial thromboplastin time (aPTT) 37.1 sec., and blood urea nitrogen (BUN) 20 mg/dl. The ammonia level was 111 μmol/L and liver function tests were elevated.

Maintenance of anesthesia was with isoflurane, nitrous oxide and oxygen (N_2O/O_2), fentanyl, midazolam, and pancuronium bromide. The arterial blood gas, Sonoclot (Sienco Inc., Arvada, CO), and Thrombelastogram (TEG model 5000; Haemoscope, Niles, IL) were monitored to correct any acid-base imbalance or electrolyte and coagulation abnormalities. The patient was hyperventilated with arterial carbon dioxide tension ($PaCO_2$) maintained between 21 and 26. ICP and cerebral perfusion pressure (CPP) were closely monitored throughout the procedure. Mannitol 25–50 g and 20 mg furosemide were given every 2 hours to maintain the ICP between 30 and 60 mm Hg. A Neo-Synephrine intravenous drip was closely titrated at 0.157–1.57 μg/kg/min to keep the mean blood pressure at 100–120 mmHg and CPP at 40–70 mmHg (Fig. 1). The OLT was successful, and ICP elevation resolved by the first postoperative day (POD). Computed tomography (CT) scan of the brain showed diffuse cerebral edema but no hypodensity. The patient made a steady recovery, regaining mental function. He was discharged on POD 38. He improved rapidly and was able to return to work after 3 months.

Presented at the Fifth Biennial Meeting of the American Hepato-Pancreato-Biliary Association, Fort Lauderdale, Florida, April 14–17, 2005.
From the Department of General Anesthesiology, Section of Liver Transplantation, Cleveland Clinic Foundation, Cleveland, OH (A.G.); Summer Research Student for the Cleveland Clinic Foundation (K.R.B.), Cleveland, OH.
Reprint requests: Dr. Alexandru Gottlieb, Cleveland Clinic Foundation, 9500 Euclid Ave.E-31, Cleveland, OH 44195. e-mail: gottlia@ccf.org

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.06.005

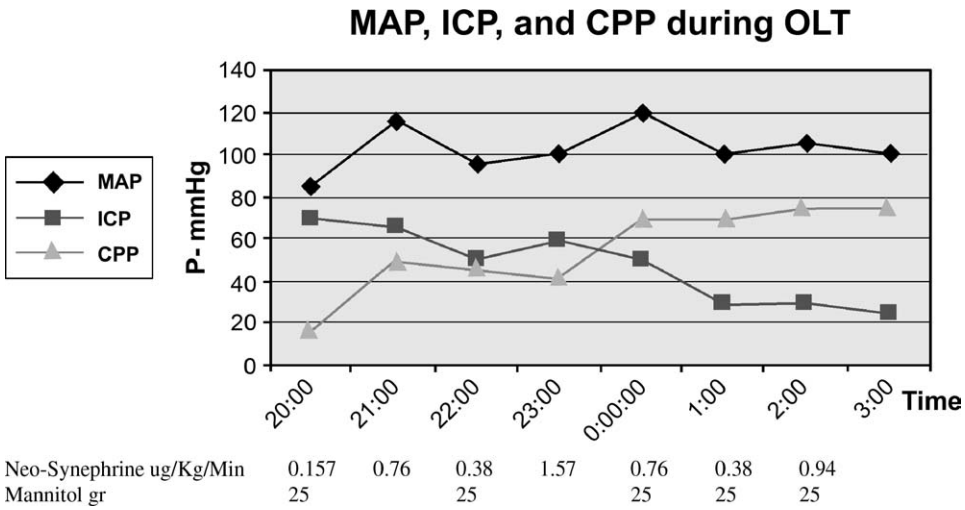

Fig. 1. Intraoperative, hemodynamics, intracranial pressure, and cerebral perfussion pressure. MAP = mean arterial pressure, CPP = cerebral perfussion pressure, ICP = intracranial pressure, OLT = orthotopic liver transplantation.

DISCUSSION

Our patient was typical in that his presentation of ALF included an increase in ICP. He was at exceedingly high risk, since patients with an ICP of greater than 40 mmHg or a CPP of less than 50 mmHg have been shown to be poor candidates for OLT. This subset of patients is more susceptible to critical elevations of ICP during OLT. An increase in ICP may cause a higher incidence of perioperative cerebral bleeding and neurologic damage brought about by a potential for brain herniation and brainstem coning. These patients should be closely monitored and treated to preserve viable CPP,[2] as was done in our case.

The mechanism by which ICP increases in patients with ALF is unclear. Hyperammonemia is known to interfere with ion homeostasis, membrane potentials, and neurotransmission, thus decreasing the cerebral metabolism rate and affecting the cerebral blood flow (CBF). However, in severe cases of hyperammonemia as in ALF or Reye's syndrome, there is also a failure of CBF autoregulation with further aggravation in the brain supply-demand ratio. Brain lactate was correlated with increased ICP in patients with ALF.[3] It is possible that glycolysis with lactate accumulation is causing brain vascular vasodilation and increased ICP.

Monitoring of ICP is useful, if not essential, in patients with signs of encephalopathy from ALF. In more than 25% of patients with brain damage, there are no early clinical signs of raised ICP. Monitoring ICP can provide critical information including CPP, CBF regulation, and CSF dynamics. It can also help in demonstrating the impact of therapy and predicting the prognosis of the patient. Monitoring of ICP requires using an invasive device, but there is a hazard associated with their implantation. Blei et al[4] conducted a survey among centers that performed OLT in the United States (n = 262); epidural transducers had a complication rate of 3.8%, subdural bolts had a complication rate of 20%, and parenchymal or intraventricular catheters had a complication rate of 22%. Although epidural transducers had the lowest complication rate, we chose the Camino intraparenchymal monitor due to its increased accuracy. We chose to be more invasive by using a Camino intraparenchymal monitor for ICP monitoring; even though it had the highest complication rate, it was the most precise. Other noninvasive methods like CT scanning, magnetic resonance imaging, or transcranial Doppler have a poor correlation with ICP. Ultrasound studies of the optic nerves provide an unquantitative measurement of the ICP, but correlate well with prognosis of ALF in pediatric patients.[5] The marker S-100 was used as an early detection marker for increased ICP in experimental ALF pigs.[6]

In patients with ALF and elevated ICP, OLT is effective and is best performed before the patient reaches grade IV encephalopathy.[2] Treatment of ICP in patients with ALF is not well established. Reducing the level of ammonia with lactulose, L-ornithine, or L-aspartate may offer some promise but do not always improve outcome. Others[7,8] showed that treatment

with 30% hypertonic saline or indomethacin increased CPP without compromising CBF and also significantly reduced ICP. An extracorporeal hepatic support device was used successfully in nine ALF patients. Hemofiltration with albumin of "hepatic toxins" significantly reduced the incidence of encephalopathy and ICP elevation.[9] Similarly, extracorporeal liver perfusion with human or porcine liver stabilized patients with ALF while waiting 5 days for OLT.[10] The bioartificial liver support system (BLSS or BAL), made of cultured porcine hepatocytes, prolonged survival time in the canine model and in the human with ALF.[11] Mannitol, which was used for this patient, remains the treatment of choice for increased ICP in patients with ALF. Because of the important role of cerebral hyperemia in the pathogenesis of increased ICP, hyperventilation and medications like thiopental sodium, propofol, or *N*-acetylcysteine are all suggested. The use of mild hypothermia after head trauma has been shown to improve outcome. It can be potentially beneficial in ALF as well, but is not widely acceptable. Jalan et al[12] used moderate hypothermia (33.4°C) in 5 of 16 OLT patients with uncontrolled ICP. The control groups demonstrated a further increase in ICP and CBF during reperfusion, whereas the treatment group did not. It is possible that mild hypothermia can restore the CBF autoregulation as demonstrated by restoration of reactivity to carbon dioxide.[13] We did not actively induce hypothermia, but our patient's temperature decreased to 36°C during the surgery.

CONCLUSION

We presented a patient for OLT with ALF and progressive deterioration in mental functioning due to severe encephalopathy and a critical rise in ICP. We used a Camino cranial bolt for ICP measurement and vasopressors to elevate the MAP and CPP while ICP was controlled with mild hypothermia, hyperventilation, mannitol, and furosemide. As a result, we maintained a viable CPP and prevented irreversible brain damage during OLT.

The authors would like to thank Tanya D. Callaway, B.A., P.A. for reviewing and editing the manuscript.

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Development of a Dedicated Hepatopancreaticobiliary Program in a University Hospital System

Steven R. Granger, M.D., Robert E. Glasgow, M.D., Jean Battaglia, R.N., Ruey-Min Lee, M.D., Courtney Scaife, M.D., Dennis C. Shrieve, M.D., Ph.D., David Avrin, M.D., Ph.D., Sean J. Mulvihill, M.D.

In 2001, a dedicated hepatopancreatobiliary (HPB) cancer program was established at a large, university hospital. Changes included recruitment of specialized HPB faculty, standardization of patient protocols, development of coordinated multidisciplinary research and clinical efforts, collection of prospective surgical outcomes data, and construction of a dedicated cancer hospital. The aim of this study was to evaluate the impact of this program on a university health system including effects on patient volume, surgical volume, outcomes, costs, resident education, and research productivity. Hospital and departmental databases were reviewed for all records pertaining to HPB surgical cases, diagnosis, and financial information over a 6-year period, including 2 years before (1999–2000) and 4 years after (2001–2004) HPB program development. A more than two-fold increase in the number of distinct patients who had HPB diagnosis was seen across all pertinent departments. A five-fold increase in surgical volume was observed. A multidisciplinary approach to care was implemented, leading to a four-fold increase in sharing of patients across departments. Improvements in operative mortality, hospital contribution margin, resident operative experience, and research productivity were observed. The implementation of a dedicated HPB cancer program with coordinated and standardized research, educational, and clinical efforts had measurable institutional benefit. (J GASTROINTEST SURG 2005;9:891–895)

KEY WORDS: Liver, biliary, pancreas, surgery, cancer

Hepatopancreatobiliary (HPB) diseases involve cases of high complexity and generally low volume, with associated high patient morbidity and mortality. Recent interest, at a national and international level, in centers of excellence has increased regionalization of high-risk operations and care of specific diseases. Establishment of these specialty centers, and their subsequent impact, has been reported for a variety of disease-specific and organ-based centers, including trauma,[1] oncology,[2–5] minimally invasive surgery,[6] and cardiac care.[7,8] Regionalization of HPB procedures has also been documented to be associated with improved outcomes when performed at high-volume centers,[9–15] but what has not been well documented is the impact at an institutional level on the development of an HPB program.

In 2001, a dedicated HPB cancer program was developed at an established university hospital. This tertiary center has a large referral base serving five contiguous states spread over 300,000 square miles. Before institutional program development, HPB surgery was performed by board-certified general surgeons without HPB specialty training or focus. Changes included recruitment of specialized HPB faculty, standardization of patient protocols and postoperative orders, development of coordinated multidisciplinary research and clinical efforts, prospective surgical outcomes data collection, and construction of a dedicated cancer hospital. The aim of this study was to evaluate the impact of this HPB cancer program on a university health system including effects on institution and department HPB cancer patient volume, surgery case volume, patient outcomes, hospital costs, general surgery chief resident operative experience, and institutionwide HPB-related research efforts.

Presented at the Fifth Biennial Meeting of the American Hepato-Pancreato-Biliary Association, Fort Lauderdale, Florida, April 14–17, 2005.
From the Departments of Surgery (S.R.G., R.E.G., J.B., C.S., S.J.M.), Medicine (R.-M.L.), Radiation Oncology (D.C.S.), and Radiology (D.A.), Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah.
Reprint requests: Dr. Sean J. Mulvihill, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Salt Lake City, UT 84132. e-mail: sean.mulvihill@hsc.utah.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.06.009

MATERIALS AND METHODS

Hospital and departmental databases pertaining to HPB surgical cases (by *CPT* codes), diagnoses (by *ICD-9* codes), and financial information (by DRG codes) were reviewed, encompassing a period before (January 1999 through December 2000) and after (January 2001 through October 2004) program development. We compared HPB surgical volume with that of appendectomy as a control for any overall referral and surgical volume changes at our institution. We focused on procedure codes related to major resections for neoplasms (Table 1). Procedures for non-neoplastic diseases, such as cholecystectomy and pancreatic debridement, were excluded.

ICD-9 diagnosis data were also evaluated over this 6-year period by department, including patients seen by faculty in the departments of surgery, medicine, radiology, and radiation oncology. Appendicitis was used to control for any institutional changes in patient volume or referral patterns. Focus was again made toward benign and malignant HPB diagnoses, excluding inflammatory conditions (Table 1).

Efforts to standardize patient care were initiated with HPB program development. Intraoperative as well as preoperative and postoperative protocols were determined with input from all participating caregivers and implemented in 2001. Since October 2001, all surgical outcomes data have been collected in a standardized, prospective way by a trained nurse reviewer. General surgery chief resident operative experience for major HPB procedures was also examined for the study period. HPB research studies were tabulated, including those with institutional review board approval, animal care committee approval, or intramural or extramural grant support. Retrospective chart reviews and case reports were excluded.

RESULTS

Major HBP surgical procedures increased dramatically over this study period (Fig. 1). In 1999, HPB surgical volume was 24% that of appendectomy volume, with 20 major HPB cases performed. In 2000, HPB surgical volume decreased, representing only 8% the volume of appendectomy, with 11 HPB cases performed compared with 136 appendectomies. By 2003, the number of HPB operations had increased to 89 cases, a seven-fold increase over the

Table 1. Major Liver, Pancreas, and Biliary *CPT* and *ICD-9* Codes Included in This Study

Procedure	*CPT* Code	Diagnosis	*ICD-9* Code
Major liver CPTs		Major liver *ICD-9s*	
Insertion of intra-arterial infusion pump	36260	Malignant neoplasm	155
Hepatectomy; partial lobectomy	47120	Liver, primary	155.0
Hepatectomy; trisegmentectomy	47122	Intrahepatic bile ducts	155.1
Hepatectomy; total left lobectomy	47125	Liver, NOS	155.2
Hepatectomy; total right lobectomy	47130	Major biliary *ICD-9s*	
Laparoscopy; radiofrequency ablation liver tumor	47370	Malignant neoplasm	156
Open radiofrequency ablation liver tumor	47380	Gallbladder	156.0
Major biliary CPTs		Extrahepatic bile ducts	156.1
Excision bile duct tumor; extrahepatic	47711	Ampulla of Vater	156.2
Anastomosis bile ducts and GI tract	47760	Gallbladder NOS	156.8
Anastomosis intrahepatic ducts and GI tract	47765	Other	156.9
Anastomosis Roux-en- Y extrahepatic duct	47780	Benign liver & biliary tumor	211.5
Anastomosis Roux-en- Y intrahepitic ducts and GI	47785	Major pancreatic *ICD-9s*	
Major pancreas CPTs		Malignant neoplasm	157
Excision of lesion of pancreas	48120	Head	157.0
Pancreatectomy; w/o pancreaticojejunostomy	48140	Body	157.1
Pancreatectomy; w/ pancreaticojejunostomy	48145	Tail	157.2
Pancreatectomy w/ pancreaticoduodenectomy	48150	Pancreatic duct	157.3
Pancreatectomy near-total; pancreaticojejunostomy	48153	Islets	157.4
Pancreatectomy total	48155	Other	157.8
Pancreaticojejunostomy side-side anastomosis	48180	NOS	157.9
		Benign pancreatic neoplasm	211.6
		Islet cell neoplasm	211.7

GI = gastrointestinal; NOS = not otherwise specified; w/ = with; w/o = without.
Each patient was only credited for one *CPT* procedure code and one *ICD-9* diagnosis code.

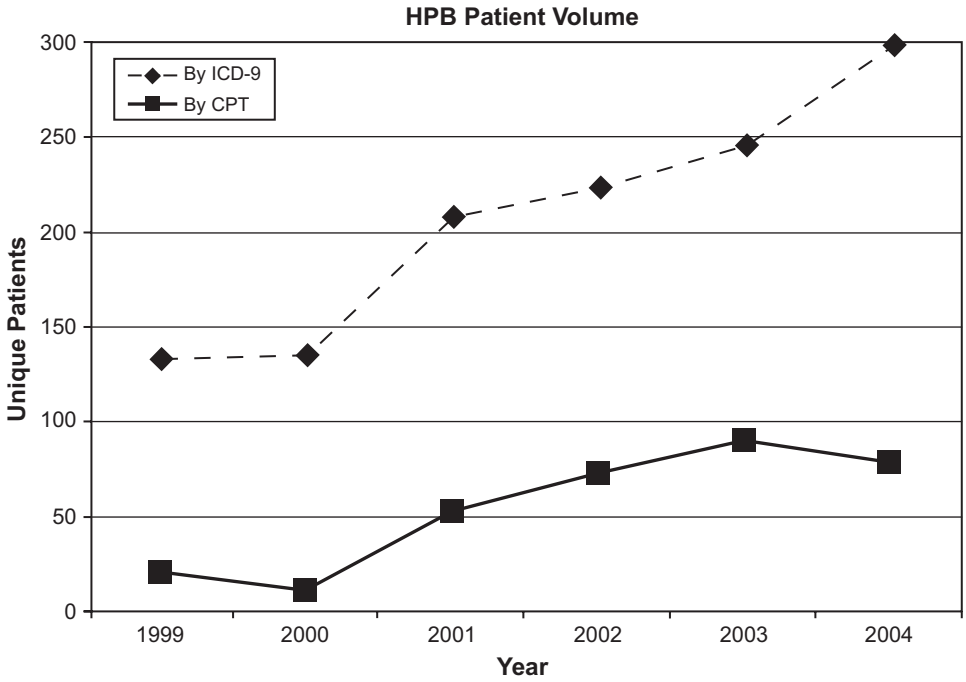

Fig. 1. HPB patient volume changes from 1999 to 2004 for major liver, pancreas, and biliary diagnoses (by *ICD-9* code) and procedures (by CPT code).

volume in 2000. HPB operative volume was 65% of the volume of appendectomy in 2003.

Increases in the number of distinct patients who had HPB diagnoses were seen across all pertinent departments as determined by *ICD-9* codes (Table 2). Each patient was allowed only one *ICD-9* code and was given credit for only one *ICD-9* entry per year per department. The Department of Surgery saw a nearly six-fold increase in unique patients evaluated per year, with only 16 unique patients seen in 2000, increasing to 94 unique patients seen in 2003. Similar increases were observed in unique patients seen in medicine, radiology, and radiation oncology.

In 1999, only 17 patients, of the 133 total unique HPB patients seen within the university system, were seen by faculty in at least one other department. This sharing of patients increased dramatically over the study period to 165 of the 299 in 2004, a 350% increase in the fraction of unique patients who were seen in at least one other department (Fig. 2).

Thirty-day mortality for HPB surgery was 11% in 1999 to 2000 and decreased to 3% in 2001 to 2003. Hospital contribution margin per case increased 50% from $9,013 in fiscal year 2000 to $13,600 in fiscal year 2003. General surgery chief resident operative experience with major HPB operations nearly doubled over the period of study (Table 3). Major HPB-related research studies increased from one in 1999 to eight in 2004.

DISCUSSION

Our institution made a commitment to the establishment of a center of excellence for benign and

Table 2. Unique Hepatopancreaticobiliary Patient Volume by *ICD-9* Codes for 1999 Through 2004 by Department

Department	1999	2000	2001	2002	2003	2004* (annualized)	Increase
Surgery	13	16	53	76	94	88	576%
Medicine	69	58	82	131	153	201	191%
Radiology	57	64	88	104	109	131	130%
Radiation oncology	11	8	14	28	25	44	300%
Total system	133	135	208	224	246	299	125%

*2004 data were collected through October 2004 and then annualized for presentation.

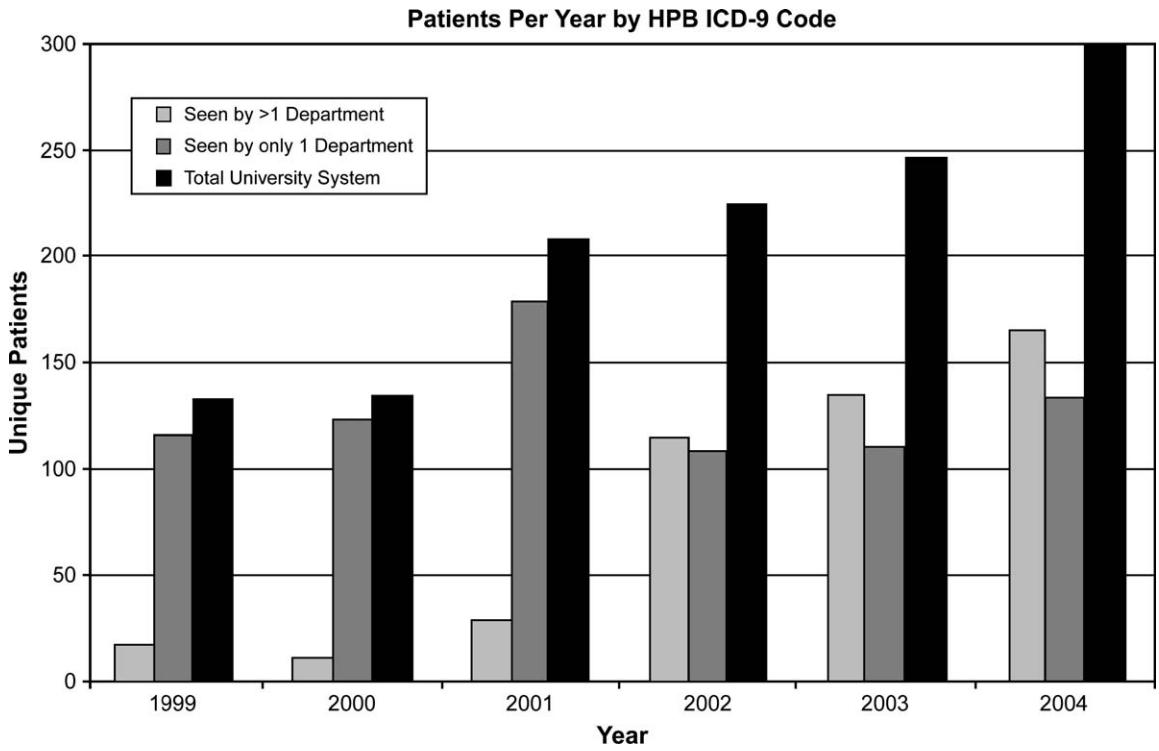

Fig. 2. Development of a multidisciplinary approach to patient care. Before program development, few patients were cared for by physicians in different departments. The proportion of "shared" patients increased dramatically after initiation of program development in January 2001.

malignant HPB diseases, beginning with recruitment of specialized HPB surgeons in late 2000. Recruitment and reassignment of resources was also initiated in medical oncology, radiation oncology, and diagnostic radiology. In 2001, plans began for building a dedicated cancer hospital adjacent to the university hospital. This cancer hospital opened in 2004.

A multidisciplinary approach to care was implemented, which included coordinated clinics and shared space between medical oncology and surgical staff. A weekly treatment planning conference was established. Initial concerns regarding patient "ownership" shifted to concerns about quality and comprehensiveness of care for the patients. No financial institutional benefits were allocated to reward participation in the multidisciplinary processes, but individual clinician recognition of improvement in quality of patient care led to support of these programs. The increase in HPB volume in conjunction with the emphasis on a multidisciplinary approach led to increases in sharing of patients across departments.

Changes also occurred at a systems level. A specialized nursing unit was established that emphasized training of nurses for consistent care of postoperative patients with HPB neoplasms. Patient protocols were developed and instituted at an institutional level; these included standardization of preoperative care, operative room preparations, and postoperative care. Dramatic improvements in operative mortality and hospital contribution margin were seen, possibly related to these process changes.

HPB surgery was fully integrated into a specific service, including chief resident coverage, clinic scheduling, and call responsibilities. General surgery chief resident experience in HPB procedures increased two-fold over the study period. Other educational benefits included the development of a defined curriculum and regular teaching conferences.

Table 3. Average General Surgery Chief Resident Operative Experience With Major Hepatopancreaticobiliary (HPB) Cases as Primary Surgeon During Chief Resident Year

Finishing Year	Major Liver Diagnosis	Major Pancreas Diagnosis	Major Biliary Diagnosis	Total—All HPB
1999–2001	3.2	6.8	1.9	11.9*
2002–2004	4.8	11.4	3.5	19.7*

*P value of $<.002$ comparing total HPB operative experience before and after establishment of the HPB program (by Student's t test).

A HPB-focused pancreatic research group was established, composed of investigators from both clinical and basic science departments. Only one National Institutes of Health–funded HPB research project was active at the time of HPB program development. In 2004, eight major HPB research projects were active, with an application for National Institutes of Health program project funding in development. In addition, a major gift was received in 2004 by a donor interested in HPB cancer research, further enhancing program development.

CONCLUSION

Implementation of a dedicated HPB program with coordinated and standardized research and clinical efforts resulted in a significant increase in the number of HPB patients and operations at this university-based academic referral center. Other beneficial effects of program development included decreased patient mortality, improved hospital contribution margin, improved educational experience, and increased research productivity. Establishment of this HPB program has had measurable institutional benefit.

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Antithymocyte Globulin Induction Therapy in Hepatitis C–Positive Liver Transplant Recipients

Peter J. Horton, M.D., Jean Tchervenkov, M.D., Jeff S. Barkun, M.D., Caroline Rochon, M.D., Prosanto K. Chaudhury, M.D., Tammy L. Znajda, M.D., John B. Martinie, M.D., Peter Metrakos, M.D.

It is unclear whether antithymocyte globulin (ATG) induction therapy in hepatitis C–positive (HCV-positive) liver transplant recipients influences the risk of developing recurrent HCV disease. Multiple acute rejection episodes and high-dose steroids and/or OKT3 used to treat acute rejection increase the risk of graft loss from HCV. We studied the impact of ATG induction on graft and patient survival in HCV-positive liver transplants performed since 1990. Recipients who died or lost their grafts within 1 month of transplantation were excluded. Second, third, and fourth grafts were excluded, as were patients with stage III or IV hepatocellular carcinoma. There were 443 cadaveric liver transplants in adult recipients, of whom 142 (32%) were HCV positive. The incidence of biopsy-proven acute rejection was less in patients who received ATG induction, 34.2% (ATG induction) versus 66.6% (no ATG induction) ($P \leqslant .01$). ATG induction did not influence the risk of graft loss from HCV-related disease ($P = .75$). When only HCV-related graft loss was considered, 10-year graft survival for HCV-positive recipients was 74% (ATG induction) versus 68.2% (no ATG induction). Whether ATG induction was given or not had no significant impact on either overall graft survival ($P = .39$) or patient survival ($P = .11$) in HCV-positive recipients. (J GASTROINTEST SURG 2005;9:896–902) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Antilymphocyte serum, liver transplantation, hepatitis C, recurrence, immunosuppressive agents

There are 4 million people with hepatitis C virus (HCV) infection in the United States. Liver transplantation is the standard of care for patients with end-stage liver disease secondary to HCV. The UNOS Registry shows that almost 40% of patients listed for liver transplantation in the United States are HCV-positive.[1] Recurrence of HCV is virtually universal post-transplantation but progression to clinical disease is variable. Overall, between 30% and 50% of recipients develop a hepatitis C viremia at some stage post-transplantation, and most recipients will have HCV-related hepatitis within 5 years. Somewhere between 10% and 40% of these recipients will progress to cirrhosis in the graft after 5–7 years.[1–6] This rate of disease progression compares with only 10% of HCV-positive people in the general population developing cirrhosis at 10 years. Hepatitis C recurrence following transplantation leads to an aggressive disease course, which translates into poor outcome.

Antibody-based induction therapy in hepatitis C virus–positive (HCV-positive) liver transplant recipients is controversial because immunosuppression may alter the risk of the patient developing recurrent HCV disease. The use of more potent immunosuppressive agents in recent years has coincided with worse graft and patient survival being reported when HCV is the indication for liver transplantation. It has not been established whether antithymocyte globulin (ATG) induction influences the risk of HCV-related graft loss, but the use of high-dose steroids and/or OKT3 to treat acute rejection and multiple acute rejection episodes are known to increase the risk of recurrent HCV.[1] Patients with recurrent HCV disease are not usually retransplanted. Induction therapy using

Presented at the Fifth Biennial Meeting of the American Hepato-Pancreato-Biliary Association, Fort Lauderdale, Florida, April 14–17, 2005.
From the Department of Surgery, Royal Victoria Hospital, Montreal, Quebec, Canada.
Reprint requests: Peter Metrakos, M.D., Royal Victoria Hospital, 687 Pine Avenue West, S 10.26, Montreal, Quebec, H3A 1A1 Canada; e-mail: peter.metrakos@muhc.mcgill.ca

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.06.020

ATG has been used as part of the standard immunosuppressive regimen since the liver transplant program at McGill University began. We looked at whether ATG induction therapy had adversely affected graft and patient survival in HCV-positive liver transplant recipients.

PATIENTS AND METHODS

The liver transplant program at the Royal Victoria Hospital (RVH) began in June 1990. The liver transplant database at the RVH was used to identify HCV-positive recipients. Recipients were divided into two groups depending on whether they were HCV-positive or HCV-negative. Graft and patient survival was analyzed on the basis of the immunosuppressive regimen that recipients were given.

Inclusion Criteria

All cadaveric liver transplants in adult recipients performed at the RVH between June 1, 1990, and December 31, 2003, were included. A minimum follow-up period of 12 months was used.

Exclusion Criteria

Liver transplant recipients who died or lost their grafts within 1 month of transplantation were excluded. Second, third, and fourth liver grafts were excluded, as were transplants in recipients diagnosed with stage III or IV hepatocellular carcinoma (HCC) pre-transplantation.

Immunosuppression

ATG induction has been used consistently since the liver transplant program at the Royal Victoria Hospital began. Methylprednisolone 500 mg intravenously is given 30 minutes before the initial dose of ATG. The first dose of ATG is usually on postoperative day 1, when the patient is likely to be hemodynamically stable. ATG is infused at 25 mg/10 kg body weight, up to a maximum of 150 mg. The maximum cumulative dose of ATG given during a course of induction therapy is 6 mg/kg. Liver transplant recipients also receive either cyclosporine (CyA) or tacrolimus (Tac); and either azathioprine (Aza) or mycophenolate mofetil (MMF); combined with steroids as maintenance immunosuppression. ATG induction has allowed the introduction of potentially nephrotoxic calcineurin inhibitors to be delayed until the recipient's serum creatinine falls below 150 μmol/L while preventing acute rejection. Ultimately, the aim has been to have recipients on calcineurin monotherapy by 1 year post-transplantation.

Statistical Analysis

Statistical analysis was performed using MedCalc for Windows, version 7.4.4.1 (MedCalc Software, Mariakerke, Belgium). Kaplan-Meier survival curves were drawn, and graft and patient survival data was analyzed with log-rank test and χ^2 test. Hazard ratios were calculated when appropriate.

RESULTS

There were 443 cadaveric livers transplanted into adult recipients during the study period, of whom 142 recipients (32%) were HCV-positive. Forty-five liver transplants in HCV-positive recipients (31.7%) were excluded for the following reasons. Thirteen recipients (9%) died or lost their graft within 1 month of transplantation; 20 recipients (14%) were retransplants, and 16 recipients (11%) had a stage III or IV HCC. Four recipients (3%) had more than one reason to be excluded. Ninety-seven HCV-positive recipients (68.3%) remained in the study, of whom 76 (78.4%) had received ATG induction.

There were 301 HCV-negative recipients transplanted during the same period. Ninety-nine HCV-negative recipients were excluded for the following reasons. Fifty-three HCV-negative recipients (17.6%) died or lost their graft within 1 month of transplantation; 43 recipients (14%) were retransplants, and 25 recipients (8%) had a stage III or IV HCC. Twenty-two recipients (7%) had more than one reason to be excluded. The outcome of 202 transplants in HCV-negative recipients (67.1%), of whom 161 (79.7%) had received ATG induction, was compared with the outcome of patients transplanted for HCV.

Donor Demographics

The median age of donors in recipients given ATG induction was 47 years (range, 8–76 years) versus 44 years (range, 15–72 years) when no ATG was used. Thirty-eight donors (50%) were male in the ATG induction group compared with 12 donors (57%) in the group not given ATG.

Recipient Demographics

The median age of HCV-positive recipients given ATG induction was 57.5 years (range, 29–73 years) versus 55 years (range, 37–69 years) when no ATG was used. Four recipients who were given ATG induction (5%) were coinfected with hepatitis B virus (HBV) compared with one recipient (5%) not given ATG. Only patients infected with HBV who were nonreplicating were transplanted. A history of significant alcohol consumption was recorded in 18 patients

(24%) who received ATG induction and 7 patients (33%) who did not. Twenty-five patients (33%) in the ATG induction group were coinfected with cytomegalovirus (CMV) compared with 9 patients (43%) in the group who did not receive ATG. In the ATG induction group, 19 HCV-positive recipients (25%) had HCC compared with 4 recipients (19%) who did not have ATG induction. Two HCV-positive patients (2.6%) in the ATG induction group were combined kidney and liver transplant recipients.

MELD Scores

The median MELD score for HCV-positive recipients given ATG induction was 24 (range, 11–54) compared with 21 (range, 9–43) in recipients not receiving ATG induction. The MELD score was not adjusted for tumor. The higher MELD scores in the patients given ATG induction was partly due to a higher prevalence of renal dysfunction. The preoperative serum creatinine was >130 μmol/L in 28 patients (37%) and >160 μmol/L in 9 patients (12%) receiving ATG induction. Five patients (24%) who did not have ATG induction had a preoperative serum creatinine that was >130 μmol/L, and only one patient (5%) had a serum creatinine >160 μmol/L.

Warm and Cold Ischemic Times

The median warm ischemic time (WIT) was 52 minutes (range, 25 minutes to 2 hours 26 minutes) in HCV-positive recipients given ATG induction and 50 minutes (range, 35 minutes to 1 hour 40 minutes) in recipients not receiving ATG induction. The median cold ischemic time (CIT) was 9 hours 42 minutes (range, 3 hours 38 minutes to 17 hours 23 minutes) in HCV-positive recipients given ATG induction and 8 hours 39 minutes (range, 5 hours 3 minutes to 15 hours 10 minutes) in recipients not receiving ATG induction.

Maintenance Immunosuppression

Maintenance immunosuppression, defined as the immunosuppression that the recipient was taking at 1 month post-transplantation with the intention of continuing in the HCV-positive ATG induction group, was 39.5% CyA (n = 30), 57.9% Tac (n = 44), 47.4% Aza (n = 36), and 43.4% MMF (n = 33). In the HCV-positive recipients not given ATG induction, it was 57.1% CyA (n = 12), 42.9% Tac (n = 9), 90.5% Aza (n = 19), and 9.5% MMF (n = 2).

Incidence of Acute Cellular Rejection

The incidence of biopsy-proven acute rejection was less in patients who received ATG induction, 34.2%, versus no ATG induction, 66.6% ($P \leq .01$).

Graft Loss From HCV-Related Disease

ATG induction did not influence the risk of graft loss from HCV-related disease ($P = .75$). The patients given ATG induction were actually less likely to have lost their graft from HCV-related disease after 10 years. When only HCV-related graft loss was considered, 10-year graft survival for HCV-positive recipients was 74% (ATG induction) versus 68.2% (no ATG induction) (Fig. 1). Recipients who lost their grafts from recurrent hepatitis C were not retransplanted; therefore, graphs for graft loss and patient death from HCV-related disease are identical.

Graft Loss From All Causes

There was no significant difference in overall graft survival between HCV-positive recipients given ATG induction and those not given ATG induction ($P = .39$). Graft survival at 10 years was 48.8% (ATG induction) versus 61.5% (no ATG induction) in HCV-positive recipients (Fig. 2). The graft survival was similar until 3 years post-transplantation, when the curves diverged slightly.

There was no significant difference in overall graft survival between HCV-negative recipients given ATG induction and those not given ATG induction ($P = .09$). Graft survival at 10 years was 58.7% (ATG induction) compared with 74.7% (no ATG induction) in HCV-negative recipients (Fig. 2). There was no significant difference in overall graft survival either between HCV-positive and HCV-negative recipients given ATG induction ($P = .15$) or between HCV-positive and HCV-negative recipients who did not receive ATG induction ($P = .18$) (Fig. 2).

Patient Death From All Causes

The difference between graft loss and patient death from all causes is accounted for by the recipients who were retransplanted. Twenty HCV-positive patients were retransplanted (26.3%) with a second liver graft, two had a third (2.5%), and one had a fourth liver graft. None of the first grafts had been lost from recurrent hepatitis C. Forty-three HCV-negative patients were retransplanted (21.3%) with a second liver graft, and five had a third (2.5%). There was no significant difference in overall patient survival between HCV-positive recipients given ATG induction and those not given ATG induction ($P = .34$). Patient survival at 10 years was 45.6% (ATG induction) versus 67.5% (no ATG induction) in HCV-positive recipients (Fig. 3).

There was no significant difference in overall patient survival between HCV-negative recipients given ATG induction and those not given ATG induction

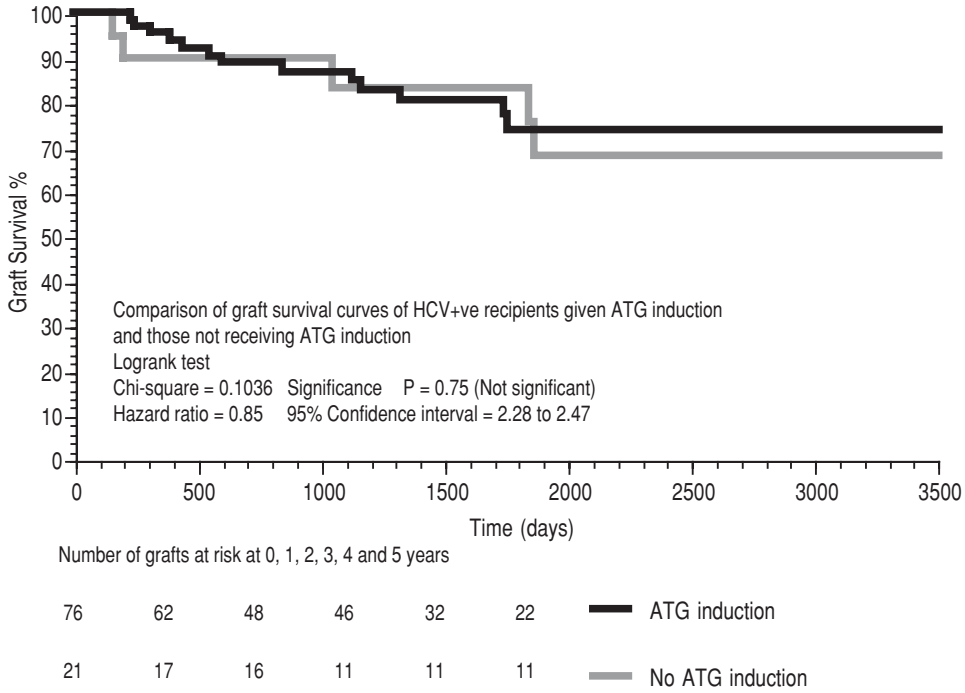

Fig. 1. Graft survival curves showing graft loss specifically from recurrent HCV-related disease. Liver transplant recipients who received ATG induction were compared with recipients who were not given ATG induction. Patients who lost their grafts from HCV were not retransplanted and so graft and patient survival curves are the same.

(P = .11). Patient survival at 10 years was 63.0% (ATG induction) versus 75.8% (no ATG induction) in HCV-negative recipients (Fig. 3).

Cumulative Dose of Steroids

ATG induction made no statistical difference to the cumulative amount of steroid administered to the recipient by 12 months post-transplantation. Most of the intravenous steroid (Solumedrol) given to patients receiving ATG induction was given as pre-medication for the ATG during the first month and was not given to treat acute rejection. The median cumulative dose of Solumedrol administered at 1 year was 0.97 g (range, 0.26–182.02 g) in recipients given ATG induction versus 1.09 g (range, 0.50–37.19 g) in recipients who were not. The median cumulative dose of prednisolone administered at 1 year was 3.09 g (range, 0.16–5.79 g) in recipients given ATG induction versus 2.61 g (range, 0.98–5.25 g) in recipients who were not.

DISCUSSION

Several consensus conferences have attempted to define the risk factors for recurrent HCV post–liver transplantation.[1,7] Pre-transplantation and post-transplantation HCV RNA levels, coinfection with CMV, possibly viral genotype 1b, and the presence of increased numbers of viral quasi-species are viral factors that increase the risk of HCV recurrence.[8–10] Using livers from older donors, transplanting female recipients and the degree of human leukocyte antigen (HLA) mismatch[11] have also been implicated on the transplant side. It is still not clear whether recipients of live donor (LD) liver grafts are at an increased risk. Multiple acute rejection episodes and the use of high-dose steroids are established risk factors for recurrence. The use of OKT3 to treat steroid resistant or severe rejection is associated with an increased incidence of recurrent hepatitis C, acute hepatitis, cirrhosis, decompensated liver disease, and death.[12,13] The use of monoclonal and polyclonal antibodies is associated with an increased incidence of hepatitis C recurrence and a more aggressive disease course.[3,12–16]

The one-year graft and patient survival following liver transplantation in HCV-positive and HCV-negative recipients are not significantly different, but at 3 years some studies demonstrate a significant difference in survival, and at 5 years there is definitely a significant difference, with HCV-positive patients doing worse (OPTN data, April 25, 2003).

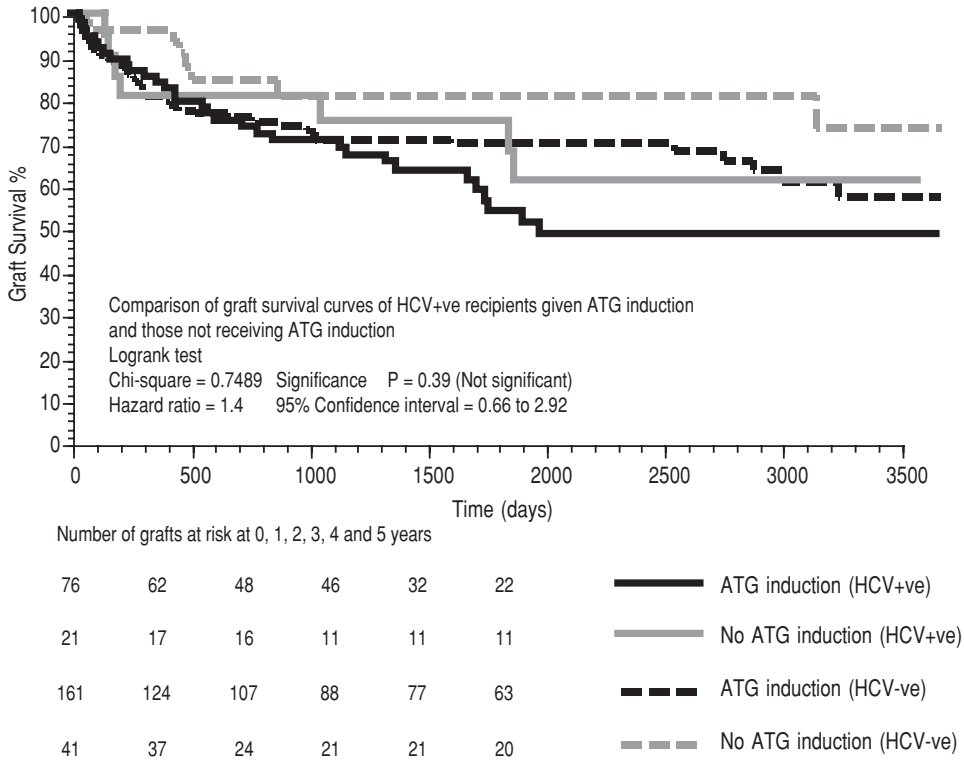

Fig. 2. Graft survival curves showing graft loss from all causes are shown. Liver transplant recipients who received ATG induction were compared with recipients who were not given ATG induction.

The incidence of hepatitis C recurrence and HCV-related disease in liver transplant recipients has increased in recent years.[5,17] Graft and patient survival is worse now than a decade ago for liver transplantation in HCV-positive recipients, the so-called era effect. It has been suggested that the overall level of immunosuppression and the era effect are linked. Potent anti-rejection agents were introduction into clinical practice during the 1990s. Immunosuppression has been blamed for the more aggressive disease seen in transplant recipients, and some authors have concluded that minimizing the amount of immunosuppression given and avoiding antibody-based induction therapy is the way forward.

There is no consensus on whether CyA is better or worse than Tac in HCV-positive patients, with some authors preferring one agent over the other and others finding no difference. There is some evidence that HCV replication increases when patients are switched from Aza to MMF, and this is worrisome; however, whether this translates into worse outcomes for the patients is not known. The combination of MMF with an interleukin-2 blocker may be bad for recurrence.[16] High-dose steroids used to treat rejection episodes have been shown to be associated with an increased risk of HCV disease recurrence and cirrhosis in the graft. However, immunosuppressive protocols that avoid steroids altogether or use rapid steroid taper post-transplantation, although popular, have not been shown to improve outcome. On this background, antibody-mediated induction therapy using ATG has been relatively ignored as an immunosuppressive strategy with a general feeling that it is a bad idea.[18] There are only a few reports concerning ATG induction therapy and HCV in liver transplantation in the literature,[19] none with long-term follow-up.[20]

ATG induction has been routinely used for induction therapy in liver transplantation at our institution since 1990. Antibody-based induction therapy can be used to protect renal function in the early post-transplant period.[21] ATG induction has allowed us to delay the introduction of calcineurin inhibitor in the early period, benefiting renal function, while simultaneously preventing rejection.

Acute cellular rejection (ACR) does not normally impact greatly on patient and graft survival following liver transplantation; however, ACR is associated with decreased long-term survival of patients transplanted for hepatitis C cirrhosis. After one or more episodes of ACR, HCV-positive recipients have an increased risk of death that is three times that of HCV-positive

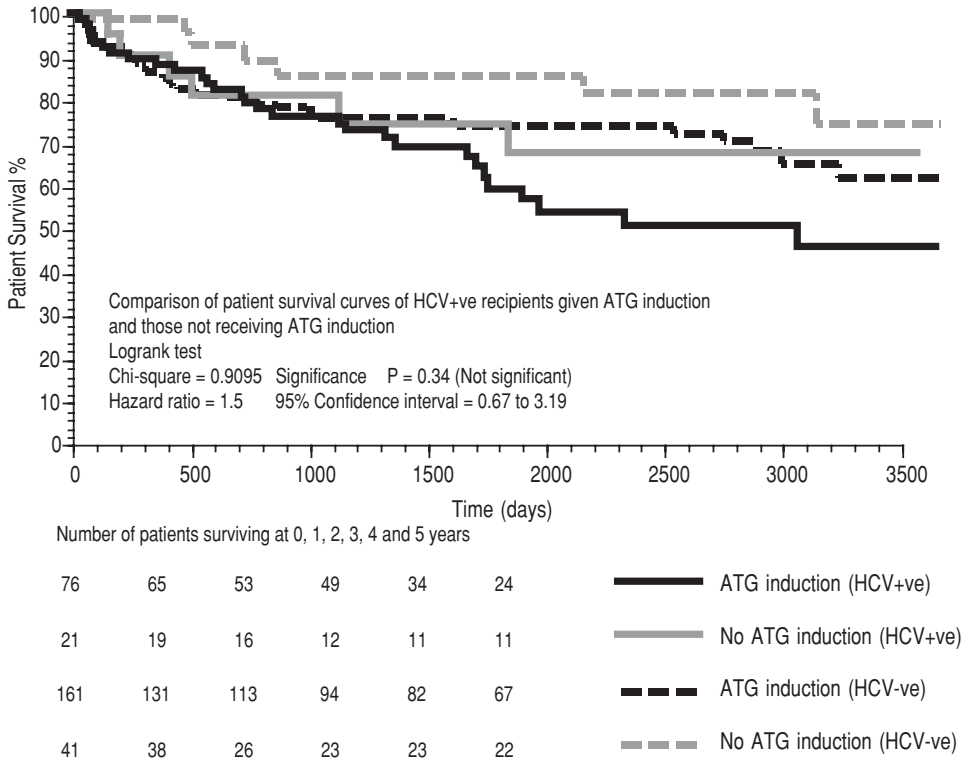

Fig. 3. Patient survival curves showing death from all causes are shown. Liver transplant recipients who received ATG induction were compared with recipients who were not given ATG induction.

recipients who are free from rejection. If ACR does not respond to high-dose pulsed steroids, the risk of death is increased to a greater-than-five-times risk.[22]

High-dose pulsed steroid therapy used to treat ACR increases baseline serum HCV RNA levels by 4–100 times. The elevation in HCV RNA levels is associated with an increased incidence of HCV-related acute hepatitis[23,24] and an increased incidence of severe hepatitis on histology.[25] The time to develop recurrent cirrhosis is accelerated following the pulsed steroids and the consequent rise in serum HCV RNA levels[23] and is associated with severe inflammation and fibrosis in the graft. Once present, these histologic changes tend to progress rapidly to decompensated liver disease and death within a few years.[12]

As viral load is known to increase dramatically following treatment for acute rejection, it may be that immunosuppressive protocols aimed at minimizing the incidence of rejection are associated with a better outcome for HCV-positive recipients. On the other hand, there are those in liver units who believe that mild ACR episodes in HCV-positive recipients, defined as Banff grade 1, are best left untreated. They believe that the rejection should "burn itself out." It may be that the absolute level of immunosuppression is less important than change in triggering HCV recurrence.[26]

The diagnosis of rejection in HCV-positive recipients is not straightforward. ACR often occurs on a background of recurrent HCV liver disease. The Banff criteria for liver allograft rejection uses interface hepatitis and injury to bile ducts to diagnose and grade the severity of acute rejection; however, recurrent chronic HCV disease can have a similar histologic appearance, creating a confusing clinical picture. This may result in acute rejection going untreated, or worse, high-dose steroids being given unnecessarily to an HCV-positive recipient. Adopting an immunosuppressive strategy associated with a lower incidence of ACR may make the decision not to treat the patient for rejection easier when the histology has been difficult to interpret.

We found that the ATG induction significantly reduced the incidence of acute rejection and did not increase the risk of graft loss or death from recurrent HCV. The graft and patient survival curves were not significantly different. Recipients given ATG induction appeared to have a slightly worse graft and patient survival after 3 years. This was not related to HCV recurrence, and only one patient who had ATG induction developed and died from a post-transplantation lymphoproliferative disease. Recipients who were given ATG induction were older, had higher MELD scores, and had a higher incidence

of renal dysfunction pre-transplantation, and these factors may help account for the difference.

CONCLUSION

ATG induction did not increase the risk of HCV-related graft loss or patient death. The significantly lower incidence of ACR in patients receiving ATG induction and the known association of recurrent HCV-related disease with the treatment of ACR and multiple acute rejection episodes provide the rational for continuing to use ATG induction therapy in HCV-positive recipients.

We acknowledge Ann Hubert, BAV, Medical Illustrator, Medical Multimedia Services, The Montreal General Hospital, 1650 Cedar Avenue, E4-310, Montreal, Quebec, Canada, who produced the images used in this report.

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Vascular Endothelial Growth Factor and *DPC4* Predict Adjuvant Therapy Outcomes in Resected Pancreatic Cancer

Alok A. Khorana, M.D., Ying Chuan Hu, M.D., Ph.D., Charlotte K. Ryan, M.D., Richard A. Komorowski, M.D., Galen Hostetter, M.D., Steven A. Ahrendt, M.D.

Angiogenesis is important for pancreatic cancer progression, but its role in predicting response to therapy is not known. We investigated the association of various angiogenic factors and intratumoral microvessel density (IMD) with adjuvant therapy and survival in resected pancreatic cancer. Tissue cores from a multi-institutional retrospective series of resected patients were used to build a pancreatic cancer tissue microarray. Vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PD-ECGF), CD31 (for IMD), and *DPC4* expression were determined using immunohistochemistry. Expression of VEGF and PD-ECGF, both proangiogenic factors, was observed in 70 (56%) and 75 (59%) of 124 tumors, respectively. Expression of *DPC4*, an angiogenesis inhibitor, was observed in 59 of 124 (48%) tumors. VEGF expression correlated significantly with increased IMD ($P = .03$), as did loss of antiangiogenic *DPC4* ($P = .05$). PD-ECGF expression did not correlate with IMD. Use of adjuvant therapy was associated with increased survival in patients with VEGF-positive tumors (18.8 [treated] versus 11.2 [untreated] months; hazard ratio [HR] = 0.38, 95% confidence interval [CI], 0.19–0.76; $P = .005$), but not in patients with VEGF-negative tumors. Similarly, improved survival was observed in patients with high IMD (16.3 [treated] versus 11.2 [untreated] months; HR = 0.44, 95% CI, 0.23–0.87; $P = .02$) and in patients with loss of *DPC4* (20.3 [treated] versus 11.2 [untreated] months; HR = 0.31, 95% CI, 0.14–0.67; $P = .002$), but not in those with low IMD or normal *DPC4* expression. VEGF (stimulator) and *DPC4* (inhibitor) are important regulators of pancreatic tumor angiogenesis and predictive of benefit from adjuvant therapy. Adjuvant therapy may have both antiangiogenic and cytotoxic effects. Addition of anti-VEGF agents to adjuvant regimens may further improve outcomes.
(J Gastrointest Surg 2005;9:903–911)

Key words: Pancreatic cancer, VEGF, *DPC4*, microvessel density

Pancreatic cancer is the fifth leading cause of cancer death in the United States. In 2004, 31,860 Americans are expected to be diagnosed with pancreatic cancer, and 31,270 will die of the disease.[1] Only a minority of newly diagnosed pancreatic cancer patients are considered eligible for resection. Five-year survival rates in those who undergo this major procedure are only 8%–24%.[2–4] Adjuvant chemoradiation or chemotherapy is usually recommended to eligible patients after the resection procedure. However, outcomes even with adjuvant therapy remain dismal, and reported median survival is less than 20 months.[5] A recent single-institution study using interferon and chemoradiation therapy reported an actuarial 5-year survival rate of 55%, although this approach awaits confirmation in a multicenter trial.[6] The results of most phase III studies suggest, however, that a large number of resected patients are treated with adjuvant chemoradiation without significant benefit.[2,4] We have previously shown that thymidylate synthase

Presented at the Fifth Biennial Meeting of the American Hepato-Pancreato-Biliary Association, Fort Lauderdale, Florida, April 14–17, 2005.
From the James P. Wilmot Cancer Center and the Department of Medicine (A.A.K., S.A.A.), and the Department of Surgery (Y.C.H., S.A.A.), University of Rochester, Rochester, NY; the Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry (C.K.R., S.A.A.), Rochester, NY; Department of Pathology, Medical College of Wisconsin, Milwaukee, WI (R.A.K.); the National Human Genomics Research Institute, National Institutes of Health, Bethesda, MD (G.H.); and Translational Genomics Research Institute, Phoenix, AZ (G.H.).
Dr. Khorana is supported by the James P. Wilmot Cancer Research Fellowship.
Reprint requests: Alok A. Khorana, M.D., 601 Elmwood Ave., Box 704, Rochester, NY 14642. e-mail: alok_khorana@URMC.rochester.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.06.021

expression is predictive of the response to 5-fluorouracil–based adjuvant therapy.[7] Further elucidation of predictive factors is necessary to select patients who are likely to benefit from adjuvant therapy.

Angiogenesis is essential for tumor growth and metastasis. Vascular endothelial growth factor (VEGF) is an important proangiogenic cytokine and is required to initiate the formation of immature vessels by vasculogenesis or angiogenic sprouting.[8] Measurement of intratumoral microvessel density (IMD) using immunohistochemistry has emerged as a reliable marker for angiogenesis in recent prognostic studies of various solid tumors.[9] Increased angiogenesis, as demonstrated by high IMD, has also been shown to be associated with a poor prognosis in pancreatic cancer.[10–12] Angiogenesis in pancreatic cancer is regulated by a balance between proangiogenic and antiangiogenic cytokines. VEGF and platelet-derived endothelial cell growth factor (PD-ECGF), also known as thymidine phosphorylase, appear to be important proangiogenic factors in pancreatic cancer. Several studies have demonstrated a correlation between VEGF expression and increased angiogenesis as demonstrated by IMD, as well as a correlation with worsened outcomes after resection.[13–15] However, the association of PD-ECGF with increased IMD and worsened survival has not been as consistently demonstrated.[16,17] A recent study in pancreatic cancer cell lines has shown that the tumor suppressor Smad4/*DPC4* (deleted in pancreatic cancer, locus 4) inhibits pancreatic cancer growth by suppressing angiogenesis.[18] The clinical significance of this observation has not been determined.

We, therefore, chose to study the expression of VEGF, PD-ECGF, and *DPC4* in resected pancreatic cancer specimens. We correlated the expression of these factors with IMD determined by CD31 staining and with survival after adjuvant therapy.

MATERIALS AND METHODS

Patient Characteristics

Formalin-fixed, paraffin-embedded tumor tissue was collected retrospectively from 138 patients who underwent pancreatic resection for pancreatic ductal adenocarcinoma at Strong Memorial Hospital/University of Rochester (n = 79) or Froedtert Memorial Lutheran Hospital/Medical College of Wisconsin (n = 59) between January 1994 and February 2002. Distal bile duct, ampullary, and duodenal adenocarcinomas as well as other pancreatic neoplasms (mucinous cystic adenocarcinoma and intraductal papillary mucinous tumors with adenocarcinoma) were excluded from this study. Any patient who received preoperative therapy (neoadjuvant chemotherapy and radiation therapy) was not eligible to participate. All pathology reports were reviewed, and TNM stage and grade were assigned using American Joint Committee on Cancer criteria.[19] Surgical margins were considered positive if infiltrating adenocarcinoma was present at the uncinate process, retroperitoneal soft tissue, or final pancreatic neck margin. Ten tumors were uninterpretable for one or more of the immunohistochemical stains. Four patients died within 30 days of surgery from perioperative complications and were also excluded from analysis.

Clinical information was obtained from a review of hospital and physician charts or from the respective hospital tumor registry. Patient follow-up was obtained through the review of hospital and physician records, direct patient contact, and the Social Security Death Index. Two patients were lost to follow-up before the completion of the study. This research protocol was reviewed and approved by the University of Rochester Research Subjects Review Board.

Construction of Pancreatic Cancer Tissue Microarray

Hematoxylin and eosin (H&E)-stained standard slides were reviewed from each pancreatic cancer, and a representative tumor region and the corresponding formalin-fixed paraffin tissue block were selected for use in the tissue microarray.[7,20] Two discrete histomorphologically representative regions were selected from each tissue block. Three 0.6-mm tissue cores were taken from each region using an automated custom-built tissue arrayer and transferred to three individual recipient blocks at defined array coordinates (six cores per tumor). In addition, tissue cores were also selected from histologically normal pancreatic acini, pancreatic ducts, and duodenal mucosa for use as controls. Five-micron sections were cut from each recipient tissue microarray block using an adhesive-coated tape system (Instrumedics, Hackensack, NJ[20]). Sections were stained with H&E to confirm the presence of pancreatic cancer within each tissue core and for immunohistochemical analysis.

Immunohistochemistry

Tissue sections from the pancreatic cancer tissue microarray were deparaffinized, rehydrated through graded alcohols, and washed with Tris-buffered saline. Expression of *DPC4*, PD-ECGF, and CD31 was determined using the streptavidin-biotin-peroxidase complex method as reported previously.[7] Antigen retrieval for *DPC4* and CD31 was performed

by microwave heating sections in 10 mmol/L sodium citrate buffer (pH 6) for 10 minutes. After endogenous peroxidase activity was quenched and nonspecific binding was blocked, monoclonal anti*DPC4* (Santa Cruz Biotechnology, Santa Cruz, CA), monoclonal antithymidine phosphorylase (PD-ECGF) (NeoMarkers Inc., Fremont, CA), and monoclonal antiCD31 (NeoMarkers Inc.) were incubated at 4°C overnight at a dilution of 1:400 for *DPC4* and PD-ECGF and 1:120 for CD31, respectively. The secondary antibody was biotinylated rabbit antimouse antibody (DAKO, Carpinteria, CA) used at a dilution of 1:200 for 30 minutes at 37°C. After washing with Tris-buffered saline, sections were incubated with StrepABComplex/horseradish peroxidase (1:100 dilution; DAKO) for 30 minutes at 37°C. Immunolocalization was performed by immersion in 0.05% 3,3′-diaminobenzidine tetrahydrochloride as chromagen.

Sections for VEGF immunostaining were treated with 3% hydrogen peroxide for 10 minutes to quench myeloperoxidase and then cleared in running water followed by a 5-minute rinse in Tris-buffered saline (TBS) at pH 7.6. Antigen unmasking with heat retrieval solution (DAKO) at pH 6.1 was accomplished by placing the slide in preheated DAKO TBS in a steamer for 30 minutes. The slide was mounted on the DAKO Autostainer and incubated with rabbit polyclonal antibody to VEGF (1:50) (Zymed Laboratories, San Francisco, CA) for 1 hour. Staining was completed using DAKO Rabbit Envision Plus Kit (DAKO). The sections were counterstained with a modified Mayer hematoxylin followed by 10 dips in 3% ammonia water.

An invasive ductal breast cancer with known VEGF positivity, a pancreatic carcinoma with known *DPC4* positivity, a breast carcinoma with known PD-ECGF positivity, and placental tissue with known CD31 positivity served as positive controls for VEGF, *DPC4*, PD-ECGF, and CD31, respectively. Negative controls were performed by replacing the primary antibody by normal serum.

All sections were reviewed independently by pathologists blinded to all clinical and pathologic information (C.K.R., Y.C.H., and R.A.K.). VEGF expression was considered positive when at least one of the pancreatic tissue cores contained cytoplasmic VEGF staining of moderate or greater intensity in greater than 5% of pancreatic cancer cells. *DPC4* and PD-ECGF were also considered as positive when more than 5% of tumor cells exhibited cytoplasmic staining, according to published criteria.[21,22]

CD31 staining was used to determine IMD. Large and small microvessels as well as single brown immunostained endothelial cells were included in the microvessel count as previously recommended in consensus guidelines.[9,23] An individual IMD was calculated from each pancreatic cancer tissue core in the microarray (single high-power field). The IMD for each tumor was defined as the mean value from all interpretable cores.

Statistical Analysis

The association between immunohistochemical expression of VEGF, PD-ECGF, and *DPC4* and individual clinical and pathologic variables (age, gender, race, tumor size, pathologic stage, pathologic grade, margin status, and operative procedure, IMD) was assessed using Fisher's exact test or χ^2 (categorical variables) or Wilcoxon's rank-sum test (continuous variables). The associations between individual clinical and pathologic variables (age, gender, race, T stage, N stage, pathologic stage, pathologic grade, margin status, operative procedure, IMD, and the expression of VEGF, PD-ECGF, and *DPC4*) and survival were assessed using the Cox proportional hazards regression model. The influence of age and IMD on survival was determined by dividing the population into similar size groups at the median value of these two variables. A stepwise variable selection procedure was used to build a Cox proportional hazards multiple regression model for time to death; a significance level of .20 was used to determine whether a variable could be entered into or removed from the regression model. Associations were quantified using hazard ratios and their 95% confidence intervals (CIs). Survival time was determined as the time from resection to death. For survivors, survival times were censored on the last date that patients were known to be alive. Survival probabilities were estimated using the method of Kaplan and Meier. Log-rank tests were used to compare survival curves among the various subgroups of patients. All statistical tests were two-tailed.

The funding source had no role in the study design, data collection and analysis, or the writing of the report.

RESULTS

Patient Characteristics

One hundred twenty-four pancreatic adenocarcinoma patients were evaluable for VEGF, PD-ECGF, *DPC4*, and CD31 staining. Patient characteristics are described in Table 1. Mean age of this population was 66.5 ± 11.4 years. Sixty-nine (56%) patients were male and 55 (44%) were female. A history of adjuvant therapy was available for 111 (90%) patients. Eighty-eight (79%) of these patients received some form of

Table 1. Clinical and Pathologic Characteristics of 124 Patients With Resected Pancreatic Cancer Evaluated for VEGF, DPC4, and CD31 Expression

	Total	VEGF Positive	VEGF Negative	*P*	DPC4 Positive	DPC4 Negative	*P*
No. of patients	124	70 (56)	54 (44)		59 (48)	65 (52)	
Age (yr)	67 ± 11	67 ± 12	65 ± 11	.19	67 ± 11	66 ± 12	.64
Gender							
Male	69 (56)	37 (53)	32 (59)	.47	34 (58)	35 (54)	.67
Female	55 (44)	33 (47)	22 (41)		25 (42)	30 (46)	
Tumor size (cm)	3.0 ± 1.1	3.0 ± 1.0	2.9 ± 1.1	.64	2.8 ± 1.0	3.2 ± 1.0	.01
T stage							
T1 and T2	50 (42)	26 (38)	24 (47)	.33	27 (47)	23 (37)	.26
T3 and T4	69 (58)	42 (62)	27 (53)		30 (53)	39 (63)	
N stage							
N0	68 (55)	38 (54)	30 (56)	.89	35 (59)	33 (51)	.34
N1	56 (45)	32 (46)	24 (44)		24 (41)	32 (49)	
Tumor stage							
I and II	67 (54)	37 (53)	30 (56)	.77	35(59)	32 (49)	.26
III and IVA	57 (46)	33 (47)	24 (44)		24 (41)	33 (51)	
Tumor grade							
Poorly differentiated	45 (38)	30 (45)	15 (28)	.08	21 (36)	24 (39)	.91
Moderately differentiated	52 (43)	27 (41)	25 (46)		25 (43)	27 (43)	
Well differentiated	23 (19)	9 (14)	14 (26)		12 (21)	11 (18)	
Margin status							
Negative	99 (80)	52 (74)	47 (87)	.08	46 (78)	53 (82)	.62
Positive	25 (20)	18 (26)	7 (13)		13 (22)	12 (18)	
Operative Procedure							
Pancreaticoduodenectomy	109 (89)	63 (91)	46 (85)	.57	52 (88)	57 (89)	.17
Total pancreatectomy	3 (2)	1 (1)	2 (4)		0 (0)	3 (5)	
Distal pancreatectomy	11 (9)	5 (8)	6 (11)		7 (12)	4 (6)	
Adjuvant therapy							
Yes	88 (79)	46 (78)	42 (81)	.72	43 (80)	45 (79)	.93
No	23 (21)	13 (22)	10 (19)		11 (20)	12 (21)	

Values given in number of patients unless otherwise indicated.

adjuvant radiation and/or chemotherapy. Eighty-two (74%) patients received external beam radiation, 85 (77%) patients received adjuvant chemotherapy, and 78 (70%) patients received combined adjuvant chemoradiation. Patients receiving adjuvant therapy were younger (64 ± 13 [adjuvant therapy] versus 73 ± 11 years [no adjuvant therapy]; $P = .001$), more likely to be male (64% [adjuvant therapy] versus 30% [no adjuvant therapy]; $P = .004$), and had larger tumors (3.1 ± 1.0 [adjuvant therapy] versus 2.6 ± 0.8 cm [no adjuvant therapy]; $P = .04$) than patients not receiving adjuvant therapy. No statistically significant differences in pathologic stage, tumor N stage, and histologic grade were noted among patients receiving and patients not receiving adjuvant therapy.

Immunohistochemistry

VEGF expression was observed primarily in tumor cells, and only rarely in stromal cells. Seventy of the 124 patients (56%) expressed VEGF in tumor cells. IMD was significantly ($P = .03$) greater in pancreatic cancer with positive VEGF expression than in tumors with negative VEGF expression. PD-ECGF expression was observed primarily in the cytoplasm of pancreatic cancer cells. Seventy-five of the 124 patients (60%) expressed PD-ECGF. No correlation was observed between PD-ECGF expression and IMD. Expression of the angiogenesis inhibitor *DPC4* was observed in 59 (48%) patients. IMD was significantly ($P = .03$) lower in pancreatic cancer with positive *DPC4* expression than in tumors with loss of *DPC4* expression.

Survival Analysis

At the time of data analysis, patients had been followed for a median period of 16 months (range, 51 days to 93 months). Actuarial survival for the entire study population at 5 years was 15%. The role of VEGF, PD-ECGF, *DPC4*, and IMD and other clinical and pathologic variables in predicting survival is

Table 2. Univariate Analysis of Prognostic Factors in Patients With Resected Pancreatic Cancer

	No. of Patients	Median Survival (mo)	Risk Ratio	95% Confidence Interval	*P*
Age (yr)					
≤67	64	18.3	1.0		.22
>68	60	13.3	1.3	0.86–1.9	
Gender					
Male	69	18.9	1.0		.05
Female	55	13.0	1.5	1.0–2.2	
T stage					
T1 and T2	50	17.1	1.0		.65
T3	69	15.4	1.1	0.73–1.7	
N stage					
N0	68	19.3	1.0		.004
N1	56	11.5	1.8	1.2–2.7	
Tumor stage					
I and II	67	19.7	1		.004
III and IVA	57	11.6	1.8	1.2–2.7	
Tumor grade					
Poorly differentiated	23	19.9	1.0		.07
Moderately differentiated	52	17.9	1.0	0.58–1.7	
Well differentiated	45	11.4	1.9	0.97–2.9	
Margin status					
Negative	99	16.4	1.0		.08
Positive	25	11.8	1.5	0.95–2.4	
Adjuvant therapy					
Yes	88	19.8	1.0		.005
No	23	11.2	0.48	0.29–0.80	
DPC4 expression					
Negative	65	15.6	1.0		.53
Positive	59	17.7	0.88	0.59–1.3	
VEGF expression					
Negative	54	19.4	1.0		.17
Positive	70	13.8	1.3	0.89–2.0	
PD-ECGF expression					
Negative	49	17.9	1		.32
Positive	75	15.3	1.22	0.82–1.84	
IMD					
≤6 per tissue core	61	19.9	1		.10
>6 per tissue core	63	13.0	1.4	0.94–2.1	

IMD = intratumoral microvessel density.

shown in Table 2. A trend toward shorter survival was observed with positive VEGF expression and with high IMD, but neither of these trends was statistically significant. *DPC4* and PD-ECGF expression were not associated with survival. Male gender, tumor N stage, and overall pathologic stage were predictive of overall patient survival. Overall survival was also prolonged in patients receiving any form of adjuvant therapy (RR = 0.48; 95% CI = 0.29–0.80, $P = .005$).

Multiple regression analysis was performed using a Cox proportional hazards model to determine variables independently predictive of survival in patients with resected pancreatic cancer. Tumor N stage, gender, histologic grade, margin status, the use of adjuvant therapy, VEGF expression, and IMD were included in the stepwise model selection process. The absence of lymph node metastases (RR = 0.55; 95% CI = 0.36–0.85, $P = .007$) and the use of adjuvant therapy (RR = 0.46; 95% CI = 0.28–0.78, $P = .004$) were both associated with a decreased risk of death in resected pancreatic cancer.

Angiogenesis Markers and Survival After Adjuvant Therapy

The interaction between the angiogenesis markers VEGF, *DPC4*, and IMD and treatment with adjuvant therapy on patient survival is shown in Table 3. No

Table 3. Effect of VEGF Expression, DPC4 Expression, IMD, and Adjuvant Therapy on Survival in Patients With Pancreatic Cancer

	Adjuvant Therapy	Patients	Median Survival (mo)	Risk Ratio	95% Confidence Interval	*P*
VEGF expression						
Positive	No	13	11.2	1.0		.007
Positive	Yes	46	18.8	0.38	0.19–0.76	
Negative	No	10	13.7	1.0		.22
Negative	Yes	42	20.7	0.61	0.28–1.4	
DPC4 expression						
Negative	No	12	11.1	1.0		.003
Negative	Yes	45	20.3	0.31	0.14–0.67	
Positive	No	11	14.3	1.0		.32
Positive	Yes	43	18.9	0.68	0.32–1.4	
IMD						
>6 per tissue core	No	16	11.2	1.0		.02
>6 per tissue core	Yes	37	16.3	0.44	0.22–0.87	
≤6 per tissue core	No	7	17.9	1.0		.51
≤6 per tissue core	Yes	51	21.2	0.73	0.28–1.9	

IMD = intratumoral microvessel density.

statistically significant differences in the expression of VEGF and *DPC4* or IMD were present between patients receiving or not receiving adjuvant therapy. Forty-six patients with VEGF-positive tumors received adjuvant therapy. Median survival among VEGF-positive patients that received adjuvant therapy was 18.8 months, a significant increase over the median survival of 11.2 months for patients who did not receive adjuvant therapy (HR 0.38; 95% CI = 0.19–0.76, $P = .007$) (Fig. 1). No statistically significant survival benefit was observed among patients with VEGF-negative tumors who received adjuvant therapy (20.7 versus 13.7 months; $P = .22$).

Forty-five patients with loss of *DPC4* received adjuvant therapy. Among patients with loss of *DPC4* expression, adjuvant therapy significantly improved overall survival (HR = 0.31, 95% CI, 0.14–0.67, $P = .003$) (Fig. 2). In patients with normal *DPC4* expression, no significant difference in survival was noted among patients managed with resection versus patients managed with resection and adjuvant therapy. Finally, adjuvant therapy significantly improved survival among patients with high IMD but not in patients with low IMD. Among patients with more than six microvessels per tissue core, adjuvant therapy significantly improved overall survival

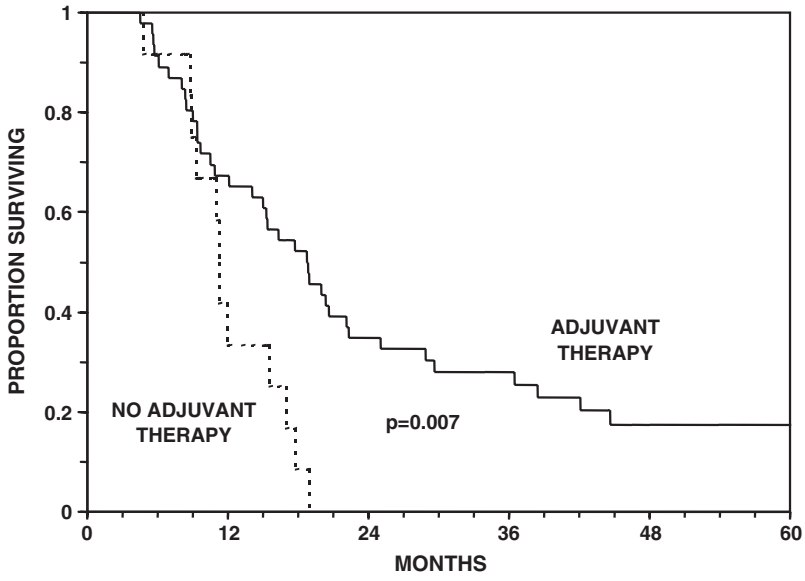

Fig. 1. In patients with VEGF-expressing pancreatic cancer, adjuvant therapy was associated with a significant ($P = .007$) increase in patient survival versus patients treated with resection alone.

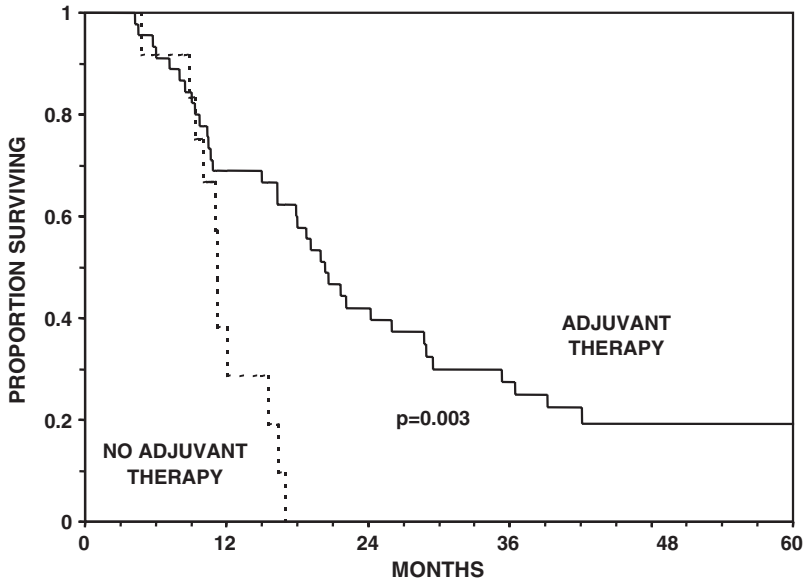

Fig. 2. In patients with pancreatic cancer lacking normal *DPC4* expression, adjuvant therapy was associated with a significant (P = .003) increase in patient survival versus patients treated with resection alone.

(HR = 0.44, 95% CI, 0.22–0.87, P = .02) (Fig. 3). PD-ECGF expression did not correlate with survival after adjuvant therapy.

DISCUSSION

Increased expression of proangiogenic VEGF, absence of antiangiogenic *DPC4* expression, and increased IMD, a surrogate for angiogenesis, were all associated with improved survival in patients who received adjuvant therapy in this retrospective analysis of resected pancreatic cancer. Both VEGF expression and the absence of *DPC4* expression correlated with increased IMD, supporting their role in the regulation of angiogenesis in pancreatic cancer. PD-ECGF expression did not correlate with IMD or survival.

The importance of VEGF as a stimulator of angiogenesis in pancreatic and other tumors is well known.

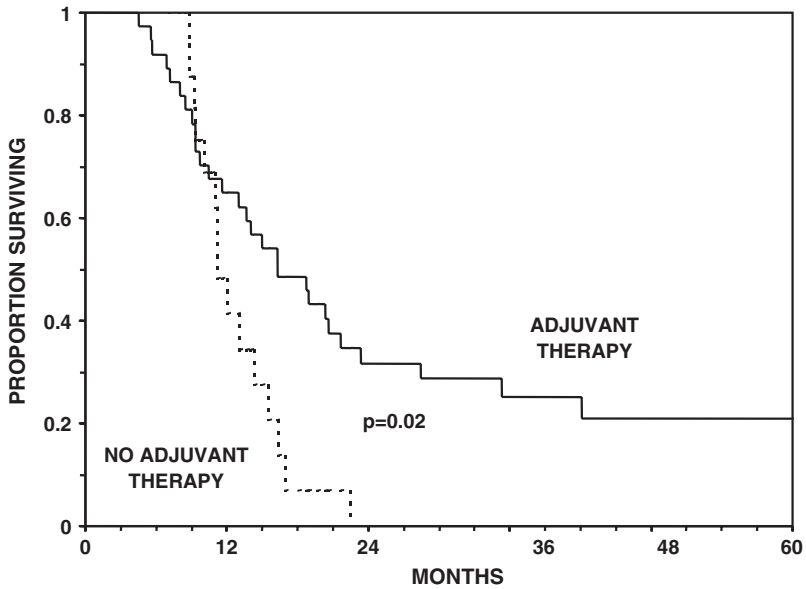

Fig. 3. In patients with pancreatic cancer with high IMD, adjuvant therapy was associated with a significant (P = .02) increase in patient survival.

Overexpression of VEGF and its receptor, VEGF-RII, has been reported in pancreatic cancer.[24] Prior clinical studies have shown an association of VEGF expression with worsened survival and increased relapses in pancreatic cancer.[13–15] Our study showed an association between VEGF expression and a trend toward worsened survival, consistent with prior reports. Although the significance of VEGF as a prognostic factor has been previously documented, its utility as a predictive factor has not been investigated. In our study, although VEGF expression was associated with worsened survival, patients with increased VEGF expression benefited from the use of adjuvant therapy. The evidence supporting adjuvant therapy is controversial.[4] In an analysis of a large U.S. database, fewer than one fifth of patients who received adjuvant therapy after resection were alive at 5 years.[25] This suggests that many patients who receive adjuvant therapy are treated without benefit. We have previously shown that 5-fluorouracil–based adjuvant therapy is most beneficial in patients with high thymidylate synthase–expressing cancers.[7] The results from our current analysis, if confirmed, could provide an additional way of discriminating patients who would be more likely to benefit from an adjuvant regimen.

DPC4 is a tumor-suppressor gene that is frequently inactivated in pancreatic and biliary tract cancers.[26] In the cytoplasm, *DPC4* mediates signals from a family of TGF-α ligands. Growth suppression and apoptotic functions of TGF-α are abrogated by inactivation of *DPC4*.[27] In addition, *DPC4* may act through a second pathway of angiogenesis inhibition, by decreasing the expression of VEGF and increasing the expression of thrombospondin-1.[18] An initial study reported that patients with pancreatic cancer had a worse survival if their cancers did not express *DPC4*.[28] However, the results of a larger series did not demonstrate a consistent effect of *DPC4* on patient survival in pancreatic cancer, and none of these studies reported data regarding adjuvant therapy.[21,28] We did not observe an association between *DPC4* expression and patient survival. However, we found that loss of *DPC4* expression was associated with an increase in IMD, suggesting that *DPC4* is important in the regulation of angiogenesis. To the best of our knowledge, this is the first report demonstrating this finding in clinical samples. Furthermore, loss of *DPC4* expression was associated with a statistically significant improvement in survival following adjuvant therapy, similar to that reported with VEGF and increased IMD.

PD-ECGF promotes angiogenesis by stimulating chemotaxis of endothelial cells.[29] Prior smaller series have reported conflicting results on its significance in angiogenesis in pancreatic cancer, and as a prognostic factor.[16,17] We found no correlation between PD-ECGF expression and IMD or survival, suggesting that PD-ECGF is not as significant as VEGF in promoting angiogenesis in pancreatic cancer.

Caution must be used in interpreting the results of our study. This analysis was retrospective, and the populations receiving or not receiving adjuvant therapy were not balanced for age or gender. The adjuvant therapy regimens used were not standardized, although a majority of patients received 5-fluorouracil–based treatment. The use of a tissue microarray could have underestimated the true frequency of the various parameters tested, particularly in patients with focal expression. However, we used three distinct arrays, each sampling different sites within each tumor to compensate for this. Our results require confirmation in a larger prospective study before clinical utilization.

The association of the angiogenesis parameters tested with benefit from adjuvant therapy raises questions about the mechanism of action of adjuvant therapy in this setting. Recent reports have suggested that scheduling chemotherapy with more frequent dosing, termed metronomic scheduling, can yield potent antiangiogenic activity in animal models.[30] Metronomic dosing of chemotherapy may preferentially target endothelial cells rather than tumor cells.[31,32] In this context, it is interesting to note that adjuvant therapy regimens for pancreatic cancer have often used frequent doses and/or a protracted venous infusion of 5-fluorouracil.[33] Furthermore, the addition of interferon, a known antiangiogenic agent, to an adjuvant protracted 5-fluorouracil–based chemoradiation regimen, has been shown to result in a substantial improvement in outcomes.[6] The results observed with this study suggest that the mechanism of adjuvant therapy in this setting may be antiangiogenic in addition to being cytotoxic. The addition of newly available angiogenic inhibitors, in particular anti-VEGF therapies, to current adjuvant therapy regimens may further improve outcomes. Such a strategy deserves to be tested in prospective clinical studies.

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Small Bowel Varices From Neuroendocrine Tumor of the Pancreas

Shimul A. Shah, M.D., Carlos M. Mery, M.D., Michael J. Zinner, M.D., F.A.C.S.

Small bowel varices (SBVs) are a rare but important cause of gastrointestinal (GI) bleeding. We present a case of SBVs caused by superior mesenteric vein thrombosis from a large neuroendocrine tumor of the pancreas. This patient presented with GI bleeding. A computed tomography scan showed an incidental hypervascular mass that was unresectable. After exhaustive work-up, the GI bleeding was in fact due to the mass by direct compression on the superior mesenteric vein. The SBVs were evident on the venous phase of a computed tomography angiogram. The patient was treated medically with octreotide, β-blockade, and external beam radiation therapy applying the physiology of esophagogastric varices to the small bowel. Persistent GI bleeding in the presence of a large central mass should always alert one to consider varices from collateral flow as a possible cause. (J GASTROINTEST SURG 2005;9:912–914)

KEY WORDS: Small bowel varices, neuroendocrine tumor, superior mesenteric vein thrombosis

Small bowel varices (SBVs) are rare compared with esophageal or gastric varices but can be equally debilitating because of repeated episodes of bleeding. Few cases have been reported in the literature, and cirrhosis is the etiology in most cases. We report a unique case of superior mesenteric vein (SMV) compression from a large neuroendocrine (NE) tumor of the pancreas resulting in SBV and recurrent lower gastrointestinal (GI) bleeding.

CASE REPORT

An 81-year-old woman presented with 1 day of crampy abdominal pain, copious melena, and small amounts of hematochezia. Her initial hematocrit was 25%, and after resuscitation, she underwent an upper and lower endoscopy. Her upper endoscopy and colonoscopy were unremarkable. She underwent an abdominal computed tomography (CT) scan that revealed a 13.1 × 7.7 × 4.7-cm solid, enhancing mass in the body of the pancreas, encasing the superior mesenteric artery and SMV with multiple solid liver lesions (Fig. 1). A CT-guided biopsy of the lesion confirmed a NE tumor.

She continued to have intermittent episodes of melena and hematochezia. Upper and lower endoscopies were repeated, showing no evidence of active bleeding, and a capsule enteroscopy demonstrated only small varices in the proximal jejunum. A small bowel follow-through radiogram using luminal contrast media was then performed, which was normal. The bleeding spontaneously stopped, and after observation for several days, the patient was discharged.

She returned to the emergency department 3 weeks later with melena combined with bright-red blood per rectum and a hematocrit of 25% (down from 32%). A tagged red blood cell scan showed evidence of possible bleeding from the stomach. An angiogram identified some hyperemia in the distribution of the left gastric artery, which was successfully embolized with gelfoam. She was discharged home with a stable hematocrit and no evidence of further bleeding.

Three hours after discharge, the patient noticed two melanotic stools, associated with dizziness, fatigue, and nausea. An upper endoscopy showed a large area of erythema with three clean-based ulcers on the lesser curvature of the stomach with no stigmata

From the Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
Reprint requests: Shimul A. Shah, M.D., Department of Surgery, Toronto General Hospital, University of Toronto, 585 University Ave., 11C-1244, Toronto, Ontario M5G 2N2, Canada. e-mail: shimul.shah@uhn.on.ca

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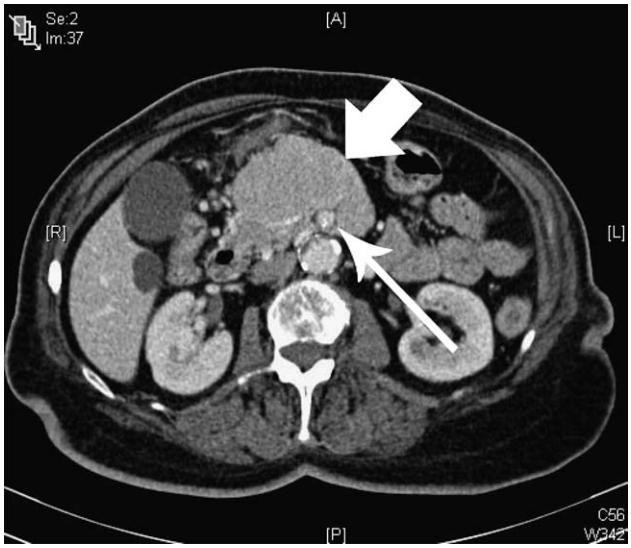

Fig. 1. CT scan showing a large neuroendocrine tumor (*arrow*) compressing the superior mesenteric vein (*small arrow*).

of acute bleeding, findings presumably secondary to the prior embolization of the left gastric artery. For the next several days, she continued to have slow GI bleeding and a hematocrit down to 26%. A repeat tagged red blood cell scan, enteroscopy, and colonoscopy were all inconclusive (Fig. 2). The patient continued to have intermittent episodes of bleeding. Magnetic resonance imaging, performed to exclude any possible source of bleeding, was unremarkable except for the known mass and a luminal varix in the fourth portion of the duodenum. Due to the different locations of varices and multiple minor bleeding points, the suspicion of diffuse SBVs was raised. A CT angiogram with emphasis on the venous phase confirmed the presence of scattered engorged veins in the duodenum and small bowel (Fig. 3).

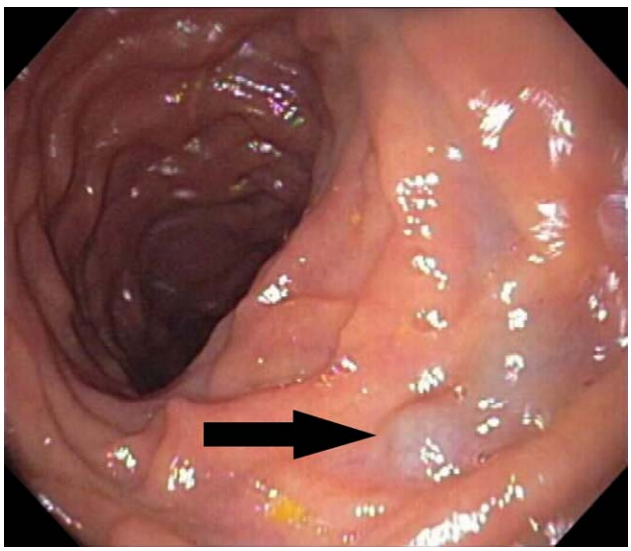

Fig. 2. Endoscopy showing old nonbleeding ulceration.

The GI bleeding was due to SBVs secondary to mesenteric hypertension from compression of the SMV by the pancreatic mass. Medical management of the SBVs was the only option, and the patient was started on propranolol and octreotide and prepared for radiotherapy (external beam radiation therapy [EBRT]).

Two weeks after discharge, she was started on EBRT (5000 cGy over 35 days), which she tolerated well. She will undergo restaging CT imaging 2 months after completion of her radiotherapy. She is currently taking propranolol and subcutaneous octreotide twice a day and has had only a single minor episode of bleeding with no change in hematocrit or need for transfusion with 1-year follow up.

DISCUSSION

SBVs are rare, with fewer than 100 cases reported in the literature. Symptomatic reports have been described due to various causes including cirrhosis, extrahepatic portal hypertension, adhesions, and Banti's syndrome.[1–6] They are persistent and can be massive or indolent. As our patient's hospital course exemplifies, this problem can often be a diagnostic dilemma. We report a rare case of SMV compression resulting in SBV from a large NE tumor of the pancreas. This patient was treated medically with octreotide, propanolol, and EBRT, applying the physiology of esophagogastric varices to the small bowel.

SBVs are supplied by the SMV and inferior mesenteric vein and then drain into the inferior vena cava through the iliac or ovarian veins. Varices can form when there is reversal from the normal hepatopetal flow of the SMV. SBVs have commonly been described with liver cirrhosis and portal thrombus.[1–4]

The most common therapy for SBV involves ligation of varices and resection of the involved portion of bowel.[4,7,8] Our patient did not have resection as an option because various portions of the duodenum and small bowel mesentery appeared to be involved, namely the root of the mesentery. Without any real decompressive treatment options of the SMV thrombosis, we elected instead to use β-blockade (propranolol), octreotide, and radiation as therapy.

Our case belies the frustration associated with SBVs. Prolonged episodes of bleeding, multiple hospitalizations, and numerous inconclusive tests are the usual course in making the diagnosis. Although initially found to have isolated jejunal varices on capsule endoscopy early in the hospitalization, we failed to recognize this as a source of GI bleeding because the

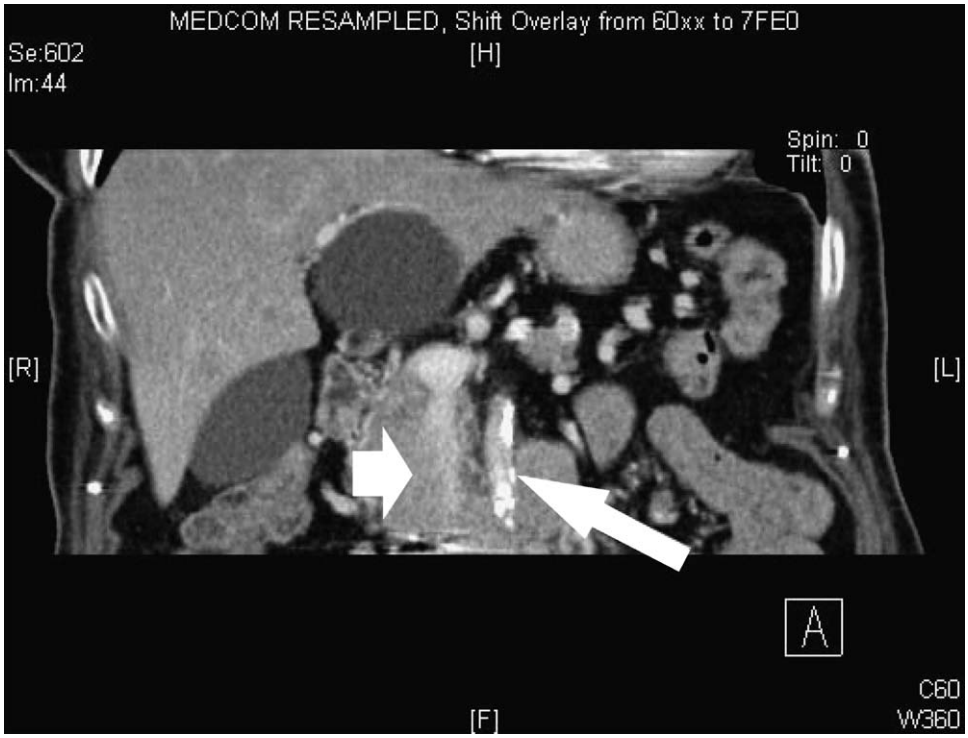

Fig. 3. Venous phase CT with scattered engorged veins in the duodenum (*large short arrow*) and small bowel (*small long arrow*).

SBVs only intermittently bled. Once the patient was diagnosed with a CT venous phase angiogram, treatment with octreotide, propranolol, and EBRT was started. The patient has done well since medical therapy with no more reported episodes of bleeding with a follow-up of 6 months. Continued radiation therapy for the large NE tumor may shrink the mass to a point where flow in the SMVs may reverse itself back to normal. This novel therapy extrapolates principles from gastric variceal therapy and applies it to the small bowel.

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Pancreaticoduodenectomy in the Presence of Superior Mesenteric Venous Obstruction

Leonidas G. Koniaris, M.D., F.A.C.S., Kevin F. Staveley-O'Carroll, M.D., Ph.D., F.A.C.S., Herbert J. Zeh, M.D., F.A.C.S., Eduardo Perez, M.D., Xiao-ling Jin, M.D., Ph.D., Warren R. Maley, M.D., F.A.C.S., Gazi Zabari, M.D., F.A.C.S., David L. Bartlett, M.D., F.A.C.S., Amit Khanna, M.D., M.P.H., Dido Franceschi, M.D., F.A.C.S., Luke O. Schoeniger, M.D., Ph.D., F.A.C.S.

The study goal was to determine the technical feasibility and outcomes associated with pancreaticoduodenectomy for periampullary malignancies with near (>80%) or complete (100%) superior mesenteric venous (SMV) obstruction. A retrospective examination of 11 patients with high-grade or complete SMV obstruction who underwent pancreaticoduodenectomy at five academic medical centers is reviewed. Pancreaticoduodenectomy for locally advanced periampullary malignancies causing high-grade or complete SMV obstruction is technically feasible. Operative approaches and outcomes are presented. One 30-day death was observed. Median survival of the cohort is 18 months. Survivals exceeding 2 years post-resection have been observed. In a number of cases, significant palliation of pain and of biliary and duodenal obstruction were achieved. Based on this initial series, pancreaticoduodenectomy in the presence of near or total SMV obstruction is feasible, may result in an R0 resection, and may be beneficial in select patients with a periampullary malignancy. We suggest such an approach be considered particularly following completion of neoadjuvant therapy without systemic progression. Further studies and more long-term follow-up at high-volume centers are required, however, to better determine the indications and potential benefit of such an undertaking. (J GASTROINTEST SURG 2005;9:915–921)

KEY WORDS: Pancreatic, pancreatitis, cancer, Whipple, neoadjuvant, technique

Surgical resection remains the best chance of cure and palliation for patients presenting with periampullary malignancies. Although historically associated with high perioperative mortality risk, pancreaticoduodenectomy currently can be performed at a number of high-volume centers with a 1%–4% periprocedural mortality rate.[1–3] Consideration for surgical candidacy is generally determined based upon computed tomography (CT) criteria.[4–6] Criteria include absence of metastatic disease, no extension into the superior mesenteric or celiac artery, and no tumor invasion into the portal mesenteric confluence. With improved surgical experience, especially over the past decade, reports from many centers with high-volume pancreatic surgeries have challenged the presence of portomesenteric invasion as a contraindication to pancreaticoduodenectomy.[7–9] Of particular significance is the report of Tseng and coworkers[10] from the M. D. Anderson cancer center who reported venous resection in 141 cases of pancreaticoduodenectomy from 1990 through 2002. This and other considerably smaller series have demonstrated that complete resection in patients with lateral tumor invasion of the superior mesenteric venous (SMV) without venous obstruction can be associated with outcomes approaching that of patients undergoing pancreaticoduodenectomy alone.[7–10]

Given the nearly equivalent long-term survival associated with venous resection for periampullary malignancies, the question of extending the benefits

From the Departments of Surgery, University of Miami School of Medicine, Miami, Florida (L.G.K., E.P., X.J., D.F.); Penn State University School of Medicine, Hershey, Pennsylvania (K.F.S.-O.); University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (H.J.Z.); The Johns Hopkins University School of Medicine, Baltimore, Maryland (W.R.M.); University of Louisiana School of Medicine, Shreveport, Louisiana (G.Z.); and University of Rochester School of Medicine, Rochester, New York (A.K., L.O.S.).
Reprint requests: Leonidas G. Koniaris, M.D., F.A.C.S., Alan Livingstone Chair in Surgical Oncology, University of Miami Miller School of Medicine, 3550 Sylvester Comprehensive Cancer Center (310T), 1475 N.W. 12th St., Miami, FL 33136. e-mail: lkoniaris@med.miami.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.005

of pancreaticoduodenectomy to those patients with extensive local burden, including complete venous occlusion, therefore arises. Of note, such an approach was initially advocated by Fortner.[11] We report herein 11 patients who presented with locally very advanced periampullary malignancies and complete or near-complete SMV occlusion. In each case, a pancreatectomy with resection of the SMV was performed. Results and complications are presented and discussed.

PATIENT SELECTION AND TECHNIQUE

Initially, patients who underwent SMV resections were limited to young, active patients in whom triple-phase CT scan suggested SMV involvement but complete occlusion was not suspected preoperatively. Resection was undertaken in these cases and complete or near-total venous obstruction noted in the resection specimen. Importantly, venous collaterals have generally not been a problem in these cases as can be found if portal obstruction is manifest. As the group's experience has developed, we have offered the procedure to young, active patients, particularly those with otherwise favorable tumors, even if triple-phase CT has suggested complete venous obstruction on triple-phase CT scan. No preoperative magnetic resonance angiograms or other venous imaging techniques have been used.

The approach used in completing pancreaticoduodenectomy with near-total or total SMV thrombosis has varied (Fig. 1). In all cases, we identify the SMV

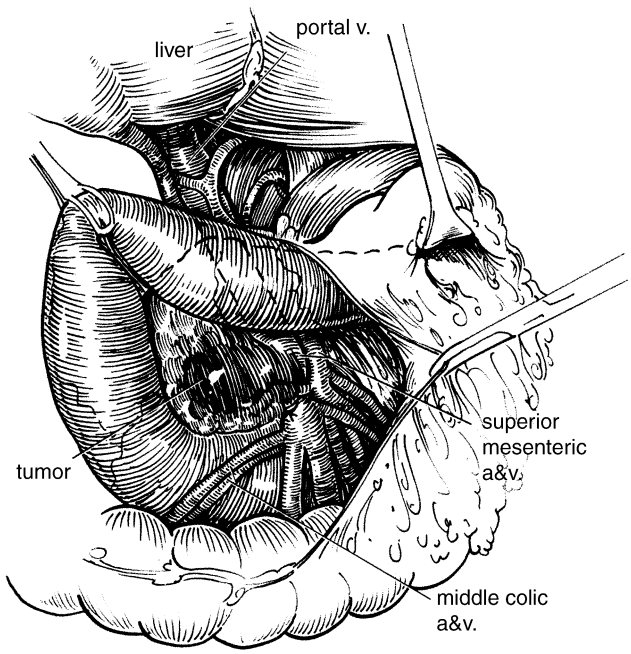

Fig. 1. Large periampullary malignancy involving the superior mesenteric vein.

inferior to the pancreas as initially described by Cameron[12] or, if the tumor is found to be extending into the transverse colon's mesentery, below the level of the middle colic veins. If possible, we attempt to define a plane between the SMV and the pancreatic neck by elevating the pancreatic neck off the SMV–portal vein confluence, working below at the level of the SMV and above at the level of the portal vein.[9,13] Division of the common bile duct is frequently undertaken to facilitate exposure of the portal vein–SMV confluence (Fig. 2, *A*, *B*). If a clear plane between the pancreatic neck and the SMV cannot be defined or if preoperative SMV obstruction was noted, we divide the pancreas more laterally, generally above the confluence of the IMV with the splenic vein, after developing the plane between the pancreas and IMV with blunt and sharp dissection (Fig. 2, *C*, *D*). Of note, this maneuver is contrary to the classic teaching of pancreaticoduodenectomy that holds an inability to define the plane between the pancreas and the SMV is a contraindication to attempted resection.[9] Following transection of the pancreas medial to the SMV, dissection and mobilization of the pancreas are continued with division of the duodenal bulb or performance of a hemigastrectomy, depending on the decision of whether to preserve the pylorus. The splenomesenteric confluence is identified and separated from the tumor and pancreatic head. The splenomesenteric confluence is left intact in all cases. Vascular control with vessel loops is generally obtained at this point. These maneuvers allow mobilization of the pancreaticoduodenal specimen with a freed portomesenteric confluence. It is not our practice to temporarily occlude the superior mesenteric artery to prevent edema. At this stage, the medial division of the pancreas allows mobilization of the medial aspect of the SMV with the specimen rather than leaving it in situ (Fig. 2, *C*, *D*).

It is generally our practice to attempt to complete the resection prior to reconstructing the SMV. Of particular help is separation of the SMA from the uncinate process and transection of the duodenal mesentery, as this allows anterior rotation of the specimen connected only by the portomesenteric venous confluence and SMV. Alternatively, in select cases where adequate collateral flow could be preserved, we have simply ligated and resected the occluded SMV without subsequent venous reconstruction (Fig. 3, *C*). If the SMV is to be ligated, however, great care must be exercised to prevent any impingement of hepatopedal splenic flow. In most cases, venous reconstruction has been undertaken. In many cases, a primary anastomosis can be performed without tension by completely mobilizing the liver and the root of the mesentery (Fig. 3, *B*). When this is not possible,

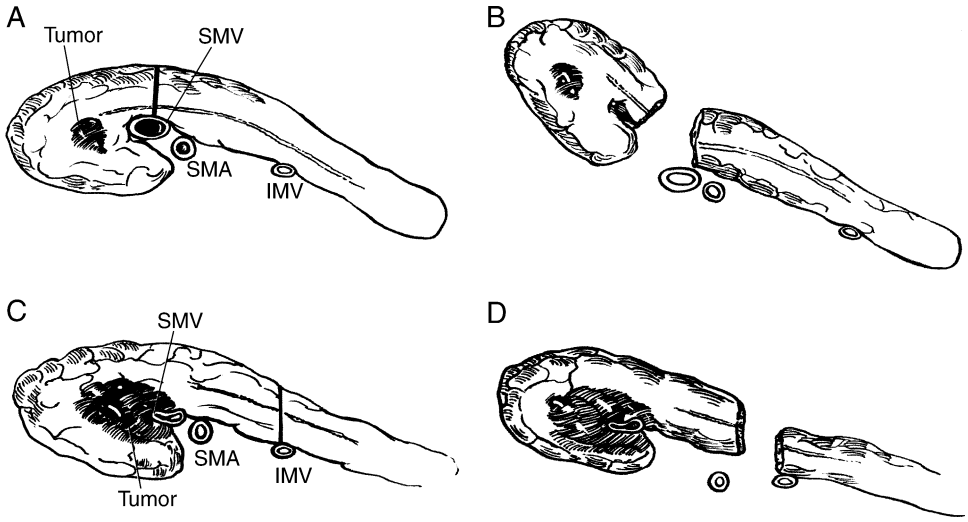

Fig. 2. Transverse views of pancreas demonstrating classic transection line of pancreas (**A, B**) and an alternative approach when the tumor has obliterated the superior mesenteric vein (SMV) and no plane is identified between the pancreatic neck and the SMV (**C, D**).

a conduit is required. For this we have used a variety of techniques, including internal jugular vein, paneled graphs (squares of saphenous vein placed together to generate a larger-diameter vessel), and artificial tetrahydrofluoride-based materials as previously described[9] (Fig. 3, *A*). The authors disagree with regard to which material is optimal for such reconstruction when needed. The group has variably re-anastomosed mesenteric vessels, like the middle colic vein, in the reconstruction. Of note, we have not encountered any infectious complications with the use of artificial materials. As well, no use of intraoperative or perioperative heparin has been required. All authors agree that if mobilization has allowed a single primary anastomosis, such a construction is preferable because it minimizes the difficulties encountered with reconstruction.

RESULTS

The described technique has been successfully applied in 11 cases. These cases and outcomes are summarized in Table 1. In all cases, high-grade stenosis was identified preoperatively and complete obstruction recognized in five cases. Neoadjuvant treatment has been used in three cases. Mean survival of the cohort is 18 months, with the longest survivor of the cohort disease free at 33 months. Median survival of the cohort is 16 months. Of note, a number of patients have derived marked palliation with the procedure, including control of endocrine symptoms (patient 3) and upper gastrointestinal bleeding with high-grade duodenal obstruction (patient 1).

As noted in the perioperative outcomes, a number of additional hours have been required to complete operative resection. Median and mean operative time was 8 hours. Median and median blood loss was 2100 and 1500 ml. Mean and median length of stay (LOS) was 17 and 13 days. Common complications included significant delayed gastric emptying in three patients and the development of significant ascites in two patients.

CONCLUSIONS

Surgical resection is the best palliation and only potentially curative therapy that can be provided to patients with localized pancreatic cancer and other periampullary malignancies. Prospective randomized trials have suggested a survival small benefit at 2 years using 5-fluorouracil–based adjuvant chemotherapy for pancreatic carcinoma[14,15]; in addition, immunotherapy has offered great promise in the treatment of these patients.[16,17] We, therefore, examined the feasibility of extending the application of pancreaticoduodenectomy to include the setting of localized disease with complete or near-complete SMV obstruction. The theoretical justification for this approach is predicated on the idea that the portomesenteric vein is not part of a pancreaticoduodenal resection margin and that large but localized tumors may have malignancies with less aggressive phenotypes. As presented, pancreaticoduodenectomy with SMV thrombosis is technically feasible, may be associated with negative margins of resection (R0), and

Table 1. Summary series of cases of high-grade and total SMV obstruction from periampullary malignancies

Patient	Age (yr)	Malignancy	Resection	SMV Status	Method of Venous Reconstruction	Course (EBL, Transfusion, Operative Time, LOS, Complications)	Outcome	Chemotherapy Used
1	49	Duodenal cancer	Classic pancreaticoduodenectomy, right hemicolectomy, portal reconstruction, R0 resection	90% Stenosis	Primary anastomosis after mobilization of the liver and mesenteric root	EBL 700 ml, 4 units PRBCs for starting HCT of 21, 9-hour case, discharge POD 7	Alive, NED 9 mo	No
2	71	Pancreatic adenocarcinoma	Pylorus-preserving pancreaticoduodenctomy, en bloc resection of 2 cm of SMV, R0 resection	80% Stenosis	Primary anastomosis after mobilization of the liver and mesenteric root	EBL 1500 ml, 2 Units PRBCs, 8 hours, Discharged POD 10, peripancreatic fluid collection requiring percutaneous drain	Asymptomatic local recurrence at 6 mo	Adjuvant
3	65	ACTH-producing neuroendocrine tumor	Pylorus-preserving pancreaticoduodenctomy, en bloc resection of 3 cm of SMV, R0 resection	>95% Stenosis	Primary anastomosis after mobilization of the liver and mesenteric root	EBL 2000 ml, 2 units PRBCs, 7 hours, discharge POD 11, DGE	Alive, NED 15 mo	Adjuvant
4	58	Pancreatic adenocarinoma	Pylorus-preserving pancreraticoduodenctomy, preservation of large collateral branch, no SMV reconstruction, R0 resection	95% stenosis	None—preserved several large collaterals (SMV ligation)	EBL 1000 ml, 2 units PRBCs, 6-hours case, discharged POD 12, fascial dehiscine	Dead of recurrent disease 16 mo	Patient treated with neoadjuvant chemoradiotherapy on protocol with CPT 11 and Celebrex
5	63	Infiltrating ductal adenocarcinoma with involvement of ampulla (probably pancreatic)	Pylorus-preserving pancreaticoduodenctomy, R1 resection	>95% Stenosis	Primary resection and reconstruction with Gore-Tex	EBL 2000 ml, 4 units PRBCs, 8 hours, discharged 30 days, DGE	11 mo, dead	Patient treated with neoadjuvant chemoradiotherapy (Gemzar and radiation)
6	59	Pancreatic adenosquamous with osteoclast giant cell features invading duodenum and splenoportal confluence	Pylorus-preserving pancreaticoduodenctomy, R status unclear	100%, occluded	Primary anastomosis after mobilization of the liver and mesenteric root	EBL 1500 ml, 3 units PRBCs, 6 hours, discharged 35 days, postoperative CVA	3 mo, dead	NA

(Continued)

Table 1. Continued

Patient	Age (yr)	Malignancy	Resection	SMV Status	Method of Venous Reconstruction	Course (EBL, Transfusion, Operative Time, LOS, Complications)	Outcome	Chemotherapy Used
7	45	Pancreatic adenocarinoma	Classic pancreaticoduodenectomy, R0 resection	100%, occluded	None—preserved several large collaterals (SMV ligation)	EBL 1.3 L, 4 units PRBCs, 5-hour case, discharge POD 14, massive ascites and UGT bleed	Alive, NED 33 mo	Patient treated with neoadjuvant chemoradiotherapy (Gemzar and radiation)
8	55	Pancreatic adenocarinoma	Pylorus-preserving pancreaticoduodenectomy, R0 resection	100%, occluded	Resection with interposition left IJ vein graft, splenic vein end to side anastomosis to interposition IJ graft	EBL 4500 ml, 8 units PRBCs, 11 hours, discharged POD 9	Alive 7 mo with liver mets	Adjuvant chemotherapy (5-FU, Gemzar)
9	58	Pancreatic adenocarcinoma	Pylorus-preserving pancreaticoduodenectomy 10 days after another surgeon and performed a distal pancreatectomy, R status under	50% Stenosis, anterior half of SMV	Resection with interposition left IJ vein graft, splenic vein not reconstructed as previously resected	EBL 3500 ml, 6 units PRBCs, 10 hours, discharded POD 17 days, DGE	Dead at 6.5 mo presumed recurrence	Adjuvant chemotherapy (5-FU, Gemzar)
10	66	Pancreatic adenocarcinoma	Classic pancreaticoduodenectomy, R status unclear	SMV occlusion	Resection with interposition left IJ vein graft, splenic vein end-to-side anastomosis to interposition IJ graft	EBL 4000 ml, 7 units PRBCs, 10 hours, discharged to rehabilitation POD 21, DGE, pancreatic fistula (closed day 14)	Deceased at 1 mo secondary to PE or aspiration	No
11	56	Pancreatic adenocarcinoma	Pylorus-preserving pancreaticoduodenctomy, R0 resection	80% Stenosis	Primary anastomosis after mobilization of the liver and mesenteric root	EBL 1000 ml, 2 units PRBCs, 6 hours, discharged 12 days	Alive, 32 mo NED	Adjuvant

ACTH = adrenocorticotropic hormone; IJ = internal jugular vein; SMV = superior mesenteric vein; EBL = estimated blood loss; LOS = length of stay; POD = postoperative discharge date; PRBC = packed red blood cell; CVA = cerebrovascular accident; DGE = delayed gastric emptying; PE = pulmonary embolism; NED = no evidence of disease.

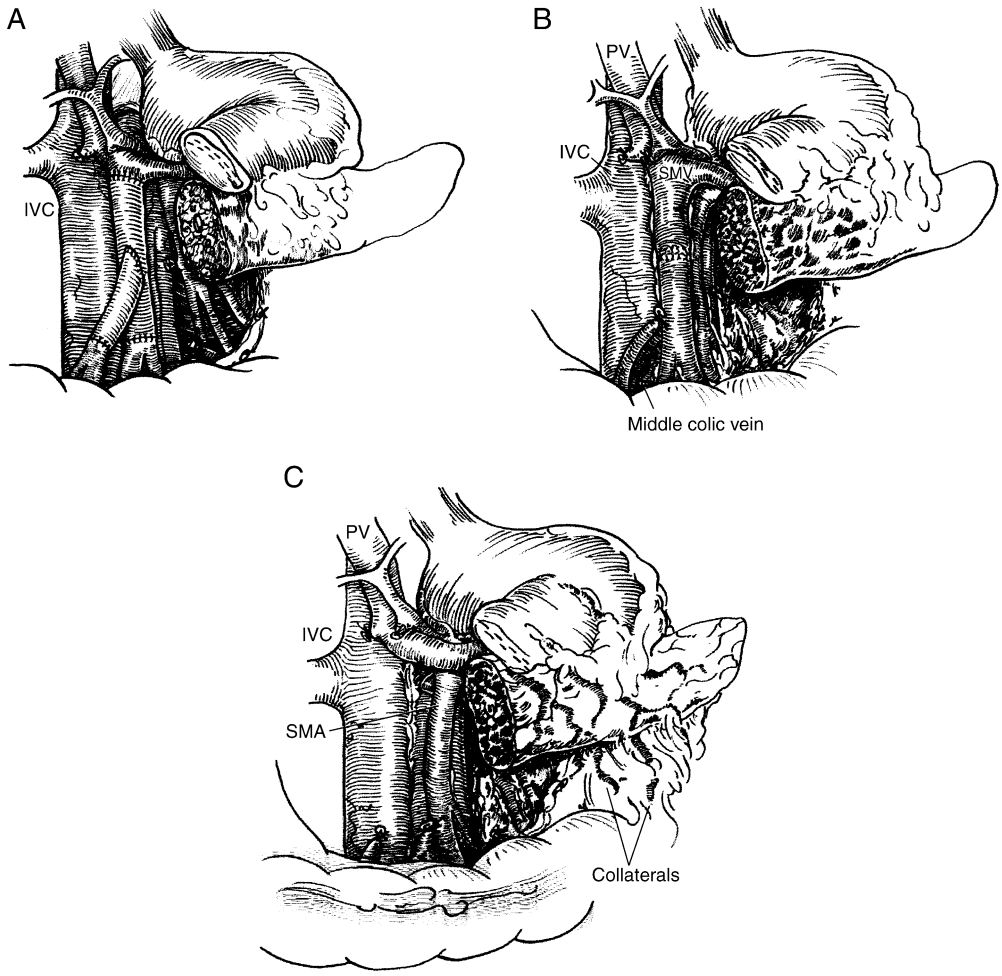

Fig. 3. Approaches used for reconstruction. **A**, Use of reversed vein or artificial conduit to reconstruct the superior mesenteric vein (SMV). Multiple venous grafts of large collaterals are demonstrated. **B**, Primary anastomosis following mobilization of the mesenteric root and ligation of the middle colic vein. **C**, Resection of the SMV without reconstruction.

may result in prolonged disease-free survival in select cases relative to historical unresected controls.

The idea that larger but not metastatic pancreatic cancers may carry a favorable prognosis has been suggested by the M. D. Anderson group[10] as well as by Snady and coworkers[18–20] at the Mount Sinai Medical Center in New York. In the Snady et al. series, which examined the potential benefits of neoadjuvant therapy in the treatment of pancreatic cancer, the authors found that survival was markedly improved in those patients who presented with larger T3 tumors and demonstrated a clinical response to chemotherapy than those presenting with resectable T1 and T2 lesions that underwent surgery followed by chemotherapy. In fact, it is our bias that the best application of the techniques described herein might be in a neoadjuvant setting, especially among those who demonstrated regression or no advancement of the tumor mass during the neoadjuvant phase.

This report demonstrates that it is technically feasible to perform a pancreaticoduodenectomy in select patients who present with complete occlusion of the SMV. Although the results are intriguing, no conclusions about the potential benefits of this approach should be made. Importantly, no prospective data were collected to evaluate quality of life in the cohort. Benefit is presumed for the group from those in whom debilitating symptoms of endocrine overproduction and ongoing tumor bleeding were encountered. Moreover, it must be stressed that the described approach has been applied in cases where the portal vein was still patent. In no cases has this been attempted in cases where portal vein obstruction has occurred. Clearly, this aggressive approach carries a major risk of death and needs further studies to determine its indications, if any. Until further evaluation is performed, this procedure should be considered investigational and limited to high-volume centers.

We ourselves favor it in younger patients who strongly desire all means of resection be pursued in order to obtain the chance of cure. Postoperative recovery is generally longer; furthermore, excellent intensive care unit care may be needed. Nonetheless, this approach is technically feasible and appears beneficial in select cases.

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Distal Pancreatectomy for Resectable Adenocarcinoma of the Body and Tail of the Pancreas

John D. Christein, M.D., Michael L. Kendrick, M.D., Corey W. Iqbal, M.D., David M. Nagorney, M.D., Michael B. Farnell, M.D.

The study goal was to analyze outcome after distal pancreatectomy for three subtypes of adenocarcinoma to determine the role of en bloc resection in surgical management. A secondary aim was to identify those clinicopathologic factors correlating with survival in an analysis limited to ductal adenocarcinoma. Medical records of consecutive patients undergoing distal pancreatectomy for adenocarcinoma between 1987 and 2003 were reviewed. A comparative analysis was undertaken of the safety and outcome of patients undergoing standard and en bloc resections. Clinicopathologic factors for patients undergoing distal pancreatectomy for ductal adenocarcinoma were subjected to both univariate and multivariate survival analyses. Ninety-three patients underwent resection for ductal adenocarcinoma (66, 71%), mucinous cystadenocarcinoma (18, 19%), or adenocarcinoma associated with intraductal papillary mucinous neoplasm (IPMN) (9, 10%). En bloc resection was required in 33 (35%) patients. There was no operative mortality. Median survival was 15.5 months, 30.2 months, and 50.7 months for ductal adenocarcinoma, mucinous cystadenocarcinoma, and adenocarcinoma associated with IPMN, respectively. Patients undergoing en bloc resection had a higher overall complication rate, required more transfusions and more intensive care unit admissions, and had a higher rate of positive margins; however, there were no deaths. For ductal adenocarcinoma, tumor size greater than 3.5 cm, age greater than 60 years, and stage were factors that correlated with survival on a univariate analysis. None were significant on multivariate analysis. Four patients with ductal adenocarcinoma were actual 5-year survivors. While en bloc resections are associated with a higher rate of complications, the majority are self-limited and mortality is low. Resection, including adjacent organs, should be performed when appropriate. Long-term survival for patients with cystadenocarcinoma or IPMN-associated adenocarcinoma can be anticipated. While rare, long-term survival for patients with ductal adenocarcinoma after distal pancreatectomy can be achieved.
(J GASTROINTEST SURG 2005;9:922–927)

KEY WORDS: Pancreatic adenocarcinoma, distal pancreatectomy, survival, pancreatic leak

Cancer of the body and tail of the pancreas has an insidious nature as patients continue to present late in the course of the disease.[1,2] Due to delayed presentation, few patients are candidates for complete resection.[3–5] Even if a potentially curative operation is performed, long-term survival rates have been discouraging. While studies have documented that long-term survival is possible and resection provides the only chance for cure,[3,4,6,7] prognostic factors associated with prolonged survival have not been elucidated in the literature.

Tumors of the body and tail of the pancreas typically present in a more advanced stage than those of the more proximal gland. Most patients with body or tail pancreatic cancer present with disease outside of the pancreatic parenchyma from direct infiltration of adjacent organs or vascular structures, via lymphatics to locoregional lymph nodes, or by hematogenous dissemination to distant organs.[3,4,6–8] Under the circumstances of direct involvement of surrounding structures, one may question whether an aggressive resection, including adjacent organs such as the colon, adrenal gland, or stomach, is warranted.

Until about a decade ago, the high rate of morbidity and mortality associated with pancreatic resection was the main argument against aggressive treatment

Presented at the Thirty-Eighth Annual Meeting of the Pancreas Club, New Orleans, Louisiana, May 16, 2004.
From the Department of Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
Reprint requests: Michael B. Farnell, M.D., Department of Surgery, Mayo Clinic and Mayo Foundation, 200 First Street S.W., Rochester, MN 55905.

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.008

of pancreatic cancer. More recently, multiple reports have been published documenting acceptable rates of morbidity[7–11] and mortality[6–13] associated with resections of the pancreas for adenocarcinoma. When occurring in the body or tail of the pancreas, adjacent organs often are involved, either by malignant infiltration or local inflammatory response. Due to this locally aggressive characteristic of pancreatic cancer, an en bloc resection is often required to achieve a negative margin.[6–8] To date, few reports have been published on the safety and efficacy of en bloc resection of pancreatic adenocarcinoma of the body and tail.[6–8]

The primary goal of this report was to perform a comparative analysis of outcome for standard and en bloc resections for three pathologic subtypes of pancreatic adenocarcinoma. Because of differing biology and the small number of patients with mucinous cystadenocarcinoma and intraductal papillary mucinous neoplasm (IPMN)-associated adenocarcinoma, the secondary aim of identifying clinicopathologic variables associated with survival was limited to patients with ductal adenocarcinoma.

METHODS

A retrospective review was undertaken of medical records of patients undergoing resection of histologically proven pancreatic body or tail adenocarcinoma between the years 1987 and 2003, at the Mayo Clinic, Rochester, MN. This review was restricted to patients diagnosed with ductal adenocarcinoma, mucinous cystadenocarcinoma, or adenocarcinoma associated with an IPMN. Patients with distant metastatic disease, those diagnosed with neuroendocrine carcinoma, and those undergoing an R2 resection (macroscopic residual tumor) were excluded. Follow-up information was gathered from the Mayo Clinic medical record, death certificates, and patient correspondence.

All pathologic subtypes were included into the comparative analysis of safety and morbidity associated with standard and en bloc distal pancreatectomy for adenocarcinoma. Survival was determined using the Kaplan-Meier method. For patients with ductal adenocarcinoma, clinicopathologic variables were analyzed for significance. Variables on a continuous scale were compared using either the two-sample t test or the Wilcoxan rank sum test. Nominal variables were compared using either the χ^2 test or the Fisher's exact test. All calculated P values were two-sided and $P < 0.05$ were considered statistically significant. Those factors reaching significance through univariate analysis were analyzed with a multivariate method.

RESULTS

Ninety-three patients with the diagnosis of pancreatic ductal adenocarcinoma, mucinous cystadenocarcinoma, or adenocarcinoma associated with an IPMN underwent an R0 or R1 distal pancreatectomy at the Mayo Clinic, Rochester, MN, between the years 1987 and 2003. This patient population was comprised of 53 males and 40 females with a mean age of 65 years (age range, 30–92 years). Median follow-up was 16.2 months and was complete for 87 (94%) patients.

Clinical Presentation

Pain was the most common presenting symptom, found in 77 (83%) patients. Forty-four patients (47%) presented with a weight loss (mean, 9.6 kg), 24 (26%) had a history of cigarette smoking, and 14 patients (15%) had new-onset diabetes mellitus. Fifty-seven (87%) of those diagnosed with ductal adenocarcinoma presented with pain.

Extent of Resection

Twelve surgeons performed distal pancreatectomy for adenocarcinoma during the study period, of which 67% were performed by the two senior authors. Standard distal pancreatectomy-splenectomy was performed in 58 (62%) cases, a spleen-sparing distal pancreatectomy in 2 for mucinous cystadenocarcinoma (3%), and an en bloc resection, including one or more adjacent organ, was necessary in 33 (35%). Multiple organs were resected in 17 (52%) of the en bloc cases. A portion of the stomach, part of the colon and its mesentery, or part of the left kidney and/or left adrenal gland was resected alone in 7, 5, and 4 cases, respectively. The median operative time was 4.5 hours. Perioperative blood transfusion was required in 36 (37%) patients, with a median of 3 units transfused. An operative drain was left in the pancreatic bed in all cases. There was no operative (30-day or in-hospital) mortality. An en bloc resection was necessary in 39% of those with ductal adenocarcinoma.

Clinical variables were compared for en bloc and standard resection for all 93 patients in order to determine safety and morbidity of the operations. Those undergoing en bloc resections had significantly more complications ($P = 0.03$), had higher estimated blood loss ($P < 0.02$) and required more transfusions ($P < 0.03$), intensive care admissions ($P < 0.01$), and R1 (microscopically positive margins) resections ($P = 0.04$). There was no statistical difference in the

en bloc resection rate for those with ductal adenocarcinoma versus the other pathologic subtypes ($P = 0.16$) (Table 1).

Hospital Course

An intensive care unit admission was required in 29 (31%) patients. The median length of hospital stay was 9 days. Complications occurred in 43 (46%) patients. Pancreatic leak was the most common complication, occurring in 19 (20%) patients. The operative drains effectively managed the leak in 15 (74%) cases. Abdominal computed tomography or ultrasound-guided percutaneous drainage was necessary to control the leak in four patients. The median time to resolution of the leak, as defined by drain removal, was 28 days. Reoperation was necessary in five (5%) patients due to postoperative bowel obstruction (one), bleeding (two), or abscess drainage (two). There was no significant difference in the pancreatic leak rate after an en bloc (27%) or a standard (17%) distal pancreatectomy ($P = 0.29$) (Table 1).

Overall Survival

The median survival for the 66 patients with ductal adenocarcinoma was 15.5 months. For 18 patients with mucinous cystadenocarcinoma and 9 patients with IPMN-associated adenocarcinoma, median survivals were 30.2 months and 50.7 months, respectively ($P < 0.01$). Kaplan-Meier survival curves for each of the three pathologic subtypes are shown in Fig. 1.

Table 1. Comparison of extent of resection for adenocarcinoma of the body or tail of the pancreas

	En bloc resection	Standard resection	*P* value
Patients (n)	33	60	NA
Operative time (hr)	4.7	4.4	0.12
Length of hospital stay (days)	10	9	0.63
Need for reoperation (%)	5	5	0.14
Pancreatic leak (%)	27	17	0.29
Ductal adenocarcinoma (%)	39	61	0.16
Other pathologic subtype (%)	26	74	
Overall complication rate (%)	58	36	0.03*
R0 resection (%)	73	90	0.044*
Estimated blood loss (ml)	750	500	0.016*
Need for transfusion (%)	55	30	0.025*
Intensive care unit admission (%)	50	21	0.004*

*Statistically significant.

Clinicopathologic Factors Associated With Survival in Ductal Adenocarcinoma

Of the 66 patients with ductal adenocarcinoma, 83% underwent an R0 resection. In all but one specimen, the status of the pancreatic neck margin was assessed microscopically; however, radial margins were reported in only 62% of specimens.

The surgical pathology grading system used at the Mayo Clinic is divided into four groups. In comparison to the traditional grading system, grade 1 correlates with a well-differentiated tumor, whereas grade 4 correlates with a poorly differentiated or high-grade tumor. Grades 2 and 3 define even divisions of progression from well to poorly differentiated. The ductal adenocarcinoma tumors were graded as G1 (2 patients), G2 (9 patients), G3 (40 patients), and G4 (15 patients).

The median tumor size was 5.5 cm (range, 2.0–13 cm). According to the American Joint Committee on Cancer (AJCC),[14] the T stage was T1 (3 patients), T2 (27 patients), and T3 (36 patients). T4 tumors are unresectable due to invasion of the celiac axis or superior mesenteric artery and were excluded from this series.

Twenty (30%) patients had lymph node metastases and were categorized as N1. In this series, the pathologic reports of 10 (15%) specimens made no comment of lymph node status or stated that no lymph nodes could be identified. The overall stage distribution was as follows: stage IA (n = 2), IB (n = 22), IIA (n = 22), and IIB (n = 20). Both stage III, which includes patients with T4 tumors, and stage IV, which denotes distant metastatic disease, were excluded from this study.

For the 66 patients with resected ductal adenocarcinoma, the overall median survival was 15.5 months, with a 3- and 5-year survival rate of 24.1% and 9.6%, respectively. Of 13 clinicopathologic variables analyzed, only age ($P = 0.04$), tumor size ($P = 0.02$), and stage ($P < 0.01$) were significant in the univariate model (Table 2). We were unable to demonstrate that these factors were independent determinants of survival in the multivariate model (Table 3).

Fifty-seven (87%) patients presented with pain and 36 (55%) had weight loss. Pain at presentation ($P = 0.88$) and history of weight loss ($P = 0.93$) did not affect survival. At the time of operation, an en bloc resection, including one or more adjacent organs, was performed on 26 (39%) patients. Extent of operation ($P = 0.88$) did not affect survival. The presence of lymph node metastases ($P = 0.82$) and margin status ($P = 0.74$) did not affect survival in those with ductal adenocarcinoma.

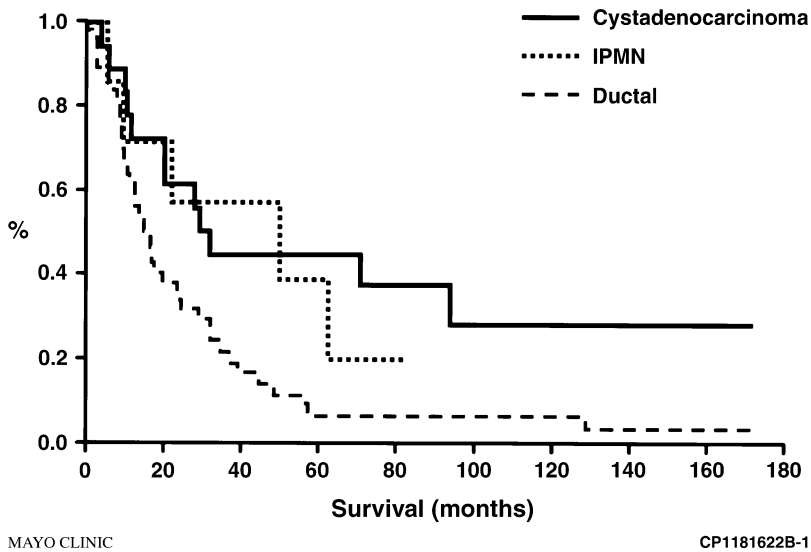

Fig. 1. Kaplan-Meier survival analysis of three subgroups (mucinous cystadenocarcinoma, intraductal papillary mucinous neoplasm–associated adenocarcinoma, and ductal adenocarcinoma) of adenocarcinoma after distal pancreatectomy.

Five-Year Survivors After Distal Pancreatectomy for Ductal Adenocarcinoma

Four patients with ductal adenocarcinoma were actual 5-year survivors after distal pancreatectomy. Two of the four patients underwent an en bloc resection. Three patients had lymph node metastases, and the margins of resection were involved with microscopic tumor in one specimen. Three patients who experienced recurrence before the 5-year mark died thereafter. One patient is alive without disease at 10 years.

DISCUSSION

Adenocarcinoma of the pancreatic body or tail occurs less frequently than adenocarcinoma of the pancreatic head.[13,15,16] Consistent with this, few studies addressing the operative management, safety, and survival of these patients have been published.[4,6–9,11,13] This is partly due to the locally aggressive nature of pancreatic body or tail adenocarcinoma and the historically dismal prognosis, which was cause for some to advocate medical and not surgical managements of locally advanced lesions. All 93 patients were included in the comparative analysis of outcome in an effort to determine the role of en bloc resection in surgical management. We found at operation that 35% of patients have involvement of surrounding structures, either by tumor infiltration or inflammatory adhesions, which in order to obtain negative surgical margins must be excised en bloc with the specimen. Other series report comparable rates of involvement of contiguous structures.[4,6–8] This series confirms that distal pancreatectomy/splenectomy, even when en bloc resection is required, can be performed without operative mortality although at the expense of an increased morbidity.

The overall morbidity rate for all 93 patients was 46%, but most complications were self-limited and managed conservatively. The constellation of complications noted including pancreatic leak or abscess, postoperative hemorrhage, surgical site infection, urinary tract infection, postoperative ileus, and line sepsis is similar to that of other large series in the literature.[6–9,11] The morbidity associated with an en bloc resection (58%) was significantly higher than that seen with standard distal pancreatectomy/splenectomy (36%) ($P = 0.03$). While pancreatic leak was the most frequent complication (overall 20%), the leak rate was no different between the en bloc (27%) and standard (17%) resection groups ($P = 0.29$).

In this series, 12 different surgeons performed distal pancreatectomy. In each instance the pancreatic duct was individually ligated; however, pancreatic transection technique, which varied per surgeon preference, included stapling and hot or cold knife dissection. A difference in leak rate as a function of technique used to secure the pancreatic stump has not been shown in the literature.[17,18] A surgical drain was placed in all cases and effectively controlled the leak in 74%. A median of 28 days was required for leak resolution, determined by radiologic imaging and time to drain removal. No chronic pancreaticocutaneous fistulas developed. It is apparent that although

Table 2. Univariate survival analysis after distal pancreatectomy for ductal adenocarcinoma

		n	Median survival (mo)	*P* value
Age (yr)	<60	17	39.4	0.04*
	>60	49	12.8	
Weight loss (kg)	Yes	36	12.6	0.93
	No	30	16.2	
Pain	Yes	57	12.8	0.88
	No	9	24.2	
CA 19-9 (U/L)	>40	16	17.8	0.18
	<40	6	63.7	
Transfusion	Yes	27	14.1	0.44
	No	39	16.2	
Adjuvant therapy	Yes	49	16.2	0.30
	No	17	11.8	
N stage	N0	46	15.2	0.82
	N1	20	14.8	
T stage	T1	3	31.9	0.96
	T2	27	12.2	
	T3	36	11.9	
Margin status	R0	52	15.2	0.74
	R1	14	11.8	
Size (cm)	<3.5	13	31.9	0.02*
	>3.5	53	11.8	
Procedure	En bloc	26	14.1	0.88
	Standard	40	16.2	
Grade	G1	2	24.2	0.39
	G2	9	24.7	
	G3	40	15.2	
	G4	15	11.3	
Stage	IA	2	19.2	<0.01*
	IB	22	15.3	
	IIA	22	16.2	
	IIB	20	11.8	

*Statistically significant.

pancreatic leak is not infrequent, it can be managed conservatively in the majority of instances.

Several clinical and operative factors were also significantly different in the en bloc resection group. The en bloc resection group had a higher R1 resection rate ($P = 0.04$), estimated blood loss ($P = 0.02$), blood transfusion requirement ($P = 0.02$), or need for an intensive care admission ($P < 0.01$) than the standard resection group. Despite this, operative time, length of hospital stay, and reoperation rate were no different. Both groups had no mortality.

Table 3. Multivariate analysis of factors affecting overall survival after distal pancreatectomy for ductal adenocarcinoma

Factor	Risk ratio	*P* value
Age >60 yr	1.84	0.07
Size >3.5 cm	1.40	0.17
Stage	0.18	0.86

Thirty percent of patients were diagnosed with N1 disease. The median survival was 14.8 and 15.2 months for those with and without lymph node metastases, respectively ($P = 0.82$). The literature has been inconclusive with regard to the effect of lymph node metastases on survival; however, the meticulous nature in which lymph nodes are examined may play an important role in the staging of patients. Several have described decreased survival[6,8] and others report similar survival to those with and without lymph node metastases.[13] The data presented herein support that for pancreatic tail lesions, lymph node metastases may not be a negative prognostic factor. However, we believe that the percentage of N1 patients (30%) found in this study may be falsely low. Other series in the literature found approximately 50% of patients to have lymph node metastases at the time of resection.[6,8,13] This understaging of patients could be due to inadequate sampling or reporting of lymph node status, which occurred in 15% of cases. Therefore, although these data suggest that lymph node status is not a negative predictor of survival; the data are far from complete. A thorough pathologic analysis is required on all patients in order to accurately analyze survival characteristics.

During operations for ductal adenocarcinoma, an R0 resection was possible in 79% of cases. As with N1 disease, an R1 resection was not shown to be a negative prognostic factor (R0, 15.2 months and R1, 11.8 months; $P = 0.74$). The literature is inconsistent with regard to the impact of margin on survival in the resection of pancreatic adenocarcinoma. Some studies show improved survival with R0 resections,[8,13] whereas others do not.[6] Although all save one pancreatic neck margin were examined histologically, in only 62% of cases were radial margins reported. This finding may have led to an overstated rate of R0 resection. As larger numbers of specimens are accurately and thoroughly reported, an impact on survival of margin status may in fact be seen. Currently, we continue to recommend complete excision of all involved portions of contiguous organs in order to obtain a negative surgical margin. This should be followed by an appropriate specimen orientation and labeling to facilitate accurate and complete margin assessment.

The patients with ductal adenocarcinoma treated with adjuvant therapy (74%) had a median survival of 16.2 months, which was not different than those not treated (11.8 months) ($P = 0.30$). This effect is difficult to interpret based on inherent selection bias; therefore, it is impossible to reach a conclusion regarding the use of adjuvant therapy with resection of pancreatic tail ductal adenocarcinoma based

on our data. Our data are retrospective and each patient's adjuvant regimen was individualized.

Long-term survival after distal pancreatectomy for ductal adenocarcinoma has been described. In a series of 57 patients, Shoup et al.[6] reported 6 patients surviving 5 years, 3 of whom experienced recurrence after 60 months and died of disease prior to 10 years. In the data presented herein, four patients with ductal adenocarcinoma survived 5 years. Of these, one is alive without disease at over 120 months. The remaining three patients sustained recurrence prior to the 5-year mark but died of disease thereafter. No patients had recurrence beyond 5 years.

CONCLUSIONS

Long-term survival following distal pancreatectomy for mucinous cystadenocarcinoma and IPMN-associated adenocarcinoma is common. While rare, long-term survival for patients with resected ductal adenocarcinoma is feasible.

For patients with ductal adenocarcinoma of the body and tail of the pancreas, neither nodal nor margin status was shown in a multivariate model to be independent determinants of survival. These results may have been confounded by understaging and suggest a need for precise specimen labeling and analysis.

Pancreatic body and tail adenocarcinoma should be treated aggressively by surgical resection. En bloc resection can be performed safely and carries a similar long-term survival to standard resection. While the complication rate is higher following an en bloc resection, the majority is self-limited and the surgical mortality rate is low. Thus, one should be prepared to perform an en bloc resection when adjacent organs are involved.

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Early Nonenhanced Abdominal Computed Tomography Can Predict Mortality in Severe Acute Pancreatitis

Austin L. Spitzer, M.D., Ruedi F. Thoeni, M.D., Anthony M. Barcia, B.S., Michael T. Schell, M.D., Hobart W. Harris, M.D., M.P.H.

We wondered whether nonenhanced computed tomography (CT) within 48 hours of admission could identify individuals at risk for higher mortality from acute pancreatitis. Data from the international phase III study of the platelet-activating factor-inhibitor Lexipafant was used to analyze noncontrast CT versus acute pancreatitis mortality. Nonenhanced CT examinations of the abdomen from the trial were classified by disease severity (Balthazar grades A–E) and then correlated with patient survival. Among the 477 individuals who underwent CT within 48 hours of admission and 220 individuals who did so over the subsequent 6 days, higher CT grades were associated with increased mortality. Each unit increase in Balthazar grade during the initial 48 hours was associated with an estimated increase in the risk of mortality of 33%, and this trend increased to 50% if pancreatic enlargement and peripancreatic stranding (grades B and C) were combined ($P < 0.05$). CT grade correlated minimally with Ranson, Glasgow, or APACHE II score during the initial 48 hours; however, this correlation improved over 3–8 days. Early nonenhanced abdominal CT in patients with acute pancreatitis is a valuable prognostic indicator of mortality in acute pancreatitis, even among patients without clinical features of severe acute pancreatitis. (J GASTROINTEST SURG 2005;9:928–933)

KEY WORDS: Computed tomography, Balthazar, pancreatitis, lexipafant

Acute pancreatitis is an inflammatory process in which the variable involvement of regional tissues or remote organ systems results in a wide spectrum of disease severity.[1] Premature activation of digestive enzymes is suspected to precipitate pancreatic acinar cell injury and leukocyte activation, which become the potential basis for the development of a systemic inflammatory response.[2–4] Advances in our understanding of the pathophysiology of pancreatitis and treatment of its complications have improved the outcome for individuals with acute pancreatitis; however, for patients with severe pancreatitis, mortality remains at 8%–15%.[5–8] Identifying patients who require aggressive resuscitation and intensive care measures therefore remains imperative.

The perpetual failure of clinical assessment to accurately predict pancreatitis severity[9,10] necessitated the development of prognostic scoring systems based on objective clinical and laboratory data by Ranson et al.,[11,12] Imrie et al. (Glasgow),[13,14] and Knaus (APACHE II).[15–19] Additionally, computed tomography (CT) examination of the abdomen can detect almost all but the mildest forms of acute pancreatitis and assist with the management of most complications.[20] However, the usefulness of CT as a prognostic indicator remains under debate.[21–24] For the most reliable staging, it has been recommended that CT scans be obtained 48–72 hours after the onset of an acute attack of pancreatitis;[25] however, this time constraint, like that of the Ranson and Glasgow prognostic systems, limits the opportunity to expeditiously focus resources appropriately.

We hypothesized that nonenhanced abdominal CT examination obtained within 48 hours of hospital admission could identify individuals at risk for increased mortality from acute pancreatitis. To demonstrate this association, we reviewed data collected during the largest prospective trial for treatment of

From the Departments of Surgery (A.L.S., A.M.B., M.T.S., H.W.H.) and Radiology (R.F.T.), University of California, San Francisco and East Bay (A.L.S.).
Reprint requests: Hobart W. Harris, M.D., M.P.H., Division of General Surgery, University of California, San Francisco, 513 Parnassus Avenue, S-301, San Francisco, CA 94143-0104. e-mail: harrish@surgery.ucsf.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.012

acute pancreatitis, the international phase III study of Lexipafant.

METHODS

The Lexipafant Study

The Lexipafant study was a randomized, international, double-blind, placebo-controlled, phase III trial to determine if an infusion of Lexipafant given within 48 hours of the onset of symptoms of pancreatitis could reduce all-cause mortality within 28 days.[26] The trial was conducted in accordance with the Declaration of Helsinki,[27] the EEC Committee for Proprietary Medicinal Products,[28] and under the supervision of the Food and Drug Administration in the United States. The data were collected between September 1996 and May 1998. The design of the trial was to treat subjects on an "intent-to-treat" basis; therefore, we included mortality in all subjects (n = 149 at 90 days, 90 of whom had an abdominal CT examination within 8 days of hospital admission) in our analyses.

Data records were downloaded into ASCII files and converted into SAS version 6.11 data sets (SAS Institute Inc., Cary, NC). The subsequent analyses were carried out using SAS version 8.2. From these data records, all information on patient demographics, including clinical outcome, mortality rate, multiple organ failure scores, and Ranson, Glasgow, and Apache II scores obtained during the initial 48 hours were extracted. Additionally, the CT data from those patients who underwent CT examination within at least 8 days following admission were collected. The time interval between hospital admission and the CT examination was noted for each patient. The CT examinations were acquired according to the Lexipafant study protocol. Specifically, the decision to perform CT examination was made under the discretion of the attending surgeon and radiologist. Typically, scans were obtained with oral contrast and at a slice thickness of 5 mm. CT grades were established based on the detailed reports of the radiologist performing the CT examinations and by using the Balthazar grading system: grade A = normal pancreas, 0 points; grade B = focal or diffuse pancreatic enlargement, 1 point; grade C = inflammation of pancreas or peripancreatic fat or both, 2 points; grade D = single peripancreatic fluid collection, 3 points; and grade E = two or more fluid collections and/or retroperitoneal air, 4 points.[29] Subsequently, the CT grades were compared with Ranson, Glasgow, and APACHE II scores for mortality prediction within 48 hours or between 3 and 8 days following admission.

Statistical analysis consisted of the following: (1) logistic regression to determine the odds ratios for CT grade prediction of death (Kruskall-Wallis P values); (2) the Mann-Whitney rank sum test to compare scores from the CT grades and clinical prognostic systems with mortality outcome at each time period; and (3) Spearman rank correlation to study associations between CT grade and clinical prognostic system mortality prediction. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1518 subjects (56% men; mean ± SD age, 61 ± 16 years) were enrolled in the Lexipafant study according to the inclusion criteria. Of these subjects, 510 were randomized to receive placebo, 498 to receive 10 mg/24 hours Lexipafant, and 510 to receive 100 mg/24 hours Lexipafant. The mean APACHE II score for each of these three groups was approximately 11 at enrollment, and their multiple organ failure scores were not significantly different. The mortality rate was approximately 8% for each group at 28 days and 10% at 90 days. When descriptive variables were compared between treatment and placebo groups, no significant differences were found. Therefore, the subjects were subsequently considered a homogeneous patient population.

Six hundred ninety-seven subjects (63% men; age, 59 ± 16 years) underwent abdominal CT examination within 8 days of hospital admission. Of these, 477 had their examination within the first 2 days of hospital admission and 220 had their examination within 3–8 days following admission. The mortality rates for the two groups were 11% and 14%, respectively.

Higher abdominal CT examination grades correlated with increased mortality (Fig. 1); specifically, within 48 hours of hospital admission, each unit increase in Balthazar grade was associated with an estimated increase in the risk of mortality of 33% ($P < 0.011$). For instance, the mortality rate was approximately 5% in patients with a grade A (grossly normal CT examination). In contrast, the mortality rate escalated to 20% in patients with a grade E examination (more than one fluid collection). Interestingly, the mortality rate was slightly higher in patients with grade B examinations than in those with grade C examinations (14% versus 10%, Fig. 1, *A*). However, if the grade B and C categories were combined, the overall odds ratio increased to approximately 1.5 (Fig. 1, *B*). This would indicate that each unit increase in Balthazar grade would be associated with an estimated increase in the risk of mortality of 50% ($P < 0.006$). The association of increased CT grade and increased mortality was similar during the subsequent 6 days but was not significant at this study power ($P > 0.06$).

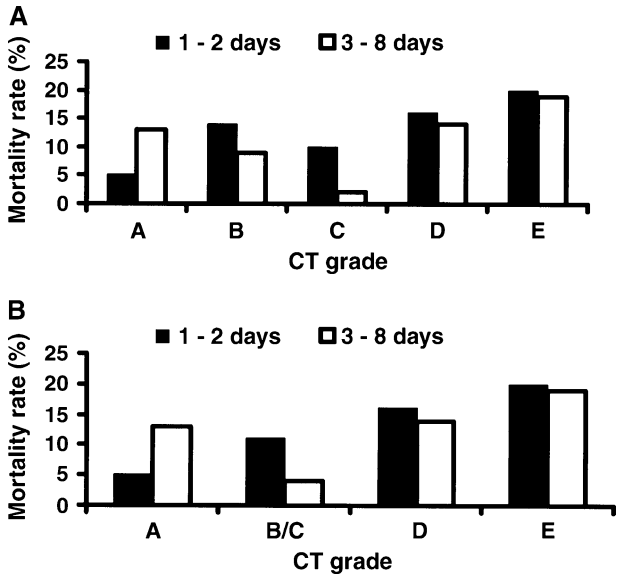

Fig. 1. The association between nonenhanced CT grade and estimated increase in risk of mortality in the Lexipafant study population. Mortality rate (%) predicted by standard Balthazar CT grades (**A**) and by Balthazar CT grades with grade B and C merged (**B**). Y-axis = mortality rate (%), X-axis = CT grade. Among the group of individuals with the shortest time from clinically suspected pancreatitis to CT examination (1–2 days), there were a total of 65 deaths (n = 477); there were an additional 25 deaths among the individuals examined between 3 and 8 days (n = 220). *P* values are from Kruskall-Wallis tests following logistic regression analysis for CT grade versus mortality <0.05 for scores from 1 to 2 days (0.004 and 0.002 for standard and merged grades, respectively) versus 3 to 8 days (0.174 and 0.0638 for standard and merged grades, respectively).

Survivors and nonsurvivors had significantly different mean CT grades and clinical prognostic scores within 48 hours (Table 1). For nonsurvivors versus survivors, the mean CT grades were 3.8 ± 1.2 and 3.3 ± 1.3 at 48 hours ($P = 0.004$) and 3.6 ± 1.6 and 3.2 ± 1.3 at 3–8 days ($P = 0.114$), respectively. Abdominal CT grades for examinations performed within the first 48 hours were not significantly correlated with Ranson, Glasgow, or APACHE II prognostic scores from the first 48 hours (Table 2). However, over the following 6 days, CT grades did correlate with the Ranson and Glasgow scores.

DISCUSSION

This study found that in patients with acute pancreatitis who undergo nonenhanced CT of the abdomen during the first 48 hours of hospitalization, increased grades according to the Balthazar CT grading system[29,30] are associated with an estimated increase in risk of mortality. Furthermore, it appears that early abdominal CT may be warranted in some patients with suspected severe acute pancreatitis because abdominal CT grade during this time period was not significantly correlated with the Ranson, Glasgow, and APACHE II prognostic scores for the same time period.

Currently, in evaluating patients with acute pancreatitis, the CT examination with contrast enhancement is recommended for those individuals with (1) questionable diagnosis; (2) increased amylase and severe clinical pancreatitis, abdominal distention and tenderness, fever, and leukocytosis; (3) Ranson score greater than 3 or an APACHE II score greater than 8; (4) minimal improvement in clinical status over 72 hours of conservative treatment; or (5) initial treatment response followed by acute change indicating a complication.[1,20] However, some variables, including suspected etiology not related to alcohol abuse, late admission, benign physical examination (lack of guarding and/or rebound), low or normal hematocrit, and nonelevated blood glucose, may render a contrast-enhanced CT unnecessary in the early stages given their high negative predictive value.[1,22]

In the past 10 years, it has been established that the increased frequency of death in acute pancreatitis is directly correlated with the development and extent of pancreatic necrosis.[1,31–37] Thus, the early detection of pancreatic necrosis signifies severe disease and is commonly used as a grave prognostic indicator in the initial evaluation of these patients.[25] Pancreatic necrosis occurs early, within the first 24–48 hours, and with few exceptions usually remains stable during a given episode of acute pancreatitis.[34,38] Because results from CT scans obtained in the initial 12 hours may be equivocal, Balthazar[25] suggested that a CT examination 2–3 days after disease onset is more reliable. However, in a previous study, Balthazar and associates[30] did not find significant prognostic differences between patients with greater than 50% necrosis and those with less than 50% necrosis. Furthermore, additional studies have not been able to demonstrate that the presence of pancreatic necrosis has prognostic value,[39,40] whereas others have shown that it only has prognostic value if CT examinations are obtained 2–3 days after disease onset.[41] More recently, Casas et al.[21] found that although necrosis did portend a more negative outcome, it did not add to the severity prediction made with the graded nonenhanced CT examination. Casas et al.[21] therefore suggested that the use of iodinated contrast material to assess pancreatic necrosis might be reserved for those patients classified as having severe disease on nonenhanced CT scan. Our results appear to support this suggestion; however, a clear

Table 1. Computed tomography (CT) grade or clinical prognostic score by survival status and shortest time from the initial clinically suspected diagnosis and study inclusion to CT scan*

Variable	Day	Status	n	Mean ± SD	Median	Median 95% confidence interval	*P* value
CT grade	1–2	Lived	412	3.4 ± 1.3	3.0	3.0–4.0	0.004
		Died	65	3.8 ± 1.2	4.0	4.0–4.0	
	3–8	Lived	195	3.2 ± 1.3	3.0	3.0–4.0	0.114
		Died	25	3.6 ± 1.6	4.0	3.0–5.0	
Ranson	1–2	Lived	197	3.4 ± 1.4	3.0	3.0–4.0	<0.0001
		Died	40	4.5 ± 1.4	5.0	4.0–5.0	
	3–8	Lived	79	3.1 ± 1.3	3.0	3.0–3.0	0.303
		Died	12	3.9 ± 2.0	3.5	2.0–6.0	
Glasgow	1–2	Lived	247	4.3 ± 1.6	4.0	4.0–4.0	<0.0001
		Died	49	5.9 ± 1.6	6.0	5.0–7.0	
	3–8	Lived	111	4.1 ± 1.4	4.0	4.0–4.0	0.0116
		Died	18	5.2 ± 1.8	5.5	4.0–7.0	
APACHE II	1–2	Lived	412	11.7 ± 4.6	11.0	10.0–12.0	<0.0001
		Died	65	18.1 ± 6.5	17.0	15.0–20.0	
	3–8	Lived	195	10.9 ± 4.3	10.0	10.0–11.0	0.0007
		Died	25	15.4 ± 6.8	14.0	11.0–19.0	

*Mann-Whitney rank sum test to compare scores.

disadvantage of our study is the fact that contrast-enhanced CT results were not available for comparison. Evidence of this limitation to our study is likely demonstrated by the inverse relationship between percentage increases in mortality and the grade B and C examinations (Fig. 1, *A*, *B*). Without the presumed advantage of contrast enhancement, differentiating between pancreatic enlargement and peripancreatic inflammation in the acute period compounds difficult interpretations and may result in equivocal readings.

A further argument for nonenhanced CT examinations is that contrast medium has been shown to impair the microcirculation and increase acinar necrosis and mortality in animal models of pancreatitis.[42–45] However, a recent study in clinical patients reported that contrast-enhanced abdominal CT did not appear to aggravate the severity of acute pancreatitis.[46] Additionally, others have reported that the most common reason for failure to estimate the severity of pancreatitis was that partial necrosis of the gland was not appreciated.[24] Although regions of pancreatic necrosis found surgically do correlate with lack of enhancement of pancreatic parenchyma on enhanced CT, peripancreatic necrosis and minor areas of focal or superficial parenchymal necrosis may not be detected on nonenhanced CT scans.[47] This limitation may partially account for the mortality in our study associated with an apparently normal CT (grade A, Fig. 1, *A*, *B*). Given that areas of pancreatic necrosis cannot be appreciated without intravenous contrast material, the subsequent clinical deterioration would likely not have been signaled by the nonenhanced CT examination.[24] These points would seem to echo Balthazar's recent comments that the most important point of the CT assessment of pancreatitis is the quality of the examination, specifically that contrast is necessary for differentiation of the pancreas from the adjacent heterogeneous fluid collections and inflammatory tissue.[25] Nevertheless, in patients with renal failure, nonenhanced CT may be the only initial imaging choice.

Table 2. Correlation of computed tomography grade within 48 hours of hospital admission versus Ranson, Glasgow, or APACHE II score

	Day	Spearman rank correlation	Spearman *P* value	Spearman 95% confidence interval
Ranson	1–2	−0.028	0.670	−0.155–0.100
	3–8	0.269	0.010*	0.066–0.450
Glasgow	1–2	0.039	0.504	−0.075–0.152
	3–8	0.321	0.0002*	0.156–0.468
APACHE II	1–2	0.052	0.258	−0.038–0.141
	3–8	0.047	0.485	−0.085–0.178

*Statistically significant.

The existing clinical prognostic systems for severe acute pancreatitis have been criticized for many reasons. For example, not all of the Ranson criteria are completed during a typical patient evaluation, which means the system does not help discriminate at the time of diagnosis. The Glasgow system, although an

improvement in terms of available variables, also requires 24–48 hours to calculate. An additional criticism of both systems is that certain variables are, in essence, duplicates (e.g., white blood cell count and lactate dehydrogenase are both nonspecific measures of inflammation) and do not actually contribute to predictive value. A distinct advantage of the APACHE II system is that it can be calculated at admission and on a daily basis to monitor changes in prognosis. Indeed, severe attacks of pancreatitis have been shown to correspond to increasing scores over the first 48 hours, whereas milder attacks demonstrate decreasing scores over time.[18] However, the APACHE II system, which reportedly has the best accuracy of the clinical scoring systems, has a sensitivity of predicting a severe attack of pancreatitis in only 61% of patients at admission.[48,49] It should be noted that a separate analysis of the predictive ability of these prognostic scoring systems found that the Ranson, Glasgow, and APACHE II scoring systems successfully predicted increased mortality in the total study population for the Lexipafant trial.[50] As a surrogate for these available clinical systems, the use of early CT examination is advantageous in that it provides both diagnostic and prognostic information.

There are limitations in our study. The inclusion criteria used for patient recruitment in the Lexipafant trial were a potential source of error in our analysis. During the trial, investigators were concerned that the APACHE II score used as an inclusion criterion overestimated mortality in acute pancreatitis.[4] This APACHE II score (>6) likely contributed to greater patient numbers through recruitment of some people who did not have pancreatitis. This may be reflected in the subjects whose CT examination was normal but who died. The cause of their death likely was not pancreatitis; therefore, the association between mortality from acute pancreatitis and a normal CT examination in this study may be an overestimation. On the other hand, it is also possible that without the benefit of contrast, more severe pancreatitis and/or necrosis was not realized. Previous authors have reported minimal to no mortality among patients with low Balthazar grade CT examinations.[21,29,30,41,51] Removal of the lowest grade (A) from our analysis would increase the significance of the relationship between the CT grade and mortality.

In conclusion, early nonenhanced abdominal CT examination in patients with acute pancreatitis is a valuable prognostic indicator of mortality even among patients without clinical features of severe acute pancreatitis. These data support the suggestion that intravenous contrast may be reserved for individuals with high-grade Balthazar CT scores on initial CT examination and/or high clinical suspicion for severe pancreatitis.

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Can Pancreaticoduodenectomy Be Used to Palliate Selective Metastatic Malignancies? Case Report of Malignant Fibrous Histiocytoma

Mindy M. Ho, B.S., Thomas J. Howard, M.D., Keith D. Lillemoe, M.D.

KEY WORDS: Obstructive jaundice, pancreaticoduodenectomy, palliation, malignant fibrous histiocytoma

Pancreaticoduodenectomy is the accepted surgical treatment for resectable periampullary malignancies.[1] These tumors are generally adenocarcinomas of the pancreas, distal common bile duct, duodenum, and ampulla of Vater and are relatively resistant to other forms of treatment (i.e., chemotherapy, radiotherapy, or both), and a margin-negative (R_0) resection is the only chance for cure.[2] The first successful pancreaticoduodenectomy was reported by Kausch in Germany in 1912 and gained notoriety in the United States after the report by Whipple in 1935.[3] Since its original description, the operation has undergone many modifications and technical refinements.[4] Over the past two decades, numerous large case series from high-volume centers have reported dramatic improvements in the operative morbidity and mortality rates associated with this operation.[1,5–8] In this report, we present a unique case of malignant metastatic fibrous histiocytoma treated by pancreaticoduodenectomy and use it as a paradigm to justify extending the indications for this operation, in select settings, for surgical palliation of selective metastatic malignancies.

CASE REPORT

The patient was a previously healthy, 43-year-old man with metastatic malignant fibrous histiocytoma. The first lesion noted by the patient was a "grape-size" mass in his left upper extremity that remained asymptomatic until April 2002, when he developed an episode of pain along his right rib. Subsequent evaluation including a chest radiograph, computed tomography (CT) scan, and bone scan showed three separate lesions (right ninth rib, left trapezius muscle, and left quadracept muscle). He underwent a right thoracotomy with wide resection of the ninth rib tumor, resection of a golf ball-size mass in the left trapezius and suprascapular muscles, and resection of a 3-cm left thigh mass. The pathology showed malignant fibrous histiocytoma with the etiology of the primary tumor thought to be his left upper extremity. More metastatic lesions were found on the posterior aspect of his right calf and medial aspect of his left upper extremity (LUE). He underwent five courses of chemotherapy (Epirubicin), with improvement in his LUE lesion, and both lesions were resected locally. Postoperatively, he received two more courses of chemotherapy (temozolamide) until an abdominal CT in October of 2004 showed two 3.5-cm lesions—one superior to the duodenum in the hepatoduodenal ligament and the other in the head of the pancreas. These lesions were causing partial gastric outlet obstruction, so in January 2004, he underwent a third operation at an outside hospital that included cholecystectomy and gastrojejunostomy without vagotomy. Resection at that point was thought to be contraindicated due to the lesion being metastatic disease.

In June 2004, he had an episode of acute pancreatitis (hyperamylasemia 1178 U/L, hyperlipasemia 8844 U/L), coffee-grounds emesis, and anemia (hemoglobin 7.0). Esophagogastroduodenoscopy showed obstruction of the gastric antrum. CT scan of the abdomen showed an increase in the size of the intra-abdominal lesion with mass effect on the inferior vena cava, pancreas, liver, and biliary system (Fig. 1). An attempt at endoscopic retrograde cholangiopancreatography revealed a large infiltrative, exophytic mass, occupying approximately 90% of the duodenal lumen circumference, that bled easily during scope

From the Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana.
Reprint requests: Thomas J. Howard, M.D., Emerson Hall #523, 545 Barnhill Drive, Indianapolis, IN 46202 e-mail: tjhoward@iupui.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.014

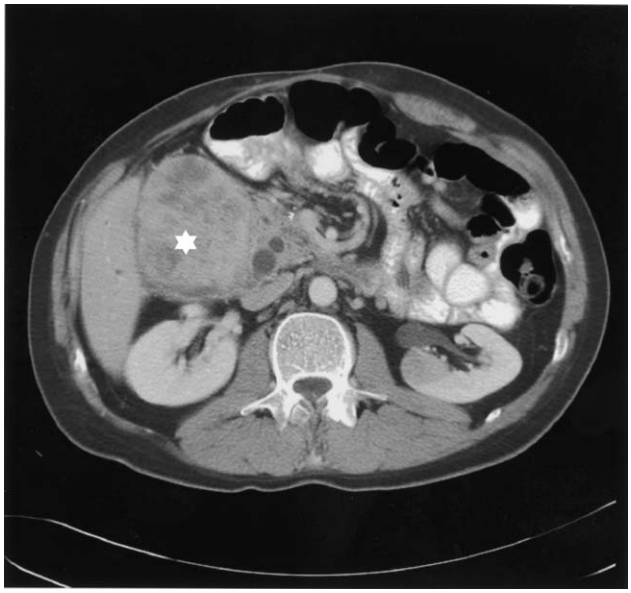

Fig. 1. Computed tomography scan showing a large, heterogeneously enhancing duodenal tumor (*star*) exerting a mass effect on the inferior vena cava, pancreas, liver, and biliary system.

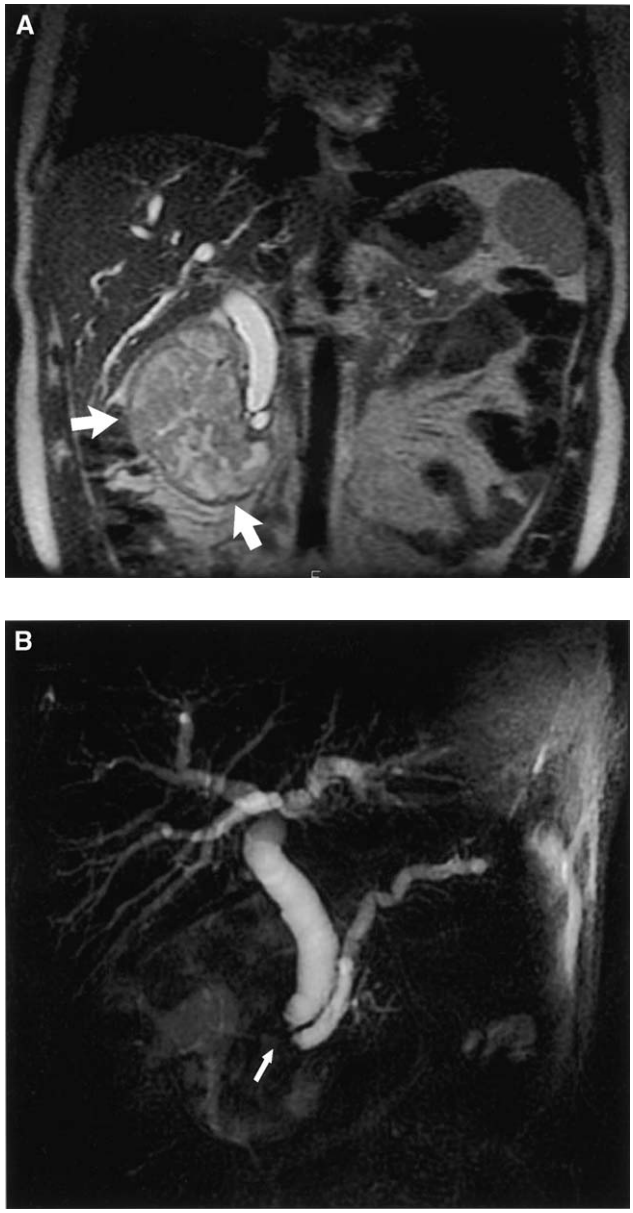

Fig. 2. Magnetic resonance imaging coronal section showing a large, bilobed soft tissue mass (*arrows*) involving the ampulla of Vater and compressing both the duodenum and head of the pancreas (**A**). MRCP study showing the mass (*arrows*) causing obstruction of both the bile and pancreatic ducts (**B**).

contact. The size and friability of this lesion precluded endoscopic investigation or stenting. Magnetic resonance cholangiopancreatography (Fig. 2) demonstrated a soft bilobar tissue mass involving the ampulla of Vater, compressing the duodenum and pancreatic head and causing both pancreatic and bile duct obstruction. Percutaneous transhepatic cholangiography confirmed these findings, and a 14 French transhepatic stent was placed through the right hepatic duct for palliation of his jaundice.

While the patient's jaundice improved, 1 week later he again had an episode of acute pancreatitis and was transferred to our facility for evaluation. Review of his CT scan and magnetic resonance images showed a resectable periampullary malignancy, and despite the presence of multiple subcutaneous metastatic fibrous histiocytoma, pancreaticoduodenectomy was recommended. At the time of operation, the mass was found to involve the duodenum, pancreatic head, transverse mesocolon, and nodal chain along the common bile duct. En bloc resection of the distal stomach, pancreatic head, distal common bile duct, right colon, and lymphadenectomy of the hepatoduodenal ligament was done. Reconstruction was done with end-to-side pancreaticojejunostomy, end-to-side hepaticojejunostomy, antecolic side-to-side gastrojejunostomy, and a side-to-side ileocolostomy. Histopathologic evaluation showed a malignant metastatic fibrous histiocytoma with negative resection margins and no lymph node involvement. The patient's postoperative course was uneventful other than a superficial wound infection treated with antibiotics and local wound care. At the time of discharge on postoperative day 8, he was tolerating a regular diet and ambulating without difficulty. At 6-month follow-up, he remains without jaundice and with minimal abdominal pain, has had no further episodes of pancreatitis or hospitalization, and continues to enjoy an excellent performance status and very good quality of life.

DISCUSSION

The role for surgical palliation of advanced gastrointestinal malignancies continues to evolve and is increasingly recognized as an important component of cancer treatment.[9] In the palliative setting, uncertain benefits of the proposed surgical treatment must be weighed against the operative morbidity and mortality rates in a situation where the goal of therapy is control of symptoms and not cure. Outcome measurements therefore are an improvement in the disease-related symptoms and quality of life rather than a significant prolongation of survival.[10]

Although our patient did not have the traditional indications for a Whipple procedure, he represented as a good candidate for palliative pancreaticoduodenectomy because his tumor caused symptomatic obstruction of his biliary system and pancreatic duct resulting in both obstructive jaundice and obstructive pancreatitis. While his jaundice could be partially relieved by transhepatic external stenting, endoscopic internal stenting of both his biliary and pancreatic duct obstruction was unfeasible due to the large tumor distorting his duodenum. Not only was his pain syndrome consistent with obstruction of his biliary system and a mass effect in his abdomen, but his recurrent episodes of obstructive pancreatitis required hospitalization and medical treatment.

In deciding to use such a large operative procedure for palliative treatment, the surgeon must take into account factors related to the patient, the tumor, and the institutional competency in which the proposed operation will take place. Patient-related factors include age, comorbidities, and nutritional status, which have been shown to directly affect the morbidity and mortality rate of pancreaticoduodenectomy.[11] Tumor-related factors that would preclude pancreaticoduodenectomy include encasement of the superior mesenteric portal venous confluence or the superior mesenteric, hepatic, or celiac arteries making resection technically unfeasible.[12] Both institution- and surgeon-related competencies are associated with procedure volumes, which have been strongly linked to operative morbidity rates, mortality rates, and even cancer outcomes.[13,14] Our patient was young and well nourished, with no significant medical comorbidities. His tumor was obstructing both his bile and pancreatic ducts and was completely resectable based on preoperative imaging studies, and there were no other effective treatment options available.[15] His metastatic subcutaneous nodules were slow growing and minimally symptomatic. Our institution is a high-volume center (130 major pancreatic resections per year) that has low operative morbidity (36%) and mortality (2%) rates.

Our review of MEDLINE querying for "histiocytoma, fibrous," limiting the subsequent search to "human subjects" and "English language" from 1966 to 2005, and limiting the subheading to surgery identified 311 papers, of which 15 reported on malignant fibrous histiocytomas of the pancreas. Most studies were catalogued in one paper that presented a case report and reviewed the literature, citing the 14 other cases of primary malignant fibrous histiocytoma of the pancreas.[16] Unlike our case report of resection for metastatic malignant fibrous histiocytoma, these reports identify primary malignant fibrous histiocytoma of the pancreas, a rare sarcoma that makes up less than 1% of all pancreatic malignancies. In our review, we identified only one other study describing pancreaticoduodenectomy for a metastatic malignant fibrous histiocytoma in the head of the pancreas.[17] Palliative pancreaticoduodenectomy has been used for other metastatic lesions, including renal cell carcinoma, one of the most common tumors known to metastasize to the pancreas. In a retrospective study of 10 patients with renal cell carcinoma metastatic to the pancreas, Sohn et al.[18] demonstrates the benefit of aggressive management with complete surgical resection to improve survival outcomes. Sperti and his colleagues[17] reported that pancreatic resection (including pancreaticoduodenectomy) should be considered in selected patients with pancreatic metastases as it provided good palliation and survival that averaged 23 months (range, 14–42 months). This series included one patient with malignant fibrous histiocytoma. Lillemoe et al.[19] also have advocated the role of pancreaticoduodenectomy in the palliation of pancreatic cancer. In their retrospective study of 126 patients, they found a statistically significant improvement in survival rates of patients undergoing palliative pancreaticoduodenectomies compared with those undergoing palliative surgical bypass. While this study deals specifically with pancreatic cancer, its data support the expanded role of pancreaticoduodenectomy, when done with a low morbidity and mortality, to provide effective palliation in patients with malignancy. Based on these observations, we believe that the indications for pancreaticoduodenectomy can be extended in carefully selected patients with metastatic malignancies in the appropriate clinical setting to provide excellent palliation and an improved quality of life.

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Laparoscopic Gastric Bypass Complicated by Gastric Pouch Necrosis: Considerations in Gastroesophageal Reconstruction

Brian K. Rundall, D.O., Chadrick E. Denlinger, M.D., Gene P. Parrino, M.D., Eugene F. Foley, M.D., David R. Jones, M.D.

Gastric pouch necrosis and intraabdominal sepsis is an uncommon complication following laparoscopic gastric bypass. The intraoperative management of this complication centers on resection of the necrotic pouch, esophageal diversion, drainage, and enteral access for nutrition. Reestablishing gastrointestinal continuity at a later surgery following this complication can be challenging. We present a case in which the colon was found to be unacceptable for use in reconstruction; the remaining stomach was used as the conduit for a transhiatal reconstruction of gastrointestinal continuity instead. (J GASTROINTEST SURG 2005;9:938–940)

KEY WORDS: Laparoscopic gastric bypass, esophageal discontinuity

Laparoscopic gastric bypass (LGB) surgery for the obese has become an increasingly common operation. While experience and surgical techniques have improved greatly, early postoperative complications continue to be a challenge to diagnose and manage. One of the most serious is early postoperative leak with resulting peritonitis and bowel compromise. Many case reports and series have reported successful repair of early, uncomplicated postoperative leaks, and their management is well delineated.[1–7] However, management of a necrotic gastric pouch has been rarely reported, and management options are not clearly delineated in the literature. We present a management strategy of reestablishing gastrointestinal continuity following an LGB procedure complicated by early gastric pouch necrosis with gross intraabdominal contamination. In addition, the initial operative management had resulted in complete esophageal discontinuity.

CASE REPORT

A 43-year-old morbidly obese female (BMI = 47) underwent an LGB and left knee arthroscopy on the same day at another institution. The patient's previous intraabdominal operations included a laparoscopic cholecystectomy, an open hysterectomy, and cesarean section. The operation was uneventful except for a misfire of the stapling apparatus at the gastrojejunal anastomosis. The stapler was reset, deployed properly, and the anastomosis was tested and found to be intact. On postoperative day 2 the patient complained of abdominal pain and was tachycardic and oliguric. She was taken to the operating room where laparoscopic reexploration was performed and gross contamination from gastrojejunostomy and jejuno-jejunal anastamoses was identified. Both anastamoses were taken down, nonviable tissue was excised, and the anastamoses were reconstructed using serial fires of the stapling device. A feeding jejunostomy tube was also placed. Unfortunately, 9 days later the patient required reexploration via laparotomy for intraabdominal sepsis. The entire proximal gastric pouch and gastrojejunal anastomosis were found to be necrotic and leaking. The distal esophagus was dissected and subsequently transected with a stapler, and the necrotic gastric pouch and jejunal segment were both resected. A gastrostomy tube was inserted. Finally, a "long" cervical end esophagostomy was made in the left neck. The patient had a prolonged postoperative course and was ultimately

From the Department of Surgery, University of Virginia School of Medicine, Charlottesville, Virginia.
Reprint requests: David R. Jones, M.D., Department of Surgery, P.O. Box 800679, University of Virginia, Charlottesville, VA 22908-0679. e-mail: djones@virginia.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.01.001

discharged from the hospital with the following foregut anatomy: a completely excluded thoracic esophagus with a cervical end esophagostomy, a gastric remnant in continuity with the rest of the gastrointestinal tract, a gastrostomy tube, and a feeding jejunostomy tube.

The patient was subsequently referred 4 months later to the University of Virginia for reconstruction of her gastrointestinal continuity. At that time she was malnourished, severely deconditioned, and had an open, granulating abdominal wound. She was advised to wait another 3 to 4 months before undergoing reconstructive surgery in order to maximize her nutrition, allow her abdominal wound to heal, and to improve her performance status through an exercise regimen. Eight months following her original procedure, preoperative colonoscopy and mesenteric angiography were performed to evaluate the colon as a possible conduit for reconstruction. These revealed no colonic lesions and a normal mesenteric arterial anatomy, including a patent marginal artery of Drummond. The patient's preoperative BMI was 35 and her serum albumin was 4.3 gm/dl.

Following an adequate bowel preparation, the patient underwent a redo laparotomy. After extensive adhesiolysis, the colonic mesentery was found to be quite foreshortened and scarred, presumably from the previous gross intraabdominal contamination and severe peritonitis. Interestingly, the remaining gastric remnant was noted to be reasonably large and the right gastric and gastroepiploic arteries were preserved. Given these findings, the patient's stomach was used as the reconstruction conduit instead of the left colon, which had been the original plan. The right crus of the diaphragm was divided to open the esophageal hiatus and allow the distal esophageal staple line to be identified. The stomach was mobilized with care taken to preserve the right gastroepiploic and right gastric arteries. A wide Kocher maneuver was performed as well as a pyloromyotomy. The previously placed gastrostomy tube was removed and the insertion site oversewn parallel to the vertical axis of the stomach. The feeding jejunostomy was left intact. The cervical esophagus was mobilized through a left neck incision. The mediastinal phase of the completion transhiatal esophagectomy was then performed, and the excluded thoracic esophagus completely excised. The stomach was then placed through the esophageal bed in the posterior mediastinum into the neck, where a side-to-side esophagogastric anastomosis was performed using a modified Orringer technique.[8] Postoperatively the patient did well, and on postoperative day 7 a gastrograffin/barium swallow showed no leak and good emptying of the stomach (Fig. 1). The patient was discharged home on postoperative day 10. At last follow-up 2 years after her reconstruction she is doing well with no dysphagia or significant reflux, and a BMI of 21.

DISCUSSION

One of the most important objectives in the early postoperative management of the gastric bypass patient is the prompt diagnosis and management of anastamotic leaks. A review of several recent series of LGB procedures reveals intestinal anastamotic leak rates of 1.6% to 5.1%.[1–7] The management of most small leaks in stable patients consists of bowel rest and percutaneous drainage of intraabdominal fluid collections.[3,7] For larger leaks, particularly with intraabdominal sepsis, operative intervention may be required.[1,2,5,7] While uncommon, frank necrosis of the gastric pouch following LGB is a life-threatening

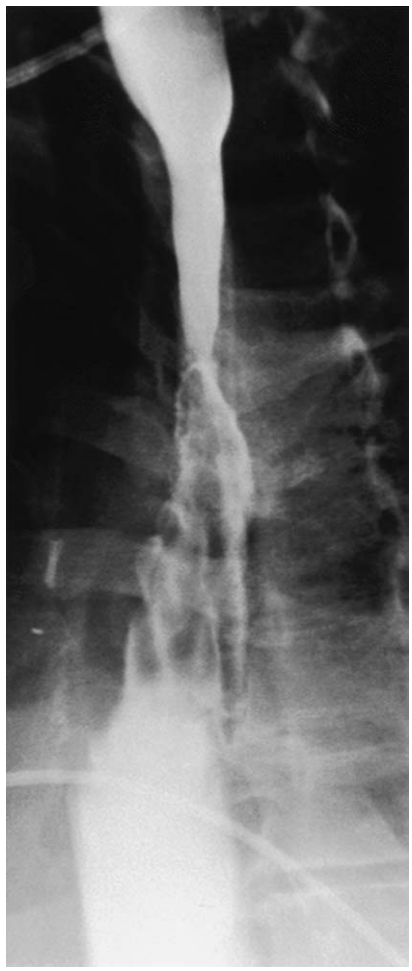

Fig. 1. Oblique view of postoperative barium swallow demonstrating passage of contrast through the cervical gastroesophageal anastomosis.

complication. Immediate operative management of this complication includes resection of the necrotic gastric pouch as well as diversion and drainage, and finally enteral access for nutrition. In this case a diverting cervical end esophagostomy was also performed to completely exclude the esophagus. This effectively ruled out use of the esophagus in reconstruction of gastrointestinal continuity at a later operation.

Reestablishing gastrointestinal continuity after total esophageal exclusion can be challenging, particularly following multiple intraabdominal surgeries accompanied by intraabdominal sepsis and abscess formation. Timing of the reconstruction should be at least 6 months or longer after the initial operation to allow adhesions to soften and all acute inflammatory processes to resolve. As noted by Barkley et al., other issues such as poor pulmonary hygiene, overall deconditioning, unhealed abdominal wounds, and malnutrition all need to be corrected prior to embarking upon reconstructive esophageal surgery.[9]

The decision regarding which conduit to use to reestablish continuity is based on the patient's prior surgical history, the existing anatomy, and the suitability of the conduit. Given that this patient had an end cervical esophagostomy, the conduit of choice had to be long enough to reach the cervical esophagus, thus effectively ruling out use of the jejunum as a conduit. Use of the colon has been well described as an effective conduit[10,11] and was our initial conduit of choice based on the patient's history of prior foregut surgery. Appropriate evaluation of the colon prior to using it for esophageal replacement includes either colonoscopy or a barium enema and mesenteric angiography. However, as demonstrated in this case, despite having a normal preoperative evaluation, there was unexpected colonic mesenteric foreshortening and scarring that would have made mobilization of the colon quite difficult, potentially resulting in ischemia and its associated sequelae.

The stomach has become the conduit of choice for esophageal replacement in many centers provided that there is an adequate amount of stomach with preservation of its blood supply. In this case we were able to use the stomach as our conduit, despite the patient having a failed LGB with gastric pouch necrosis. When performing an LGB, the amount of stomach used to create the 30 cc gastric pouch is actually quite small. Because the patient had an intact right gastroepiploic artery and there was enough residual stomach, it was possible in this case to use the stomach as the esophageal replacement.

CONCLUSION

Gastric pouch necrosis is a rare complication of LGB, and the resulting esophageal discontinuity can be challenging to correct. Consideration of the variables affecting appropriate timing of the reconstructive surgery as well as flexibility regarding the use of alternative conduits are essential if ultimate restoration of gastrointestinal continuity is to be successful. In addition, as illustrated by this case, prior failed LGB should not be considered a contraindication for use of the stomach as a conduit for reversal of esophageal discontinuity.

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Long-term Results and Gastroesophageal Reflux in a Series of Laparoscopic Adjustable Gastric Banding

Christian A. Gutschow, M.D., Peter Collet, M.D., Klaus Prenzel, M.D., Arnulf H. Hölscher, M.D., Ph.D., F.A.C.S., F.R.C.S., Paul M. Schneider, M.D., Ph.D.

During the past decade, laparoscopic adjustable gastric banding has become the most popular surgical procedure in treating morbid obesity. On the other hand, significant drawbacks such as inadequate long-term weight loss, a high prevalence of reoperations, and frequent postoperative symptoms have been reported in the literature. This analysis summarizes our Department's experience with this operation. Thirty-one patients (27 women and 4 men) with a mean body mass index of 46.5 kg/m^2 (range, 38.3–59.8 kg/m^2) were operated upon laparoscopically between September 1997 and January 2003. The preoperative work-up of all patients included a psychological evaluation. Mean follow-up was 59.3 months (range, 19–84 months). Sixteen patients had esophageal pH-metry and 18 patients had upper gastrointestinal endoscopy preoperatively and postoperatively. Data were collected prospectively during the outpatient visits. Mean preoperative excess weight was 65.6 kg (range, 37.4–96.1 kg). Mean excess weight loss after 12, 24, 36, 48, 60, 72, and 84 months was 40.3%, 50.5%, 51.9%, 48.9%, 46.2%, 51.8%, and 30.2%, respectively. In total, six patients (19.4%) had an abdominal reoperation, including four patients (12.9%) for band removal. Upper gastrointestinal endoscopy was performed in 18 patients after 30.1 months (range, 5–67 months), showing a high prevalence of esophagitis (30.0%; grade 1: n = 3, grade 2: n = 3). Conversely, postoperative esophageal pH-metry performed in 16 patients was pathologic in 43.8%. Laparoscopic adjustable gastric banding produces significant weight loss even after long-term follow-up. However, the reoperation rate is high and postoperative symptoms are frequent. The high incidence of gastroesophageal reflux and esophagitis remains a matter of concern. (J GASTROINTEST SURG 2005;9:941–948)

KEY WORDS: Laparoscopic adjustable gastric banding, gastroesophageal reflux, long-term results, morbid obesity

Morbid obesity has become one of the major health concerns of the Western world. The high prevalence of comorbidities in this specific population, particularly type 2 diabetes and hypertension, perpetuates a reduction of life expectancy and quality of life, and in turn drives the tremendous escalation of health care cost. In addition, a number of 300,000 deaths in the United States per year attributable to massive overweight is widely accepted today.[1]

As first-line conservative measures including diets, exercise, and pharmacologic treatment virtually never produce reliable long-term weight loss,[2] the interest in surgical options is rising rapidly. Besides being effective for weight reduction, it has been shown that surgical treatment efficiently reduces comorbidities and secondary costs[3] and improves quality of life.[4] Today's spectrum of surgery for obesity involves malabsorptive, restrictive, and combined procedures. The latest generation of these procedures is represented by purely restrictive gastric surgery, developed to avoid potentially deleterious side effects of the traditional malabsorptive gastric or intestinal bypass procedures. In the era of minimally invasive surgery, adjustable gastric banding has become the preferred form of bariatric surgery in many institutions in Europe and overseas because it is relatively easy to perform laparoscopically and offers the advantages of adjustability and reversibility.

On the other hand, divergent reports have been published about long-term outcome after laparoscopic adjustable gastric banding (LAGB): in contrast to a number of studies showing favorable results and consistent weight reduction,[4–6] others have reported a high reoperation rate, frequent side effects, and modest weight loss, particularly during long-term follow-up.[7–9]

From the Department of Visceral and Vascular Surgery, University of Cologne, Cologne, Germany.
Reprint requests: Christian A. Gutschow, M.D., Department of Visceral and Vascular Surgery, University of Cologne, Joseph-Stelzmann-Strasse 9, D-50931 Cologne, Germany. e-mail: ch.gutschow@t-online.de

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.02.001

Another issue of debate remains the incidence of gastroesophageal reflux (GER) after gastric banding; it is not clear whether subcardial placement of a Silastic band would promote GER and esophagitis by intraluminal stasis due to reduced clearance or whether the band would act as an antireflux mechanism similar to Angelchick's Silastic antireflux prosthesis.

In this setting, it was challenging to perform a prospective evaluation of weight evolution, incidence of complications, symptoms, and reoperations in patients operated in our department. Furthermore, we performed upper gastrointestinal (GI) endoscopies and 24-hour pH-metries in a number of patients prior to and following the operation to assess frequency and extent of gastroesophageal reflux disease (GERD) in this specific population.

MATERIAL AND METHODS

Patients

Between September 1997 and January 2003, 31 patients (27 women and 4 men) with a mean age of 37.0 years (range, 20–61 years) underwent an LAGB procedure. Mean body mass index (BMI) was 48.0 kg/m^2 (range, 38.3–59.8 kg/m^2), and mean excess body weight was 65.6 kg (range, 37.4–96.1 kg). Excess body weight was calculated as the difference between theoretical normal body weight defined by a BMI of 25 and the patient's weight at the time of surgery.

Preoperative Work-up

The inclusion criterion was a BMI greater than 40 kg/m^2 or greater than 35 kg/m^2 with significant comorbidities. All patients had a history of prior unsuccessful conservative dietetic measures. They underwent a thorough interview on diets, weight evolution, eating habits, and symptoms; special attention was paid to GER. In addition, every patient was seen by a psychotherapist to exclude those presenting with specific eating disorders. Diagnostic work-up involved physical examination, laboratory investigations, upper GI endoscopy, barium swallow, stationary esophageal manometry, and esophageal 24-hour pH-metry. Exclusion criteria for LAGB were a history of upper GI surgery, psychiatric illness, eating disorders, and severe esophagitis.

Every patient was instructed about nature, possible complications, and side effects of the procedure and signed a written consent.

Operative Technique and Immediate Postoperative Treatment

All operations were performed by or under supervision of an experienced laparoscopic surgeon (P.M.S.). The procedure involved five trocars placed in the upper abdomen. The Swedish adjustable gastric band (SAGB) was used in the whole series (Obtech Medical, Baar, Switzerland). It was placed high at the stomach from the lesser curvature near the gastroesophageal junction to the angle of His via a retrogastric tunnel created using an angulated instrument (Obtech Medical) to ensure minimal posterior dissection, thus avoiding band migration. The gastric pouch was calibrated to a size of 15 ml using an inflatable balloon placed on a gastric tube. Band migration was prevented by suturing the gastric fundus over the anterior aspect of the band with three nonabsorbable sutures. In all patients, a contrast esophagogram was performed the morning after the operation to exclude perforation and to determine band position. The patients started on oral liquids on the first postoperative day and resumed a soft diet on day 2. Soft diet was maintained for 6–8 weeks before returning to solid foods.

Outpatient Visits at Follow-up

All patients were set on a strict follow-up protocol. The first visit was realized 1 month postoperatively, followed by further visits every 2 months during the first year, every 3 months during the second year, and every 6 months thereafter. During the visits, actual weight and GI symptoms were assessed.

The band was filled via a subcutaneous port system placed in the epigastrium with water-soluble contrast medium. Initial band inflation was performed 3 months after surgery with 2 ml of contrast medium. During the following visits, subsequent filling to a maximum load of 7 ml was performed only if indicated (there was inadequate weight loss).

In addition, patients were regularly instructed by a clinical dietitian regarding fat, protein, carbohydrate, and vitamin intake. Laboratory investigations to exclude nutrition deficiencies were also performed regularly.

In the case of regurgitation or severe dysphagia, contrast esophagograms were performed to exclude band dislocation or pouch distention. After a follow-up greater than 6 months, all patients were offered a 24-hour pH-metry and an upper GI endoscopy.

Patients not willing to attend the outpatient follow-up visits were contacted by telephone at the end of the evaluation period.

Upper Gastrointestinal Endoscopy and 24-Hour pH-metry

Gastroscopy was performed with a PQ-20 upper GI endoscope (Olympus Corporation, Tokyo, Japan). Macroscopic lesions were classified according to the

Savary-Miller classification. Biopsy samples were taken only if macroscopically lesions were present.

For 24-hour pH monitoring, a portable datalogger (Digitrapper Mark III; Medtronic Germany GmbH, Düsseldorf, Germany) connected to a multiuse antimony pH catheter (Medtronic) was used. The system was calibrated before each study in buffer solutions with a known pH of 4.0 and 7.0. From a practical standpoint, pH probes were passed transnasally into the esophagus. Under fluoroscopic control, the tip of the probe was positioned 5 cm above the upper border of the lower esophageal sphincter. Patients were asked to follow a strict study protocol: they were instructed to take three meals per day with no liquids allowed between meals. Recumbent phases of recording were permitted only at night. Patients were asked to keep a diary with exact specification of meals, supine and erect phases of measurement, as well as sensations of heartburn and regurgitation. After completion of the measurements, probes were withdrawn from the patients, and data were stored via an interface on an IBM-compatible computer equipped with Polygram software (Medtronic).

Assessment of Data and Statistical Analysis

All data collected during the follow-up visits were entered into an Excel Spreadsheet (Microsoft Office 2000; Microsoft Corporation, Redmond, WA). Statistical analysis was performed with Statistica (StatSoft, Tulsa, OK). Wilcoxon matched-pair and χ^2 tests were used as appropriate. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Follow-up and Postoperative Visits

Data were collected from 31, 29, 24, 20, 16, 10, and 3 patients after 12, 24, 36, 48, 60, 72, and 84 months, respectively. There were no deaths during the follow-up period. Mean follow-up was 59.3 months (range, 19–84 months); it was incomplete in 3 patients. Four bands (12.9%) had to be removed. Conversely, complete follow-up was available in 24 patients.

The median number (range) of postoperative outpatient visits per patient after 12, 24, 36, 48, 60, 72, and 84 months was 7 (2–12), 2 (0–11), 1 (0–8), 0 (0–6), 1 (0–5), 0.5 (0–4), and 0 (0–2), respectively.

Postoperative Evolution of Weight

Postoperative reduction of BMI after 12, 24, 36, 48, 60, 72, and 84 months was 8.7 ± 4.2, 11.3 ± 6.1, 12.3 ± 7.7, 11.9 ± 7.5, 11.5 ± 7.8, 12.8 ± 9.5, and 7.5 ± 8.8 kg/m^2, respectively (Fig. 1). Conversely, percentage of excess weight loss after 12, 24, 36, 48, 60, 72, and 84 months was 40.3%, 50.5%, 51.9%, 48.9%, 46.2%, 51.8%, and 30.2%, respectively (Fig. 2).

There was a tendency for better weight loss in patients adhering strictly to the follow-up protocol (⩾7, 3, 2, 2, 2, 2, and 2 outpatient visits during follow-up) than in those attending the appointments less regularity; however, this difference was not significant (Fig. 3).

After 12, 24, 36, 48, 60, 72, and 84 months, a 50% excess weight loss was achieved in 35.5%, 48.3%, 50.0%, 50.0%, 31.3%, 50.0%, and 33.3%, respectively.

At the end of the evaluation period, one patient (3.2%) had gained weight despite a functioning band and two patients (6.4%) had a BMI of less than 25, thus being within the range of normal weight.

Complications and Reoperations

There were no conversions to open surgery during the primary operation. A colonic lesion that became apparent during the immediate postoperative course and needed urgent open reoperation was the only major perioperative complication of the series. After reoperation, the patient had an uneventful postoperative course.

As minor postoperative complications, four wound infections (12.9%) were seen.

Including the case mentioned above, a total of six patients (19.4%) needed an abdominal reoperation. Laparoscopic band removal was performed in four patients (12.9%) for pouch distention due to slippage, regurgitation, and aspiration pneumonia (n = 2), recurrent pancreatitis (n = 1), and psychosomatic reasons (n = 1). Another patient had laparoscopic correction of band position for slippage (n = 1). Other indications for minor reoperations were reconnection of catheter at the access port (n = 1), and excessive scar formation (n = 1).

Gastroesophageal Reflux and Dysphagia

Symptoms of GERD were common among our patients. The preoperative prevalence of heartburn (19.4%) was reduced immediately after surgery (3.2%, 9.7%, and 12.9% after 3, 6, and 12 months, respectively) and rose during further follow-up to 24.1%, 25.0%, 25.0%, 31.3%, and 33.3% at 24, 36, 48, 60, 72, and 84 months. However, differences to preoperative values were not statistically significant. Similarly, the prevalence of regurgitation rose significantly from 0.0% preoperatively to 38.7%, 37.9%,

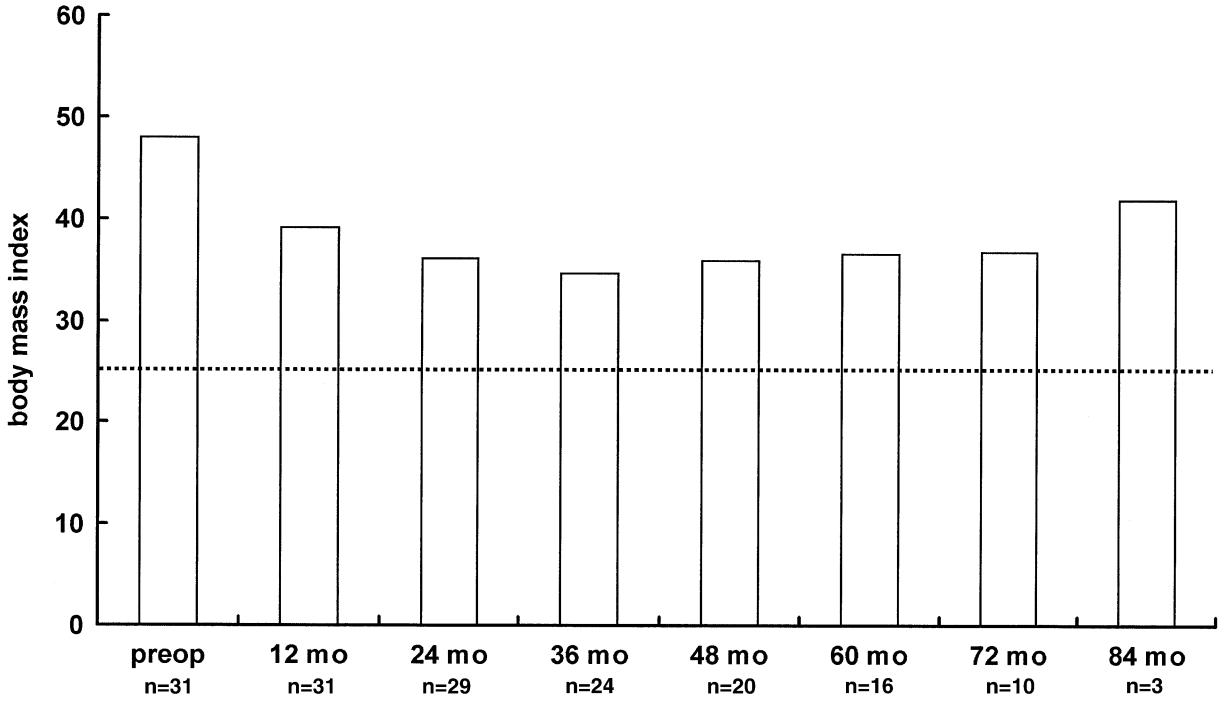

Fig. 1. Evolution of body mass index (BMI) during follow-up. Dotted line represents the threshold for normal BMI (BMI $\leqslant$ 25).

45.8%, 35.0%, 53.3%, 50.0%, and 33.3% after 12, 24, 36, 48, 60, 72, and 84 months ($P \leqslant 0.008$ except for 84 months). Dysphagia was the most common symptom found during follow-up: prevalence rose from 0% preoperatively to 29.0%, 44.8%, 44.0%, 35.0%, 56.3%, 40.0%, and 0.0% after 12, 24, 36, 48, 60, 72, and 84 months ($P \leqslant 0.004$ except for 84 months) (Fig. 4).

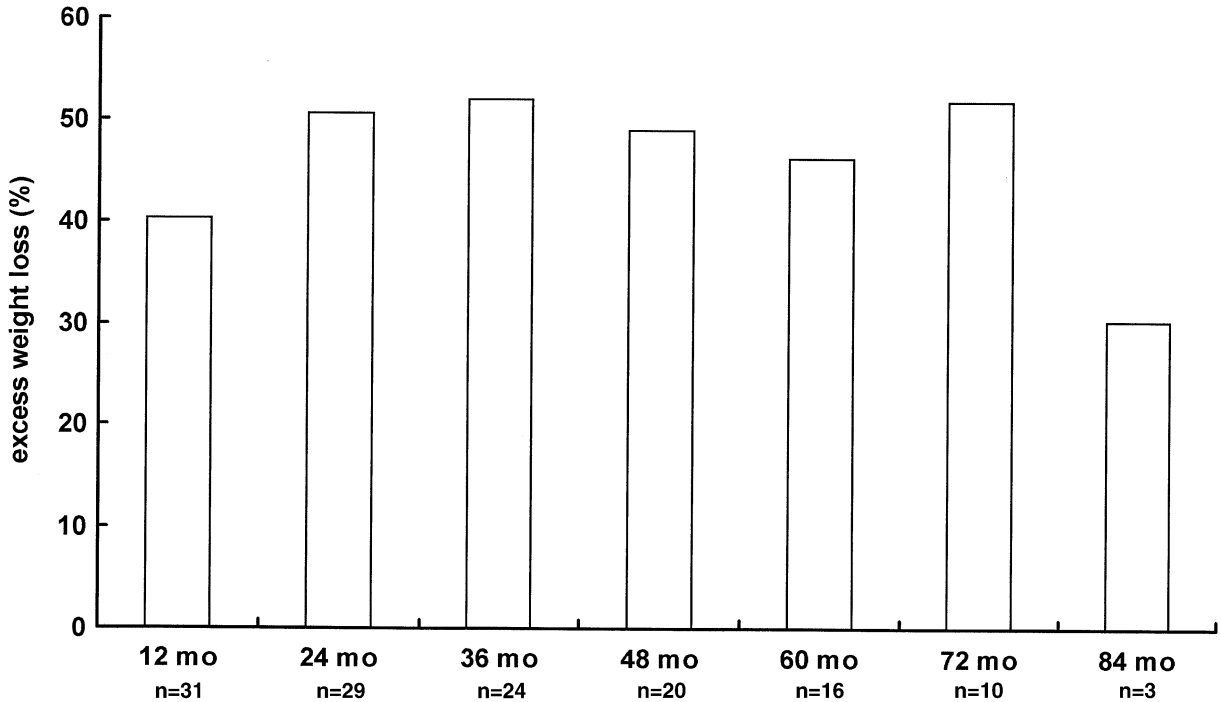

Fig. 2. Percentage of excess weight loss during follow-up.

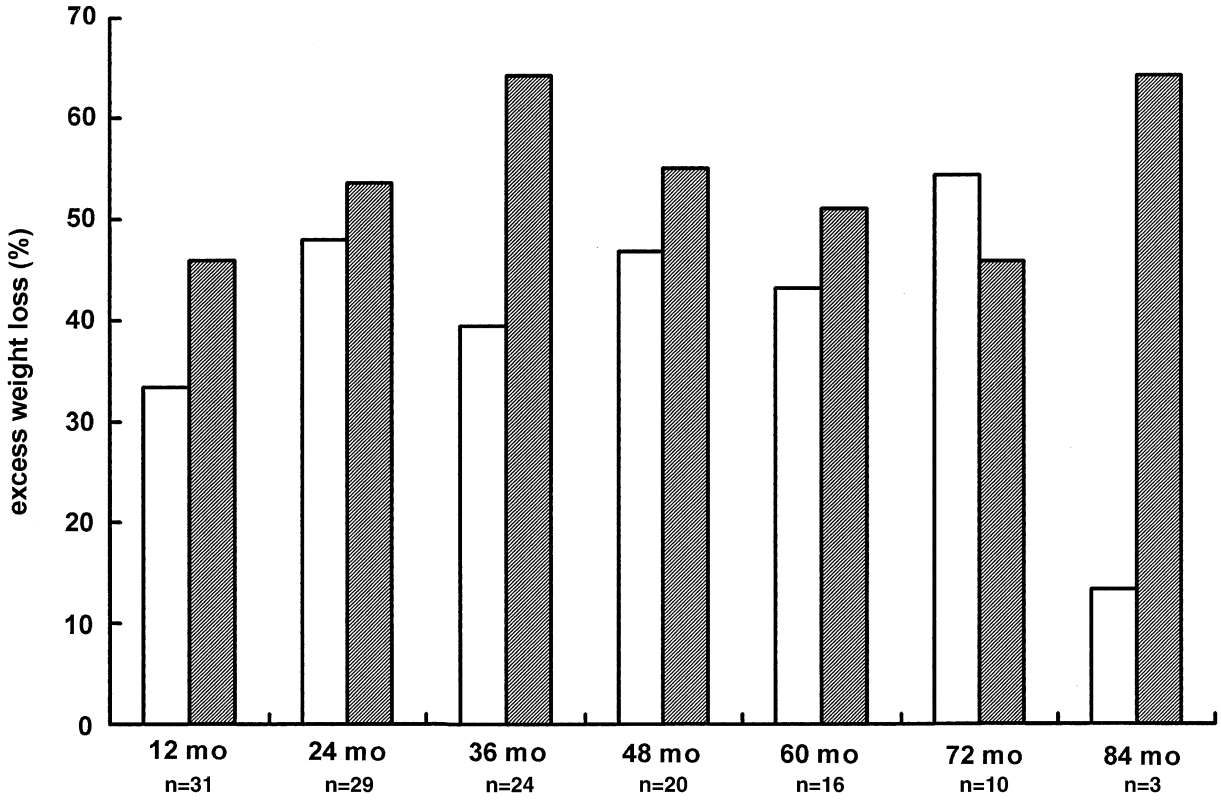

Fig. 3. Percentage of excess weight loss during follow-up according to whether the patients attended the outpatient appointments regularly (shaded bars) or did not adhere to the appointment program (plain bars).

Eighteen patients agreed to undergo upper GI endoscopy after a mean follow-up of 30.1 months (5–67 months); the prevalence of esophagitis was 30.0% (preoperative prevalence of esophagitis, 16.7%). Esophagitis grades 1 and 2 were found in three patients each. Five of the 15 patients with a negative preoperative endoscopy developed esophagitis; conversely, two of three patients with esophagitis before surgery had a negative endoscopy at follow-up (Fig. 5).

pH-metry was performed in 16 patients after a mean follow-up of 23 months (range, 7–40 months); a pathologic result was found in 43.8%. The mean percentage of pH $<$ 4 during total time measurement rose from 4.3% to 7.9%; however, this was not statistically significant. Six of the 11 patients with negative preoperative pH-metry became positive during follow-up and four of five patients with a positive preoperative pH test became negative (Fig. 6). Twelve patients had both postoperative pH-metry and endoscopy. A pathologic pH-metry was found in the two patients who agreed to undergo the test and who had esophagitis grade 2 (100%), in one of three patients with esophagitis grade 1 (33.3%), and in four of seven patients with esophagitis grade 0 (57.1%).

Contrast radiographs were obtained in 20 patients after a median follow-up of 42.5 months (range, 7–74 months). Dilation of the distal esophagus was seen in six patients (30.0%). Median follow-up of patients with dilation of the distal esophagus was longer (56 months) than that of those showing a normal esophageal lumen (32 months). No correlation could be seen between esophageal dilation and the prevalence of reflux symptoms: 5 of 14 patients without and 1 of 6 patients with dilation complained of heartburn, whereas 8 of 14 patients without and 2 of 6 patients with dilation had regular regurgitation of ingested foods.

DISCUSSION

The evolution of weight loss in our series compares favorably with that of other long- and mid-term studies.[4–6,10,11] Similar to the results reported by others, impressive reduction of excess weight was found up to mid-term follow-up ($\leq$36 months). Later, most

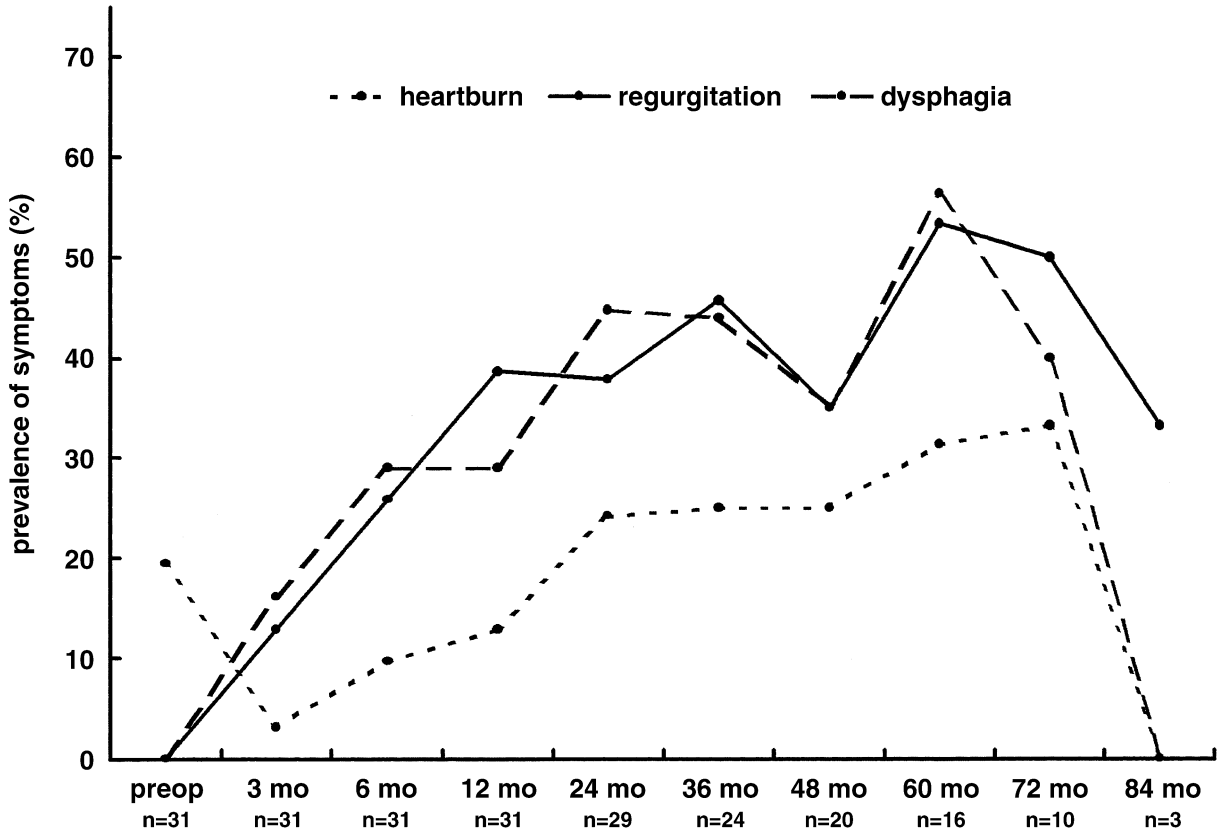

Fig. 4. Evolution of postoperative symptoms during follow-up.

patients experienced a stable steady state until the end of the evaluation period. However, we would like to stress that only two patients achieved the theoretical goal of a "normal" BMI $\leqslant 25$, and one patient even gained weight with a functioning band in place. Furthermore, despite strict preoperative evaluation of eating habits, patients with unsatisfactory weight loss often admitted to consuming large amounts of sweets or soft drinks during follow-up. In agreement with others,[12–14] we believe that patients with poor weight loss despite a functioning band should be offered the option of a laparoscopic gastric bypass procedure early during follow-up. On the other hand, this opinion is challenged by a large French monocentric study; the author claimed that conservative measures can be successful in the vast majority of patients presenting with poor weight loss.[15]

Of our patients, 19.4% needed an abdominal reoperation for complications. We believe that our low incidence of slippage and pouch distention (9.7%) compared with other series is largely attributable to our operative policy involving strictly minimal dissection of the retrogastric tunnel with the so-called Goldfinger instrument (Obtech) in combination with fixation of the band by a fundic wrap. Furthermore, we would like to stress the importance of not filling the band earlier than 3 months after the intervention and to start inflation slowly, taking into account the occurrence of gastrointestinal symptoms. Another important point is a careful instruction by a dietitian. Patients were advised to eat a soft diet during the first 6–8 weeks, to take frequent small meals without fibrous contents, and to adapt quantity and consistency of the diet to the presence of gastrointestinal symptoms. Erosion of the SAGB through the gastric wall was not seen in this series; however, according to others, this phenomenon has become a rarity since introduction of the highly compliant Swedish silicone gastric band engineered to exert much less pressure on the gastroesophageal junction.[5]

There are divergent reports in the literature about the incidence of GER after LAGB. Like others,[16–18] we were impressed by the progressive incidence of reflux symptoms in our population (Fig. 4). The prevalence of regurgitation and dysphagia showed a steady increase during follow-up and peaked after 60–72 months. Interestingly, the prevalence of heartburn was reduced during early follow-up ($\leqslant$12 months) compared with the preoperative situation, that is, during a phase when the band was not or was just slightly inflated: reflux symptoms disappeared after surgery in all six patients with preoperative heartburn.

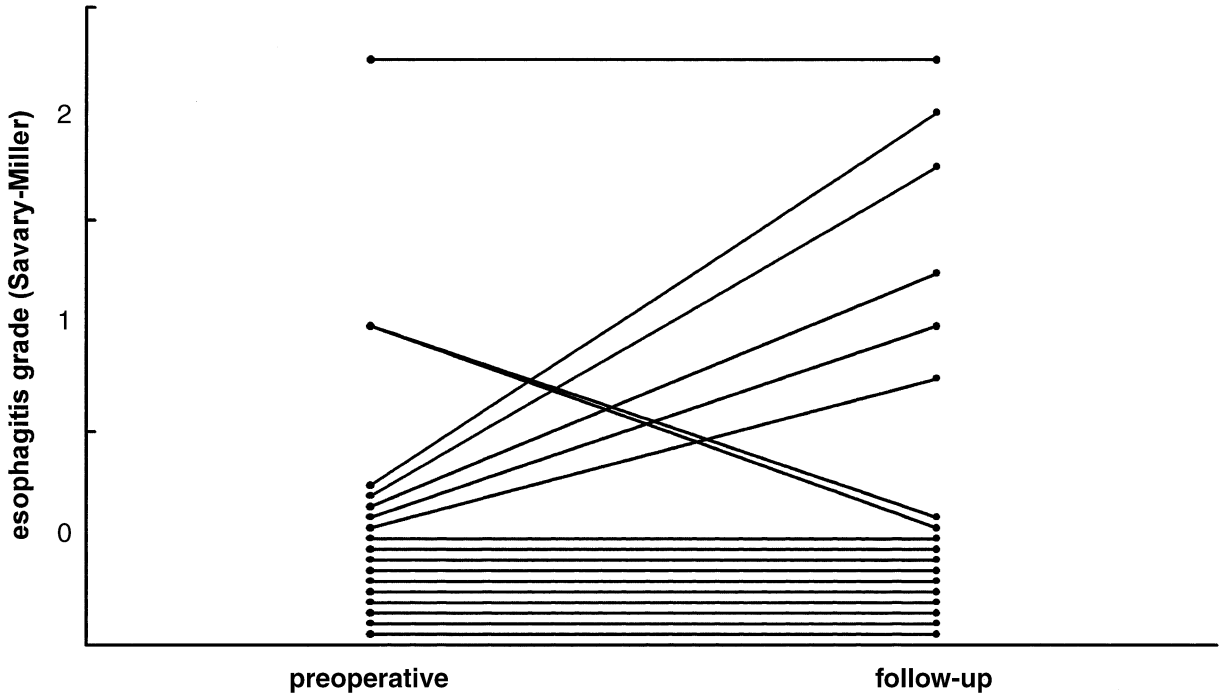

Fig. 5. Results of preoperative and postoperative endoscopies according to the Savary-Miller classification (n = 18).

This phenomenon is paralleled by the observation of de Jong et al.,[19] who found the unfilled band acting as an effective antireflux device. Likewise, Dixon and O'Brien[20] reported a dramatic decrease of reflux symptoms during early follow-up in their series. In contrast, during mid- and long-term follow-up, the inflated band reduces transstomal flow by narrowing the esophageal outlet. As a consequence, esophageal

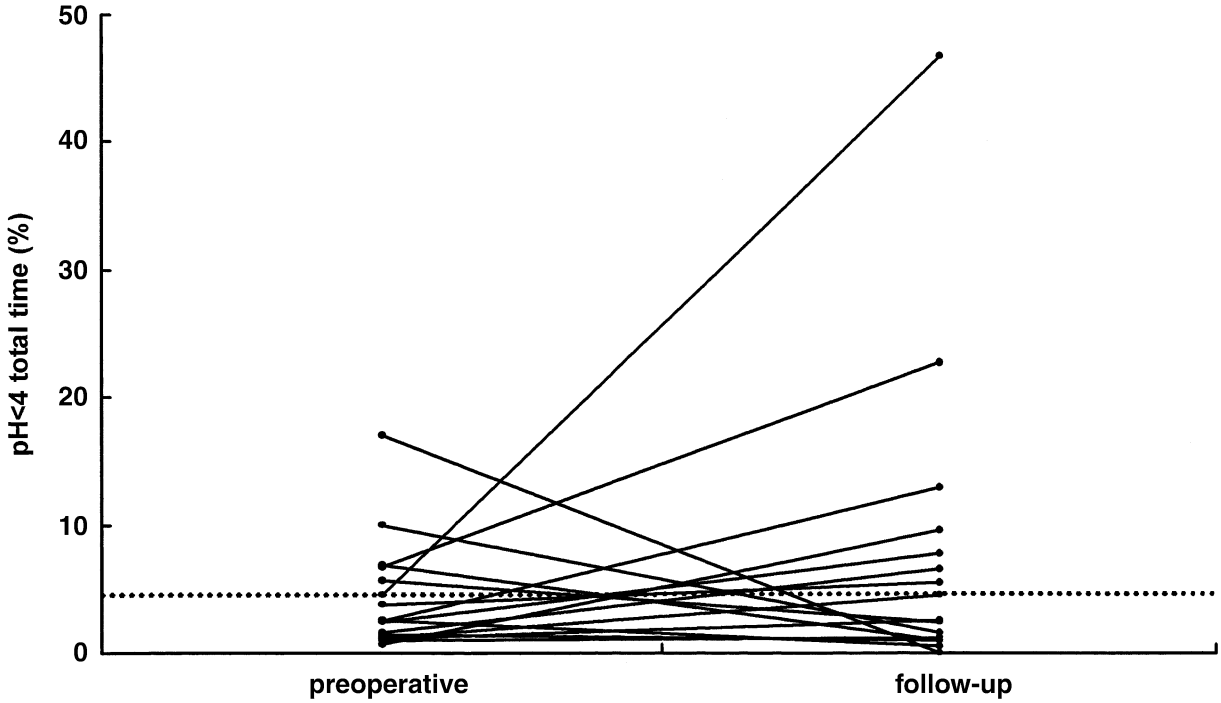

Fig. 6. Results of preoperative and postoperative 24-hour pH-metries showing the percentage of pH < 4 during total time measurements (n = 16). Dotted line represents threshold of normal pH-metry.

clearance is progressively reduced, leading to stasis of ingested food and refluxed acidic material. This development is followed by increasing rates of heartburn, regurgitation, and dysphagia, especially if proximal pouch formation occurs.[19]

In conclusion, our experience confirms the findings of other groups: LAGB is a safe and effective operation to reduce massive overweight in the majority of patients. However, we believe that a strict patient selection is crucial to obtain good results and that alternative procedures should be within the surgeon's armamentarium to treat those patients experiencing failure despite a functioning band. This is even more crucial as the high incidence of GER and esophagitis remains an alarming problem and is inherent to the operative technique. Longstanding reflux disease is known to promote development of Barrett's esophagus and a case of adenocarcinoma of the gastroesophageal junction was recently described after LAGB.[21] Therefore, regular endoscopy and biopsy are recommended, and band removal should be considered in reflux resistant to conservative management.

We thank Marlies Janson for her helpful assistance and Dr. Cátia A.Gradil for careful revision of the manuscript.

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Obesity Is Not a Contraindication to Laparoscopic Nissen Fundoplication

Matthew J. D'Alessio, M.D., Dean Arnaoutakis, B.S., Natalie Giarelli, R.N., M.S., Desiree V. Villadolid, B.S., Alexander S. Rosemurgy, M.D.

Obesity has been shown to be a significant predisposing factor for gastroesophageal reflux disease (GERD). However, obesity is also thought to be a contraindication to antireflux surgery. This study was undertaken to determine if clinical outcomes after laparoscopic Nissen fundoplications are influenced by preoperative body mass index (BMI). From a prospective database of patients undergoing treatment for GERD, 257 consecutive patients undergoing laparoscopic Nissen fundoplication were studied. Patients were stratified by preoperative BMI: normal (<25), overweight (25–30), and obese (>30). Clinical outcomes were scored by patients with a Likert scale. Overweight and obese patients had more severe preoperative reflux, although symptom scores for reflux and dysphagia were similar among all weight categories. There was a trend toward longer operative times for obese patients. Mean follow-up was 26 ± 23.9 months. Mean heartburn and dysphagia symptom scores improved for patients of all BMI categories ($P < 0.001$). Postoperative symptom scores and clinical success rates did not differ among BMI categories. Most patients undergoing laparoscopic Nissen fundoplication are overweight or obese with moderate dysphagia and severe acid reflux. Clinical outcomes after laparoscopic Nissen fundoplication did not differ among patients stratified by preoperative BMI. Obesity is not a contraindication to laparoscopic Nissen fundoplication. (J GASTROINTEST SURG 2005;9:949–954)

KEY WORDS: Laparoscopic fundoplication, antireflux surgery, gastroesophageal reflux disease, obesity

Laparoscopic antireflux surgery has become accepted treatment for patients with gastroesophageal reflux disease (GERD) refractory to medical therapy or as an alternative to maintenance antisecretory treatment.[1,2] The safety and effectiveness of laparoscopic Nissen fundoplication have been well established in controlling the symptoms and preventing the adverse sequelae of chronic gastroesophageal reflux.[3,4] Obesity is a rapidly growing health problem in the United States and is thought to be a predisposing factor in the development of GERD. Obese individuals are nearly three times more likely than their normal-weight counterparts to develop symptoms related to acid regurgitation.[5,6] Furthermore, obesity has been associated with adenocarcinoma of the esophagus, a well-established consequence of chronic reflux.[7]

Notwithstanding the potential benefits of operative therapy for GERD, obesity has long been held as a predisposing factor to failure of antireflux surgery. Obesity is thought to contribute to poor outcomes by multiple factors. Increased intra-abdominal fat increases the difficulty of the operation and can interfere with proper placement of the wrap. Furthermore, increased intra-abdominal pressure from obesity leads to tension and excess wear on the hiatal reconstruction. Previously published reports address the influence of body mass index (BMI) on outcome after antireflux surgery. In a single-institution series of 224 patients having undergone antireflux operations, Perez et al.[8] reported a recurrence rate of 31% in obese (BMI > 30) patients, compared with 4% for those of "normal" weight (BMI <25) ($P < 0.001$), concluding that obesity adversely affects outcomes after antireflux surgery. Conflicting with these results, Fraser et al.[9] reported their single-institution experience with 194 patients who had undergone laparoscopic Nissen fundoplication. In their series, no

Presented at the Forty-Fifth Annual Meeting of The Society for Surgery of the Alimentary Tract, New Orleans, Louisiana, May 15–19, 2004.
From the Department of Surgery, University of South Florida College of Medicine, Tampa, Florida.
Reprint requests: Alexander S. Rosemurgy, M.D., Department of Surgery, University of South Florida College of Medicine, P.O. Box 1289, Room F-145, Tampa, FA 33601. e-mail: arosemur@hsc.usf.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.019

correlation was found between BMI and any of the clinical outcome variables studied. Of interest, postoperative heartburn symptom scores were significantly higher in normal-weight subjects. These authors concluded that obesity does not adversely affect clinical outcome after laparoscopic Nissen fundoplication.

It is our practice to recommend aggressive weight loss to overweight and obese patients seeking surgical therapy for GERD. Despite this, the majority of our patients undergoing antireflux operations have a BMI greater than 25 at the time of surgery. This study was undertaken to determine if clinical outcomes after laparoscopic Nissen fundoplications are influenced by preoperative BMI. Our hypothesis was that overweight and obese patients have poorer outcomes after laparoscopic Nissen fundoplication than patients of normal BMI.

METHODS

Patients

From a prospectively collected database of patients who underwent antireflux operations at the University of South Florida/Tampa General Hospital, Tampa, FL, from 1993 to 2002, we identified a cohort of 257 consecutive patients who underwent primary laparoscopic Nissen fundoplication for GERD. All patient information was collected and handled in concordance with a protocol approved by the institutional review board. Patients were stratified based on preoperative BMI: normal (BMI <25), overweight (BMI 25–30), and obese (BMI >30). Patients undergoing fundoplication had chronic GERD symptoms that were medically refractory or required continued use of antisecretory medications. All patients had objectively documented acid reflux by 24-hour ambulatory pH monitoring and/or findings of GERD demonstrated by flexible endoscopy. If symptoms were predominantly obstructive in nature, ambulatory pH study was not undertaken. Esophageal motility was assessed in all patients by stationary water perfusion esophageal manometry or contrast esophagography undertaken in the 15-degree Trendelenburg position.[10]

Clinical Scoring

Preoperative and postoperative symptom scores for the frequency and severity of heartburn and dysphagia, among many symptoms, were graded by patients with a Likert scale (analog, range 0–10) as described previously.[11,12] Overall result and willingness to repeat the operation, if necessary, were assessed. Clinical follow-up was obtained at 1, 3, and 12 months and then annually thereafter. Extended follow-up was obtained in the clinic, by mail, or by telephone, as necessary.

Technique of Fundoplication

Laparoscopic Nissen fundoplication was undertaken with the patient supine using a five-port technique. The left lobe of the liver was retracted ventrally using a fan retractor. Ultrasonic shears (Auto-Sonix; US Surgical Corporation, Norwalk, CT) were used for all dissection. The right crus was first identified and freed. The esophageal hiatus was then dissected, freeing the posterior esophagus and identifying the left crus. The esophagus and fundus were fully mobilized, with division of all short gastric vessels. Any hiatal hernia was completely reduced and the hernia sac excised, as much as possible. An adequate length of esophagus approximating 8 cm was delivered into the abdominal cavity to ensure a tension-free, intra-abdominal placement of the wrap. The gastroesophageal fat pad was routinely excised. The anterior and posterior vagus nerves were carefully spared. A posterior cruroplasty using 0-gauge braided polyester sutures was always constructed using the Endostitch (Surgidac; US Surgical Corporation). A 360-degree Nissen fundoplication was formed over a 52–60 French bougie and secured to the esophagus well above the gastroesophageal junction using 0-gauge braided polyester sutures. The fascia of all port sites was closed with absorbable monofilament suture using the EndoClose device (US Surgical Corporation). Operative time was measured as the difference in minutes between the time of skin incision and the time the surgical dressings were applied. Patients were generally started on a clear liquid diet when awake and discharged home on the first postoperative day, taking a mechanical soft diet.

Statistical Analysis

Statistical analysis was undertaken using True Epistat computer software (Epistat Services, Richardson, TX). Preoperative and postoperative symptom scores were compared using the paired Student's t test. Similarities among groups were analyzed using χ^2 analysis for discrete variables and Kurskal-Wallace ANOVA for continuous variables. Statistical significance was considered to be two-tailed $P \leqslant 0.05$.

RESULTS

Preoperative patient characteristics stratified by BMI are shown in Table 1. Of the obese patients, only 3 of 62 had a BMI greater than 35. The mean

Table 1. Preoperative characteristics of patients undergoing laparoscopic Nissen fundoplication stratified by preoperative body mass index (BMI)

	Normal weight	Overweight	Obese	*P* value
n	79	116	62	—
Gender (% male)	42	48	44	NS*
Age (mean ± SD)	52.3 ± 17.5	54.1 ± 13.7	50.2 ± 13.5	NS†
BMI (mean ± SD)	22.5 ± 2.1	27.3 ± 1.5	33.1 ± 2.6	—
DeMeester score (mean ± SD)	43.6 ± 53.5	51.7 ± 44.0	51.0 ± 35.4	0.03†
Hiatal hernia present	58%	67%	63%	NS*
Esophagitis present	37%	33%	42%	NS*
Dysmotility present	31%	28%	32%	NS*
Current PPI therapy	86%	91%	87%	NS*
Reflux Score (mean ± SD)	7.3 ± 3.1	7.3 ± 3.4	7.3 ± 3.6	NS†
Dysphagia Score (mean ± SD)	3.7 ± 3.9	4.8 ± 3.7	5.2 ± 4.1	NS†
Operative time (min)	90.8	105.9	115.5	NS†
Follow-up (mo) (mean ± SD)	28.8 ± 24.7	21.8 ± 23.1	28.3 ± 23.9	NS†

NS = not significant ($P > .05$).
*χ^2 analysis.
†Kurskal-Wallace ANOVA.

preoperative DeMeester score was lower in the normal weight patients; however, the mean DeMeester scores were highly elevated above normal for patients of all BMI categories. Laparoscopic Nissen fundoplication was completed in all 257 patients. The mean ± SD operative time was 102.5 ± 32.1 minutes. There was a trend toward shorter operative times for the patients of normal BMI ($P = 0.07$) (Table 1). Average hospital length of stay was 1.7 ± 2.0 days. Median length of stay was 1 day. Mean length of stay was similar among patients stratified by BMI (P = NS).

Overall, 8% of patients experienced complications. Complication rates were similar among patients of all BMI categories: 10% for normal weight, 7% for overweight, and 8% for obese patients (P = NS). A total of 25 complications occurred in 21 patients. Most complications were minor and included urinary retention (n = 5), uncomplicated CO_2 pneumothorax (n = 4), atelectasis (n = 4), urinary tract infection (n = 2), atrial fibrillation (n = 2), superficial wound infection (n = 2), DVT (n = 1), ileus (n = 1), pleural effusion (n = 1), and pneumonia (n = 1). One major complication (0.4%) occurred in a patient with BMI of 27, a small bowel perforation requiring celiotomy and repair on postoperative day 5 in a patient who has had previous abdominal operations. There were no myocardial infarctions, strokes, pulmonary emboli, or deaths.

Mean ± SD follow-up was 25.5 ± 23.9 months. Mean preoperative and postoperative symptom scores stratified by BMI are depicted in Figure 1. Patients of all BMI categories had elevated mean preoperative symptom scores for heartburn and dysphagia. Statistically significant reductions in symptom scores for both heartburn and dysphagia were recorded at follow-up for patients of all weight categories ($P < 0.001$ all groups). There was no significant difference in the mean postoperative dysphagia (P = NS) and heartburn (P = NS) symptom scores among patients stratified by preoperative BMI. Overall, 86% of patients had reductions in their heartburn score. Dysphagia was exacerbated in 16% of patients. This occurred at similar rates among BMI categories: 14% for normal weight, 14% for overweight, and 22% for obese patients (P = NS).

Patient reported overall clinical outcomes are depicted in Figure 2. The outcome of laparoscopic Nissen fundoplication was rated to be excellent or good by 80% of patients. Eighty-five percent of patients reported that they would undergo the operation again if they knew then (i.e., before fundoplication) what they know now. The proportions of patients reporting excellent or good outcomes and willingness to repeat the operation were similar among all BMI categories (P = NS).

DISCUSSION

Obesity has become a major public health problem in the United States, affecting over 20% of the U.S. adult population.[13] Obesity adversely affects health by predisposing patients to a number of chronic medical

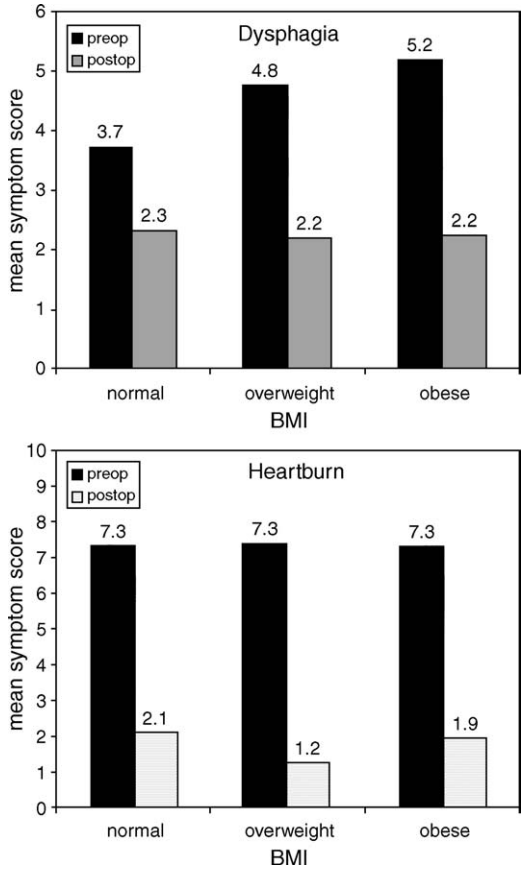

Fig. 1. Mean symptom scores for heartburn and dysphagia before and after fundoplication for patients stratified by preoperative body mass index (BMI). Reductions in severity of symptoms after fundoplication were statistically significant ($P < 0.001$, paired Student's t test) for all comparisons. No significant differences (P = NS Kruskal-Wallis ANOVA) in postoperative symptom scores were found among the three patient groups.

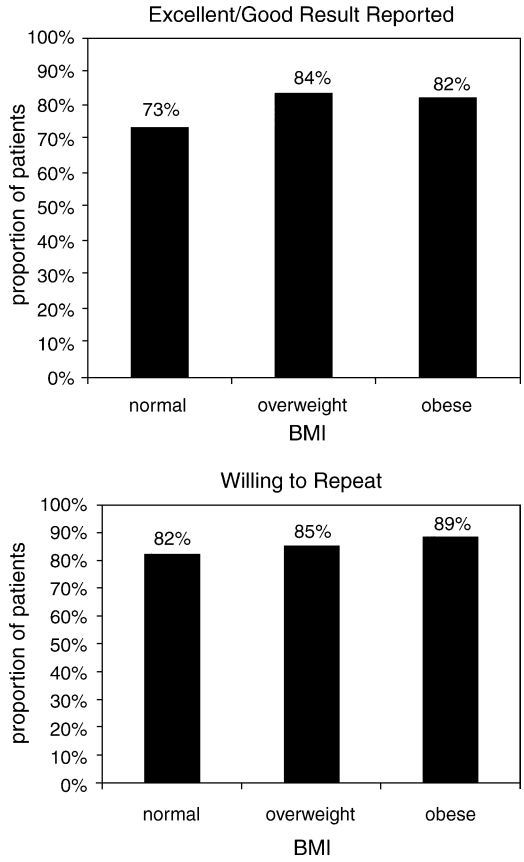

Fig. 2. Overall clinical outcomes after laparoscopic Nissen fundoplication reported by patients stratified by preoperative body mass index (BMI). Proportions were similar among BMI categories for overall outcome ratings and willingness to repeat the operation, if necessary (P = NS χ^2).

conditions such as diabetes mellitus, hypertension, and obstructive sleep apnea.[14] The association between obesity and GERD is becoming more clear, with overweight persons 1.8 times more likely to experience GERD symptoms, and obese patients nearly three times more likely to experience reflux-related symptoms compared with individuals of normal BMI.[5,6] Furthermore, evidence associating obesity and adenocarcinoma of the esophagus is growing.[7] Laparoscopic Nissen fundoplication has been accepted as standard operative therapy for medically refractory GERD or as an alternative to chronic medical therapy in patients with GERD requiring maintenance antisecretory medications.[1,2] It would seem logical that overweight and obese patients would comprise a majority of those seeking surgical therapy for reflux. Nonetheless, the efficacy of laparoscopic Nissen fundoplication in overweight and obese patients has not been conclusively demonstrated, and the risk of laparoscopic fundoplication in these patients has not been established. This report documents the efficacy of laparoscopic Nissen fundoplication in overweight and obese patients and establishes that the associated procedural morbidity for these patients is appropriately low.

Although surgeons have traditionally held obesity as a relative contraindication to antireflux surgery, nearly 70% of patients in this study had an elevated BMI (>25) at the time of fundoplication. However, only a small minority (5%) of obese patients in this study who underwent laparoscopic Nissen fundoplication had a BMI of greater than 35, and each of them had achieved significant weight loss prior to fundoplication. It is becoming common practice that morbidly obese patients with severe reflux are offered Roux-en-Y gastric bypass because the gastric bypass controls acid reflux symptoms and brings about the

added benefit of weight loss.[15,16] While this represents a viable (and perhaps preferable) surgical option for those with morbid obesity, gastric bypass is generally reserved for patients whose BMI is greater than 35.

For obese patients requiring surgical correction of GERD who are not candidates for gastric bypass, conflicting evidence exists as to whether obesity adversely affects outcomes after fundoplications. Perez et al.[8] reported on 224 patients who underwent antireflux operations in a single institution series. These patients underwent either laparoscopic Nissen or Belsey Mark IV fundoplications. The obese patients experienced a significant increase in recurrences compared with overweight and normal-weight subjects. These authors reported a relatively high recurrence rate (31%) in their obese subjects. It should be noted, however, that nearly half of the obese patients with recurrences had undergone the Belsey Mark IV operation.[8] In contrast, Fraser et al.[9] reported their single-institution series of 194 patients, all of whom underwent laparoscopic Nissen fundoplication. These authors found that increased BMI had no detrimental effect on outcome after laparoscopic Nissen fundoplication for any of the outcome measures studied.

In our single-institution study of 257 patients, the largest to date addressing obesity and laparoscopic Nissen fundoplication, we found that laparoscopic Nissen fundoplication was safe and effective therapy for chronic and medically refractory GERD, resulting in excellent or good overall clinical outcome scores in 80%–85% of patients. When patients were stratified by preoperative BMI, we found no significant differences among the BMI categories for any of the clinical outcome measures studied. Relative to normal weight patients, there was a nonsignificant trend ($P = 0.07$) toward longer operative times for obese patients, perhaps indicating increased technical difficulty of the operation when undertaken on overweight and obese patients. Notwithstanding, obesity was not associated with an increase in hospital length of stay or perioperative morbidity. Given the small number of patients with a BMI greater than 35 and given those patients had lost weight prior to laparoscopic Nissen fundoplication, no meaningful comments can be derived from our data about the role of and success after laparoscopic Nissen fundoplication in morbidly obese patients.

With a mean length of follow-up of over 2 years, this cohort represents medium-term follow-up. At the time of follow-up, similar reductions in mean symptom scores for heartburn and dysphagia were seen for patients of all BMI categories. Furthermore, patient ratings for overall result of fundoplication and willingness to repeat the operation were similar among all BMI categories. Our findings document similar clinical success rates to those reported by Fraser et al., as well as in other comparable studies.[3,9,11,16,17] Our series does show that after laparoscopic Nissen fundoplication, a small yet significant portion of patients continue to experience dysphagia. In this series, persistent dysphagia occurred at similar rates for patients of all BMI categories. In most patients undergoing laparoscopic Nissen fundoplication, postoperative dysphagia is transient; however, persistent dysphagia remains a clinically significant problem.[18,19] Patients with persistent exacerbation of dysphagia after fundoplication were more than three times more likely to report an overall outcome score of fair or poor or to respond that they would not be willing to repeat the operation. In other words, patients with dysphagia were more likely to state that they would not undergo laparoscopic fundoplication again if they had known then (i.e., before fundoplication) what they know now.

In this era of emerging, minimally invasive antireflux therapies, laparoscopic Nissen fundoplication retains its status as a safe and highly effective definitive therapy for chronic and refractory GERD.[1–3,11,12] With the excellent results and safety of the operation shown in patients with elevated BMI, it is important to consider the technical factors that may play a role in a successful outcome. Operative technique is undoubtedly important, such as complete excision of the gastroesophageal fat pad and any hernia sac, as well as division of the short gastric vessels close to the stomach, thereby minimizing the amount of perigastric fat incorporated into the wrap.[19] Because dysphagia is a major source of patient dissatisfaction, the importance of constructing a tension-free, calibrated fundoplication in an effort to avoid postoperative dysphagia cannot be overemphasized. Furthermore, liberal mobilization of the esophagus to allow the fundoplication to reside within the abdominal cavity without tension seems critical in optimizing outcomes.

In our institution, overweight and obese patients are generally required to lose approximately 10% of their body weight prior to surgery (the more, the better). While this may be a factor in the favorable results experienced by our overweight and obese patients, this issue is not specifically addressed by this study. Further study is warranted in order to determine what effect, if any, preoperative weight loss has on outcome of fundoplication in patients with an elevated BMI.

CONCLUSION

The results of this study demonstrate that laparoscopic Nissen fundoplication is a safe and effective

therapy for symptom reduction in patients with chronic or refractory GERD. This effect is experienced by patients with normal BMI, as well as overweight or obese patients. After laparoscopic Nissen fundoplication, similar rates of perioperative morbidity, symptom reduction, and patient satisfaction are seen in normal-weight, overweight, and obese patients. Obesity should not be considered a contraindication to laparoscopic Nissen fundoplication.

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Alendronate Improves Vitamin D–Resistant Osteopenia Triggered By Gastrectomy in Patients With Gastric Cancer Followed Long Term

Yutaka Suzuki, M.D., Yoshio Ishibashi, M.D., Nobuo Omura, M.D., Naruo Kawasaki, M.D., Hideyuki Kashiwagi, M.D., Katsuhiko Yanaga, M.D., Masahiro Abo, M.D., Mitsuyoshi Urashima, M.D., Ph.D.

Gastrectomy/gastric bypass has been used for patients with gastric cancer, and its application is now expanding to treating patients with morbid obesity, the prevalence of which is increasing worldwide. It is well known that gastrectomy leads to osteopenia, but the underlying pathophysiology and optimum treatments for this disorder have not been delineated. We followed 13 patients who showed progressive osteopenia (bone mineral density T-score <-2.4 SD) after gastrectomy/gastric bypass due to gastric cancer and who were resistant to long-term treatment (mean, 6 years) of active vitamin D_3 and prospectively studied the effects of alendronate, a bisphosphonate, on osteopenia-related parameters for 2 years. Oral administration of alendronate in addition to vitamin D_3 led to remarkable improvement within 2 years, not only in clinical symptoms, such as radial bone fractures and lumbar pain, but also in parameters for osteopenia, including decreased bone mineral density of the lumbar spine ($P < 0.01$), decreased concentrations of calcium ($P < 0.05$), increased urine levels of deoxypyridinoline ($P < 0.01$), increased serum levels of bone-specific alkaline phosphatase ($P < 0.01$), increased serum levels of osteocalcin ($P < 0.01$), and increased serum levels of intact parathyroid hormone ($P < 0.05$), although body weight did not alter. These results suggest that bisphosphonate may improve osteopenia after gastrectomy/gastric bypass. (J GASTROINTEST SURG 2005;9:955–960)

KEY WORDS: Bisphosphonate, osteomalacia, osteopenia, gastrectomy, bone mineral density

Gastrectomy/gastric bypass (GX/GB) is commonly used for patients with gastric cancer, and its application is now expanding to the treatment of morbid obesity.[1,2] The prevalence of gastric cancer in Japan is 90:100,000, and long-term survival of these patients has been improved because of recent advances using a combination of surgery and chemotherapy.[3] Moreover, the incidence of morbid obesity, defined as a body mass index greater than 40 kg/m^2, is rapidly increasing in developed countries.[4] Thus, in developed countries including Japan, the number of patients who are candidates for GX/GB may increase exponentially in the near future.

GX/GB is known to reduce bone mineral density (BMD) in gastric cancer patients[5–9] as well as in morbidly obese patients.[10] The decrease in BMD is subsequently associated with an increased risk of bone fracture. Thus, exponential use of GX/GB for morbid obesity may increase bone fractures in these patients. However, the pathophysiology of osteopenia after GX/GB and its appropriate treatments has not yet been delineated: neither vitamin D nor calcium supplements have been confirmed to be effective in correcting osteopenia after GX/GB,[11–14] or these treatments are still controversial.[15–18] Using a rat model, we have demonstrated GX/GB-induced osteoporosis mixed with osteomalacia and its improvement with the oral administration of bisphosphonate demonstrated with morphometrical techniques and measurements of biochemical markers.[19]

We therefore selected 13 patients who showed progressive osteopenia (BMD T-score < -2.4SD) after GX/GB due to gastric cancer and who were resistant to long-term treatment (mean, 6 years) of

From the Department of Surgery (Y.S., Y.I., N.O., N.K., H.K., K.Y.), Department of Rehabilitation (M.A.), and Division of Clinical Research and Development (M.U.), Jikei University School of Medicine, Tokyo, Japan.
Reprint requests: Mitsuyoshi Urashima, M.D., Ph.D., M.P.H., Division of Clinical Research and Development, Jikei University School of Medicine, Nishi-shimbashi 3-25-8, Minato-ku, Tokyo 105-8461, Japan. e-mail: urashima@jikei.ac.jp

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.020

active vitamin D_3 and prospectively studied the effects of alendronate, a bisphosphonate, on osteopenia-related parameters for 2 years.

PATIENTS AND METHODS

Patients and Treatment

Patients with gastric cancer who underwent GX/GB at the Jikei University Hospital between February 1979 and July 1997 represented the source population. In this source population, 13 long-term survivors with no relapse of gastric cancer for more than 7 years and no fractures in the vertebral bones were selected based on their continuous decrease in BMD (T-score at the start of bisphosphonate therapy, < -2.4 SD) despite active vitamin D_3 treatment for more than 4 years. Written informed consent to use oral alendronate sodium hydrate (ALN) in combination with vitamin D_3 to improve osteopenia was obtained from all 13 patients.

All 13 patients had either stage I or II cancer. The mean age of patients was 54 ± 9.2 years, and they were followed for a mean of 12 ± 4.6 years after GX/GB (Table 1). Either total GX (n = 3) or partial GX (n = 10) was performed without major complications. Reconstruction after GX consisted of Billroth I, Billroth II, Roux-en-Y gastric bypass, or ileocolon interposition. Oral administration of active vitamin D_3 (alfacalcidol, 1 μg/day), with (patients 1, 7, 8, 10, and 13) or without (patients 2–6, 9, 11, and 12) vitamin K_2 (menatetrenone 45 mg/day), was started a mean of 4.0 ± 4.3 years (range, 1–17 years; median, 2 years) after GX/GB to treat progressive osteopenia; this treatment was continued for a mean of 5.9 ± 6.0 years (range, 4–8 years; median, 6 years). Next, oral administration of both ALN (5 mg/day) and alfacalcidol (1 μg/day) were continued for 2 years, as a prospective intervention study.

Osteopenia Parameters

The lumbar spine (L1–4) BMD (g/cm^2) was measured using an osteodensitometer in the hospital and converted to a Z-score. The Z-score is the standard deviation (SD) from the normal mean value of a reference population of the same age and gender and is represented as a percentage. The T-score (SD) is defined similarly but uses young adult controls of the same gender as the reference. Measurements took place before starting active vitamin D_3 treatment, at the starting point of ALN (0 months), and 3, 6, 12, 18, and 24 months after starting ALN. Biochemical measurements, including serum calcium (Ca) and phosphate (Pi), were measured with an autoanalyzer in the hospital. Bone-specific alkaline phosphatase (BSAP) was measured at SRL laboratory (SRL Co. Ltd. Hachioji, Tokyo, Japan). Serum osteocalcin, a biochemical marker of bone turnover, was measured with radioimmunoassay at SRL Inc. (Tokyo, Japan). Urinary deoxypyridinoline (DPD) concentrations were measured by high-performance liquid chromatography and corrected by urinary creatinine concentration at SRL Inc. Serum intact parathyroid hormone (iPTH) was determined with an immunoassay at SRL Inc.

Table 1. Patient Characteristics

Patient No.	Date of Operation	Age at Operation (yr)	Gender	Type of Gastrectomy	Reconstruction	Starting Date of Vitamin D_3	Starting Date of Alendronate Bisphosphonate	Lumbar Pain	Nail Deformity	Bone Fracture
1	1993/5	55	F	P	B-I	1994/5	2002/3	Frequent	Yes	No
2	1988/5	39	F	P	B-I	1994/9	2002/4	No	Yes	Radial
3	1994/5	67	M	P	B-I	1998/1	2002/4	No	No	No
4	1994/4	52	M	P	B-I	1996/2	2002/4	Sometimes	No	No
5	1995/5	64	F	T	Roux-en-Y	1996/8	2002/3	Frequent	No	No
6	1992/3	44	M	P	B-I	1997/3	2002/4	No	No	No
7	1994/4	66	F	T	Roux-en-Y	1997/7	2002/4	No	Yes	Radial
8	1997/7	52	F	P	B-I	1998/4	2002/4	No	Yes	No
9*	1991/1	55	M	P	B-I	1997/9	2002/4	No	No	No
10	1996/1	52	F	T	Ileocolon interposition	1998/1	2002/4	No	No	No
11*	1979/2	44	F	P	B-II	1996/7	2002/4	Frequent	Yes	Radial
12	1992/4	50	M	P	B-I	1994/6	2002/4	No	No	No
13	1992/5	66	F	T	Roux-en-Y	1994/1	2002/4	No	No	No

P = partial gastrectomy, T = total gastrectomy; B-I = Billroth I; B-II = Billroth II; Roux-en-Y = Roux-en-Y gastric bypass.
*Patients 9 and 11: stage II; all others: stage I.

Statistics

Changes in parameters before and after treatment with active vitamin D_3 were evaluated using the Wilcoxon signed rank test. We used a nonparametric Kruskal-Wallis test developed by Cuzick[20] for time trends of osteopenia-related parameters. All statistical analyses were performed using STATA 8.0 (STATA Corporation, College Station, TX).

RESULTS

Three patients had a radial fracture during treatment with vitamin D_3 alone (Table 1). Moreover, 4 patients had been complaining of lumbar pain and 5 patients had noticed a deformity in their nails during vitamin D_3 treatment; this deformity disappeared soon after starting ALN therapy. Body weight decreased during active vitamin D_3 therapy ($P = 0.0013$) but did not change during the following 2 years when ALN treatment was added to the regimen (Fig. 1).

A mean of 4 years after GX/GB and before vitamin D_3 treatment, the median BMD, T-score, and Z-score of L1–4 BMD were 0.81 g/m^2, −2.63 SD, and −0.58 SD, respectively. Even after administration of vitamin D_3, with or without vitamin K_2 , for a mean of 6 years, these levels decreased further to a median of 0.73 g/m^2, −3.18 SD, and −1.34 SD, respectively ($P = 0.0015$ for all values). However, BMD values increased to 0.82 g/m^2, −2.54 SD, −0.52 SD, respectively, after administration of ALN for 2 years ($P < 0.01$ for all values) (Fig. 2, *A–C*). Similarly, concentrations of serum calcium were decreased after vitamin D_3 ($P = 0.004$) (Fig. 3) and improved after ALN ($P < 0.05$), whereas concentrations of serum Pi were not altered. Levels of DPD, BSAP, osteocalcin, and iPTH, which already tended to be higher than the upper limit of normal before starting vitamin D_3 therapy, were not changed by the administration of vitamin D_3. However, these values decreased to almost normal levels after administration of ALN for 2 years (DPD, $P < 0.01$; BSAP, $P < 0.01$; osteocalcin, $P < 0.01$; iPTH, $P < 0.05$) (Fig. 4, *A–D*).

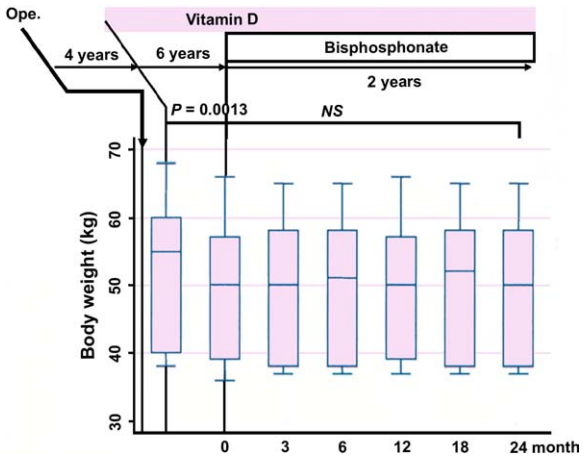

Fig. 1. Changes in body weight of 13 patients before and a mean of 6 years after active vitamin D_3 treatment (0 month after starting ALN), 3, 6, 12, 18, and 24 months after starting ALN. Box plots in each time point show the 25th/50th/75th percentiles and adjacent values with outliers. The changes of parameters before and after use of active vitamin D_3 were evaluated using Wilcoxon signed rank test. We used a nonparametric test developed by Cuzick for trends across ordered groups.

DISCUSSION

Bisphosphonate is a potent inhibitor of bone resorption via induction of osteoclast apoptosis.[5] These clinical effects have been well established in various bone disorders, including osteoporosis in women[21,22] and men[23,24] and bone resorption disorders associated with multiple myeloma[25] and bone metastasis of the breast[26] and prostate cancer.[27,28] In this study, we demonstrated a clear "V"-shaped recovery in BMD as well as improvement in clinical symptoms: a decrease during active vitamin D_3 treatment and an increase after starting ALN treatment in combination with vitamin D_3. To our knowledge, there are no reports to prove the clinical effectiveness of bisphosphonate therapy in patients with osteopenia after GX/GB, although the effectiveness of bisphosphonates for GX/GB-induced osteopenia has been implied using rat models including our previous study.[19,29] The small sample size is a limitation of this study, but all patients were followed for a very long duration—a mean of 12 years after GX/GB—and osteopenia-related parameters were compared before and after the administration of ALN.

Body weight did not change for 2 years after starting ALN, although weight decreased for a mean of 6 years during vitamin D_3 administration. This finding suggests that mere malnutrition triggered by GX/GB may not explain osteopenia, as suggested with the rat model.[30] A deficiency of active vitamin D_3 due to malnutrition after GX/GB may not be a plausible etiology for osteopenia, as administration of active vitamin D_3 did not improve BMD or other parameters related to bone metabolism. The duodenum and the upper jejunum are the major sites of Ca absorption and vitamin D receptors,[31,32] and the altered stream of digested food that occurs after GX/GB can impair absorption of calcium and vitamin D

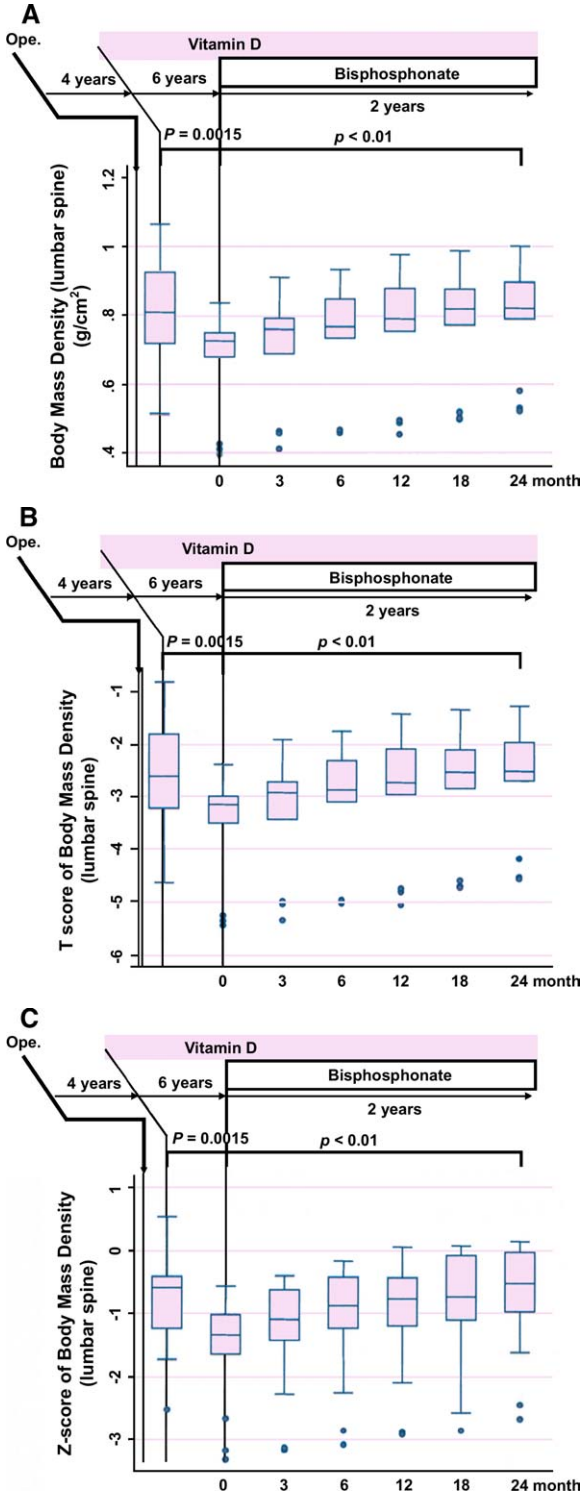

Fig. 2. Bone mineral density (BMD) of the lumbar spine. *A*, Raw value of BMD (g/cm^2). *B*, T-score of BMD (SD). *C*, Z-score of BMD (SD). Statistical evaluations were performed in the same way as in Fig. 1.

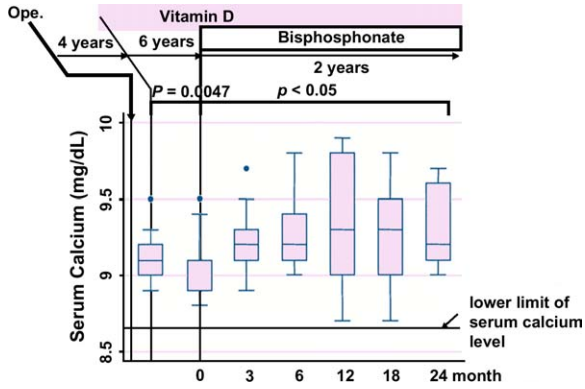

Fig. 3. Serum levels of calcium are shown in each time point with box plots. Statistical evaluations were performed in the same way as in Fig. 1.

in these sites. Thus, osteomalacia induced by GX/GB may be not due to malnutrition associated with reduced supplementation of calcium and vitamin D, but rather due to malabsorption of calcium and vitamin D, which may explain why peroral administration of active vitamin D_3 is ineffective after GX/GB. The malabsorption specific to GX/GB treatment may also stimulate iPTH secretion followed by increased osteoclast activity,[33] resulting in facilitation of bone turnover with increases in bone resorption, represented by higher osteocalcin and DPD levels. In fact, iPTH, osteocalcin, and DPD tended to be higher than the upper limit of normal range in this study.

Within 2 years, oral administration of alendronate, in addition to vitamin D_3, led to remarkable improvements in biochemical parameters with an increase in serum concentration of calcium; decreases in serum levels of osteocalcin, BSAP, and iPTH; and a decrease in urine levels of DPD. Decreased calcium absorption after GX/GB may stimulate iPTH secretion to maintain physiologic levels of calcium, resulting in osteopenia. Bisphosphonate was proved to improve osteoporosis related to hyperparathyroidism, but it did not decrease levels of iPTH.[34,35] Thus, the combination with vitamin D_3 may play a role in improving levels of iPTH associated with osteopenia after GX/GB, although controls of ALN alone should be used to prove this hypothesis.

In conclusion, total GX/GB for gastric cancer led to impaired BMD of the lumbar spine in 13 patients. These changes worsened during active vitamin D_3 administration for 6 years but improved after ALN coadministration for 2 years. These results suggest the potential benefits of ALN therapy for GX/GB-treated patients.

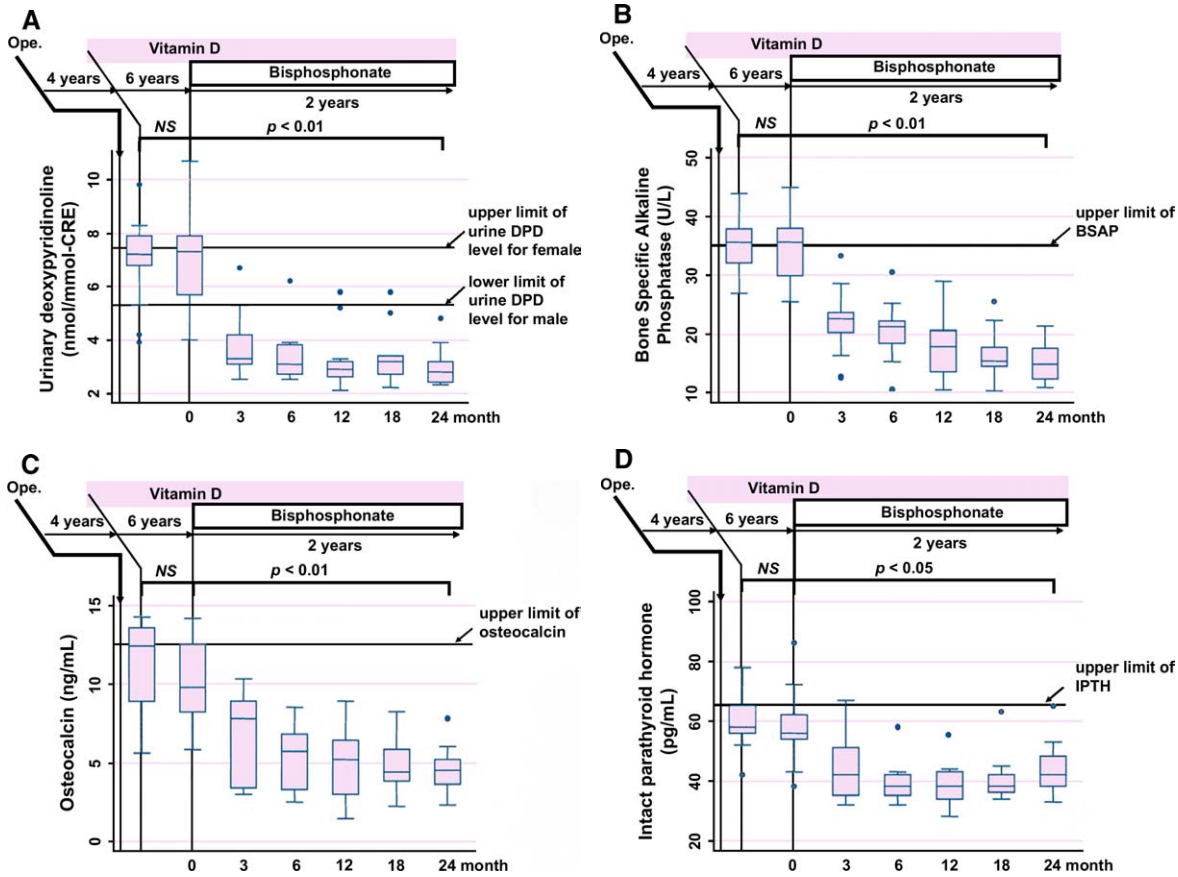

Fig. 4. (**A**), Urinary levels of deoxypyridinoline (normal range: males, 2.1–5.4 nmol/cre; females, 2.8–7.6 nmol/creatinine). (**B**) Bone-specific alkaline phosphatase (normal range, 9.6–35.4 U/L). (**C**) Osteocalcin (normal range, 2.5–13 ng/mL). (**D**) Intact parathyroid hormone (normal range, 10–65 pg/mL). Values are shown at each time point with box plots. Statistical evaluations were performed in the same way as in Fig. 1.

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Prospective Evaluation of Endoscopic Ultrasonography in the Diagnosis of Biliary Microlithiasis in Patients With Normal Transabdominal Ultrasonography

Seyed Amir Mirbagheri, M.D., Mehdi Mohamadnejad, M.D., Jafar Nasiri, M.D., Ahad Atef Vahid, M.D., Ramin Ghadimi, M.D., Reza Malekzadeh, M.D.

Prior investigators have proposed microlithiasis as a causative factor for occult gallbladder diseases. Endoscopic ultrasonography (EUS) is potentially far more sensitive than transabdominal ultrasonography (TUS) in visualizing small stones. The aim of this study was to investigate the role of endoscopic ultrasonography (EUS) in the diagnosis of microlithiasis in patients with upper abdominal pain and normal TUS. Thirty-five patients with biliary-type abdominal pain and normal TUS results were prospectively studied. All patients underwent radial EUS by means of a GF UM-20 echoendoscope (Olympus Optical, Tokyo, Japan). Of 35 patients, 33 were revealed to have gallbladder sludge or small stones, and 21 had CBD sludge or microlithiasis. Nine patients were not available for follow-up; of the remaining patients, 13 underwent combined endoscopic biliary sphincterotomy and cholecystectomy, 10 underwent cholecystectomy, and 3 underwent biliary sphincterotomy alone. In a postoperative follow-up at 9.2 months, 25 patients (96.2%) were symptom free. EUS is an important diagnostic tool in patients with unexplained biliary colic. Cholecystectomy with or without EUS is an effective treatment modality in these settings. (J GASTROINTEST SURG 2005;9:961–964)

KEY WORDS: Endoscopic ultrasonography, microlithiasis, transabdominal ultrasonography

Most people with gallstones are clinically asymptomatic. The most common symptom of gallstones is intermittent epigastric or right upper quadrant pain, probably caused by stone impaction in the cystic duct. This biliary pain is generally a steady pain that can last for several hours. Multiple etiologic factors have been proposed for biliary-type abdominal pain. Determining the etiology is of utmost importance because it helps to direct therapy, limits further unnecessary tests, and may improve a patient's long-term prognosis.[1]

Patients with cholelithiasis are more likely to become symptomatic when they have microlithiasis; this is particularly true because they are more likely to develop choledocholithiasis and associated severe complications such as pancreatitis and cholangitis.[2] Microlithiasis is referred to as sludge, biliary sand, biliary sediment, microcrystalline disease, pseudolithiasis, and reversible cholelithiasis.[1] Although prior investigators have raised controversies about the true definition of microlithiasis, most refer to microlithiasis as stones of less than 3 mm in diameter.[3,4]

The sensitivity of transabdominal ultrasonography (TUS) for the diagnosis of microlithiasis is limited to 50%–60%.[1] This may be even less in obese patients and those with an ileus due to acute illness. The gold standard imaging method for diagnosis of common bile duct (CBD) stone is endoscopic retrograde cholangiopancreatography (ERCP), which has the advantage of permitting intervention if stones are

Presented in part as a poster at the Forty-Fifth Annual Meeting of The Society for Surgery of the Alimentary Tract, New Orleans, Louisiana, May 15–19, 2004.

From the Department of Internal Medicine (S.A.M., R.G.), School of Medicine, Tehran University of Medical Science, Tehran, Iran; Gastrointestinal and Liver Disease Research Center (M.M.), Iran University of Medical Sciences, Tehran, Iran; Digestive Disease Research Center (J.N., R.M.), Tehran University of Medical Science, Tehran, Iran; and Department of Surgery (A.A.V.), Mehr General Hospital, Tehran, Iran.

This study was supported by local funds from Digestive Disease Research Center, Tehran University of Medical Sciences, and has had no external financial support.

Reprint requests: Prof. Reza Malekzadeh, Digestive Disease Research Center, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Avenue, Tehran 14114, Iran. e-mail: malek@ams.ac.ir

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.03.002

present,[5] but it is invasive and may cause complications such as pancreatitis. Furthermore, very small stones may be missed on ERCP. Therefore, it is desirable to confirm the presence of CBD stones before embarking upon an ERCP. The two most widely used techniques for detecting microlithiasis are endoscopic ultrasonography (EUS) and bile microscopy. Microscopy of the aspirated bile from the gallbladder or CBD is a relatively invasive procedure, and microscopic examination of duodenal bile for diagnosis of microlithiasis has low sensitivity (~65%).[6] Contrary to bile microscopy, EUS is less invasive and has been shown to have a high positive predictive value for unexplained upper abdominal pain.[7] On the other hand, EUS minimizes the influence of bowel gas or subcutaneous tissue on image quality and produces higher image resolution with a better sensitivity (nearly 95%) for the diagnosis of microlithiasis.[6,8]

The aim of this study was to prospectively evaluate the role of EUS in the diagnosis and management of acute biliary-type upper abdominal pain in patients with clinical diagnosis of microlithiasis but normal TUS results.

PATIENTS AND METHODS

From January 2001 to September 2003, 80 consecutive patients with acute biliary-type abdominal pain were referred to the emergency department of a tertiary referral hospital in Tehran, Iran. Initial evaluation, including a comprehensive history, physical examination, and routine laboratory tests (complete blood cell count, prothrombin time, liver function tests, and blood biochemistry), was performed shortly after admission. Meanwhile, conventional TUS was performed on all patients by expert radiologists with 2- to 4-MHz TUS probes. The initial scan was usually performed during the acute illness; however, if no stones were identified or if unsatisfactory biliary scans were obtained, ultrasonography was repeated once. Of 80 patients, 45 were found to have acute pancreatitis based on acute abdominal pain and a serum amylase level greater than three times the upper limit of normal (normal <110 U/L). They were not included in our study. For the remaining 35 patients in whom our initial evaluation as well as TUS and upper gastrointestinal endoscopy failed to reveal any definite diagnosis, further investigations were requested. These patients were scheduled for radial EUS using a GF UM-20 echoendoscope (Olympus Optical, Tokyo, Japan).

The examination was performed with the patient in the left lateral decubitus position under mild intravenous sedation with midazolam. The patient was closely monitored during the procedure using pulse oximetry in addition to clinical observation. US images of gallbladder and bile duct were obtained with the instrument placed in the first and second parts of duodenum and at the level of the distal antrum and pylorus. Biliary tract images were obtained at different angles by adjusting the position of the probe. The presence of stones or microlithiasis was noted, as was the presence of other pathologies. Stones were identified as hyperechoic structures casting an acoustic shadow. Hyperechoic, rather mobile images with or without posterior acoustic shadow were considered to be sludge or microlithiasis, based on standard US criteria.[9] The normal range of thickness of the gallbladder wall on EUS was considered to be 3 mm, and the diameter of the CBD, 6 mm or less.

Patients with biliary microlithiasis or gallbladder wall thickness on EUS were offered cholecystectomy. Preoperative ERCP and biliary sphincterotomy was also achieved for patients with dilated CBD, sludge in CBD, or increased level of alkaline phosphatase (ALP). However, in a few patients who refused or were considered unsuitable for cholecystectomy, biliary sphincterotomy was the only therapeutic approach. Cholecystectomy was performed laparoscopically in all except one who underwent open surgery. All patients were closely followed for recurrence of symptoms after the therapy.

Informed consent for the study and the endoscopic procedures was obtained from all patients. The study protocol was approved by the ethics committee of the Digestive Disease Research Center, Tehran University of Medical Sciences.

RESULTS

The study population included 14 males and 21 females with the mean ± SD age of 47.7 ± 13.1 years. EUS was performed successfully in all patients. EUS findings are summarized in Table 1 according to gender.

Table 1. Endosonographic findings in 35 patients with acute biliary-type abdominal pain and normal transabdominal ultrasonography according to gender

Endosonographic findings	Males (n = 14)	Females (n = 21)	Total (n = 35)
Gallbladder sludge/ small stones	12	21	33 (94.3%)
Gallbladder wall thickness	6	18	24 (68.6%)
Common bile duct sludge/small stones	3	18	21 (60%)
Dilated common bile duct (>6 mm)	0	3	3 (8.6%)

Gallbladder sludge and/or microlithiasis was evident in 33 (94.3%) patients as hyperechoic specks of calcification, with or without posterior acoustic shadowing readily distinguishable from the hypoechoic contents of normal gallbladder; among these, 20 patients had also thick-wall gallbladder.

Sludge and/or microlithiasis of the CBD was noted in 21 patients. Among them, 18 patients had normal CBD diameter and in 3, the diameter was greater than 6 mm.

Nine patients were dropped during the follow-up; of the remaining 26 patients (11 males and 15 females) were followed for an average of 9.2 months (range, 3–13 months). Of 26 patients, 4 (15.4%) were found to have elevated serum ALP levels and 3 (11.5%) had elevated aspartate aminotransferase and alanine aminotransferase levels.

Combined endoscopic biliary sphincterotomy and cholecystectomy was achieved in 13 (50%) patients. Ten patients (38.5%) underwent cholecystectomy alone, and 3 (11.5%) underwent biliary sphincterotomy alone.

ERCP with sphincterotomy was performed successfully in all 16 patients. Histology of all removed gallbladders revealed chronic cholecystitis. Meanwhile, cholestrolosis was found in three cases, of which two were verified by EUS prior to the surgery.

At the end of the follow-up, 25 (96.2%) patients remained symptom free. Types of therapeutic procedure and patient outcomes are shown in Table 2.

DISCUSSION

Evaluation of pancreatobiliary diseases continues to evolve as new diagnostic modalities are developed. EUS, a fairly recent development in biliary-tract imaging, has been proved to be a minimally invasive technique with a low morbidity and proven efficacy in the diagnosis of gallbladder and pancreas diseases.

Table 2. Types of therapeutic procedures and treatment outcomes in 26 patients who were followed after treatment

Type of treatment	No. of patients	Mean duration of follow-up ± SD (months)	No. (%) of responding patients*
Cholecystectomy alone	10	10.3 ± 1	10 (100)
Cholecystectomy plus ES	13	8.5 ± 3.2	12 (92)
ES alone	3	8 ± 3.5	3 (100)
Total	26	9.2 ± 2.6	25 (96.2)

ES = endoscopic biliary sphincterotomy.
*Number (%) of patients who became symptom free after the procedure was performed.

Lithiasis of the CBD and gallbladder is a frequent complication. The biochemical abnormalities and symptoms associated with these complications are neither sensitive nor sufficiently specific. The inadequacies of TUS and computed tomography for the diagnosis of microcholedocholithiasis and microcholelithiasis are now well known.[1] EUS, with its high-image resolution and close proximity to the biliary system during the examination, is considered to be superior to TUS for gallbladder imaging.

Patients presenting with recurrent biliary-type abdominal pain in whom conventional TUS is negative present a clinical challenge. These patients frequently undergo a wide range of different examinations in order to exclude choledocholithiasis, biliary dyskinesia, chronic pancreatitis, and peptic ulcer disease. These examinations may not only impose high expenses on the patients and society but also be associated with an increased risk of mortality and morbidity.

For patients with acute recurrent pancreatitis, the role of EUS for diagnosing microlithiasis of the gallbladder or CBD is obviously established.[10,11] Although the role of microlithiasis as a cause of acute recurrent pancreatitis[1,9,12] or idiopathic acute cholangitis[13] has been well established, to our knowledge there is only one study that has shown that EUS can identify biliary microlithiasis in patients with biliary-type pain and normal TUS.[8]

In the present study, EUS revealed microlithiasis or sludge in gallbladder in 33 of 35 examined patients. Choledocholithiasis was found in 20 patients. Following the therapeutic approaches, 96% of the patients became symptom free, a figure similar to the previous study regarding biliary pain due to microlithiasis.[8] Our study clearly supports the great value of EUS in the detection of cholelithiasis and choledocholithiasis in patients with negative TUS results.

Microscopic examination of bile also has been suggested for the diagnosis of microlithiasis. Bile microscopy is a relatively invasive procedure with an overall sensitivity of 65%–90%.[1] Its diagnostic yield varies with respect to the site of bile aspiration—greatest when bile is collected from the gallbladder and lowest when it is collected from the duodenum. In contrast to bile microscopy, EUS is less invasive and can accurately diagnose biliary microlithiasis. Thus, we believe that EUS is the best diagnostic method in patients who have biliary-type pain with normal TUS results and suspected microlithiasis.

Some critical points should be considered regarding our study. First, there may be a possible bias in selecting the patients. Another possibility of bias is that the EUS is an operator-dependent procedure.

Our small sample size should be kept in mind, but the major limitation probably is the fact that it was an uncontrolled trial. On the other hand, 13 patients underwent combined endoscopic biliary sphincterotomy/cholecystectomy, and it is unclear whether cholecystectomy alone was sufficient for these patients. However, despite these critical points, the high rate of response to the therapeutic procedures is in agreement with the effectiveness of our approach.

In summary, EUS seems to be a promising diagnostic modality in patients with a clinical suspicion of cholelithiasis and choledocholithiasis and a normal TUS results. Larger, long-term, controlled prospective studies are needed to form a better understanding of the role of EUS in detecting pathogenesis, clinical significance, and optimum form of therapy for patients with microlithiasis. In conclusion, in patients with biliary type abdominal pain and normal transabdominal ultrasonography, EUS is a useful diagnostic modality and it can influence the management plan.

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Prophylactic Cholecystectomy in Transplant Patients: A Decision Analysis

Lillian S. Kao, M.D., Christopher Flowers, M.D., M.S., David R. Flum, M.D., M.P.H.

Prophylactic laparoscopic cholecystectomy should be performed in solid organ transplant patients with asymptomatic cholelithiasis. Modeled, decision analytic techniques were used to evaluate the different management strategies for asymptomatic cholelithiasis in cardiac and pancreas/renal transplant recipients. The clinical outcomes of expectant management, pretransplantation prophylactic cholecystectomy, and posttransplantation prophylactic cholecystectomy were analyzed for each population. The probabilities and outcomes were derived form a pooled analysis of published studies. One- and two-way sensitivity and cost analyses were performed. Prophylactic posttransplantation cholecystectomy is favored for cardiac transplant recipients with asymptomatic cholelithiasis, resulting in 5:1000 deaths versus 80:1000 for pretransplantation cholecystectomy and 44:1000 for expectant management. In distinction, expectant management for asymptomatic cholelithiasis is favored in pancreas/renal transplant patients, resulting in 2:1000 deaths compared with 5:1000 for prophylactic cholecystectomy. After heart transplantation, a strategy of routine, prophylactic cholecystectomy is anticipated to result in a cost savings of $17,779 per quality-adjusted life-year. Prophylactic posttransplantation cholecystectomy is the preferred management strategy for cardiac transplant patients with incidental gallstones, resulting in decreased mortality and significant cost savings per quality-adjusted life-year. Expectant management is the preferred strategy for pancreas and/or kidney transplant recipients with asymptomatic cholelithiasis. (J GASTROINTEST SURG 2005;9:965–972)

KEY WORDS: Laparoscopic cholecystectomy, transplant recipients, immunosuppression, asymptomatic cholelithiasis, decision analysis

In the general population, the standard of treatment for asymptomatic gallstones is expectant management.[1,2] However, this strategy for solid organ transplant recipients has been questioned based on reports in the literature of an increased prevalence of gallstones in transplant patients,[3–6] increased risk of infectious morbidity from posttransplantation biliary complications due to immunosuppression,[7] and increased mortality associated with emergency cholecystectomy posttransplantation.[7–10] Previous recommendations have been based on limited case series and have encompassed the full range of options including expectant management,[6,11] routine screening with pretransplantation cholecystectomy,[8] and prophylactic cholecystectomy posttransplantation.[10,12,13] These different management strategies have not been systematically evaluated or compared.

A recent collective review of this subject found that while the baseline prevalence of cholelithiasis in solid organ transplant candidates is equivalent to that of the general adult population, there is an increased prevalence of gallstones after transplantation, a quicker progression to symptoms, and a fairly low rate of morbidity and mortality associated with elective surgery, either before or after the transplantation.[14] However, urgent posttransplantation cholecystectomy is associated with significant morbidity and mortality (44% and 37% for heart transplant patients[7,8,10,13,15–17] and 33% and 5.6% for renal transplant patients[18,19]). When there are multiple components of a medical/surgical decision, a formalized modeled analysis can aid in structuring the decision-making process and determine the preferred strategy. Because there are a number of competing variables that are involved in both the decision to

From the Department of Surgery (L.S.K.), LBJ General Hospital, University of Texas Health Science Center at Houston, Houston, Texas; and the Departments of Internal Medicine (C.F.) and Surgery (D.R.F.), University of Washington Medical Center, Seattle, Washington.
Reprint requests: Lillian S. Kao, M.D., Department of Surgery, University of Texas Health Science Center at Houston, 5656 Kelley Street, Suite 30S 62008, Houston, TX 77026. e-mail: Lillian.S.Kao@uth.tmc.edu

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.011

perform surgery and the timing of an operation in pretransplant patients with incidental cholelithiasis, we hypothesized that a decision analysis would help determine the situations when surgical intervention would be a favored strategy.

MATERIAL AND METHODS

Decision Model

Two decision models were developed using Decision Analysis software (Treeage Software Inc, Williamstown, MA) to compare pretransplantation prophylactic cholecystectomy, posttransplantation cholecystectomy, and expectant management of incidental gallstones. One model compares these management strategies for patients undergoing cardiac transplantation, and the other applies to patients receiving kidney and/or pancreas transplants. This analysis did not consider patients undergoing liver transplantation because the gallbladder is routinely removed during this procedure.

Transition probabilities and outcomes were derived from published sources and available primary data (Tables 1 and 2). In patients undergoing noncardiac solid organ transplantation, the probabilities for outcomes were identical for both pre- and post transplantation cholecystectomy, so in Model 2, these strategies have been consolidated to "prophylactic cholecystectomy."

Outcome Assessment and Sensitivity Analyses

The primary outcome measured was probability of death. One-way sensitivity analyses were conducted to evaluate the uncertainty in the model and to incorporate the full range of data from all sources. These analyses were performed by varying one parameter while holding the other fixed. Values were varied in the sensitivity analyses to include all values described in the literature. These ranges were selected to attempt to include the true variability in these estimates present across a variety of health care settings. Variables that had the greatest impact on the model were evaluated in two-way sensitivity analyses, varying these parameters through the full range of reported estimates while holding the other variables constant.

For analyses that suggested prophylactic cholecystectomy as the preferred strategy, an incremental cost-effectiveness analysis was performed using estimates of the cost of cholecystectomy provided in the literature.[20] Additional costs associated with the development of symptomatic cholelithiasis and other costs for patients undergoing emergency cholecystectomies were not considered in this analysis to provide a conservative bias. An estimated median survival of 8 years after cardiac transplantation[21,22] and a median quality of life score of 0.81[23] (with 1.0 representing perfect health) were used to compute the incremental cost per quality-adjusted life-year (QALY).

RESULTS

For cardiac transplant patients with incidental gallstones, the preferred management strategy was prophylactic posttransplantation cholecystectomy (Fig. 1 *A*, *B*). This strategy resulted in 5 deaths per 1000 patients compared with 80 per 1000 for pretransplantation cholecystectomy and 44 per 1000 for expectant management. The relatively high rate of mortality with pretransplantation cholecystectomy, the higher rate of mortality with posttransplantation emergent cholecystectomy, and the lower rates of mortality with elective or posttransplantation cholecystectomy were the most influential parameters in the complete model.

As depicted in Figure 1, *B*, in cardiac transplant patients, the main determinants of mortality for the expectant management were the likelihood of developing symptoms from gallstone disease posttransplantation (38%), the likelihood of requiring an

Table 1. Summary of variables used in cardiac analysis

Variable	Baseline estimate (%)	Range (%) (References)
Mortality rate (pretransplantation cholecystectomy)	8	0–33[3,8,31–33]
Mortality rate (posttransplantation, prophylactic cholecystectomy)*	0.05	0.01–3[7,9,10,13]
Mortality rate (emergency cholecystectomy posttransplantation)	37	0–43[7,8,10,13,15–17,34]
Mortality rate (posttransplantation elective cholecystectomy)	0.05	0.01–3[7,10,13]
Likelihood of developing posttransplantation biliary symptoms	38	6–58[4,6,11,13]
Likelihood of requiring an emergency cholecystectomy posttransplantation (emergency cholecystectomy posttransplantation)	25.8	14–41[7,8,10,13,15–17,34]

*No data are available on the mortality of patients undergoing prophylactic, posttransplantation cholecystectomy. The mortality rate and range were assumed to be the same as for patients undergoing posttransplantation elective cholecystectomy.

Table 2. Summary of variables used in kidney/pancreas analysis

Variable	Baseline estimate (%)	Range (%) (References)
Mortality rate (pretransplantation cholecystectomy)	0.05	0.01–3[18]
Mortality rate (posttransplantation, prophylactic cholecystectomy)*	0.05	0.01–3[19,35]
Mortality rate (emergency cholecystectomy posttransplantation)	5.6	0.05–17[18,19]
Mortality rate (posttransplantation elective cholecystectomy)	0.05	0.01–3[19,35]
Likelihood of developing posttransplantation biliary symptoms	13	No range[36]
Likelihood of requiring an emergency cholecystectomy posttransplantation	26.4	23–37.5[18,19]

*No data are available on the mortality of patients undergoing prophylactic, posttransplantation cholecystectomy. The mortality rate and range were assumed to be the same as for patients undergoing posttransplantation elective cholecystectomy.

emergent cholecystectomy if symptoms developed (30%), and the risk of death from an emergent cholecystectomy (63%). The mortality associated with elective posttransplantation cholecystectomy is less than 1% and therefore negligible in the model. A two-way sensitivity analysis was performed in order to evaluate the robustness of the model and was constructed by varying the rate of developing symptoms from biliary disease and the mortality rate associated with emergency cholecystectomy, the two most influential parameters for this arm of the decision analysis model (Fig. 3). Because of the lack of prospective data regarding the likelihood of developing symptoms from incidental gallstones posttransplantation, the model must be based on the best estimates from the literature, which span a wide range of values, from 6% to 58%.[4,6,11,13] The resultant graph results in two zones, one in which expectant management is favored (striped zone) and one in which prophylactic cholecystectomy is favored (hatched zone). Over wide variation in the model parameters, posttransplantation prophylactic cholecystectomy results in lower mortality than expectant management and therefore is the dominant or favored strategy. However, in certain situations, expectant management may be favored; that is, when the intersection of the x-axis value (mortality of emergent cholecystectomy) and the y-axis value (rate of symptom development) falls into the striped zone, expectant management results in a lower mortality rate compared with prophylactic cholecystectomy. For example, an institution with a mortality rate of 5% for emergency cholecystectomies and an incidence of posttransplantation biliary symptoms of 12% among their patients should practice a policy of expectant management.

Because in this analysis prophylactic cholecystectomy after heart transplantation was the favored strategy, we performed a cost-effectiveness analysis of this strategy to determine the incremental cost per QALY. Using cost estimates derived from a recently published review of the cost-effectiveness of various components of biliary surgery[20] and the expected outcomes from the base case model, we estimated the costs/QALY of a strategy of routine prophylactic cholecystectomy. Actuarial data indicate that the median survival after heart transplantation is 8 years with a patient-derived quality of life score of 0.8 (scale 0–1). Using this model a strategy of routine, prophylactic cholecystectomy after heart transplantation is associated with a cost of $115,000 per life saved and a cost of $17,779 per QALY.

For patients undergoing renal/pancreas transplantation, the favored strategy was expectant management rather than prophylactic cholecystectomy (Fig. 2 *A*, *B*). The mortality associated with expectant management resulted in 2 deaths per 1000 patients compared with 5 deaths per 1000 patients with prophylactic therapy. The low mortality rate associated with elective cholecystectomy in patients post–kidney/pancreas transplantation was the factor with the greatest influence on the modeled outcomes. A two-way sensitivity analysis using the mortality rate for emergency surgery (x-axis) and the rate of symptom development (y-axis) indicated that there were situations when alternatively prophylactic cholecystectomy was a favored strategy in this population (Fig. 4). For example, when the mortality rate for emergent cholecystectomy was greater than 17% and the rate of symptom development was greater than 35%, then prophylactic cholecystectomy was the dominant strategy. However, these values are well beyond those found in any clinical report and therefore are not likely to approximate most clinical settings.

DISCUSSION

Determining the best management strategy for asymptomatic gallstones in solid organ transplant recipients requires an appraisal of the probability that the gallstones will cause harm if left in situ counterbalanced with the risk that the cholecystectomy itself will cause harm. The options for incidental gallstone

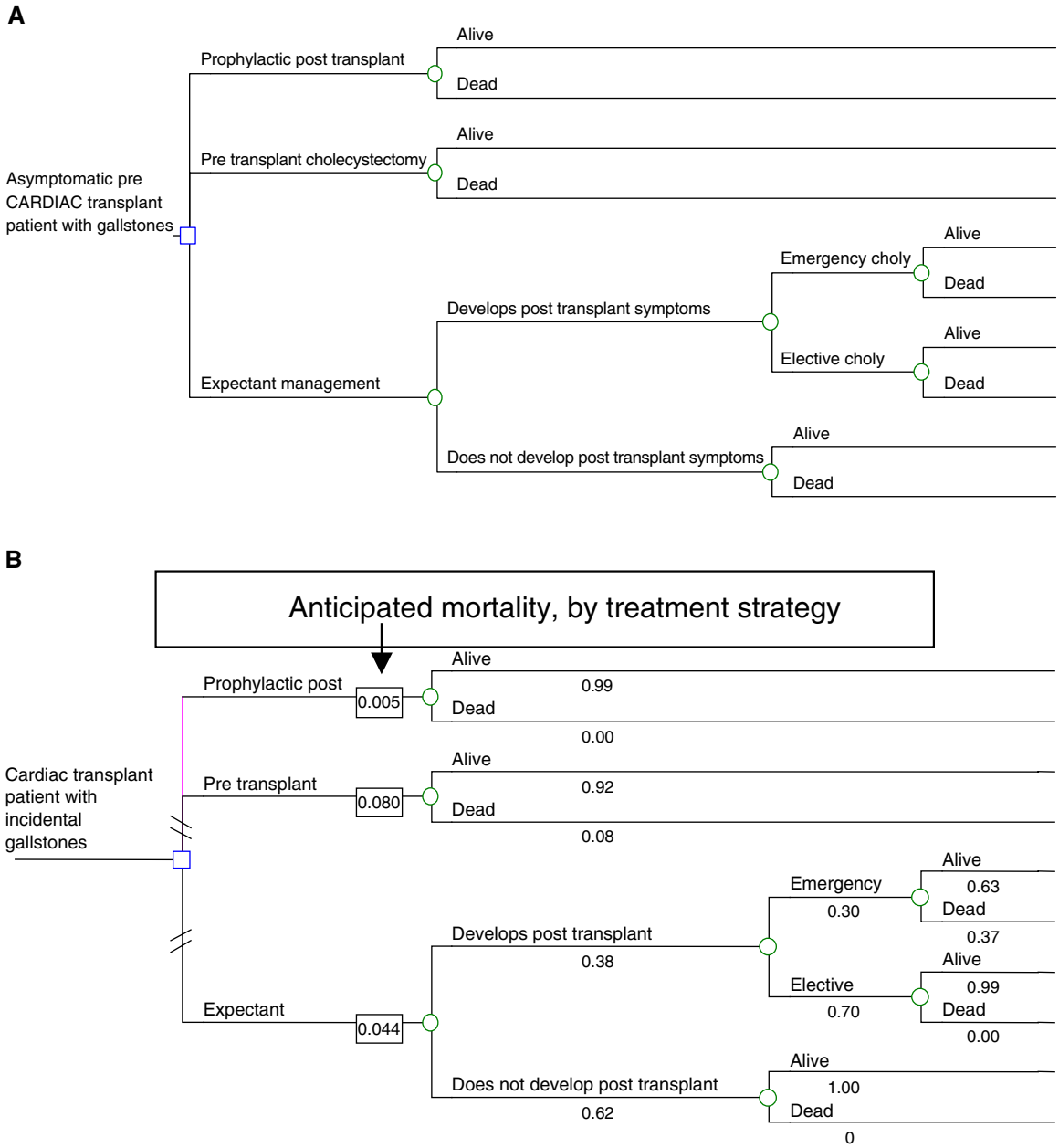

Fig. 1. (A) Decision model incorporating the three strategies for management of asymptomatic gallstones in cardiac transplant patients and the potential outcomes using each strategy. **(B)** The base-case estimates derived from the literature were inserted into the decision model in order to obtain the probability of death for each management strategy.

management include prophylactic cholecystectomy (either pre- or posttransplantation) versus expectant management. Despite the lack of consensus regarding the optimal treatment strategy, many transplantation programs incorporate or recommend routine ultrasonographic screening either pretransplantation,[3,6,10,11] posttransplantation,[9] or both.[4,5] Yet they do not have standardized guidelines for the management of incidentally detected stones. Because there is wide variability in the reported mortality rates associated with cholecystectomy at various stages of a transplant patient's life, the overall assessment of risk is difficult for clinicians to make for any given patient. In the absence of prospective data, modeled analyses such as this one offer an attractive alternative to "back of the envelope" estimates.

Although the base estimates were derived from the best available data, one critique of the analysis is that

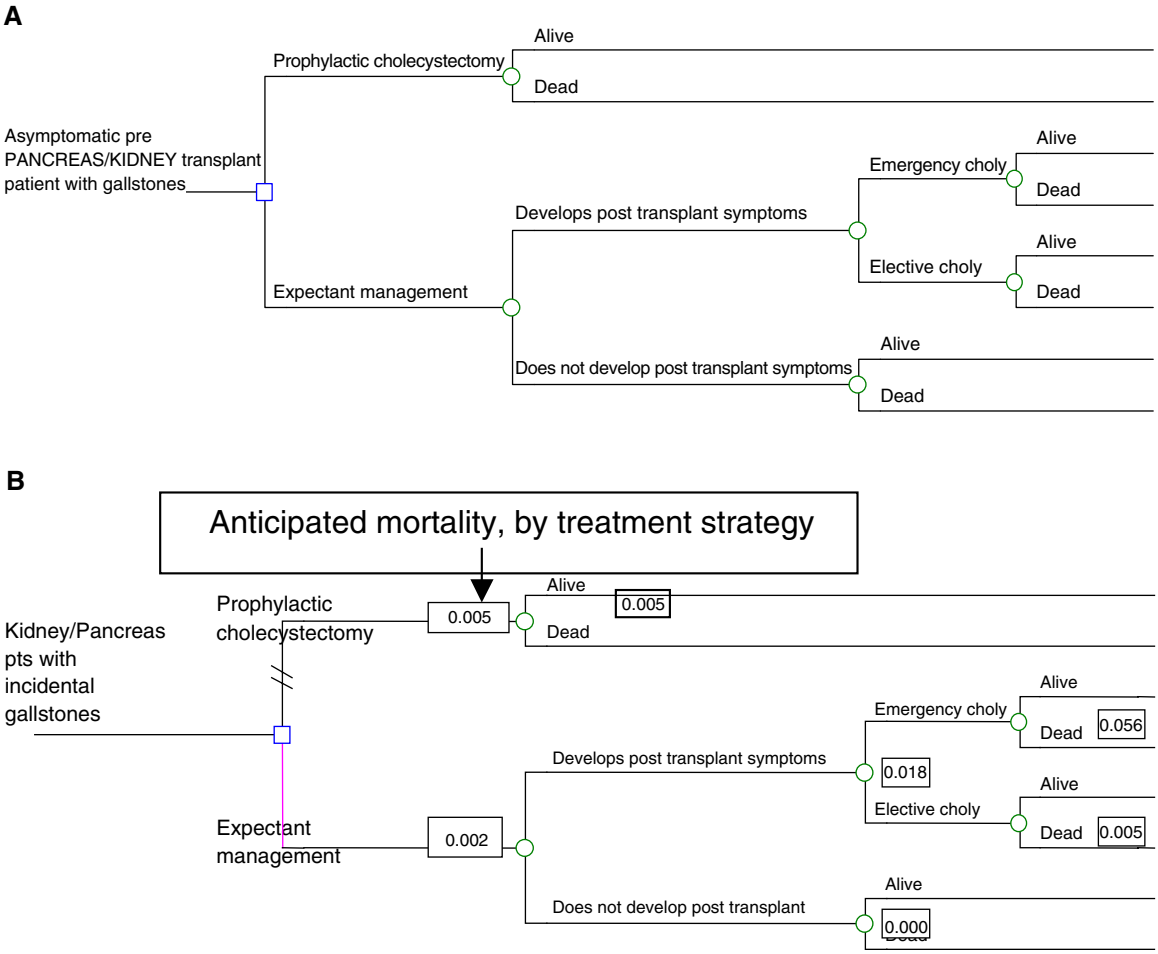

Fig. 2. (A) Decision model incorporating the strategies for management of asymptomatic gallstones in kidney/pancreas transplant patients and the potential outcomes using each strategy. Because the probabilities for pre- and posttransplantation prophylactic cholecystectomy were identical, these two strategies were consolidated into one arm, prophylactic cholecystectomy. Therefore, unlike the decision model for cardiac transplant patients, this model contains two management arms. **(B)** The base-case estimates derived from the literature were inserted into the decision model in order to obtain the probability of death for each management strategy.

the mortality rates were calculated from heterogeneous data from different time periods in the field of transplantation spanning more than a decade. Furthermore, much of the available data was derived from retrospective studies collected more than 15 years ago such that base estimates of mortality after emergent cholecystectomy exceeding 30% may no longer be realistic. Nonetheless, use of data from the most recent large case series still supports a strategy of posttransplantation cholecystectomy. Richardson et al.[9] evaluated 518 patients who underwent cardiac transplantation between 1985 and 2000. Excluding patients who died in the immediate posttransplantation period who would not have benefited from a strategy of prophylactic posttransplantation cholecystectomy, 2/24 (8%) of patients requiring emergent surgery for acute cholecystitis or pancreatitis died. The rate of progression of gallstones to symptoms was at least 33% based upon the percentage of patients who progressed to cholecystectomy. Based on the two-way sensitivity analysis depicted in Figure 3, prophylactic posttransplantation cholecystectomy is still the favored management strategy for that scenario. Given the advancements in immunosuppression, increased selectivity of donors and recipients, and improvements in surgical technique, survival after cardiac transplantation is increasing.[22] Eventually, when the mortality of emergent cholecystectomy for acute cholecystitis approaches that for the general population, expectant management may become the favored strategy.

Although this study attempted to encompass a broad range of plausible clinical strategies, another

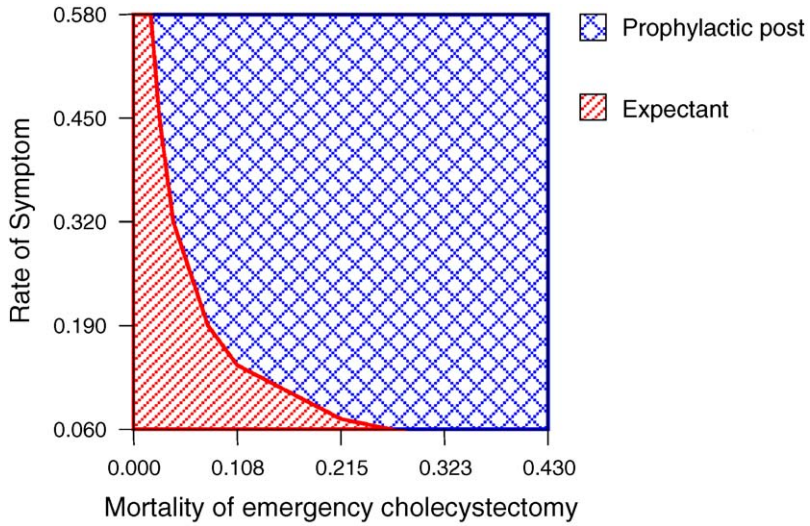

Fig. 3. The two dominant determinants influencing gallstone management strategy in cardiac transplant patients were mortality of emergent cholecystectomy (horizontal axis) and the rate of progression to symptoms (vertical axis). The *striped area* represents the range of mortality and symptom progression rates for which expectant management is the dominant strategy, while the *hatched area* represents the range of mortality and symptom progression rates for which prophylactic posttransplantation cholecystectomy is the dominant strategy. If the mortality rate for emergent cholecystectomy were less than 5%, then expectant management would be favored regardless of the rate of progression to symptoms. On the other hand, if the rate of progression to symptoms were greater than 60%, then prophylactic cholecystectomy would be the preferred strategy. Using the base estimates derived from the literature (37% and 38% for mortality of emergent cholecystectomy and rate of progression to symptoms, respectively), prophylactic posttransplantation cholecystectomy is the preferred strategy for cardiac transplant patients.

limitation of modeled analysis is that the base estimates may not reflect all clinical situations. However, the use of sensitivity analyses allows for the incorporation of uncertainty in the parameters into the model. Thus, while the base-case values and the reasonable range of values supported prophylactic post–cardiac transplantation cholecystectomy, this study also detailed the clinical situations when alternative strategies would be recommended such that each institution can apply actual values to the model to determine an individualized preferred treatment strategy.

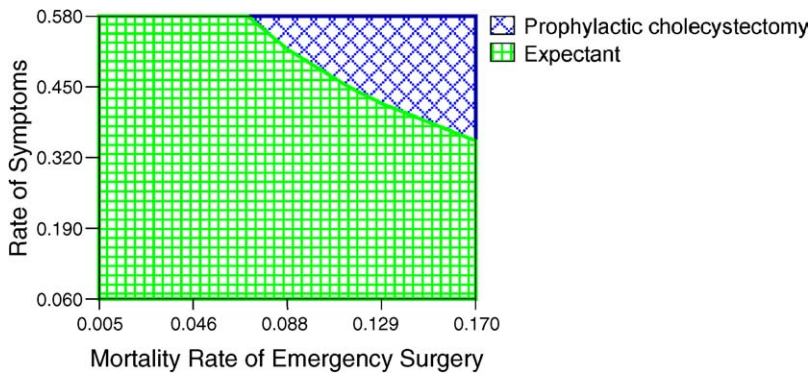

Fig. 4. The two dominant determinants influencing gallstone management strategy in kidney/pancreas transplant recipients were mortality rate of emergency cholecystectomy (horizontal axis) and the rate of progression to symptoms (vertical axis). For kidney/pancreas transplant patients, expectant management (represented by the checkered area) is the dominant strategy over a wide range of rates of mortality for emergent cholecystectomy and symptom progression. Using the base estimates derived from the literature (5.6% and 26% for mortality of emergent cholecystectomy and rate of symptom progression, respectively), expectant management is the preferred strategy.

The results of the decision analysis should not be interpreted independent of the literature. The modeled analysis should be used in conjunction with more up-to-date evidence, as it becomes available. A recent retrospective chart review was performed of patients receiving renal transplantation between 1994 and 2000.[24] The authors concluded that prophylactic pre–renal transplantation cholecystectomy was not warranted and that there was no increase in morbidity related to gallstones posttransplantation. The results of this study are consistent with our model, which demonstrated expectant management to be the dominant strategy for renal transplant patients.

Another limitation is that the model does not address all of the issues that arise in treating solid organ transplant recipients with asymptomatic gallstones such as minimum frequency for ultrasonographic screening or optimum timing for posttransplantation cholecystectomy in cardiac transplant recipients. Based on a review of the literature[14] and the results of this decision analysis, prophylactic cholecystectomy should be performed after transplantation, before the development of symptoms, and after the initial recovery period. Because of higher levels of immunosuppression, there is an increased risk of gastrointestinal complications within the first 6 months of cholecystectomy, and if required, surgical intervention should be performed aggressively.[25] However, because higher levels of immunosuppression are associated with increased surgical morbidity and mortality,[7,25,26] prophylactic cholecystectomy should probably be deferred until after the initial recovery period. Of note, the overall strategy of performing prophylactic cholecystectomy will not benefit patients who develop severe complications of biliary disease early in the posttransplantation period (acute cholecystitis and pancreatitis)[9]; these patients have a significantly higher mortality due to sepsis and multiple organ failure.[7,9] Further studies are still necessary to better address these remaining issues.

There are several other limitations to this study design, one of which is that multiple assumptions are incorporated into the structure of the model. As in any modeled analysis, the base-case values derived from the assumptions influence model outcomes. One assumption of the model is that there are no deaths associated with gallbladder disease that is not treated by cholecystectomy and that all patients with symptoms will undergo cholecystectomy. Furthermore, it assumes a constant rate of symptom development over time and that there is no difference in transplantation-related survival based on biliary disease. This model assumes a stable rate of posttransplantation survival regardless of management strategy. Last, the model assumes that a need for emergency cholecystectomy and symptomatic biliary disease has no impact on costs and quality of life beyond the cost of the cholecystectomy itself.

Given the currently available data, post–cardiac transplantation prophylactic cholecystectomy appears to be a reasonable strategy. When recommending the prophylactic use of cholecystectomy, the cost implications should be addressed. From a cost perspective, applying a strategy of routine cholecystectomy in post-cardiac transplantation patients may also be reasonable. At $17,779/QALY, prophylactic cholecystectomy appears to be a cost-effective intervention, given that interventions resulting in a cost-effectiveness ratio of less than $50,000 per QALY are generally considered to be acceptable.[27–29] Comparable strategies that have been deemed cost-effective include gastric bypass surgery to prevent the complications of morbid obesity (11,000 pounds/QALY or ~$19,000/QALY)[30] and use of intraoperative cholangiography to prevent common bile duct injury ($13,500/QALY).[20]

In conclusion, for patients undergoing kidney or pancreas transplantation found to have incidental gallstones, expectant management is favored. However, among patients undergoing cardiac transplantation, prophylactic posttransplantation cholecystectomy appears to reduce the risk of biliary tract–related mortality. Our study also indicates that routine post–cardiac transplantation cholecystectomy provides benefits to this population that justifies its financial costs.

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The Real Value of Lower Esophageal Sphincter Measurement for Predicting Acid Gastroesophageal Reflux or Barrett's Esophagus

Oscar Alonso, M.D., Diego Hernández, M.D., Enrique Moreno, M.D., F.A.C.S., Alejandro Manrique, M.D., Almudena Moreno, M.D., Álvaro García-Sesma, M.D., Jorge Calvo, M.D.

The study goal was to ascertain the true value of lower esophageal sphincter measurement in order to establish the risk of presenting gastroesophageal reflux or Barrett's esophagus. Of 671 patients assessed for symptoms of gastroesophageal reflux, 459 were included in a prospective study, practicing esophagogastroscopy, esophageal manometry, and 24-hour pH-metry. The risks of presenting a pathologic DeMeester score or Barrett's esophagus were estimated according to different values for the lower esophageal sphincter parameters. The risk of a pathologic DeMeester score only increased when pressure was less than 6 mm Hg, total length was less than 2 cm, or abdominal length was less than 1 cm; regardless of which parameter was affected, the risk being greater when the three parameters were altered (odds ratio = 2.4, 3.1, and 4 for one, two, and three altered parameters). Male sex, sphincter pressure, and DeMeester score were associated with Barrett's esophagus ($P < 0.05$) but not total or abdominal length. Pressure and total and abdominal lengths have a similar influence over establishing the risk of pathologic acid reflux, but only pressure may indicate the risk of Barrett's esophagus.
(J Gastrointest Surg 2005;9:973–979)

Key words: Manometry, pH monitoring, gastroesophageal reflux, Barrett

The structural characteristics of the lower esophageal sphincter (LES) play a fundamental role in the physiopathology of gastroesophageal reflux (GER). Manometry is considered a key test in the study of GER, because it enables the characteristics of the LES to be established, to estimate the risk of GER and its probable response to medical treatment, and to evaluate the motility of the esophageal body, with a view to selecting the most suitable surgical technique.[1] Many studies have shown that the risk of pathologic acid GER increases when a structural defect of the LES exists.[1–3] In general, a structural defect of the LES is considered to be when pressure at rest (PR), total length (TL), and/or abdominal length (AL) are below 6 mm Hg, 2 cm, or 1 cm, respectively, regardless of which or how many of these three structural parameters are altered.[1–4] Nevertheless, it is not precisely known whether any of these three structural parameters of the LES are more important than the other two in the physiopathology of GER nor what is the difference in the risk between there being one single altered parameter or the three being affected. We also know that pathologic GER increases the risk of Barrett's esophagus and that these patients frequently have some structural defect of the LES.[4,5] However, pH-metry does not detect pathologic GER in all subjects with a structural defect, nor does endoscopy always detect Barrett's esophagus. Can the risk of pathologic GER or Barrett's esophagus be predicted from the structure of the LES? How reliably? How many subjects with normal manometry have pathologic GER or Barrett's esophagus? How many subjects with structural defects do not have pathologic GER or Barrett's esophagus? The objective of this study was to ascertain the true value of manometry, in order to establish the risk of presenting GER or Barrett's esophagus on the basis of LES values, as well as the effect of each one of the three LES parameters on that risk.

From the Department of Surgery and Abdominal Organ Transplantation, "12 de Octubre" University Hospital, Madrid, Spain.
Reprint requests: Dr. Oscar Alonso, Servicio de Cirugía Digestiva y Trasplante de Órganos Abdominales, Hospital "12 de Octubre," 4ª planta, Avenida de Córdoba Km 5.4, Madrid 28041, Spain. e-mail: montsemc@jazzfree.com

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.013

MATERIAL AND METHODS

Between January 1993 and January 2004, 671 adult patients (>14 years old) were admitted to our service for study of GER disease. On the basis of the symptomatology and response to treatment, in 459 cases a complete study using esophagogastroscopy, stationary esophageal manometry, and 24-hour pH-metry was indicated and undertaken in this order. These 459 subjects were included in a prospective study in order to analyze the capacity to predict the existence of pathologic acid reflux or Barrett's esophagus from LES manometric values. For this purpose, the following variables were collected: age, gender, presence of Barrett's esophagus in endoscopy, PR, TL, and AL values for the LES, and DeMeester score. All of the manometries and pH-metries were undertaken by the same surgeon, who did not know the result of the endoscopy at the moment of undertaking these, in order to avoid the result influencing his interpretation of the tests.

Esophagogastroscopy

A flexible esophagogastroscopy model Olympus GIF-1T or 2-T series (Lake Success, NY) was used. The presence or otherwise of esophagitis was inspected, as well as columnar epithelium, considering the length in centimeters. For the histopathologic study, biopsy samples were taken of the four quadrants every 2 cm of columnar epithelium and in regions suspected of presenting Barrett's esophagus. The histologic study was undertaken by the same pathologist. Barrett's esophagus was defined as substitution of the normal stratified squamous epithelium for a columnar epithelium, regardless of its length but present during endoscopy, and specialized intestinal metaplasia on the biopsy sample.

Stationary Manometry

Manometry was undertaken following the technique of stationary withdrawal described previously,[6–8] using a polygraph (Synectics Medical, Inc, Irving, TX) connected to a personal computer. For this study PR, TL, and AL values were taken. On the basis of the results of a published study undertaken in our laboratory with 24 healthy subjects,[6,8] we consider that the PR, TL, and AL variables were normal when 10 mm Hg or greater, 3 cm or greater, and 2 cm or greater, respectively; "diminished" when these values were between 6 and 10 mm Hg, 2 and 3 cm, and 1 and 2 cm, respectively; and "very diminished" when they were less than 6 mm Hg, less than 2 cm, and less than 1 cm, respectively. We use the term "mechanically deficient" LES when one of the parameters is diminished, and "mechanically incompetent" when at least one is very diminished.

Ambulatory 24-Hour Ph-Metry

The 24-hour monitoring of esophageal pH was undertaken with a crystal (Mettler-Toledo, Urdorf, Switzerland) or an antimony (Synectics Medical, Stockholm, Sweden) microelectrode (by date undertaken), placed 5 cm above the upper rim of the LES, defined manometrically. (In order to verify correct placement of the probe, lateral radiography of the thorax was undertaken.) Any medication that interfered with gastrointestinal motility or gastric secretion had been suspended 48 hours earlier. The readings stored in a portable recorder (Synectics Medical, Inc.) were entered into a personal computer for analysis using a computing program (Gastrosoft Inc., Dallas, TX) that calculated the score previously described by Jonson and DeMeester. The plots were also revised visually. Based on the results of the study with 24 healthy subjects already mentioned,[6,9] it was considered that the DeMeester score was pathologic when it was greater than 15.5 (95th percentile).

Statistical Analysis

First, a univariate and multivariate study was run on the variables associated with a pathologic DeMeester score and Barrett's esophagus. The prevalence of both pathologic DeMeester score and Barrett's esophagus was then analyzed for different groups of subjects, depending on the values of the three LES parameters (diminished, very diminished, one, two, or three altered parameters, etc.) and was compared with that of subjects with normal values for the three parameters. The risk of presenting a pathologic DeMeester score or Barrett's esophagus was calculated, depending on the different possible values of the LES parameters. Last, we calculated the sensitivity, specificity, and positive and negative predictive values (S, SP, PPV, and NPV, respectively) of different changes in LES (diminished or very diminished pressure, all three parameters very diminished, etc.) in order to detect pathologic DeMeester score or Barrett's esophagus. Quantitative variables were expressed as a mean and standard deviation, and the qualitative variables as percentages. In order to compare quantitative variables, the Student's *t* test was used, and for qualitative variables, the χ^2 test (with Fisher correction where necessary) was used. The multivariate analysis was undertaken using logistic regression analysis for "pathologic DeMeester score" dependent qualitative variables (first) and "Barrett's esophagus" (later). The confidence level was 95%. It was considered that

$P < 0.05$ was statistically significant. The estimation of the risk of pathologic DeMeester score or Barrett's esophagus was undertaken using the odds ratio (confidence interval 95%). The analysis was undertaken with the statistical program SPSS for Windows version 9.0.

RESULTS

Of the 459 patients studied, 212 (46%) were male and 247 (54%) were female. The mean age was 48.7 ± 17 (16–79) years. Esophageal manometry showed that in 117 cases (25%), the three LES parameters were normal; 144 (31%) presented one or more diminished parameter; and 198 (43%) had one extremely diminished parameter. pH-metry showed pathologic DeMeester score in 284 (62%) patients. The esophagoscopy found Barrett's esophagus in 58 subjects (12% of 459; 8% of the 671 patients who consulted for symptoms of GER).

Capacity to Predict Pathologic Acid GER on the Basis of the Three LES Structural Parameters

Among the subjects with a pathologic DeMeester score, the PR and TL (9.9 ± 7.1 mm Hg and 3.1 ± 1.4 cm) were significantly lower than in subjects with normal DeMeester score (11.8 ± 6.8 mm Hg and 3.4 ± 1.2 cm) ($P < 0.05$). The AL was also lower (1.1 ± 2.2 versus 1.5 ± 2.4 cm), but the difference was not statistically significant ($P = 0.093$). The average age was higher in subjects with pathologic DeMeester score (46.1 versus 37.5 years; $P < 0.001$), as was the percentage of men (72.3% versus 43.1%; $P < 0.001$). In the multivariate analysis, PR, TL, age, and male gender variables were associated independently with the existence of a pathologic DeMeester score ($P < 0.05$) but not AL.

The risk of presenting a pathologic DeMeester score on the basis of the individual value of each LES parameter is shown in Table 1. Total length was the parameter that least frequently was found to be changed. Among the subjects with diminished PR, the percentage of patients with a pathologic DeMeester score did not increase significantly in comparison with those who had normal PR. The same occurred between the subjects with diminished TL or AL. Only when PR, TL, or AL was very diminished did the risk of presenting a pathologic DeMeester score increase, this being slightly higher when the TL was very diminished (odds ratio = 2.4; 2.8 and 2.3, respectively). Table 2 shows the S, SP, PPV, and NPV for each LES parameter considered individually, in order to detect a pathologic DeMeester score. It was observed that the PPV and SP were somewhat higher when the TL was very diminished, but S was lower.

When we analyzed the ability to predict a pathologic DeMeester score on the basis of PR, TL, and AL values taken together, the result was as follows: of the 117 subjects who had normal values for the three parameters, 51% had a pathologic DeMeester score on pH-metry. When none of the three parameters were very diminished, the percentage of patients with pathologic DeMeester score did not increase significantly, even when the three parameters were diminished (data not shown). Only when one of the parameters was very diminished did the risk of presenting a pathologic DeMeester score increase. This was greater with the greater number of very diminished parameters (Table 3). Among the subjects with only one very diminished parameter, the percentage who presented a pathologic DeMeester score on pH-metry was similar, regardless of whether it was PR, TL, or AL that was altered. The same was the case when two parameters were very diminished. Table 4 shows the S, SP, PPV, and NPV of one, two, or three very diminished parameters in detecting a pathologic DeMeester score.

Table 1. Risk of presenting a DeMeester score > 15.5 depending on the individual lower esophageal sphincter value of pressure at rest (PR), total length (TL), and abdominal length (AL)

	n	Normal DS (%)	DS > 15.5 (%)	P*	OR (95% Confidence Interval)
PR ⩾ 10 mm Hg	206	45.3	54.7		
PR = 6–10 mm Hg	129	36.9	63.1	0.125	
PR < 6 mm Hg	124	25.6	74.4	<0.001	2.4 (1.5–3.9)
TL ⩾ 3 cm	272	43.5	56.5		
TL = 2–3 cm	106	35.5	64.5	0.148	
TL < 2 cm	81	21.4	78.6	<0.001	2.8 (1.6–5)
AL ⩾ 2 cm	216	43.1	56.9		
AL = 1–2 cm	137	40.9	59.1	0.686	
AL < 1 cm	106	24.5	75.5	0.001	2.3 (1.4–3.9)

DS = DeMeester score; OR = odds ratio.
*Compared with normal values for PR, TL, or Al.

Table 2. Sensitivity, specificity, and predictive values for each structural parameter of lower esophageal sphincter observed individually

	S (%)	SP (%)	PPV (%)	NPV (%)
PR = 6–10 mm Hg	41	67	63	45
PR < 6 mm Hg	44	75	74	45
TL = 2–3 cm	31	75	65	43
TL < 2 cm	30	87	79	43
AL = 1–2 cm	40	62	59	43
AL < 1 cm	39	78	75	43

S = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; PR = pressure at rest; TL = total length; AL = abdominal length.

Table 4. Sensitivity, specificity, and predictive values of one, two, or three very diminished structural parameters of lower esophageal sphincter to detect DeMeester score > 15.5

No. of Very Diminished Parameters	S (%)	SP (%)	PPV (%)	NPV (%)
One, two, or three	71	52	75	49
One	58	63	72	49
Two	21	88	77	39
Three	12	94	81	36

S = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value.

Ability to Predict Barrett's Esophagus on the Basis of the Three LES Structural Parameters

Of the 58 subjects with Barrett's esophagus, in 10 cases (17%) PR, TL, and AL were normal, in 13 (22%) one or more of the three parameters were diminished, and in 35 cases (60%) one of the three parameters was very diminished (in subjects with no Barrett's esophagus, these percentages were 30%, 27%, and 43%, respectively; $P = 0.082$). The mean pressure was significantly lower in subjects with Barrett's esophagus (7.9 ± 5.4 versus 10.7 ± 7.1 mm Hg; $P < 0.01$) but not the TL (3 ± 1.4 versus 3.2 ± 1.3 cm) or the AL (1.4 ± 1.5 versus 1.3 ± 2.2 cm). pH-metry showed pathologic acid GER in 49 cases (79%), a significantly higher percentage than for subjects with no Barrett's (55%; $P < 0.001$). The mean DeMeester score was 66 ± 65 in the former case and 33 ± 41 in the latter ($P < 0.001$), and when only subjects with pathologic DeMeester score were considered, this was 82 ± 31 in the former case and 55 ± 26 in the latter ($P < 0.01$). Age was higher in subjects with Barrett's (49.7 versus 41.2 years; $P < 0.01$), as was the percentage of men (72% versus 43%; $P < 0.001$). The multivariate analysis showed that PR, male gender, and DeMeester score were associated independently with the presence of Barrett's esophagus ($P < 0.05$).

The risk of presenting Barrett's esophagus at the time of manometry, on the basis of the individual value of each LES parameter, is shown in Table 5. The percentage of subjects with Barrett's was significantly higher among those who had very diminished PR (19.6% compared with 7.6% in subjects with normal PR; $P < 0.001$). It was also higher when TL ($P < 0.05$) or AL (not significant) was diminished but not when these were very diminished.

When we considered PR, TL, and AL values jointly, among the subjects with one, two, or three diminished parameters, the percentage of subjects with Barrett's did not increase significantly (data not shown). Among the subjects with any very diminished parameters (Table 6), this percentage only increased significantly when there was one very diminished parameter and this was PR. This did not increase neither when TL or AL was very diminished, when PR was greater than 6 mm Hg, nor when there were two or three very diminished parameters. Among subjects with PR less than 6 mm Hg, TL of 2 to 3 cm, and AL of 1 to 2 cm (n = 25), 36% of cases presented Barrett's esophagus ($P < 0.001$; odds ratio = 6 (2.1–17.1).

S, SP, PPV, and NPV for detecting Barrett's esophagus from the variables associated with this were as follows: PR less than 6 mm Hg: 44%, 62%, 19%, and 92%, respectively; TL of 2 to 3 cm: 42%,

Table 3. Risk of presenting a DeMeester score > 15.5 depending on the number of lower esophageal sphincter structural parameters with very diminished values

No. of Very Diminished Parameters	n	Normal DS (%)	DS > 15.5 (%)	P*	OR (95% Confidence Interval)
One	116	28	72	.001	2.4 (1.4–4.1)
Two	51	23	77	.002	3.1 (1.5–6.5)
Three	31	19	80	.003	4 (1.5–10.4)
Normal PR, TL, and AL	117	49	51		

DS = DeMeester score; OR = odds ratio; PR = pressure at rest; TL = total length; AL = abdominal length.
*Compared with subjects with normal PR, TL, or AL.

Table 5. Risk of presenting with Barrett's esophagus, depending on the individual value of pressure at rest (PR), total length (TL), and abdominal length (AL) for lower esophageal sphincter

	n	No Barrett's Esophagus (%)	Barrett's Esophagus (%)	*P**	OR (95% Confidence Interval)
PR ⩾ 10 mm Hg	206	92.4	7.6		
PR = 6–10 mm Hg	129	90	10	.493	
PR < 6 mm Hg	124	80.4	19.6	<.001	2.9 (1.6–5.6)
TL ⩾ 3 cm	272	90.7	9.3		
TL = 2–3 cm	106	83.6	16.4	.031	1.9 (1–3.5)
TL < 2 cm	81	87.5	12.5	.355	
AL ⩾ 2 cm	216	90.3	9.7		
AL = 1–2 cm	137	85	15	.077	
AL < 1 cm	106	89.8	10.2	.892	

OR = odds ratio.
*Compared with normal values for PR, TL, or AL.

73%, 16%, and 91%, respectively; and one very diminished parameter: 73%, 51%, 19%, and 92%, respectively.

DISCUSSION

PR and TL and AL parameters that we considered as normal on the basis of the study with 24 healthy subjects were similar to the values considered by other authors.[3,6,10–12] This study shows that these values make it possible to detect a moderate percentage of patients with a higher risk of presenting pathologic GER. However, there are many limitations in view of the S, SP, PPV, and NPV. When we considered PR, TL, and AL individually, the three parameters established a similar risk of pathologic GER when these were very diminished. Although there were no significant differences in AL in the univariate and multivariate analyses, the fact of having an AL less than 1 cm established a risk of pathologic DeMeester score similar to that of having a PR less than 6 mm Hg.

Only TL determined a somewhat higher risk, which, linked to the fact that this was the parameter that was least frequently altered, made the S somewhat lower and the SP and PPV somewhat higher. Among the subjects with normal DeMeester score, only 13% would have a TL less than 2 cm, whereas 25% would have PR less than 6 mm Hg. When TL was less than 2 cm, 80% would have pathologic DeMeester score, whereas when PR less than 6 mm Hg or AL less than 1 cm, 75% would have a pathologic DeMeester score. This may be due to the fact that in subjects with small hiatus hernias, it is sometimes impossible, within the region of high pressure, to differentiate between a rise in pressure due to LES and a rise due to esophageal hiatus of the diaphragm. This artificially prolongs the TL of the LES. Therefore, TL would be the least reliable parameter. Nevertheless, when TL is diminished, there is greater probability of the subject having pathologic GER.

When we considered the three parameters jointly, the test's sensitivity increased if we considered the test positive when any of the parameters was very diminished, even when the NPV remained low.

Table 6. Risk of presenting with Barrett's esophagus, depending on the number of lower esophagus sphincter structural parameters with very diminished values

No. of Very Diminished Parameters	n	No Barrett's Esophagus (%)	Barrett's Esophagus (%)	*P**	OR (95% Confidence Interval)
One	116	81	19	.007	2.8 (1.3–6)
PR < 6 mm Hg	76	77	23	.001	3.4 (1.5–7.7)
TL < 2 cm	9	82	18	.249	
AL < 1 cm	33	89	11	.549	
Two	51	90	10	.663	
Three	31	85	15	.229	
PR. TL, and AL normal	117	92	8		

OR = odds ratio; PR = pressure at rest; TL = total length; AL = abdominal length.
*Compared with subjects with normal PR, TL, or AL.

SP and PPV increased when the number of very diminished parameters increased but at the expense of a decrease in S. The fact is that a manometrically normal LES is of no value in being able to rule out GER. In up to 51% of subjects with the three parameters normal, pH-metry showed pathologic acid GER. When any of the parameters was diminished (mechanically deficient LES), the risk of pathologic GER did not increase significantly. Therefore, even when the three parameters are diminished, if none of them is very diminished, we cannot say whether this subject is at greater risk of pathologic GER than another with normal LES. Only in subjects with any very diminished parameter (PR <6 mm Hg, TL <2 cm, or AL <1 cm), we can say that the risk of pathologic GER is greater. In view of the results, we can talk of mechanically incompetent LES with a risk of GER when there is one very diminished parameter, a high risk of GER when there are two, and a very high risk of GER when PR, TL, and AL are very diminished. As we have said, PPV and SP rise if we consider the test positive with two or three very diminished parameters but a high percentage of false-positive results is maintained (19% of subjects with three very diminished parameters did not have pathologic GER on pH-metry), and S greatly decreased (only 12% of subjects with pathologic GER will have all three parameters very diminished). NPV was low in any case. Therefore, manometry may detect a percentage of subjects with a higher risk of pathologic GER (subjects with one or more very diminished parameters) but it must be borne in mind that up to 25% of these subjects will have normal pH-metry. With that NPV, in no case can pathologic GER be ruled out when manometry is normal.

Among subjects with Barrett's esophagus, 83% had some alteration in the LES, although in only 60% of cases could we talk of mechanically incompetent LES, in contrast to the DeMeester et al.[4] study in which 100% of the subjects with Barrett's had some structural defect of the LES. It would be logical to think that if the three LES structural parameters have a similar influence in establishing the risk of GER, this would be the same for Barrett's esophagus, or that there is no structural association between LES and Barrett's esophagus, because other factors exist that affect the physiopathology of Barrett's.[7,13–15] Nevertheless, this was not the case. Pressure was the only LES parameter, along with male gender and DeMeester score, that was associated with Barrett's esophagus in the univariate and multivariate study. Moreover, the subjects with very diminished PR and normal TL and AL were the only ones in which the prevalence of Barrett's was significantly higher. Curiously, the percentage of subjects with Barrett's among those who had two or three very diminished parameters was not significantly higher. Apparently PR has more influence than TL or AL over the risk of Barrett's esophagus. This may be explained in the following way: PR usually is affected at the same time as TL and AL. PR decreases as a consequence of a progressive decrease in TL and/or AL. In the subjects with Barrett's, it seems that PR is affected before TL and AL, that is to say, there may be primary involvement of pressure (functional change) not secondary to the structural defect of the LES smooth musculature (lower TL) and to the lesser influence of abdominal pressure (less AL) (anatomic change).

Given that we know the importance of biliary reflux in the physiopathology of Barrett's esophagus,[13,14,16,17] this functional alteration of the LES may be accompanied by an alteration, also functional, in the pressure of the pylorus, this all favoring duodenogastric and gastroesophageal reflux. Lower PR of the LES, with normal TL and AL, or only diminished, could reflect diminished pressure of the pylorus. Therefore, in subjects with these LES structural characteristics, Barrett's esophagus should be ruled out, and even if this is not detected, surgical treatment considered, if the pH-metry is pathologic, not treated only with antacids or antisecretors. Along with LES PR, male gender and DeMeester score were associated with Barrett's esophagus in the multivariate analysis, a result that coincides with that of other authors.[18,19] Therefore, male gender and a high DeMeester score (>60) will support the need for surgical treatment.

Despite the fact that LES PR appears to play a major role in the physiopathology of Barrett's esophagus, the PPV of an LES PR less than 6 mm Hg is not very high for predicting Barrett's esophagus. If a subject's PR is less than 6 mm Hg, he or she is more likely to have Barrett's than is a subject with normal LES, but one would have to bear in mind other factors (age, gender, DeMeester score, esophageal motility, biliary reflux) in order to ascertain with greater precision the risk of Barrett's esophagus and act accordingly.

CONCLUSION

The values of LES parameters considered internationally as normal and pathologic make it possible to detect a moderate percentage of subjects at greater risk of presenting pathologic GER. Nevertheless, the low NPV of manometry must be underlined. This means that 24-hour pH-metry must be undertaken on all subjects studied for GER clinical symptoms, even if manometry is normal. In subjects with LES

PR less than 6 mm Hg with normal or diminished TL and/or AL, the risk of Barrett's esophagus is greater. This must be born in mind for treatment and follow-up, above all in males with DeMeester score greater than 60.

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Closed Rectopexy With Transanal Resection for Complete Rectal Prolapse in Adults

Ahmed E. Lasheen, M.D., Samy Khalifa, M.D., Salah M. El Askry, M.D., Awni A. Elzeftawy, M.D.

Many techniques have been described for repair of complete rectal prolapse in adults. The results of abdominal approaches are superior to those of perineal approaches, but they carry the risks of major abdominal surgery. Twenty-seven patients (15 females and 12 males) were included in this study, with a mean age of 46 years. Nine of these patients had fecal incontinence. The operation can be performed under spinal or general anesthesia. The operation involves transanal resection of the redundant part of the rectum followed by rectopexy through small postanal incisions. The mean follow-up period was 24 months. One patient developed infection in one stab incision 6 months after the operation. Two patients had hematoma formation, which were managed conservatively. During the 2-year period of follow-up, no recurrence was observed in any of our patients. Fecal incontinence improved in the nine incontinent patients. The technique is simple, easy, and less invasive with good results and less morbidity and is not associated with serious complications. (J GASTROINTEST SURG 2005;9:980–984)

KEY WORDS: Closed, rectopexy, adult, rectal prolapse

Rectal prolapse (RP), a distressing condition in which part or all of the layers of the rectum are extruded through the anal sphincter, usually occurs at the extreme ends of age, particularly in elderly women and infants. The causes of RP are not clearly understood, and the best method of management is debated.[1] There is controversy as whether RP is due to a sliding hernia, an intussusception, or a combination of the two.[2] Many surgical techniques for treatment of RP have been described but none have been shown to be ideal. The procedure chosen is usually based on the fitness of the patient and the surgeon's familiarity and preference for a particular surgical approach.[3] This report describes a new technique that has the simplicity of a perianal approach and the good results of an abdominal approach.

PATIENTS AND METHODS

The study included 27 patients (15 females and 12 males) with complete RP for a period ranging from 9 to 21 months. The mean age was 46 years (range, 33–57 years). Nine patients had fecal incontinence. The RP involved a full-thickness, circumferential RP, and the shortest length of prolapse was 5 cm. The initial management included assessment and correction of the predisposing factors. Systemic antibiotics and intestinal antiseptics were given orally 24 hours preoperatively. Anorectal preparation was done by repeated enema the night before operation.

TECHNIQUE

With the patient under spinal or general anesthesia and in lithotomy position, the submucosa above the dentate line is injected with a dilute epinephrine solution 1:200,000. This maneuver aids in identifying the dissection plane and makes the field bloodless. The mucosa 1 cm above the dentate line is incised circumferentially and then dissected from the underlying muscle for the length of the part of the rectum that passes through the pelvic floor muscles (about the lower half of the rectum). Then, the dissection beyond this level is deeper, excising the full thickness of the rectal wall. The dissection is complete when the rectal

From the General Surgery Department, Faculty of Medicine, Zagazig University, Sharkia, Egypt.
Reprint requests: Dr. Ahmed E. Lasheen, General Surgery Department, Faculty of Medicine, Zagazig University, Sharkia 44519, Egypt. e-mail: Lasheenahmed@yahoo.com

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.007

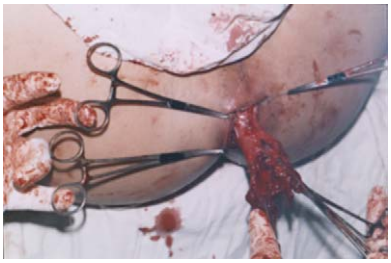

Fig. 1. Dissection of redundant rectal mucosa and plication of rectal muscle were completed.

mucosa cannot be pulled down any farther (Fig. 1). The redundant rectal muscle is then vertically plicated by two rows of sutures, one at the right side and the other at the left side, by using polypropylene No. 0 in continuous manner, starting at the apex of the dissection and continuing down to the distal cut edge of mucosa in the anal canal. As they are tied, the muscle is plicated. The excess mucosa is then excised, and anastomosis of distal mucosa to proximal mucosa is performed by using absorbable suture. After that, three postanal small stab incisions are made at 9, 3, and 6 o'clock positions about 0.5 cm in length and 1.5 cm in depth. The top hole needle is a lazy S-shape needle of 25–30 cm in length with a very pointed tip and a lateral hole immediately behind the tip, as designed for this procedure. This needle has a handle at its proximal end, which is used to direct it (Fig. 2). The top hole needle tip is introduced through one

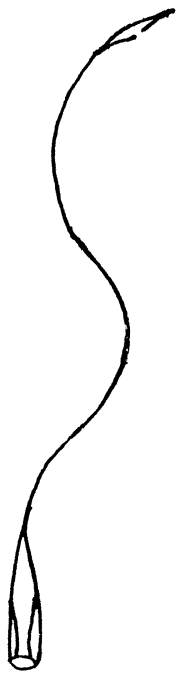

Fig. 2. Top hole needle.

end of the stab incision into the presacral fascia following the sacral curvature with a guiding finger through the anus high as possible. The needle handle is directed backward to penetrate the colonic wall (Fig. 3, *A*) at the apex of the previous dissection by the needle tip and the needle hole appears from inside the rectum. One end of nonabsorbable monofilament thread (polypropylene No. 1) is threaded through the hole of the needle, and the needle is withdrawn to bring the end of the thread through the stab incision (Fig. 3, *B*). This suture end is then detached from the needle. The needle tip is introduced again through another end of the same stab incision but this time passes into the plicated muscle of the rectum and is directed aborad up through the colonic wall before penetrating into the lumen at the same level as the previous step. Then, the needle tip appears from inside the colon at the same opening through which the thread appears (Fig. 3, *C*). The other suture end is threaded through the needle hole, and then the needle is withdrawn again to bring the other suture end through from the same stab incision. The two strands of the suture are tied subcutaneously through the stab incision thereby serving to fix and stabilize the rectal muscle.[4] Three inverted U-shaped nonabsorbable monofilament sutures are used to produce good fixation (Figs. 4, 5). The inverted U-shaped sutures at the 9 and 3 o'clock positions entrap the plication sutures, which had been placed previously in the redundant muscles. A third inverted U-shaped suture was placed at the 6 o'clock position. The stab incisions were left open for drainage and not closed with any stitches. The systemic antibiotics and intestinal antiseptics were continued for 7 days after operation. The follow-up period was ranged from 12 to 36 months (mean period, 24 months) for recurrence, incontinence, and special complications.

RESULTS

The mean time of the operation by this technique was 45 minutes (30 minutes for transanal resection and 15 minutes for closed rectopexy). Two patients developed a pararectal hematoma, which was treated conservatively. There has been no recurrence during the period of follow-up. Rectal examination confirmed that the stab incisions and sphincteric tone had healed well in about 3 weeks. One patient developed perianal suppuration at the site of one stab incision after 6 months of the operation, which was drained and healed after two weeks without other complications. There have been no complaints of constipation or stenosis on rectal examination in this group of patients treated by this technique.

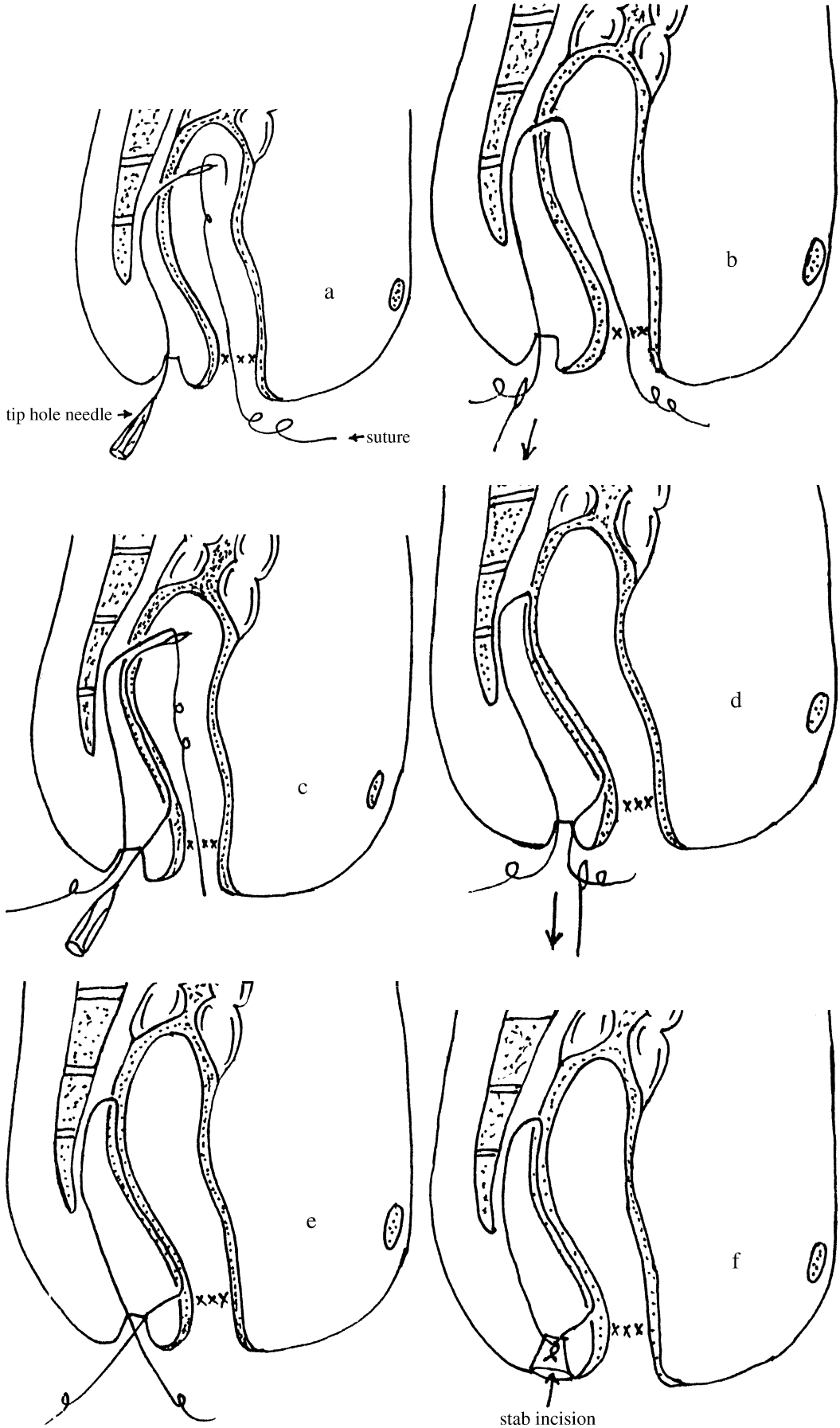

Fig. 3. Steps in rectopexy operation.

Fig. 3. (a) The top hole needle tip is passed through one stab incision, the presacral fascia, and the colonic wall, and the end of the suture is threaded in the needle hole from inside the colon. **(b)** The needle and suture are withdrawn. **(c)** The tip of needle is passed through the same stab incision into the colonic wall in a submucosal plane and appears from inside the colon through the same hole as in the previous step. The other end of the suture is then threaded in the needle hole. **(d)** The needle and suture are withdrawn. **(e)** The two suture ends are tied subcutaneously through the stab incision. **(f)** After excess parts of two suture ends are cut.

DISCUSSION

In complete RP, controversy persists as to whether it is due to sliding hernia, an intussusception, or both. Moschcowitz[5] considered PR as a sliding hernia and advised repair of the levator hiatus and obliteration of the peritoneal sac in combination with amputation of the prolapse. But this procedure was associated by a high rate of recurrence.[6] Cine-radiographic studies suggest that RP is an intussusception.[7] The RP is described at the start as a protrusion of the rectum through the levator ani muscle, and as rectum descends, it intussuscepts upon itself.[8] Generally, RP repairs are categorized into abdominal and perineal approaches. Each approach has its own risks and benefits. The abdominal operations may be categorized as those using resection alone, resection with rectopexy, or rectopexy alone. The recurrence rate has ranged from 7% to 0%, and relief of incontinence was 90%.[8,9] The abdominal approaches may be associated with postoperative constipation, injury to presacral plexus of the nerves and the veins, in addition to the risks of a major abdominal operation.[10,11] The abdominal procedures can be done laparoscopically but special instrumentation and special skills are needed, and there are complications of laparoscopic abdominal surgery.[12,13] The perineal approaches which include the Thiersch loop, the Delorme repair, and rectosigmoidectomy operations, are less invasive and less morbid, have a recurrence rate of 10%, and have less incontinence improvement.[14–16] Our technique included transanal resection of the redundant rectal mucosa only, with or without sigmoid colon and rectopexy by inverted U-sutures through three postanal stab incisions. This technique has good results with no recurrence and improvement of incontinence and is less invasive, less morbid, and easy to do. Closed rectopexy with transanal resection technique is simple, easy, less invasive, and less morbid; has good results; and is free of special complications in management of complete RP in adults.

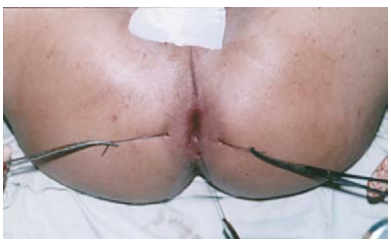

Fig. 4. Three inverted U-shaped sutures through three stab incisions.

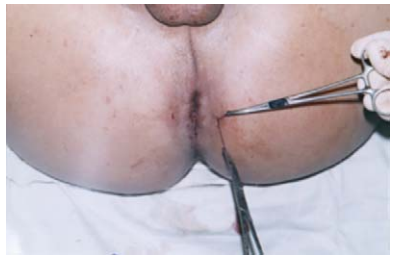

Fig. 5. The last inverted U-shaped suture is tied subcutaneously through the stab incision.

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Laparoscopic Nissen Fundoplication: The "Right Posterior" Approach

Attila Csendes, M.D., F.A.C.S. (Hon), Patricio Burdiles, M.D., F.A.C.S., Owen Korn, M.D., F.A.C.S.

The main steps for performing a laparoscopic Nissen fundoplication are described: They start with a "right approach" by dissection of the high lesser curve, near the esophagogastric junction. Then the posterior surface of the stomach is easily visualized by the "posterior approach." The fat pad and both vagal trunks are displaced to the right, avoiding any vagal injury. Two to three short gastric vessels are divided, leaving a loose gastric fundus. A 360° total symmetric and geometric fundoplication is then performed, including the esophageal wall in the most proximal and distal stitch. A final stitch for an anterior fundophrenopexy is performed. This surgical approach has been used in 225 patients with severe chronic pathologic reflux with a 1.3% conversion rate, no mortality, and only one significant postoperative complication. Late evaluation at 5 years after surgery has shown excellent or good results in 85% and fair or poor results in 15% of the patients. (J GASTROINTEST SURG 2005;9:985–991)

KEY WORDS: Laparoscopic, Nissen fundoplication, reflux esophagitis

Nissen fundoplication is the "gold standard" procedure in most surgical centers to treat pathologic gastroesophageal reflux.[1] The laparoscopic approach has shown excellent results in patients with noncomplicated reflux esophagitis and has replaced completely the open approach.[1,2] According to the literature from dedicated centers in North America and Europe, the standard Nissen fundoplication includes the following steps:

- Division of short gastric vessels from a left approach allowing the mobilization of the gastric fundus. However, with this approach, the posterior short gastric vessels are not divided, making this mobilization incomplete.
- Opening of the lesser omentum usually dividing the hepatic branch of the left (anterior) vagal nerve, which represents a risk of late gallstone disease.[3]
- Isolation of the abdominal esophagus through a careful dissection between the right crus and the posterior wall of the esophagus.

With these steps, a floppy wrap can be obtained; nevertheless, one or both vagal trunks may be included in the plication, as well as the gross fatty tissue.

The purpose of the present report is to show how we perform a laparoscopic Nissen fundoplication by a different surgical approach, to see clearly all structures of the esophagogastric junction, to keep fatty tissue away from the plication, to construct a symmetrical plication, and to preserve intact both vagal trunks outside the wrap.

METHODS

We approach the esophagogastric junction via what we call "the right posterior approach." We start the operation by dissecting the lesser curve (right approach) 2–3 cm distal to the esophagogastric junction, just where the anterior and posterior layers of the lesser omentum insert into the lesser curvature.

From the Department of Surgery, University Hospital, Santiago, Chile.
Reprint requests: Attila Csendes, F.A.C.S, Department of Surgery, Clinical Hospital, University of Chile, Santos Dumont 999, Santiago, Chile. e-mail: acsendes@machi.med.uchile.cl

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2004.12.007

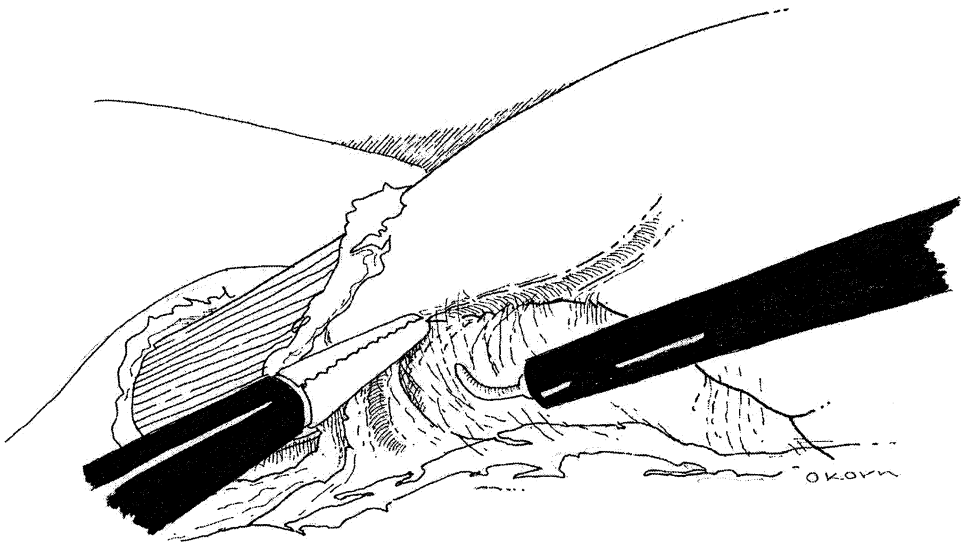

Fig. 1. The beginning of the operation via the "right approach" starts with the section of the anterior and posterior layer of the lesser omentum along the proximal lesser curve, 2–3 cm distal to the cardia.

In this way, we are sure to preserve Latarjet's nerve (Fig. 1). The phrenoesophageal ligament and the fat pad are dissected from the esophagogastric junction and are displaced to the right, including the anterior and posterior vagal trunks, together with the celiac and hepatic branches. Then by the posterior wall of the

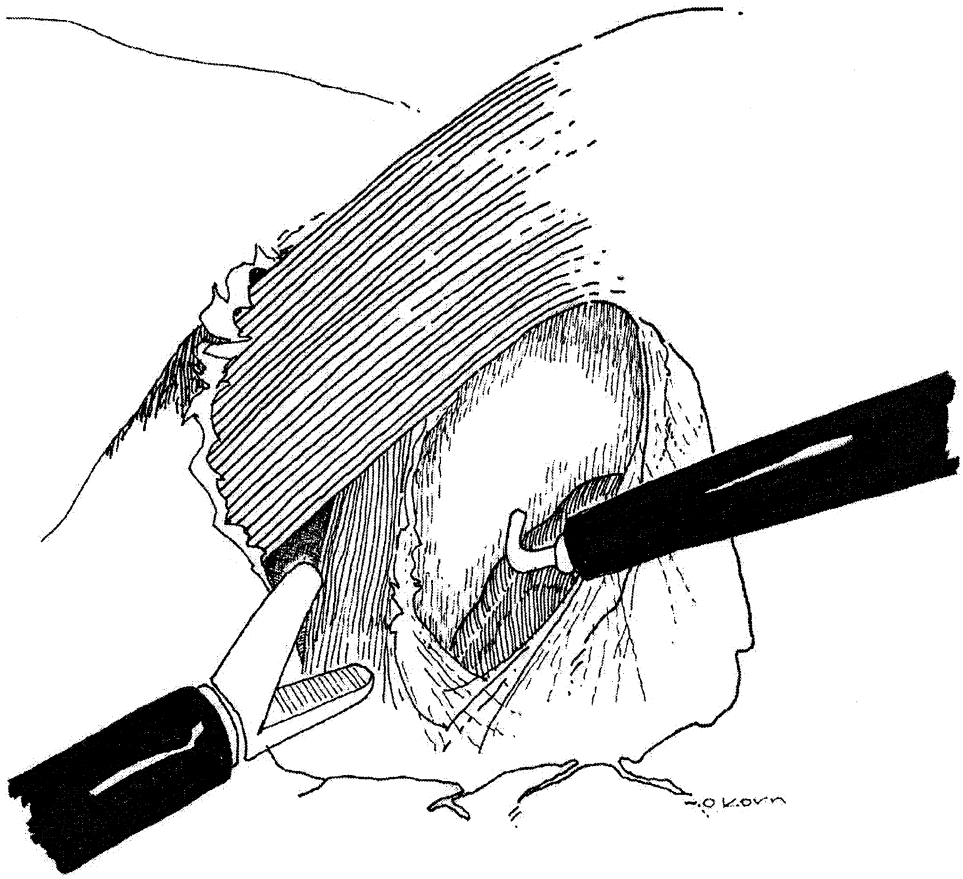

Fig. 2. The "posterior approach" to the short gastric vessels behind the posterior surface of the stomach allows a very clear view of the first short gastric vessels.

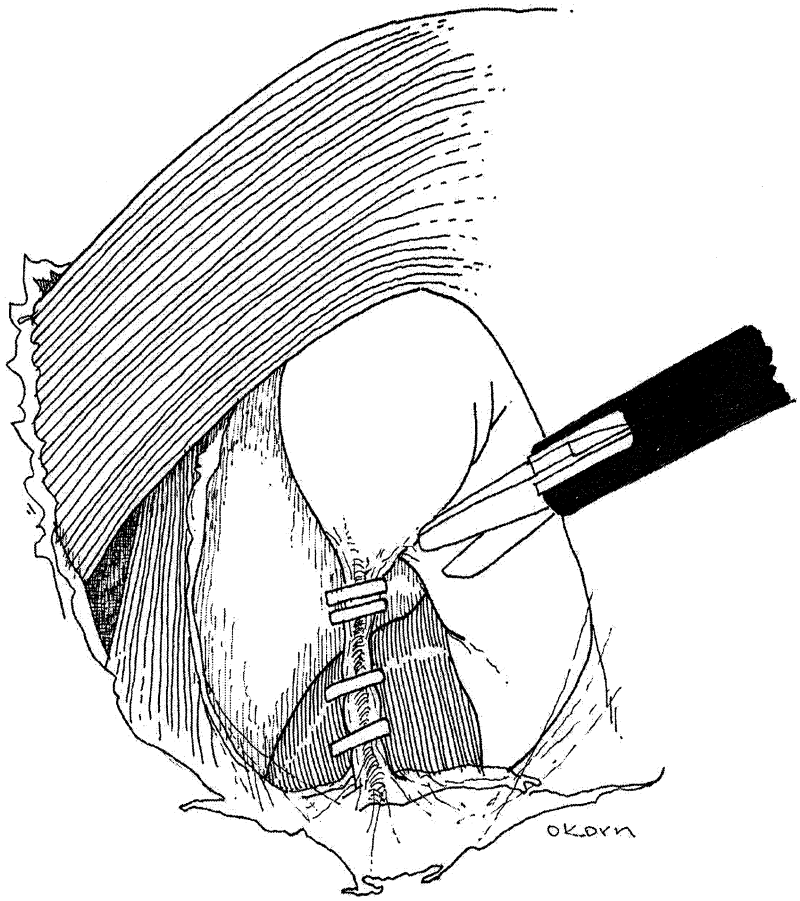

Fig. 3. Section of the first two short vessels with clips or by ultrasonic dissection.

stomach (posterior approach), we approach the short gastric vessels, through the lesser sac (Fig. 2). In this way, the first and second short gastric vessels, which form the retroperitoneal vessels, are easily divided by clips (Fig. 3) or with the ultrasonic dissector. We are convinced that this posterior approach is much

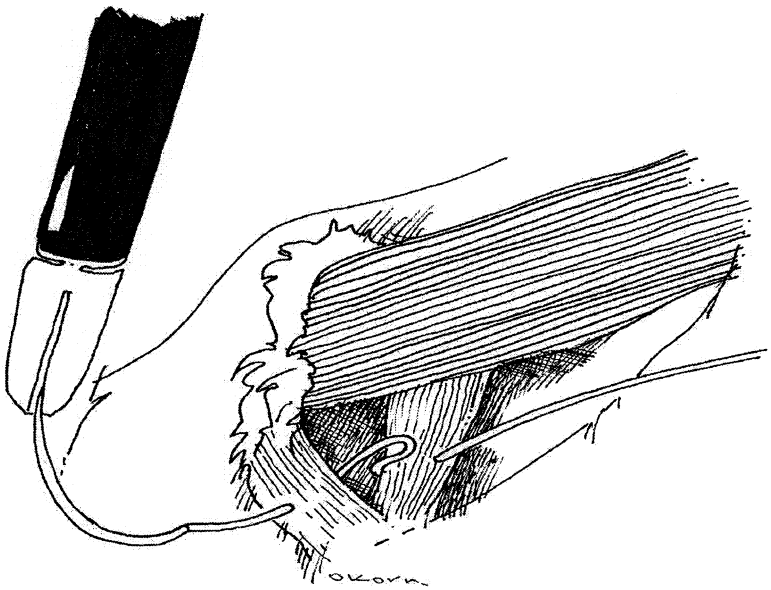

Fig. 4. Closure of the hiatus by two or three nonabsorbable stitches.

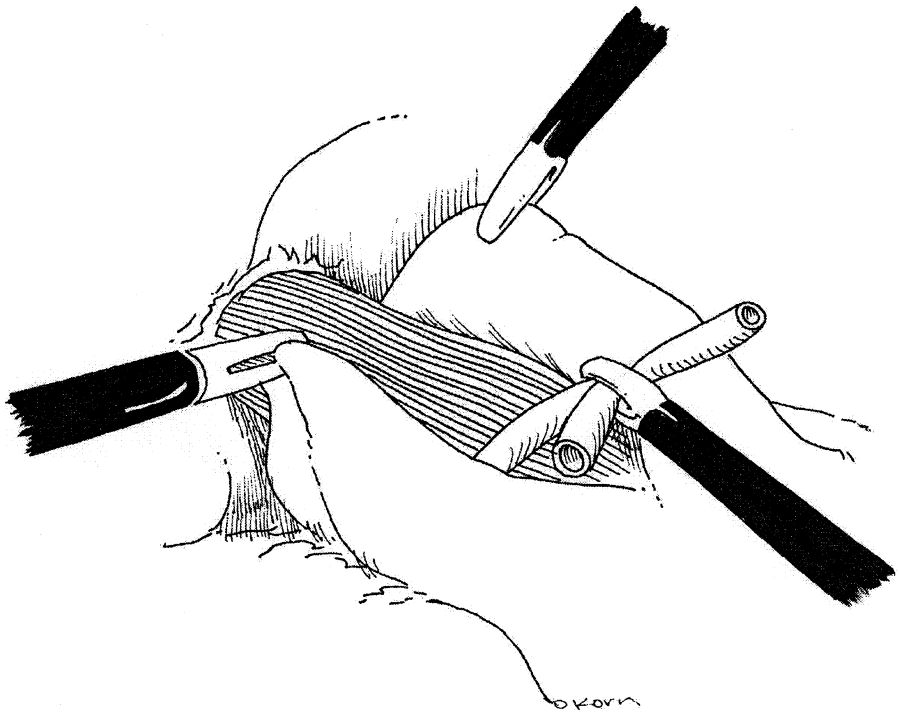

Fig. 5. "Shoe-shine" maneuver clearly demonstrates the looseness of the gastric fundus for a symmetric and geometric fundoplication.

easier than the left-side approach to visualize these vessels. After completing the division of other short gastric vessels, which connect the greater curvature with the spleen, the gastric fundus is loose, not tense, and adequate for a "floppy" fundoplication. The next step is to close the diaphragmatic crura with two or three nonabsorbable stitches (Ethibond 2-0), having displaced the posterior vagal trunk to the right

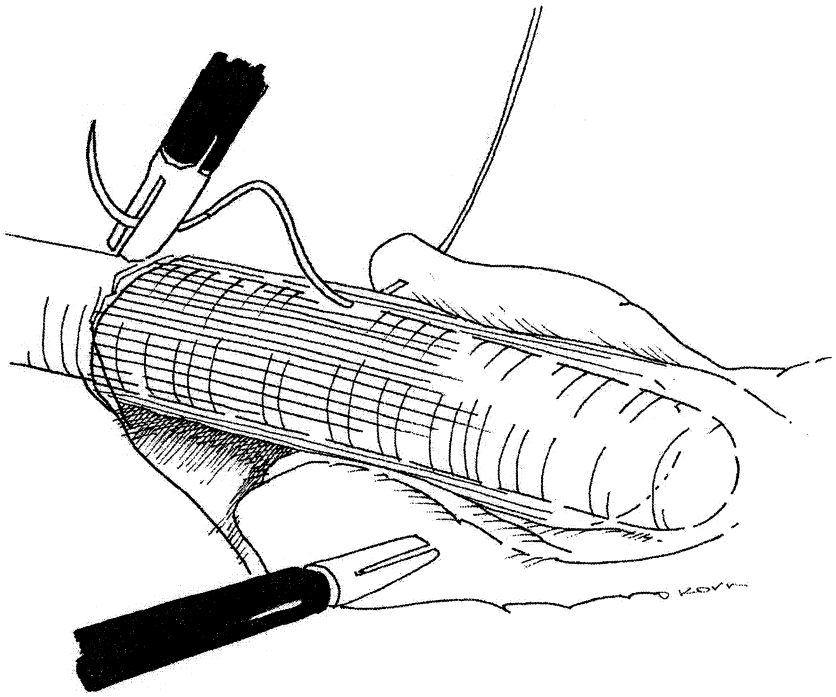

Fig. 6. Proximal stitch of the fundoplication, which includes the esophageal muscular coat, with the bougie inside the esophageal lumen.

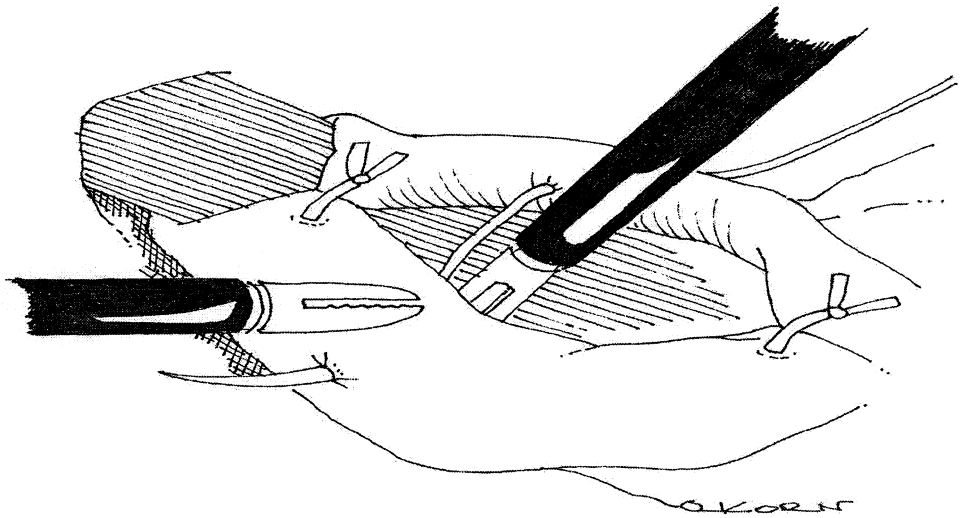

Fig. 7. Distal stitch of the fundoplication, including the esophageal wall.

(Fig. 4). Now it is very easy to perform the "shoe-shine" maneuver, which demonstrates the looseness of the gastric fundus (Fig. 5). A short piece (± 12–15 cm) of soft Nelaton catheter encircles the esophagogastric junction to pull it down in the caudal direction. A 32 F bougie is inserted into the esophagus, together with a nasogastric tube (14–16 F), which gives a total of 46–48 F. The first stitch is the most proximal, which includes the esophageal wall, to avoid displacement or slipping of the wrap (Fig. 6). In the same way a

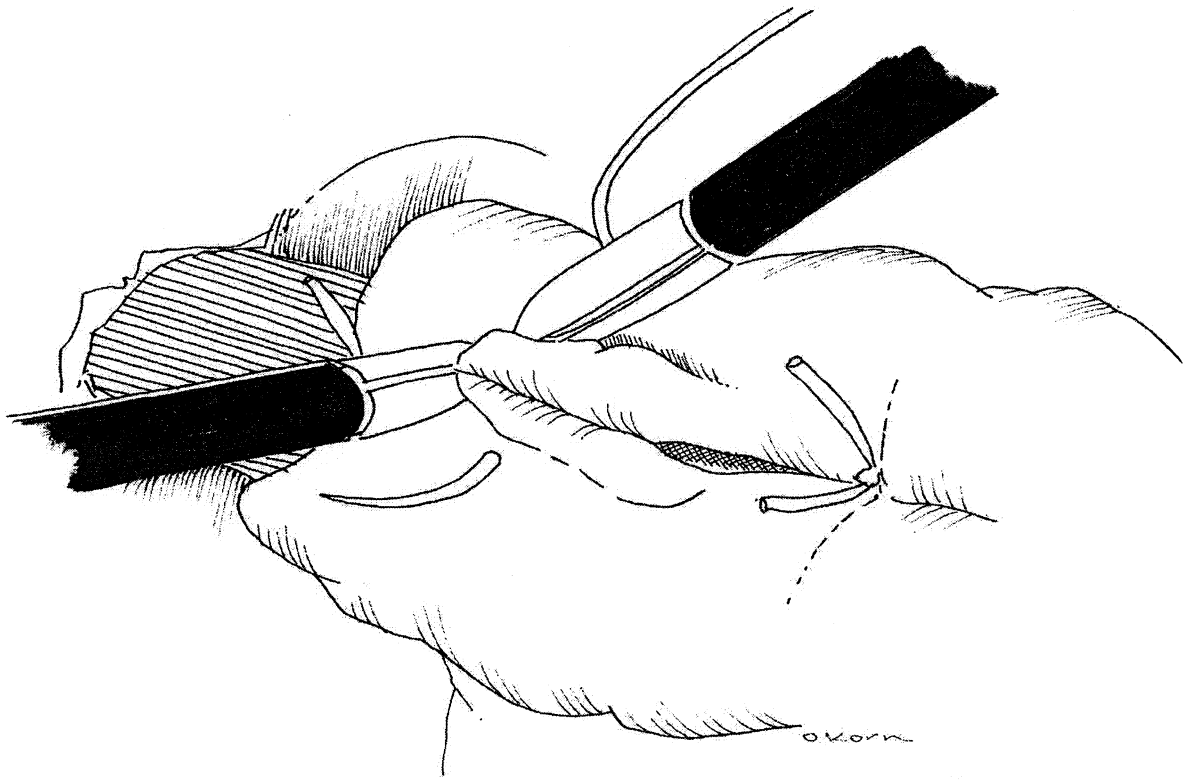

Fig. 8. Mid-stitches of the fundoplication, always using nonabsorbable sutures, which do not include the esophageal wall.

second stitch is placed at the distal portion of the wrap, also including esophageal wall (Fig. 7). The sutures used are nonabsorbable Ethibond 2-0 sutures and the knots are all intracorporeal. The operation is completed by two stitches between the previous ones, which do not include esophageal wall (Figs. 7 and 8). In this way, we construct a 360° fundoplication of 4-cm length. The bougie is removed and introduced again into the stomach gently, to exclude an excessive tightness of the distal esophagus by the wrap. The operation is completed by placing a stitch between the gastric fundus and the anterior hiatus, which we designate as an "anterior fundophrenopexy," to avoid an anterior iatrogenic paraesophageal hernia (Fig. 9). The nasogastric tube is removed the next day, and oral feeding is started. The usual hospital stay is 2–3 days.

RESULTS

From 1993 through July 2004, the laparoscopic Nissen has been performed on a total of 225 patients with severe gastroesophageal reflux disease. All patients had an abnormal 24-hour pH study, together with an incompetent lower esophageal sphincter. There have been three conversions due to a large fixed intrathoracic hiatal hernia (1.3%). No other intraoperative complication such as esophageal or gastric perforation or splenectomy has occurred. The average duration of the operation was 75 minutes (60–90 minutes). There was no operative mortality and only one postoperative morbidity (0.4%) due to necrosis of the lesser curve of the stomach, which was repaired 6 days after the operation via a laparoscopic approach, with an uneventful recovery. The late evaluation 4–5 years after surgery has shown Visick I and II results in 85% of the patients and Visick III and IV results in 15% of them.[4]

DISCUSSION

The principles that antireflux surgery should accomplish have been enumerated by us and other

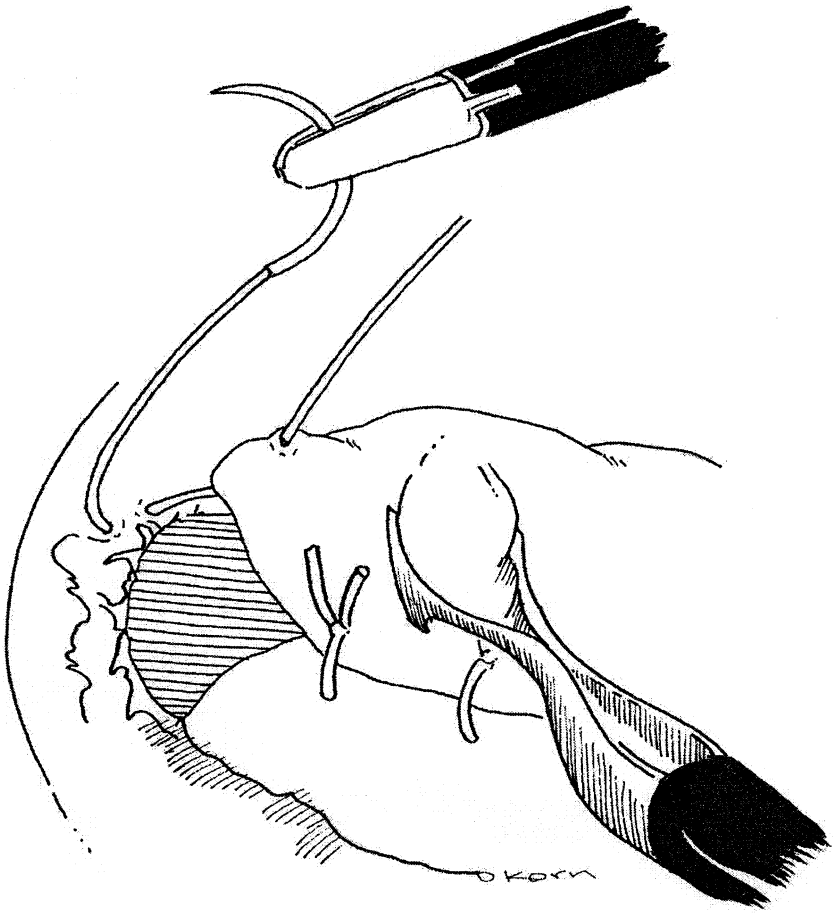

Fig. 9. Final stitch in performing an anterior fundophrenopexy, to avoid a late anterior paraesophageal hernia.

esophageal surgeons.[4–9] They include the creation of a long intra-abdominal segment of esophagus,[5] calibration of the cardia[10] by applying the principle of the Law of La Place, and restoration of the normal length-tension relationship of the muscle responsible for the lower esophageal sphincter.[5,7,8] Nissen fundoplication achieves all of these principles and is the most used laparoscopic procedure for patients with chronic gastroesophageal reflux disease.

In the present study we describe how we perform this operation. The main difference with other surgeons that we have observed performing Nissen fundoplication, is the initial surgical approach. We believe that the "right posterior" approach has two main advantages over the "left side first" approach: (1) it clearly preserves the vagal trunks, the anterior (hepatic) and posterior (celiac) branches, and the nerves of Latarjet, avoiding complications such as slow gastric emptying, gastric ulcer, gas bloat syndrome, and diarrhea, and (2) it allows a very easy approach to the first short gastric vessels, which fix the gastric fundus to the retroperitoneum. In this way a floppy Nissen can be constructed. We are aware of the four randomized trials comparing this specific point,[1] which refer to the section of the short gastric vessels. However, for surgeons with great experience in this field, it is more desirable to divide the short vessels than to not divide them, to achieve a loose gastric fundus. We always close the hiatus with two or three nonabsorbable stitches, as do the majority of surgeons. The length of fundoplication is near 4 cm, because that is the normal length of the lower esophageal sphincter. Other surgeons perform a wrap of 2- to 3-cm length,[11–13] to decrease the incidence of postoperative dysphagia. However, in our follow-up, postoperative dysphagia has not been a problem and only two patients (0.9%) required endoscopic dilatation after surgery. Dysphagia has been mild and almost gone 3 months after surgery.

We have had concerns in performing a Nissen fundoplication when patients have poor or weak peristalsis. In our experience, weak peristalsis has recovered when reflux is stopped after surgery, with identical results to those reported by Patti et al.[14]

In summary, classic Nissen fundoplication, as described in 1956,[15] has undergone several technical modifications in the past 48 years: However, the main principles of this operation have been maintained[10]: (1) preparation of the hiatal and fundic region by dissection of the esophagogastric junction through the "right posterior" approach, (2) preservation of vagal branches, (3) division of the proximal short gastric vessels, (4) closure of the hiatus, and (5) construction of a total 360° symmetric floppy fundoplication. If these principles are adhered to, late clinical results will be favorable.

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Review Article

Current Management of Portal Hypertension

Andrew S. Wright, M.D., Layton F. Rikkers, M.D.

Portal hypertension can lead to life-threatening hemorrhage, ascites, and encephalopathy. This paper reviews the pathophysiology and multidisciplinary management of portal hypertension and its complications, including the indications for and techniques of the various surgical shunts. Variceal bleeding is the most dreaded complication of portal hypertension. It may occur once the portal-systemic gradient increases above 12 mm Hg, occurs in 30% of patients with cirrhosis, and carries a 30-day mortality of 20%. Treatment of acute variceal bleeding includes resuscitation followed by upper endoscopy for sclerosis or band ligation of varices, which can control bleeding in up to 85% of patients. Medical therapies such as vasopressin and somatostatin can also be useful adjuncts. Shunt therapy, preferably the placement of a TIPS, is indicated for refractory acute variceal bleeding. Recurrent variceal bleeding is common and is associated with a high mortality. Therapies to prevent recurrent variceal bleeding include chronic endoscopic therapy, nonselective beta-blockade, operative or nonoperative (TIPS) shunts, devascularization operations, and liver transplantation. Recommendations and a treatment algorithm are provided, taking into account both the etiology and the manifestations of portal hypertension. (J GASTROINTEST SURG 2005;9:992–1005)

KEY WORDS: Portal hypertension, liver, cirrhosis, variceal hemmorhage

Portal hypertension can lead to life-threatening variceal hemorrhage or development of morbid ascites and encephalopathy. In the end stages of portal hypertension secondary to cirrhosis, the hepatorenal syndrome culminates in kidney and liver failure and carries an extraordinarily high mortality rate. Management of portal hypertension and its attendant complications requires a multidisciplinary approach combining medical and endoscopic management, surgical or nonsurgical portosystemic shunting, and in some cases liver transplantation.

ETIOLOGY AND PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Portal hypertension is most often due to increased portal venous resistance, and is generally classified by the site of increased resistance as prehepatic, intrahepatic, or posthepatic (Table 1). The most common cause of prehepatic portal hypertension is portal vein thrombosis. Isolated splenic vein thrombosis causes left-sided portal hypertension, usually as a result of pancreatic inflammation or neoplasm. In this case there is venous hypertension of the gastric and splenic veins with normal portal and superior mesenteric pressures. Gastric rather than esophageal varices predominate in this disease because of collateralization of the gastroepiploic vein. Isolated left-sided portal hypertension is reversed by splenectomy alone.

Intrahepatic portal hypertension stems from increased vascular resistance at the presinusoidal, sinusoidal, and/or postsinusoidal levels. The most common cause of presinusoidal portal hypertension is schistosomiasis. Nonalcoholic cirrhosis may also cause presinusoidal portal hypertension, especially early in the

From the Department of Surgery, University of Wisconsin Medical School, Madison, Wisconsin
Reprint requests: Layton F. Rikkers, M.D., H4/710 CSC, University of Wisconsin Hospital and Clinics, 600 Highland Ave., Madison, WI 53792. e-mail: rikkers@surgery.wisc.edu

1091-255X/04/$—see front matter
doi:10.1016/j.gassur.2004.09.028

Table 1. Classification of portal hypertension

Extrahepatic
Portal vein thrombosis
Splenic vein thrombosis
Intrahepatic
Presinusoidal
Schistosomiasis
Primary biliary cirrhosis
Sarcoidosis
Myeloproliferative disease (Hodgkin's disease, myelogeneous leukemia)
Gaucher's disease
Congenital hepatic fibrosis
Arsenic toxicity
Sinusoidal
Alcoholic cirrhosis
Storage diseases
Hemochromatosis
Wilson's disease
Postsinusoidal
Alcoholic cirrhosis
Veno-occlusive disease
Posthepatic
Budd-Chiari syndrome
Right-sided heart failure
Constrictive pericarditis
High-flow portal hypertension
Hepatic artery–portal vein fistula
Splenic arteriovenous fistula
Massive splenomegaly

course of the disease. Sinusoidal portal hypertension is most often due to alcoholic cirrhosis, with deposition of collagen in the space of Disse. Alcoholic cirrhosis may also cause increased postsinusoidal resistance as regenerating nodules compress small hepatic veins.

Postsinusoidal syndromes are rare, but include Budd-Chiari syndrome (thrombosis of hepatic veins), right heart failure, and constrictive pericarditis. Portal hypertension may rarely be caused by increased portal venous flow alone, due to either massive splenomegaly or a splanchnic arteriovenous malformation.

PATHOPHYSIOLOGY AND PROGNOSIS OF ACUTE VARICEAL HEMORRHAGE

Portal hypertension is characterized by a gradient of greater than 5 mm Hg between the portal venous and central venous pressures. After a pressure gradient of 8 to 10 mm Hg is reached, esophageal and gastric varices arise from a collateral network through the coronary and short gastric veins into the azygous vein. Bleeding can occur once the gradient increases above 12 mm Hg.[1,2] Other sites of collateralization include retroperitoneal vessels, the hemorrhoidal venous plexus, a recanalized umbilical vein, and intrahepatic shunts.

Esophageal varices are common in cirrhotic patients and frequently progress over time. In one longitudinal series, new varices arose in 5% of cirrhotic patients within 1 year and in 28% of patients within 3 years.[3] Progression was predicted by Child-Pugh score, the presence of red wale markings on the varices, and an alcoholic etiology of cirrhosis. In patients with small varices at initial endoscopy, the 2-year risk of variceal bleeding is 12%. Thirty-day mortality of variceal bleeding ranges from 20% to 29%.[4]

The pathogenesis of variceal rupture is related to physical factors within the wall of the varix. Portal pressure, variceal size, and epithelial thickness all contribute to the likelihood of variceal rupture as related by the law of Laplace.[5] The risk of bleeding is independently associated with varix size for both esophageal[6] and gastric varices.[7] Physical appearance can also predict bleeding, including red wale markings, cherry red spots, hemocytic spots, and diffuse erythema.[3,7,8] Location of varices is important, with isolated gastric varices being more likely to bleed and having a greater transfusion requirement than esophageal varices.[8]

Over 90% of active gastrointestinal hemorrhages in the setting of portal hypertension are caused by varices,[6] but bleeding may also stem from peptic ulcer disease, Mallory-Weiss tears, or gastric antral vascular ectasia. Portal hypertensive gastropathy (PHG) is an additional nonvariceal source of upper gastrointestinal bleeding in patients with portal hypertension.[9] The frequency is unknown but seems to increase after endoscopic treatment of esophageal varices. PHG consists of erythematous areas of the gastric fundus and body that are enclosed by a white reticular network. The appearance of granular mucosa with cherry-red spots indicates a more severe form of PHG and a higher risk of rebleeding.

Acute variceal bleeding has a mortality of 25% to 30%, accounts for one-third of deaths among patients with cirrhosis, and occurs in 25% to 40% of patients with cirrhosis.[10] Risk of death is related to the underlying hepatic functional reserve. About half of patients will stop bleeding following resuscitation alone.[11] Spontaneous cessation of hemorrhage is less likely in patients with Child-Pugh class C cirrhosis or with large, actively spurting varices.[12]

Rebleeding is common following variceal hemorrhage. More than 50% of all recurrent bleeding occurs within the first 10 days, with a period of greatest risk within the first 72 hours. Risk factors for early rebleeding include large varices, severe initial bleeding (hemoglobin <8 g/dl), renal failure, and

age more than 60 years.[13] After 6 weeks the risk of rebleeding returns to baseline.[14]

PROPHYLACTIC THERAPY

Because of the high mortality and morbidity of variceal bleeding, primary prevention of bleeding is a major goal in the management of portal hypertension. Nonselective beta-blockers such as propranolol and nadolol reduce portal venous inflow by blocking adrenergic dilatation of mesenteric arterioles. Beta-blockers reduce the risk of first variceal bleeding by 45% to 50% compared to placebo; however, a survival advantage has not been demonstrated.[15,16] Nitrates also reduce portal pressure and have been compared to beta-blockers in several trials. Although bleeding rates appear to be similar, long-term survival rates are lower in patients receiving nitrates.[17] Results with combination therapy have been inconclusive.[18,19]

Throughout the late 1960s and early 1970s, several groups investigated use of the portacaval shunt for prevention of variceal bleeding. Although surgery was highly successful in reducing the incidence of bleeding, encephalopathy was frequent, and there was a survival benefit to medical therapy.[20–22] There are no data regarding the transjugular intrahepatic portosystemic shunt (TIPS) in the prevention of primary variceal bleeding, and it is not currently recommended for this purpose. Some early reports recommend sclerotherapy for prophylaxis of primary variceal bleeding,[23] but more recent studies show no benefit[16] or higher mortality in groups receiving sclerotherapy.[24] A meta-analysis comparing esophageal banding and beta-blockers showed decreased risk of bleeding with banding but no difference in mortality.[25] Recurrence of varices is high, and banding is currently recommended only for patients who are at high risk of bleeding and who cannot tolerate beta-blockers.

MEDICAL AND ENDOSCOPIC MANAGEMENT OF ACUTE VARICEAL BLEEDING

A patient with suspected variceal bleeding must first be appropriately resuscitated and hemodynamically stabilized. The stomach should be evacuated with a large-bore gastric lavage tube. Transfusions of blood, and when appropriate fresh frozen plasma, should be used to restore adequate blood volume and correct coagulopathy. Platelet counts often drop within the 48 hours following an acute bleed, and platelets should be transfused as necessary. Correction of coagulopathy may not be successful with fresh frozen plasma alone. In a small pilot study, 10 patients with active variceal bleeding were given a single dose of recombinant human factor VIIa. Prothrombin time normalized in all patients within 30 minutes, with immediate control of bleeding.[26]

Patients with acute variceal bleeding are at risk of serious morbidity due to decompensated hepatic function, encephalopathy, coagulopathy, and poor nutrition. Primary bacterial infections are present in 20% of cirrhotic patients with gastrointestinal bleeding, and secondary infections may occur in up to 50%.[27] A meta-analysis of more than 800 patients showed a reduction in mortality with administration of prophylactic antibiotics.[28] There is no consensus regarding the antibiotic regimen of choice.

Endoscopy should be performed as soon as the patient is resuscitated. Band ligation and sclerotherapy control bleeding in more than 85% of patients (Fig. 1).[29,30] A meta-analysis comparing band ligation with sclerotherapy found lower rebleeding and mortality with ligation.[31] Band ligation, however, is technically more difficult, and either treatment option is considered acceptable.

After endoscopic treatment, a repeat endoscopy should be planned in 4 to 6 days. Minor complications are common, including chest pain, ulceration, and fever. Major complications include perforation, hemorrhage, aspiration, and late stricture formation. These complications are less frequent following banding compared to sclerotherapy. Mortality secondary to the procedure ranges from 1% to 3%. Endoscopic therapy should be considered a failure if hemorrhage is not controlled after two sessions, at which point mortality increases to 60% without further intervention.

Vasopressin is a splanchnic vasoconstrictor that reduces portal flow and portal pressure. Vasopressin controls acute hemorrhage in up to 60% of patients, but has limited efficacy in preventing early rebleeding and does not improve survival. It has been shown in a meta-analysis to be more effective than placebo.[29] Vasopressin should be used in an intensive care setting because of its side effects, including hypertension, bradycardia, coronary vasoconstriction, and decreased cardiac output. Vasopressin is usually administered as a bolus of 0.4 units, followed by a drip at a rate of 0.4 to 1 units per minute. Nitroglycerin, given in combination with vasopressin, enhances reduction in portal pressure while counteracting systemic vasoconstriction. Combined therapy results in more frequent cessation of bleeding (68% vs. 44%) and reduced morbidity (3% vs. 21%) compared to vasopressin alone.[32]

Somatostatin and its analog, octreotide, indirectly decrease portal flow by inhibiting the vasodilatory effects of glucagon. A meta-analysis comparing somatostatin to vasopressin found better bleeding control and

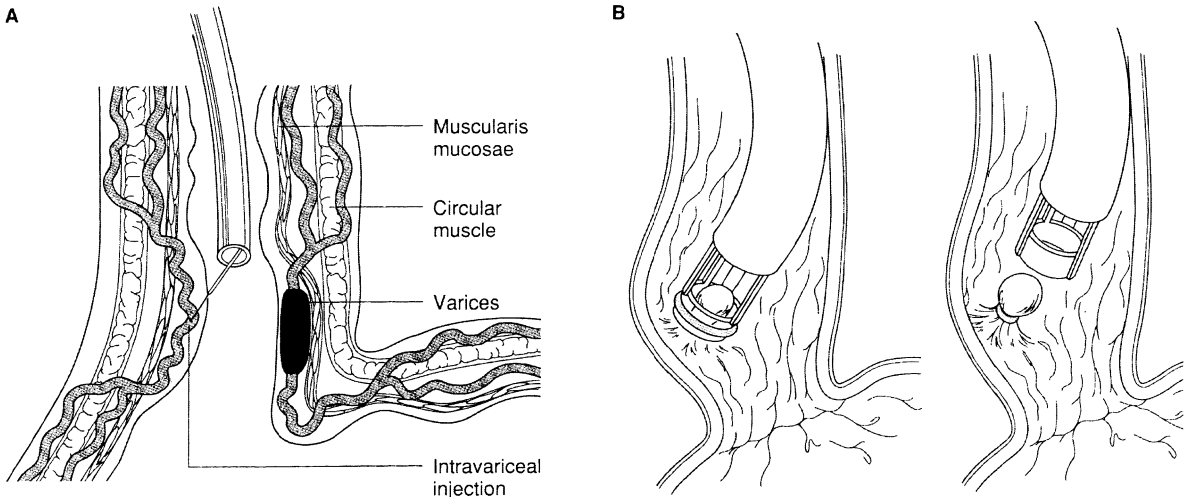

Fig. 1. Techniques of (**A**) sclerotherapy and (**B**) endoscopic band ligation. (Adapted from Marvin MR, Emond JC. Cirrhosis and portal hypertension. In Greenfield LJ, Mulholland MW, Oldham KT, Zelenock GB, Lillemoe KD, eds. Surgery: Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, p 971.) Reprinted with permission.

fewer adverse effects (0% vs. 10%) with somatostatin.[33] Compared with sclerotherapy, both somatostatin[34] and octreotide[35] have equivalent rates of bleeding control, early rebleeding, and mortality. Combination of somatostatin or octreotide with sclerotherapy appears to be more effective than drug therapy, sclerotherapy, or band ligation alone.[36–38]

In patients with life-threatening bleeding that cannot be successfully stopped by endoscopy, balloon tamponade can be used as a temporizing measure (Fig. 2). The Sengstaken-Blakemore tube stops acute variceal bleeding in up to 85% of patients, but the risk of recurrent hemorrhage following deflation is up to 50%.[39] The device is uncomfortable for the patient and carries a 14% risk of serious complications. Intraesophageal inflation of the gastric balloon can result in esophageal perforation, while ischemic necrosis of the esophagus can occur because of overinflation of the esophageal balloon. Complications appear to be more common when balloons are placed by inexperienced personnel.[39] Because of the high risk of rebleeding, definitive therapy should be planned in all patients treated with balloon tamponade.

SHUNT THERAPY IN THE MANAGEMENT OF ACUTE VARICEAL BLEEDING

With failure of endoscopic and pharmacologic therapy, the portal system should be decompressed via a shunt between the portal and systemic venous circulations. Shunting of portal blood, however, may result in adverse effects due to diversion of hormones, nutrients, and toxins around the liver, leading to encephalopathy and accelerated hepatic failure.

In most institutions the transjugular intrahepatic portosystemic shunt (TIPS) has become the emergent shunt procedure of choice. After the internal jugular vein is accessed, a wire is threaded into a hepatic vein and then punctured through the liver into a branch of the portal system (Fig. 3). A tract is developed using a balloon dilator, and an expandable metal stent is inserted to maintain patency of the shunt. TIPS placement requires an expert interventional radiologist and may not be available in all centers. Because TIPS completely diverts portal flow, it is considered a nonselective shunt.

TIPS achieves hemostasis in the majority of patients with bleeding refractory to endoscopic management.[40,41] In patients with refractory bleeding who are at prohibitive risk for emergent surgery (because of sepsis, coma, multisystem organ failure, or severe comorbidities), TIPS is successful at achieving hemostasis in 90%, with a 63% 30-day survival.[42] TIPS may also be useful in patients with severe hepatic dysfunction (i.e., Child-Pugh class C), who may not be well served by emergency operation.

TIPS is especially useful as a short-term bridge to liver transplantation, because the TIPS procedure does not disturb the anatomy of the liver or portal triad. A lower portal pressure may make transplantation technically easier. Absolute contraindications to TIPS are polycystic liver disease and right heart failure, while relative contraindications include portal vein thrombosis, hypervascular liver tumors, and encephalopathy.

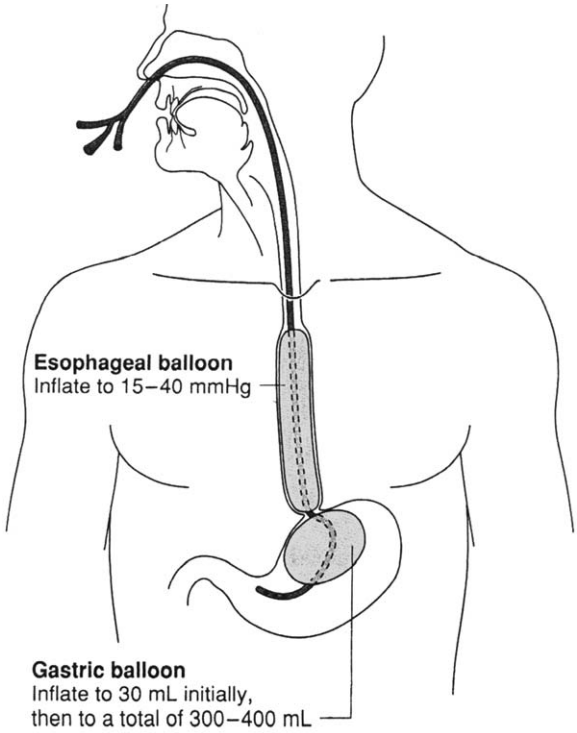

Fig. 2. The Sengstaken-Blakemore tube, used to tamponade bleeding gastroesophageal varices. Patients should also be endotracheally intubated to protect the airway. (Adapted from Marvin MR, Emond JC: Cirrhosis and portal hypertension. In Greenfield LJ, Mulholland MW, Oldham KT, Zelenock GB, Lillemoe KD, eds. Surgery: Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, p 972.) Reprinted with permission.

Urgent or emergent surgery is required when endoscopic and pharmacologic therapies are unsuccessful and TIPS placement is contraindicated, unavailable, or unsuccessful. Orloff and colleagues have reported 99% success in control of acute variceal bleeding with the portacaval shunt in 400 patients.[43] Although 30-day survival was only 58% in the first 15 years of the series, survival increased to 85% in the final 12 years. In the latter group, 5-year survival was 78%. Encephalopathy occurred in only 9% of patients. It should be noted, however, that no one else has been able to duplicate the results of this single-center experience.

MEDICAL AND ENDOSCOPIC THERAPY IN THE PREVENTION OF RECURRENT VARICEAL BLEEDING

Recurrence of variceal bleeding is common and occurs in up to 70% of patients following medical and endoscopic management.[44] Mortality in the first year following variceal hemorrhage is as high as 70% in untreated patients, due to recurrent bleeding, liver failure, and infections. Prevention of rebleeding and preservation of liver function are therefore the two long-term goals of therapy.

Chronic endoscopic therapy is currently the most common means for long-term prevention of recurrent variceal bleeding. Compared to medical treatment, sclerotherapy decreases 40-day mortality by 43%.[45] Repeat sclerotherapy can eradicate varices in 88% of patients surviving longer than 3 months, but varices eventually recur in most of these patients.[46] A meta-analysis has shown endoscopic band ligation to be superior to sclerotherapy, with less rebleeding, death, and esophageal stricture formation.[47] Fewer treatments are required to eradicate varices with band ligation. The combination of sclerotherapy and band ligation appears to decrease efficacy and increase complication rates, and is therefore not recommended.

Just as propranolol has been shown to be effective prophylaxis against initial episodes of variceal hemorrhage, it is also useful in prevention of recurrent bleeding. The risk of recurrent bleeding is lessened by about 40%, and the risk of death by 20%.[48] Combination therapy with a beta-blocker and a long-acting nitrate is probably more effective than beta-blockade alone.[49] A response to medical therapy, as indicated by a reduction in hepatic venous pressure gradient or measured variceal pressure, predicts a lower risk of rebleeding.[50]

Pharmacologic therapy with propranolol is probably somewhat less effective than endoscopic management, with one meta-analysis finding 45% of patients rebleeding with sclerotherapy compared to 61% with medical managment.[29] A combination of nadolol and isosorbide mononitrate has been shown to be more successful than endoscopic ligation (33% vs. 49% rebleeding), with better efficacy in patients with a hemodynamic response to medication.[52] Because of the risk of rebleeding, long-term pharmacotherapy should be used only in compliant patients with close physician monitoring. There appears to be no added benefit with combined beta-blockade and sclerotherapy.[53]

SHUNT THERAPY IN THE PREVENTION OF RECURRENT VARICEAL BLEEDING

Both nonoperative and surgical shunts play a role in the prevention of recurrent variceal bleeding. Portosystemic shunts are classified as nonselective, selective, and partial, depending on how much hepatic portal flow is preserved. Nonselective shunts decompress the entire portal system by diverting all portal

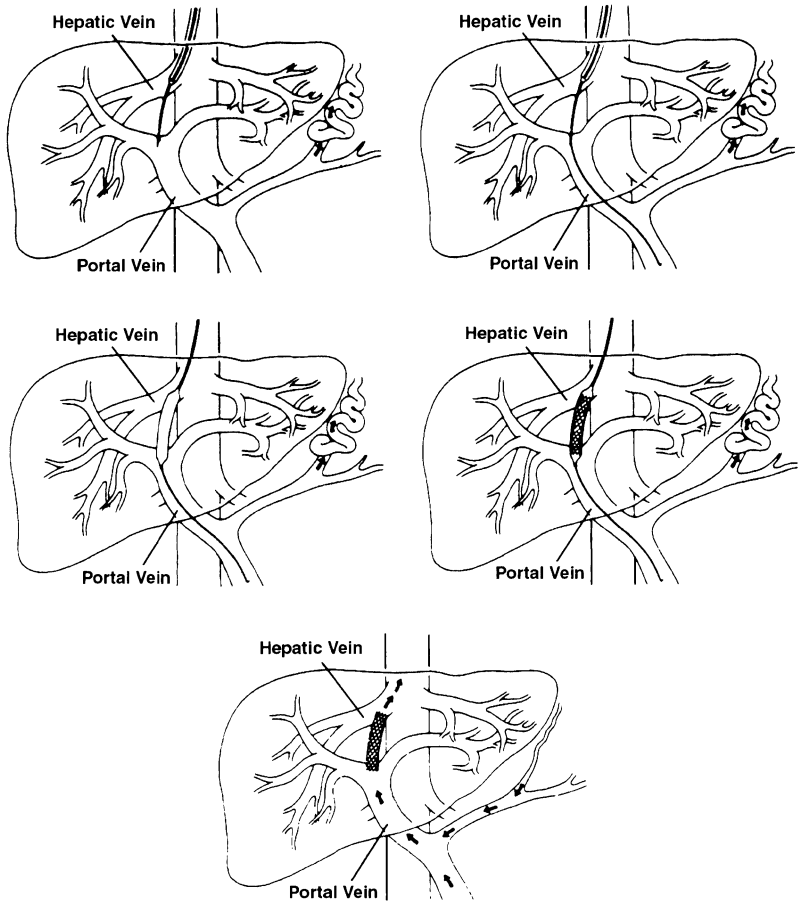

Fig. 3. Technique for placement of a transjugular intrahepatic portasystemic shunt (TIPS). A needle is placed from the hepatic into the portal vein via a transjugular approach. A guidewire is then advanced and used to dilate a tract and place an expandable stent. (Adapted from Zemel G, Katzen BT, Becker GJ, Benenati JF, Sallee DS. Percutaneous transjugular portosystemic shunt. JAMA 1991;266:390.) *Copyrighted © 1991 American Medical Association.* All rights reserved.

blood flow. Selective shunts attempt to decompress only the variceal-bearing compartment of the portal venous system while preserving some portal flow to the liver. Partial shunts, in contrast, incompletely decompress the portal system and maintain some portal flow.

Non-selective shunts include TIPS, the Eck fistula (end-to-side portacaval shunt), the side-to-side portacaval shunt, interposition shunts, and the conventional splenorenal shunt (Fig. 4). Numerous studies have compared TIPS with endoscopic management in prevention of recurrent bleeding. Although TIPS reduced the rate of rebleeding in a meta-analysis of 811 patients, overall survival was unchanged and the rate of encephalopathy was increased.[54] The primary reasons for recurrence of bleeding following TIPS are shunt thrombosis and stenosis, which occur in over 50% of patients within the first 2 years.[55] Although these problems may be managed by balloon dilatation or placement of a second shunt, there is relatively little data regarding long-term shunt patency. Because of frequent shunt failure, many patients require multiple interventions over time. In most series, both the number of interventions and overall costs are higher following TIPS compared to endoscopic therapy.[56] TIPS is therefore recommended only as salvage therapy in patients failing medical and endoscopic therapy.[42]

The end-to-side portacaval shunt has been compared to medical therapy in 4 randomized trials, none of which demonstrated a difference in survival.[29] All of the studies had a crossover bias in favor of medical management, because some patients received shunts for failure of medical therapy. Shunted patients had excellent control of bleeding, but encephalopathy was severe in up to 40% of patients. Although bleeding was the most common cause of death in medically

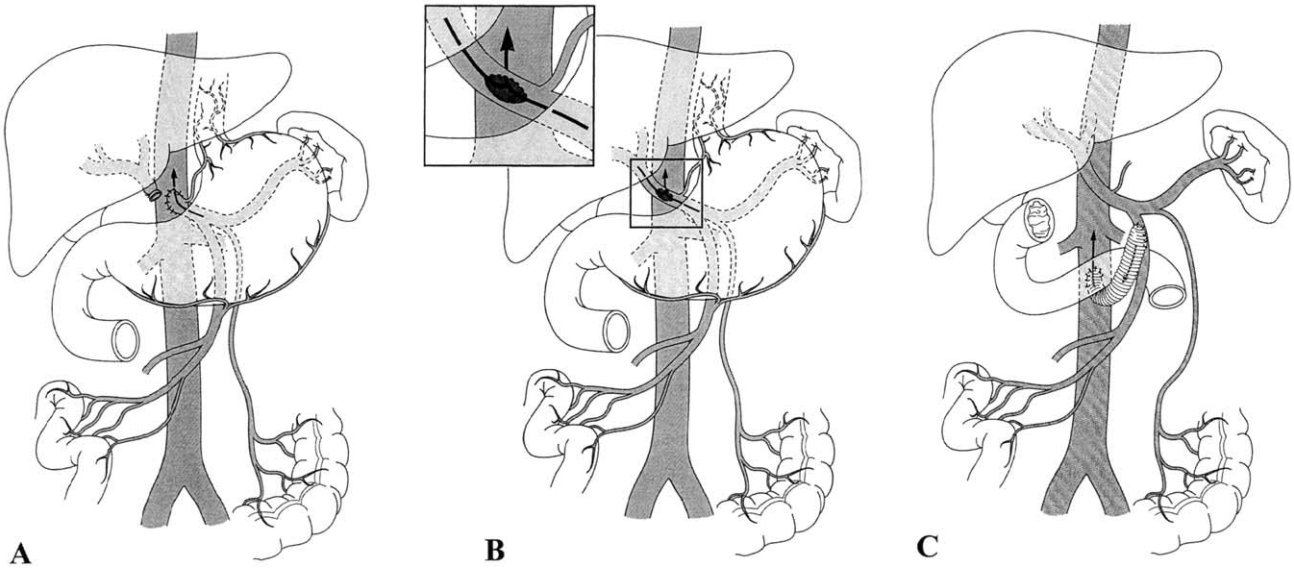

Fig. 4. Nonselective portasystemic shunts: (**A**) the end-to-side portacaval shunt (Eck Fistula), (**B**) the side-to-side portacaval shunt, and (**C**) the interposition mesocaval shunt. (Adapted from Marvin MR, Emond JC. Cirrhosis and portal hypertension. In Greenfield LJ, Mulholland MW, Oldham KT, Zelenock GB, Lillemoe KD, eds. Surgery: Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 974–975.) Reprinted with permission.

managed patients, accelerated hepatic failure was the leading cause of mortality following operative shunting.

The distal splenorenal shunt is considered to be a selective shunt because it can preserve superior mesenteric blood flow to the liver. The distal splenorenal shunt includes an anastomosis of the distal splenic vein to the renal vein and interruption of all collateral vessels connecting the superior mesenteric and gastrosplenic components of the portal system (Fig. 5). This leaves a decompressed gastrosplenic circuit and a high-pressure superior mesenteric circuit that continues to perfuse the liver. Ascites may be worsened by the distal splenorenal shunt, as mesenteric venous hypertension continues and retroperitoneal lymphatics are disrupted. A small diameter splenic vein (<7 mm) is a relative contraindication to the distal splenorenal shunt because of a high incidence of shunt thrombosis.

Collateralization between circuits following the distal splenorenal shunt leads to a loss of portal flow in approximately 50% of patients by 1 year. This occurs primarily in patients with alcoholic cirrhosis, while portal flow seems to be better maintained in patients with nonalcoholic cirrhosis and noncirrhotic portal hypertension.[57] Failure to ligate the coronary vein leads to rapid collateralization. Collaterals may also form through the pancreas (pancreatic siphon). This can be prevented by splenopancreatic disconnection, which consists of dissecting the full length of the splenic vein from the pancreas. This procedure, however, adds considerably to the technical difficulty of the operation.

There have been several controlled studies comparing the distal splenorenal shunt to nonselective shunts, none of which have demonstrated a survival advantage for either type of procedure.[58] Among patients with presinusoidal portal hypertension, encephalopathy is reduced following selective as opposed to nonselective shunting.[59] Of note, six of the seven controlled studies included a preponderance of alcoholic cirrhotics. Three of these have shown a decreased rate of encephalopathy following the selective shunt. Because encephalopathy appears to be less following the selective shunt, it can be recommended even in alcoholic patients.[60] Survival after the distal splenorenal shunt may be higher among those with nonalcoholic cirrhosis,[61] perhaps because of better preservation of hepatic portal perfusion.

In a meta-analysis of 4 trials comparing the distal splenorenal shunt and sclerotherapy, the relative risk of rebleeding was 0.16 with surgical shunting.[62] Neither survival nor encephalopathy was significantly different between the two interventions. The settings of the four studies were different, perhaps obscuring some differences between sclerotherapy and shunting. In a major metropolitan center, survival was significantly better with sclerotherapy than the distal splenorenal shunt.[63] Thirty-five percent of sclerotherapy patients required surgical rescue, and 85% of these patients were successfully salvaged. On the other hand, survival in a more rural setting was significantly better

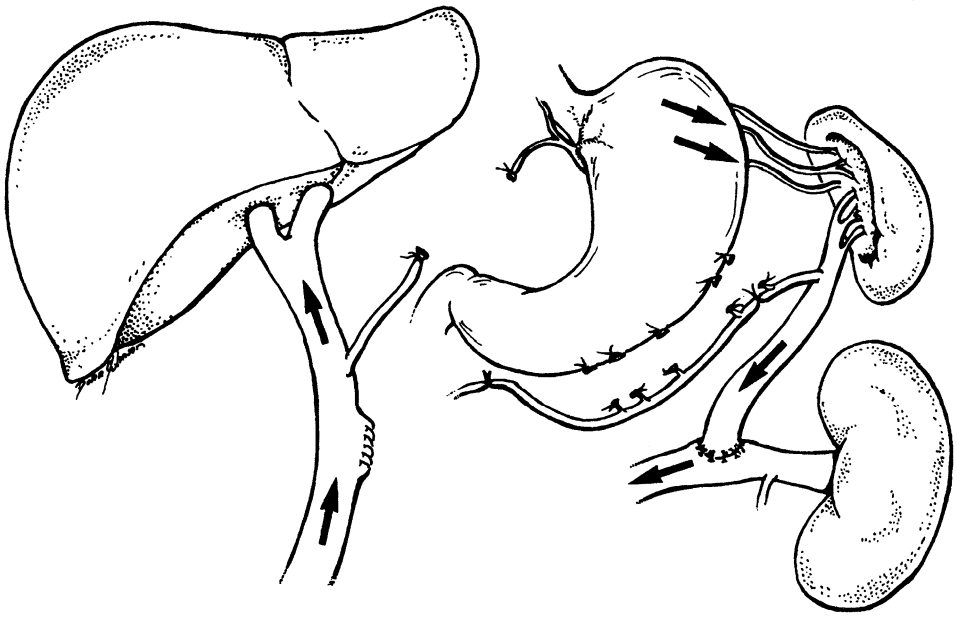

Fig. 5. The distal splenorenal shunt. (From Salam AA. Distal splenorenal shunts: Hemodynamics of total versus selective shunting. In Baker RJ, Fischer JE, eds. Mastery of Surgery, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1357–1366.) Reprinted with permission.

following surgery (53% 6-year survival, compared to 26% for sclerotherapy).[64] In this study only 31% of sclerotherapy failures were able to be salvaged with a surgical shunt. Given these disparate findings, a reasonable approach is endoscopic therapy with salvage shunting in patients with ready access to medical care. Primary shunting may be beneficial in rural areas or in patients unlikely to be compliant with ongoing medical management.

Like selective shunts, partial shunts aim to decompress varices while maintaining hepatic portal flow. Most small-diameter venous partial shunts either thrombose or dilate over time, thereby becoming nonselective. A small diameter polytetrafluoroethylene (PFTE) shunt, when combined with coronary vein ligation and division of collaterals, provides a fixed resistance and is more likely to maintain hepatopetal portal flow (Fig. 6).[65] Compared with larger, nonselective portocaval interposition shunts, the smaller (8 mm) PTFE shunt is followed by improved survival and less encephalopathy in some studies.[66,67]

The choice of surgical shunting versus TIPS is still in question. A randomized trial comparing TIPS and an 8 mm H-type portacaval prosthetic shunt found a lower failure rate with surgical shunting.[68] Rebleeding, liver transplantation, and late death were more frequent following TIPS. A separate, nonrandomized series found that rebleeding, encephalopathy, and shunt thrombosis are less but ascites is worse following a distal splenorenal shunt compared to TIPS.[69] In a decision-analysis economic model, the distal splenorenal shunt was significantly less expensive than TIPS, with fewer procedures required.[70] A multicenter randomized trial comparing TIPS with the distal splenorenal shunt is ongoing.

NONSHUNT SURGICAL THERAPY IN THE PREVENTION OF RECURRENT VARICEAL BLEEDING

There are a number of nonshunt surgical alternatives for the management of variceal bleeding. Simple esophageal transection is as effective as sclerotherapy, but variceal recurrence and rebleeding are common.[71] The Sugiura procedure (esophagogastric devascularization with splenectomy and preservation of the coronary and para-esophageal veins) had a rebleeding rate of less than 10% in a Japanese series (Fig. 7).[72,73] Modifications of this procedure have not been as successful in North America, likely due to a difference in the proportion of patients with alcoholic cirrhosis.[74] The Sugiura procedure is especially useful for patients who are unable to undergo shunting because of extensive portal, splenic, and superior mesenteric vein thrombosis.

LIVER TRANSPLANTATION

Liver transplantation is the only therapy that addresses both portal hypertension and the underlying

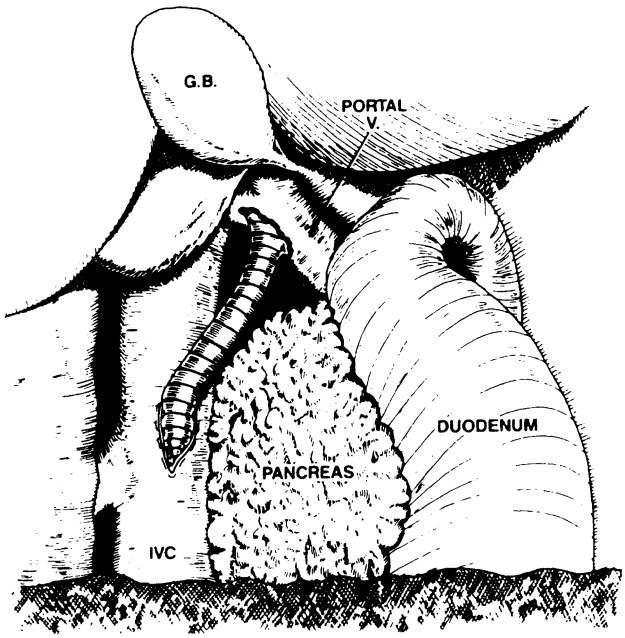

Fig. 6. The small-diameter diameter portacaval H graft interposition (partial) shunt. (From Sarfeh IJ, Rypins EB, Mason GR: A systematic appraisal of portacaval H-graft diameters: Clinical and hemodynamic perspectives. Ann Surg 1986;204:356–363.) Reprinted with permission.

liver disease. About 6000 liver transplants are performed annually in the United States, far more than the number of surgical shunts. Transplantation should be a consideration in all patients with end-stage liver failure. At the University of Wisconsin overall patient survival following liver transplantation is 89%, 79%, and 74% at 1, 3, and 5 years respectively. Transplant is most appropriate for patients with nonalcoholic cirrhosis or abstinent patients with alcoholic cirrhosis.

Shunt surgery may be used as a bridge to transplant in selected patients. In a series of 77 patients receiving a surgical shunt, 44 were considered eligible for later liver transplant.[75] Seven of these ultimately underwent transplantation, and only two died of liver failure without transplant. Survival of the transplant candidates who underwent a distal splenorenal shunt with transplantation as a salvage therapy was significantly better than that of patients receiving a transplant without a prior shunt operation.

In patients with a previous portasystemic shunt, the shunt should be taken down at the time of transplant surgery to preserve hepatic blood flow. Ligation of a distal splenorenal shunt is more difficult, and can best be managed via splenectomy or ligation of the renal vein.

ASCITES

Development of ascites is a sign of progressive liver dysfunction, and portends a worsening prognosis. Two-year survival with controlled ascites is 50%,[76] but mortality of patients with refractory ascites is 50% at 6 months and 75% at 1 year.[77] With development of the hepatorenal syndrome, mortality approaches 100% without liver transplant.[78]

Development of ascites is due to an imbalance in net capillary permeability and hydraulic and oncotic pressure gradients. Ascites does not occur until the portal-systemic pressure gradient is greater than 12 mm Hg,[79] and disappears if the gradient falls below 12 mm Hg following shunting.[80] Ascites was once thought to be primarily due to obstruction of portal venous outflow. Animal models and in vivo human data, however, suggest that increased portal inflow is more important. This increase in portal flow is due to nitric oxide–mediated vasodilatation of the splanchnic bed. Chronic vasodilatation activates the renin-aldosterone system, leading to sodium retention by the kidneys.

If possible the underlying source of cirrhosis should be treated. Ascites related to alcoholic cirrhosis will improve with abstinence,[81] while patients with autoimmune hepatitis may improve with steroid therapy. Salt restriction and diuretic therapy are the mainstays of medical therapy for ascites. Dietary changes alone (usually a limit of 2000 mg of sodium per day) are effective in only a small subset of patients. Spironolactone is the first-line diuretic of choice, as it is an aldosterone antagonist. The addition of furosemide, although not confirmed in randomized trials, is thought to prevent hyperkalemia. The initial goal of diuretic therapy should be a weight loss of approximately 1 pound per day. Patients refractory to medical therapy require more aggressive intervention, often including large-volume paracentesis with or without albumin infusion.[82,83]

TIPS is effective in 80% of patients with medically intractable ascites, but carries the risk of encephalopathy in 30% of patients.[84] Although ascites appears to be better controlled with TIPS than serial paracentesis, survival is not improved.[85] Surgical portasystemic shunting is occasionally indicated for patients with ascites and variceal bleeding who fail TIPS. Peritoneovenous shunts are rarely indicated; they have a high rate of infection and thrombosis and may lead to disseminated intravascular coagulation.[86] In a recent prospective randomized trial, control of ascites and overall survival were significantly better following TIPS compared to peritoneovenous shunting.[87] Liver transplantation should be considered when ascites complicates chronic liver disease.

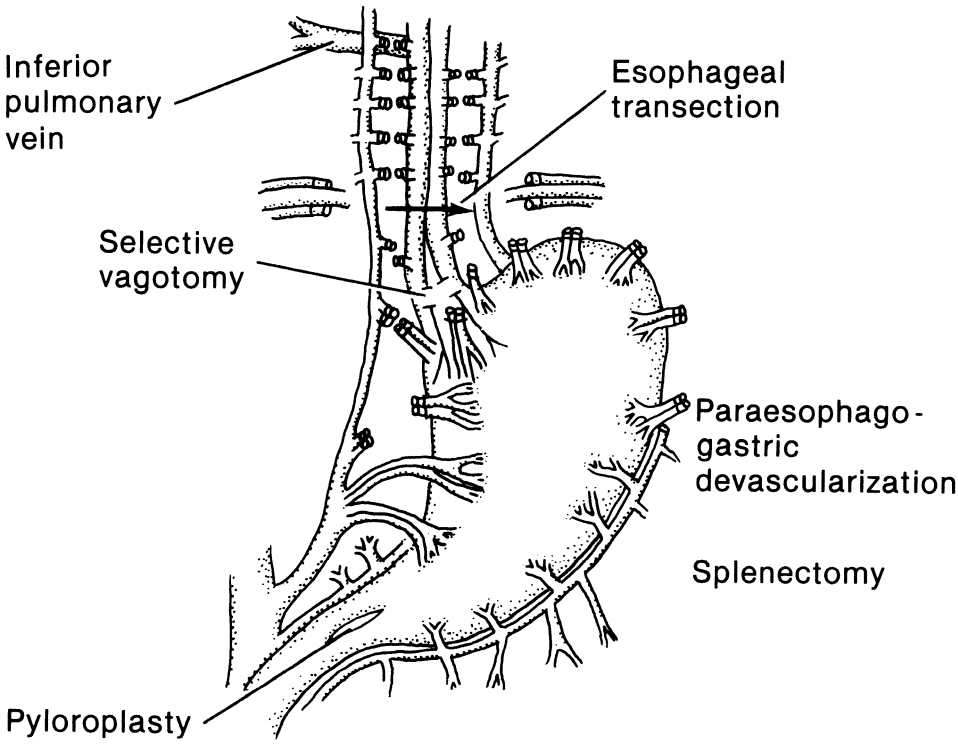

Fig. 7. Esophageal transection with esophagogastric devascularization (Sugiura procedure). (Modified from Sugiura M, Futagawa S: Further evaluation of the Sugiura procedure in the treatment of esophageal varices. Arch Surg 1977;112:1317.)

RECOMMENDATIONS

Treatment of variceal bleeding and portal hypertension has changed markedly over the last 30 years with the development of endoscopic therapies, improved medical management, liver transplantation, and TIPS. Management of acute variceal bleeding begins with adequate resuscitation and correction of coagulopathy followed by endoscopic control of bleeding. Band ligation is more successful but also more technically demanding than sclerotherapy, and either technique is acceptable. Medical therapy with vasopressin and nitroglycerin or with octreotide is also useful, with a combination of octreotide and endoscopic therapy being the most effective. Antibiotics should be given during an episode of variceal bleeding to prevent secondary complications. With failure of medical and endoscopic surgery, emergent nonoperative or surgical shunting should be considered.

Long-term management of varices now relies on the relative appropriateness of liver transplantation. Suitable patients with decompensated hepatic function (Child-Pugh classes B and C) or a poor quality of life secondary to liver disease should undergo transplantation as soon as possible. If a transplant is not readily available, or if a patient is not suitable for transplant, medical and endoscopic therapy should be the first line of treatment.

Good risk (Child-Pugh classes A and B) patients with refractory variceal bleeding despite pharmacotherapy and/or endoscopic therapy should receive a selective shunt or small diameter PTFE partial shunt. Operative shunting is also indicated as primary therapy for noncompliant patients and for patients who live in remote areas. Data comparing TIPS and surgical shunting in this patient population are not yet available. Although TIPS has replaced surgical shunting in many institutions, the distal splenorenal shunt has better patency and less rebleeding. Nonselective shunting (TIPS or side-to-side portosystemic shunt) is indicated for patients with intractable ascites and variceal bleeding. TIPS is especially indicated for patients with failure of endoscopic therapy who may be transplant candidates in the near future and for poor risk (Child-Pugh class C) nontransplant candidates (e.g., active alcoholics) who are unlikely to outlive their TIPS. A recommended treatment algorithm for variceal bleeding is shown in Fig. 8.

Ascites carries high morbidity and mortality. Initial treatment consists of managing the underlying cause

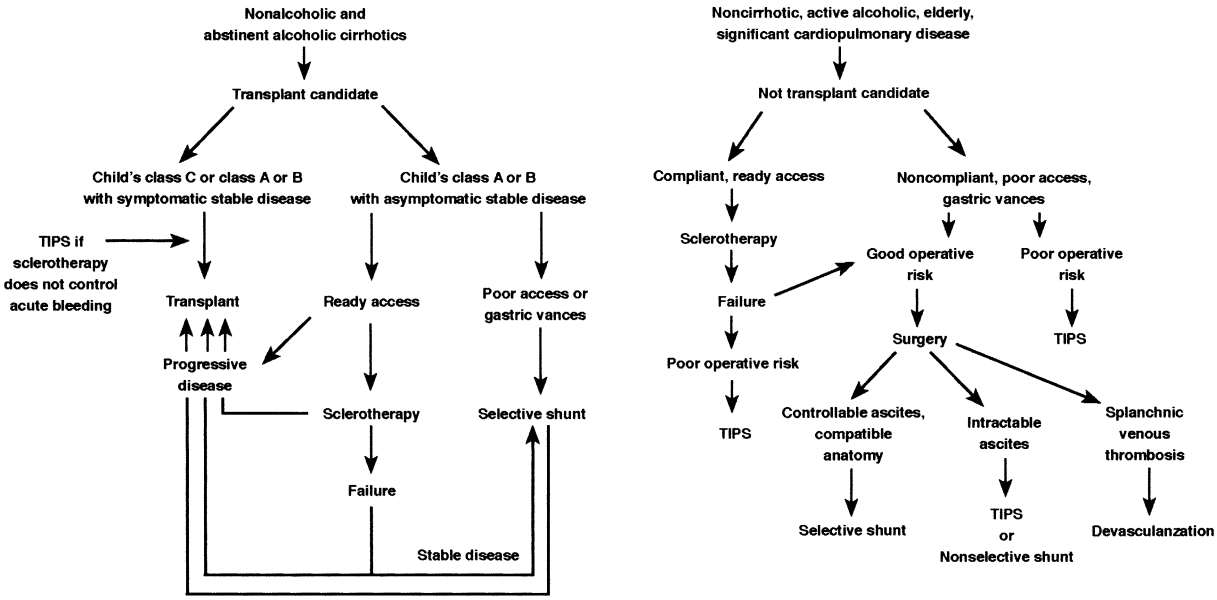

Fig. 8. Recommended treatment algorithm for definitive therapy of variceal bleeding. (From Rikkers LF. Surgical complications of cirrhosis and portal hypertension. In Townsend CM Jr, ed. Sabiston Textbook of Surgery, 17th ed. Philadelphia: Elsevier; 2004. p. 1592.) Reprinted with permission.

of cirrhosis. Salt restriction alone (<2000 mg/day) is successful in only a small number of patients. A combination of spironolactone and furosemide improves ascites by targeting the renin-aldosterone system while preventing hypokalemia. With failure of medical therapy, both large-volume paracentesis and TIPS are useful. Liver transplantation should be considered in all patients with chronic liver disease and ascites.

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Benign Mesenteric Schwannoma

Shigeki Minami, M.D., Kazuya Okada, M.D., Mitsutoshi Matsuo, M.D., Tomayoshi Hayashi, M.D., Takashi Kanematsu, M.D., F.A.C.S.

KEY WORDS: Schwannoma, mesentery, benign

Schwannoma is a benign spindle cell tumor derived from Schwann cells that line the nerve sheaths. Schwannoma rarely occurs in the mesentery. We report a case of an asymptomatic jejunal mesenteric schwannoma that was found incidentally.

CASE REPORT

A 54-year-old woman was admitted to our department for an abdominal mass. The 8-cm mass with elastic hard consistency at the upper middle abdomen was found on physical examination, computed tomography (CT) scan, and magnetic resonance (MR) imaging. She had no clinical symptoms or history of von Recklinghausen's disease. Laboratory studies including tumor markers showed no abnormal findings. An ultrasonographic examination showed a well-circumscribed 7 × 5-cm mass, including a hypoechoic region, inferior to the pancreas and anterior to the superior mesenteric artery and vein. The mass was found to be mobile on change of position during the ultrasonographic examination. Barium study did not show any abnormality of the duodenum, jejunum, and colon. CT scan demonstrated a well-defined, low-density tumor just anterior to the duodenum and the superior mesenteric artery and vein. Enhanced CT scan after intravenous contrast administration showed a locally enhanced round tumor with a cystic component. No calcification was demonstrated. On T1-weighted MR images, the tumor was isointense with skeletal muscle, and no high-intensity area was seen (Fig. 1, *A*). On T2-weighted images, the mass was predominantly hyperintense (Fig. 1, *B*). There was no evidence of invasion of the adjacent organs. No encasement of vessels or tumor stain was visualized on abdominal angiography. These findings suggested a benign solid tumor, such as gastrointestinal stromal tumor or neurogenic or myogenic tumor originating in the mesentery.

A laparotomy revealed an encapsulated, noninvasive tumor in the jejunal mesentery. Simple enucleation of the tumor was performed without bowel resection. The cut surface of the tumor revealed an 8.0 × 7.0 × 4.8-cm encapsulated mass. The tumor was yellowish and showed cystic change with hemorrhage (Fig. 2, *A*). Histologically, the tumor was composed of an Antoni A–type component featuring spindle-shaped cells with nuclear palisading (Fig. 2, *B*). The tumor also had an Antoni B–type component. No mitotic figures and no atypical appearance was observed. Immunohistochemically, the tumor cells were diffusely positive for S-100 protein but negative for smooth muscle actin. These findings were compatible with a benign mesenteric schwannoma without any malignant transformation.

The patient had an uneventful postoperative course. She remains well 5 months after her operation, without any signs of recurrence.

DISCUSSION

Schwannomas may occur nearly anywhere in the body but are rare in the mesentery. Common locations include the lower extremities, upper extremities, trunk, head and neck, retroperitoneum, mediastinum, and pelvic space. Schwannomas usually occur in young to middle-aged adults, and women are affected twice as often as men. The tumors are generally asymptomatic and are discovered incidentally. Simple

From the Department of Surgery (S.M., K.O., M.M., T.K.), Nagasaki University Graduate School of Biomedical Sciences, and Department of Pathology (T.H.), Nagasaki University Hospital, Nagasaki, Japan.
Reprint requests: Shigeki Minami, M.D., 1-7-1 Sakamoto, Nagasaki city, Nagasaki 852-8501, Japan. e-mail: shiminami-gi@umin.ac.jp

1091-255X/05/$—see front matter
doi:10.1016/j.gassur.2005.04.018

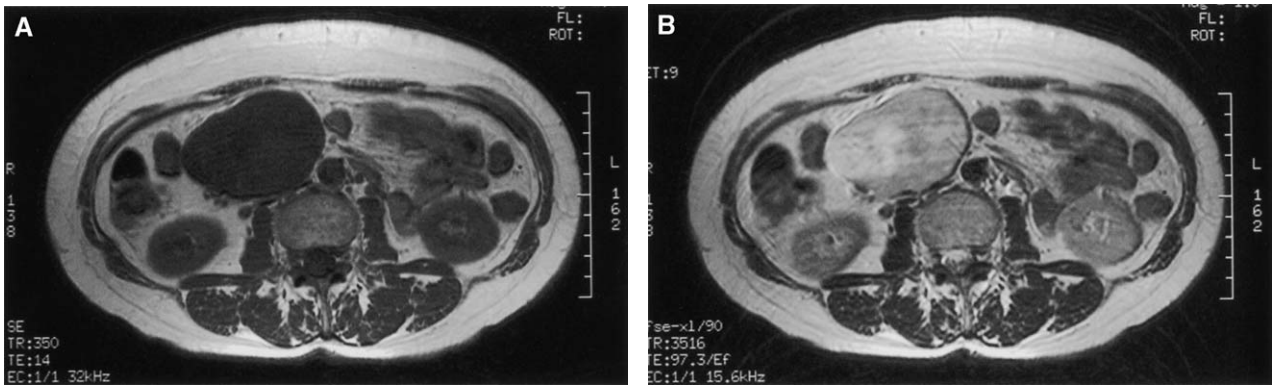

Fig. 1. (**A**), T1-weighted MR image shows a round mass of homogeneous intermediate signal intensity similar to skeletal muscle in the right anterior mid abdomen. (**B**), T2-weighted MR image shows an increased signal intensity in the mass.

enucleation is usually adequate for mesenteric schwannoma.

At CT scanning, schwannomas appear as well-circumscribed round or oval homogeneous masses with CT densities ranging from near that of water to that of muscle.[1] On enhanced CT, schwannomas demonstrate variable homogeneous or heterogeneous enhancement due to pathologically confluent areas of hypocellularity adjacent to dense cellular or collagenous regions, xanthomatous change, and/or cystic degeneration.[2,3] In our case, on enhanced CT, a moderately enhanced area and an area of low density were intermingled with hypercellular tissue and a cystic component.

MR findings in schwannomas have been described as masses with low-intensity on T1-weighted images and with high-intensity on T2-weighted images due to Antoni A and B areas and secondary degenerative changes.[2,4] In this case, the tumor exhibited mixed signal intensity on T2-weighted images. The hyperintense area on T2-weighted images correlated with the cystic portion and the relatively hyperintense area corresponded to the solid components of the tumor.

Microscopically, schwannomas are encapsulated and composed of various mixtures of hypercellular component (Antoni A area) and loose hypocellular component (Antoni B area). Immunostaining for S-100 protein is uniformly positive.[5] There is, however, overlap of these two types. Verocay bodies (palisaded nuclei) may be present in the Antoni A area. Central necrosis, hemorrhage, calcification, and cyst formation may be seen in large lesions.[5] In this case, the tumor consisted of an Antoni A component and an Antoni B area and had hemorrhagic change in the central lesion. Immunohistochemically, the tumor

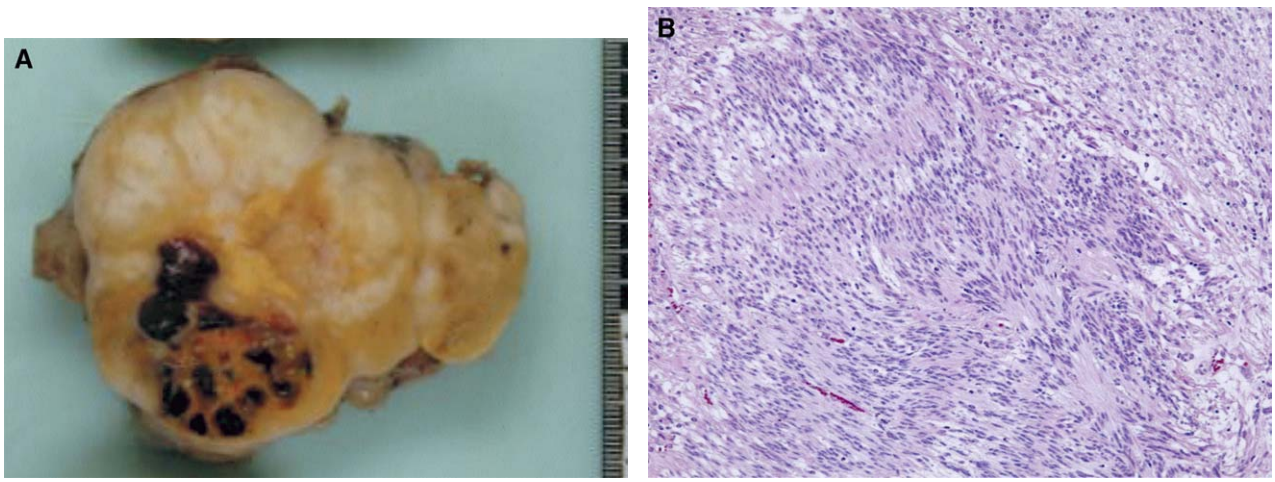

Fig. 2. (**A**), Cut surface of the tumor shows an encapsulated mass with cystic change. (**B**), Microscopic section of the tumor shows an Antoni type A component with palisading nuclei.

also showed positivity for S-100 protein. We, therefore, diagnosed the tumor as benign mesenteric schwannoma.

In summary, tumors have been found incidentally in recent years because of advances in diagnostic imaging. With regard to the differential diagnosis of mesenteric tumors, the possibility of mesenteric schwannoma should be considered. Preoperative diagnosis is difficult, but CT scanning and MR imaging are useful and effective methods for diagnosing mesenteric schwannoma. Accurate preoperative localization and characterization are important in allowing a surgical approach.

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