Editorial

New Sections for Our Journal

Keith A. Kelly, M.D., John L. Cameron, M.D., Co-Editors

The Co-Editors of the JOURNAL OF GASTROINTESTINAL SURGERY (JOGS) are pleased to introduce two new sections in our JOURNAL, one entitled "How I Do It" and the other, "Gastrointestinal Images." These new sections appear for the first time in this issue and will appear periodically in subsequent issues.

The quality of the operations surgeons perform influences the outcomes of these operations. Operations done well, for the right indications and in the right patients, generally result in good outcomes. In contrast, patients may have complications after operations that are poorly done, and so have less favorable outcomes. The quality of the operation is of primary importance to the patient and to the surgeon.

Surgeons learn from their teachers and from others about how to perform operations. They practice what they learn and modify their techniques, as needed, to improve their operations. We write a good deal in our journals about the indications, outcomes, and quality of life after operations, but less about the actual techniques of these operations, especially the techniques used by recognized experts in the field. We all recognize, however, that the tips about operating that we learn from others sometimes enable us to perform better operations—that is, operations that result in more favorable outcomes.

One good way to improve is to watch others operate, especially those who are experts in the operation in question. Many of us have had the experience of watching an expert operate and learning a new way of exposing the field, placing sutures or staples, avoiding bleeding or controlling it, and reconstructing the field after resection. The newly learned points often result in a faster recovery after operation and a better result for our patients.

Some surgeons travel, either by themselves or in groups, to other locations to watch experts perform operations as part of their continuing education in surgery. One of the oldest and yet still active traveling groups is the Society of Clinical Surgery. This Society, founded more than 100 years ago by Doctors Harvey Cushing, Will Mayo, and others, has endured, in part, because its members recognize the value of watching others operate in their own operating rooms. Unfortunately, with the pressures of today's practice, most of us do not have the opportunity to travel to other locations on such a mission as often as we would like, if at all.

With these points in mind, we are bringing to our readers a new section in the JOURNAL—a "How I Do It" section that is written and illustrated by experts in the field. We expect that reading this section will be the next best thing to being in the operating room with these experts, watching them operate. We anticipate that these reports will be of benefit to surgeons who read them and to their patients who might subsequently undergo a better operation.

The other section we are adding is entitled "Gastrointestinal Images." An old saying comes to mind: "One good picture is worth a thousand words." How many times have we seen a picture once and remembered it forever? So it can be with images important to gastrointestinal surgery. Stored away in our memory, they can be recalled in the future for use in the care of our patients. We think you will find these images useful.

We encourage surgeons and others interested in gastrointestinal disease to submit material for consideration for publication in the new "How I Do It" and "Gastrointestinal Images" sections of the JOURNAL. We believe these sections will be well received by our readers and will help them to serve their patients better.

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Proctocolectomy With Ileoanal Anastomosis

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INTRODUCTION

Until about 25 years ago, proctocolectomy with a Brooke ileostomy was the only reliable surgical option for patients with chronic ulcerative colitis (CUC) or familial adenomatous polyposis (FAP). Despite the fact that this operation eliminated all diseased tissue and the risk of primary malignant transformation, it was poorly accepted by patients and their physicians because of the significant psychological and psychosocial implications associated with a permanent, incontinent abdominal ileostomy, particularly in young and physically active patients. It is for this reason that surgeons sought other alternatives to total proctocolectomy and ileostomy that could provide the patient with continence and acceptable function.

Early attempts at continence, such as the continent ileostomy or Kock pouch,[1] were fraught with technical complications. Kock's original continent ileostomy was constructed entirely from terminal ileum with an ileal pouch that served as a reservoir and an ileal conduit connecting the pouch to a cutaneous stoma. Poor functional results soon led to a modification that included an intestinal nipple valve between the pouch and the stoma. Despite its problems, patients undergoing total proctocolectomy could, for the first time, be offered an option for continence. Although the Kock pouch remains an option for patients who wish to remain continent but are either not candidates for or have failed an ileoanal procedure or who, for other reasons, prefer a permanent ileostomy, it has limited clinical usefulness and few such pouches are currently being constructed despite a recent study that reports satisfactory long-term function in more than two thirds of patients up to 30 years after operation.[2]

More than 50 years ago, two surgical pioneers, Mark Ravitch and David Sabiston,[3] proposed the original concept of restorative proctocolectomy with anal sphincter preservation. Rather than ablating the entire rectum, anus, and anal sphincter during a standard proctocolectomy, they purported that because CUC and FAP are mucosal diseases, they could selectively dissect away all the disease-bearing rectal mucosa down to the dentate line of the anus, thereby preserving the rectal muscular cuff and anal sphincter apparatus. The continuity of the intestinal tract could then be reestablished by extending the terminal ileum into the pelvis endorectally, and circumferentially suturing it to the anus in an end-to-end fashion (Fig. 1). The potential advantages of this novel surgical approach included preservation of parasympathetic innervation to the bladder and genitals, elimination of the abdominal perineal proctectomy and, if performed carefully, preservation of the anorectal sphincter. However, and most important, the permanent abdominal stoma was eliminated and continence was maintained. Even though poor functional results forced the operation to be largely abandoned, due in part to a poor understanding of anal sphincter physiology at the time, the pioneering efforts of Ravitch and Sabiston set the stage for what has become the definitive procedure for patients seeking surgical intervention for CUC and FAP.

Since the resurgence of the ileoanal procedure nearly 25 years ago led by Utsunomiya et al.[4] and Parks and Nicholls,[5] the procedure has undergone a number of technical refinements, including the introduction of an ileal pouch,[6,7] that have greatly improved function and reduced the complication rate. Since then, there has been a dramatic increase in the use of restorative proctocolectomy, especially as

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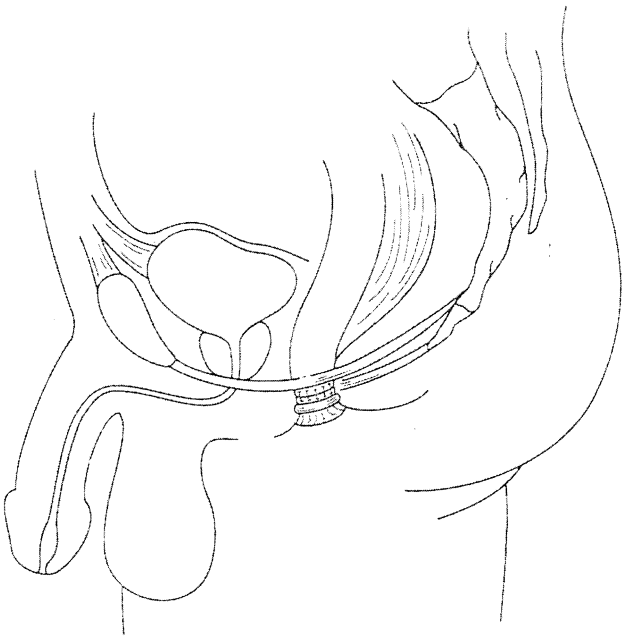

Fig. 1. End-to-end ileoanal anastomosis after colectomy, mucosal proctectomy, and endorectal ileoanal pull-through. (Adapted from Becker JM, Stucchi AF. Ulcerative colitis. In Greenfield LJ, et al., eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

surgeons became more familiar with the technical aspects of the procedure. Despite the controversies surrounding technical issues such as mucosectomy, diverting loop ileostomy, pouch configurations, and staged procedures, most surgeons agree that restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the definitive operation for the surgical treatment of patients with CUC, FAP, and more recently hereditary nonpolyposis colorectal cancer. Although this procedure is generally contraindicated for patients with Crohn's disease, there are reports of acceptable long-term outcomes in select patients.[8]

SURGICAL INDICATIONS

Recent reports estimate that 30% to 40% of patients with CUC undergo total proctocolectomy, in part because of the chronic nature of the disease, the tendency for relapse, and the significant risk of malignant degeneration.[9] The indications for surgical intervention vary widely, and these differing indications each have implications for the timing of surgery. Indications for surgical intervention of CUC include the following: (1) massive or unrelenting hemorrhage; (2) toxic megacolon with imminent or frank perforation; (3) fulminating acute ulcerative colitis that is unresponsive to medical therapy; (4) obstruction from stricture; (5) significant dysplasia or suspected or frank colon cancer; (6) systemic or extracolonic complications; and, (7) intractability.[10] In children and adolescents, failure to thrive, retardation of growth and development, and failure to mature at an acceptable rate are also indications for surgery. For most patients with CUC, however, surgical intervention becomes necessary when the disease becomes refractory to medical management or becomes a physical and social burden to the patient. With the advent of the sphincter-sparing IPAA, it is critically important to avoid standard proctectomy whenever possible and to distinguish diagnostically patients with CUC from those with Crohn's disease.

TOTAL PROCTOCOLECTOMY WITH ILEAL POUCH–ANAL ANASTOMOSIS

Just before surgery, flexible sigmoidoscopy is performed to confirm the diagnosis and to assess the status of the inflammatory process, especially of the rectal mucosa. In patients with active disease of the rectum, steroid or salicylate treatment is accelerated in the immediate preoperative period.

Although patient selection criteria have become less stringent as surgeons have become more familiar with this operation, there remain established factors associated with improved outcomes. Perhaps one of the more important preoperative criteria that can be a useful predictor of a successful outcome with acceptable continence postoperatively is adequate anal sphincter function. We routinely use anorectal manometry to establish preoperative sphincter tone. Although IPAA is contraindicated in patients found to have poor preoperative manometric results, we find that most patients, even into their sixties and seventies have acceptable results. This also raises the confidence of both the patient and the surgeon that the outcome will be acceptable. However, it is vitally important in proposing IPAA that the patient fully understands the physiology and technique of the operation and has realistic expectations about the outcome.

Because an inverse relationship was found between ileal compliance and stool frequency in patients after an end-to-end or straight ileoanal anastomosis,[6] surgeons sought to accelerate the process of ileal adaptation to improve function. An important technical advance that greatly improved the functional outcome was the surgical construction of an ileal pouch or reservoir proximal to the ileoanal anastomosis.[11] Although a number of pouch configurations such

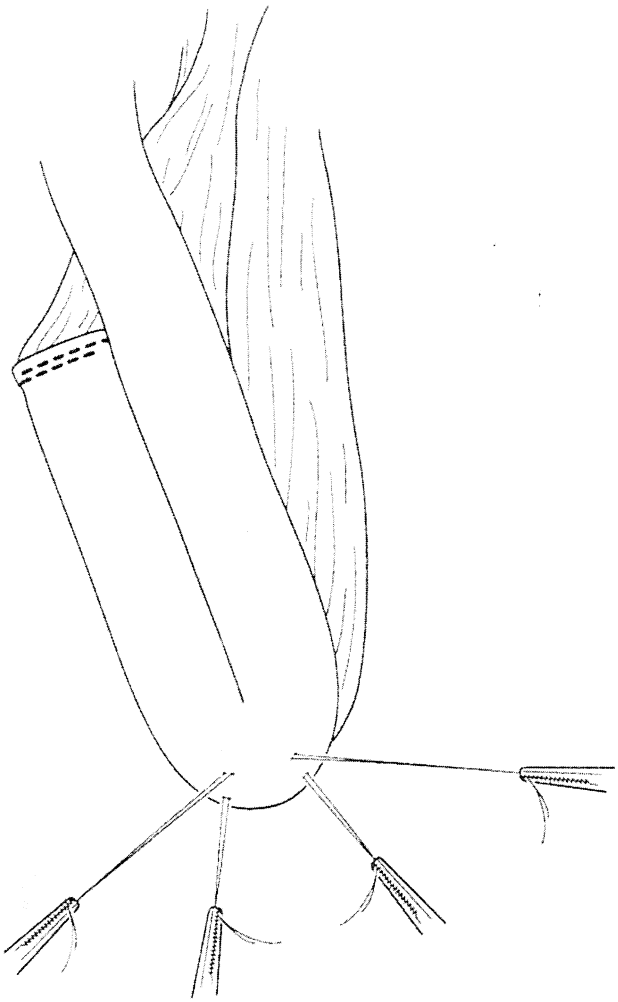

Fig. 2. Ileal J-pouch configuration in patients undergoing ileal pouch–anal anastomosis. (Adapted from Becker JM, Stucchi AF. Ulcerative colitis. In Greenfield LJ, et al., eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

as the S-pouch, W-pouch, and the lateral side-to-side isoperistaltic pouch have been used, the most commonly used configuration accompanying IPAA at major centers, and the one that is used at this center, is the 15 cm ileal J-pouch (Fig. 2).

A similarly important technical addition to the IPAA was the construction of a temporary diverting loop ileostomy. This allows diversion of the fecal stream during the early weeks of ileal pouch and ileoanal anastomotic healing, significantly reducing the potential risk of pelvic sepsis and ileal pouch and ileoanal anastomotic dehiscence. Thus at most major centers, including this one, the operation is typically performed in two "stages." The first stage consists of colectomy, mucosal proctectomy, endorectal IPAA, and diverting loop ileostomy. Approximately 8 weeks after the initial operation, the second stage is performed in which the loop ileostomy is closed. Although some surgeons have eliminated the loop ileostomy in low-risk patients, most reports have indicated that the 30-day complication rate is substantially reduced in patients with a temporary diverting ileostomy despite the need for a second surgical procedure to close the loop ileostomy.

At this center, colectomy with mucosal proctectomy and ileoanal anastomosis is performed as a two-team operation with the patient placed on the operating table in a modified lithotomy position (Fig. 3). One team carries out a standard colectomy through a midline abdominal incision. The mesentery of the colon is divided at a convenient distance from the bowel wall (Fig. 4). The proximal rectum is mobilized and transected above the levator ani sling. Simultaneously the transperineal rectal mucosal dissection is accomplished by the rectal team. Exposure is facilitated by a Lone Star retractor and hooks (Lone Star Medical Products, Houston, TX) (Fig. 5). The submucosa of the anal canal then is infiltrated with a dilute (1:200,000) solution of epinephrine. A circumferential incision is made at the dentate line with a needle-tip electrocautery, and the rectal mucosa is carefully dissected away from the anal sphincter and then the rectal muscularis (Fig. 6). The largely

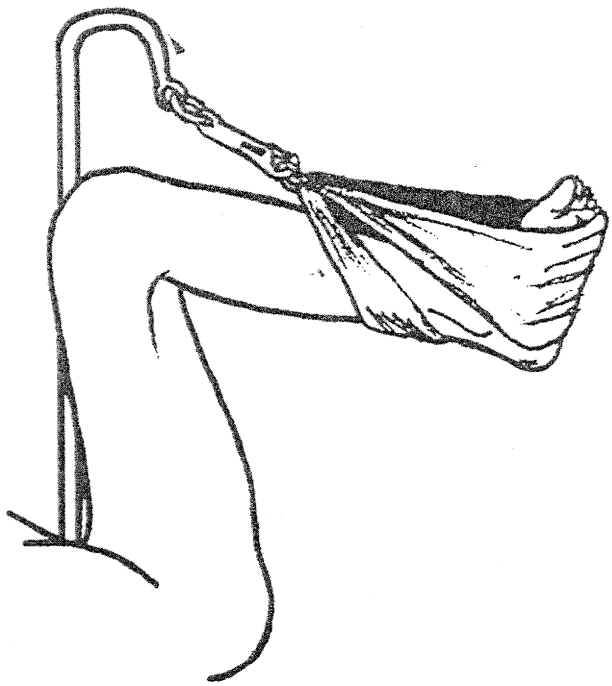

Fig. 3. The patient is placed on the operating table in the lithotomy position. (Reprinted with permission, *AORN Journal*, 55 [April 1992], p. 1012. Copyright © AORN, Inc., 2170 S. Parker Road, Suite 300, Denver, CO 80231.)

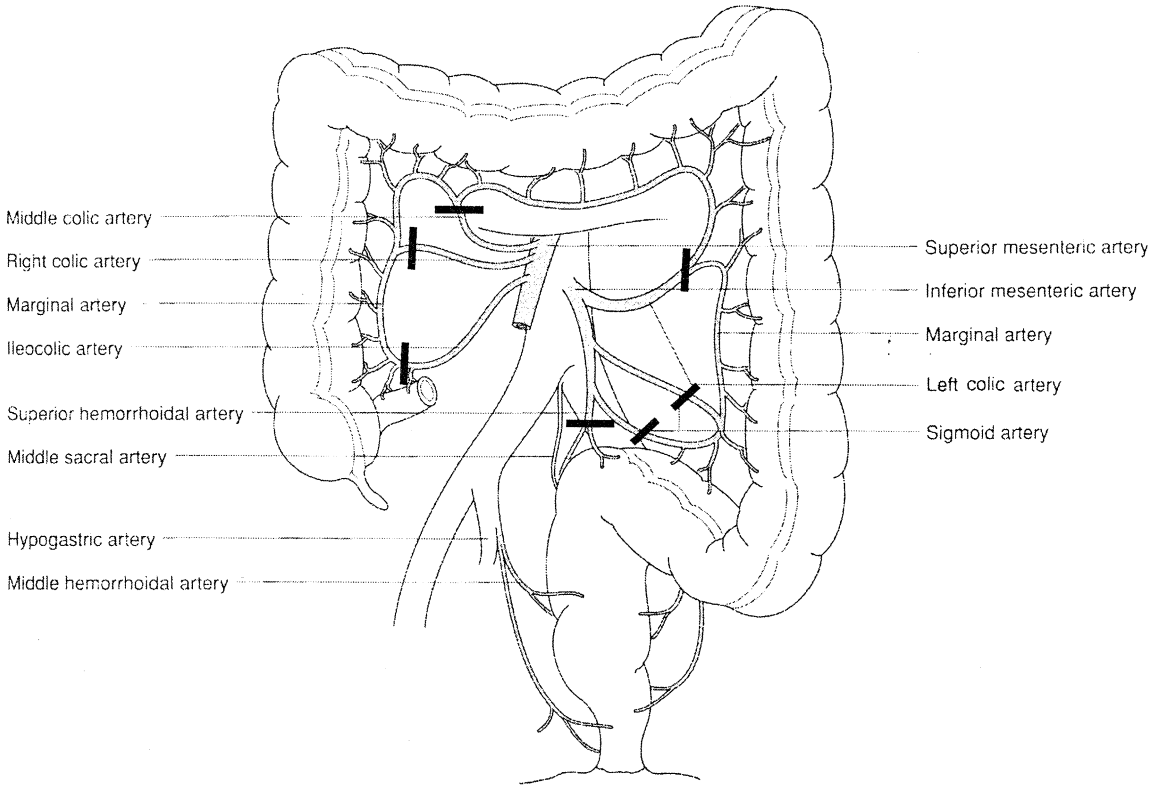

Fig. 4. Arterial blood supply to the colon showing mesenteric divisions. (Adapted from Sweeney JF. Colonic anatomy and physiology. In Greenfield LJ, et al, eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1063–1070.)

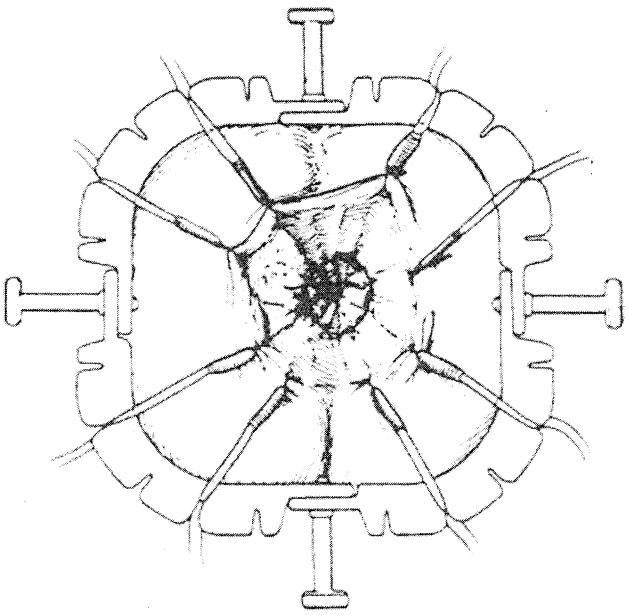

Fig. 5. Lone Star retractors used to facilitate the transanal mucosal proctectomy. (Adapted from Sagar PM, Pemberton JH. Role of the ileal pouch procedure-pouch construction, and the ileoanal anastomosis. In Allen RN, et al, eds. Inflammatory Bowel Diseases, 3rd ed. New York: Churchill Livingstone, 1997, pp 781–791.)

blunt dissection is facilitated by electrocautery or harmonic scalpel for hemostasis.

With the mucosal dissection completed, a 15 cm ileal J-pouch is constructed using two firings of a mechanical stapler applied sequentially through an enterotomy in the apex of the pouch (Fig. 7). Electrocautery is used to create the enterotomy at the apex of the 15 cm loop of terminal ileum. The forks of a 75 mm intestinal anastomosing stapler (PROXIMATE Linear Cutter; Ethicon-Endosurgery, Inc., Piscataway, NJ) are passed into the intestinal limbs, and the instrument is fired. This is repeated while the limbs are telescoped onto the stapler, until a 15 cm side-to-side anastomosis is completed. The apical enterotomy is closed with a simple 2-0 polypropylene purse-string suture. The newly constructed pouch is then filled with saline solution via a catheter to measure pouch volume at a fixed intraluminal pressure of 10 cm of H_2O and to assess leakage of the staple lines.

The ileal pouch is extended into the pelvis endorectally and fixed to the sphincter in four quadrants with 2-0 polyglycolic acid sutures. Its apex is opened and sutured circumferentially to the dentate line with interrupted 3-0 polyglycolic acid sutures (Fig. 8). To allow adequate mobility of the terminal ileum, the

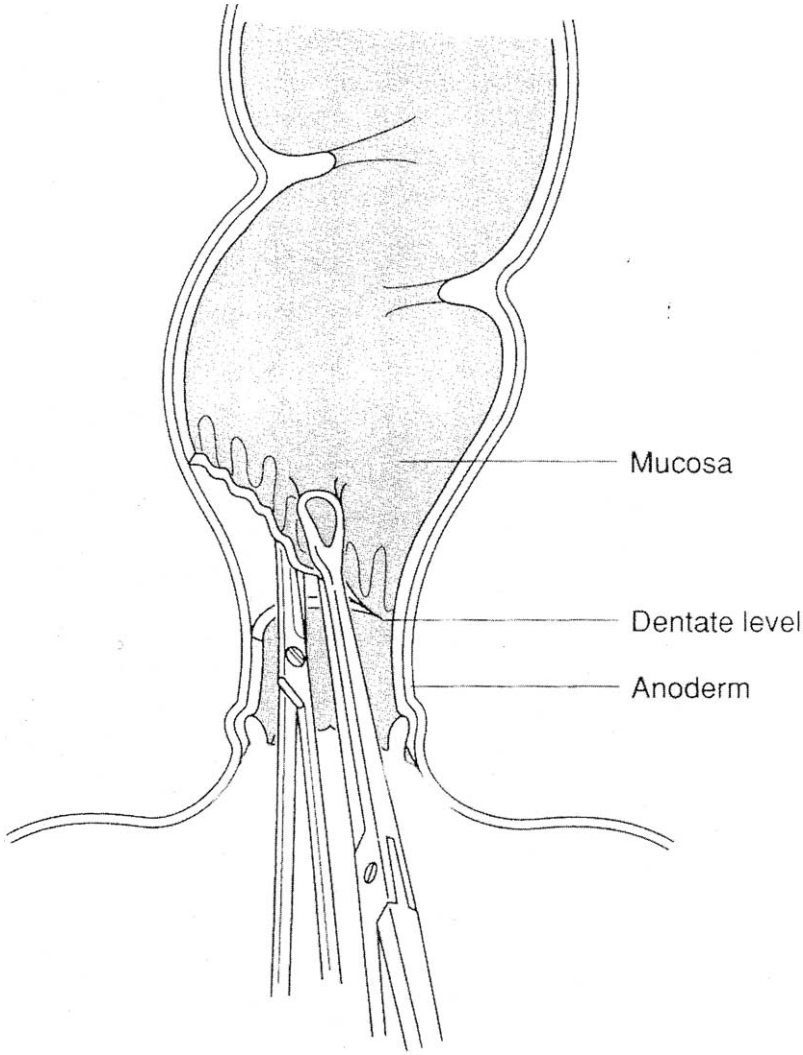

Fig. 6. Transanal mucosal proctectomy. A circumferential incision is made at the dentate line, and the rectal mucosa is carefully dissected away from the anal sphincter and the rectal muscularis. (Adapted from Becker JM, Stucchi AF. Ulcerative colitis. In Greenfield LJ, et al, eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

ileal branch of the iloecolic artery must be ligated and divided and the superior mesenteric artery mobilized to where it arises from below the pancreas.

With the ileal pouch–anal anastomosis completed, the patient is taken out of the lithotomy position. Gloves and instruments are replaced, and the abdomen is redraped. A closed-suction drain is placed in the pelvis and a mobile loop of ileum, approximately 40 cm proximal to the ileal pouch, is brought out through the abdominal wall in a previously marked ostomy site and suspended over an ostomy rod. The fascia and skin are closed, and the ileal loop is opened and the loop ileostomy is sutured with interrupted 4-0 polyglycolate acid sutures (Fig. 9).

Approximately 4 weeks after the initial operation, a standardized radiographic study is performed to assess integrity of the ileal pouch and the ileoanal anastomosis. Eight weeks after ileoanal anastomosis, anal manometry is repeated, and the ileal pouch capacity is measured. The loop ileostomy is then closed using a stapling technique, which has greatly simplified this operation (Fig. 10). A transverse elliptical incision is made around the loop ileostomy. The loop is then dissected free from the subcutaneous tissue and the fascia. The afferent and efferent limbs are divided with a stapling device. A side-to-side functional end-to-end anastomosis is then created between the two limbs with a 75 mm stapler. The enterotomy is closed with a 60 mm PROXIMATE Linear Stapler. The anastomosis is then placed back into the peritoneal cavity, and the fascia, subcutaneous tissue, and skin are closed. By protocol,

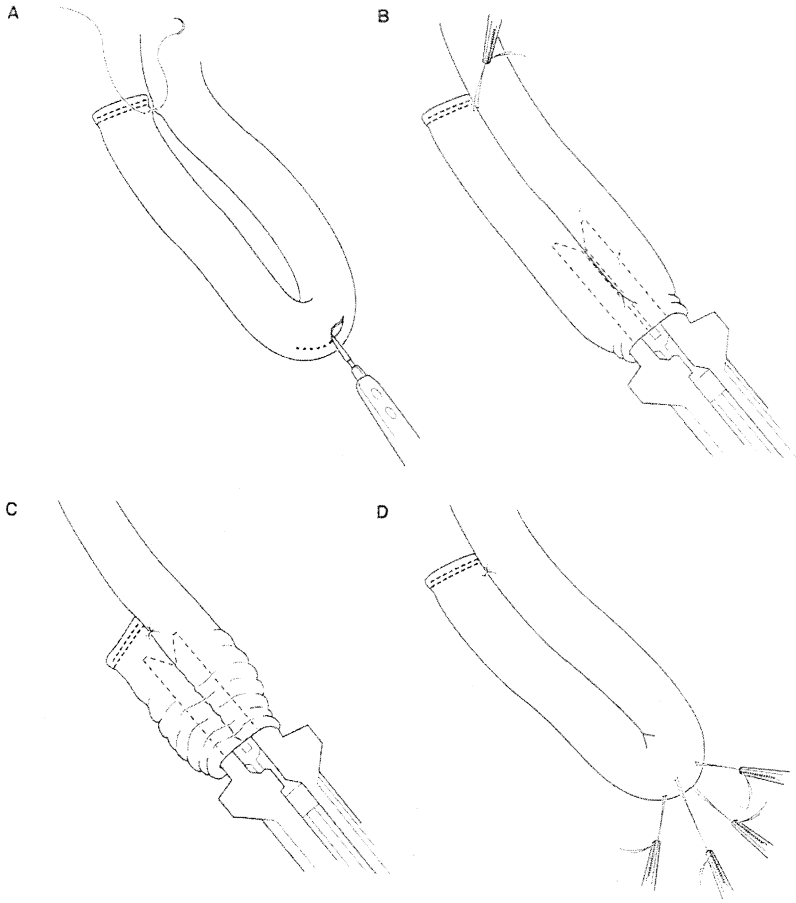

Fig. 7. Ileal J-pouch construction. **A**, An electrocautery is used to create an enterotomy at the apex of the 15 cm loop of terminal ileum. **B**, The forks of a 75 mm intestinal anastomosing stapler are pressed into the intestinal limbs, and the instrument is fired. **C**, This is repeated while the limbs are telescoped onto the stapler, until a 15 cm side-to-side anastomosis is completed. **D**, The apical enterotomy is closed with a simple purse-string suture. (Adapted from Becker JM, Stucchi A. Ulcerative colitis. In Greenfield LJ, et al, eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

patients are followed at 1 month, 3 months, 6 months, and 12 months after closure of the ileostomy, and then are seen at yearly intervals for follow-up. Anal rectal manometry is performed at 1 year. Every 5 years, the patients undergo flexible fiberoptic pouchoscopy with surveillance biopsies of the ileal pouch.

OUTCOMES

A number of large series now report that restorative proctocolectomy with IPAA is a very safe procedure with excellent long-term function and a high degree of patient satisfaction.[12–14] In our own experience with nearly 700 patients in whom IPAA has been performed using mucosal proctectomy and a hand-sewn anastomosis over a 20-year period, nearly 90% of those operations were performed in patients with CUC, and the remainder were performed in patients with FAP or a genetic variant (Table 1). The mean age is 36 years (range 11 to 76), but it has slowly increased as we have become more confident about offering the operation to older patients. Because it is a much better surgical alternative, there has also been a trend toward earlier surgical intervention. A significant improvement in the quality of life of patients who have undergone IPAA,[15,16] especially in those patients with CUC, supports consideration of the surgical treatment option much earlier in the course of the disease. In addition, we and others[12] have had excellent results in older patients and feel confident in offering the operation to patients over 65 years of age as long as they meet the preoperative manometric criteria.

The postoperative morbidity and complication rate after IPAA in the 570 patients for whom we

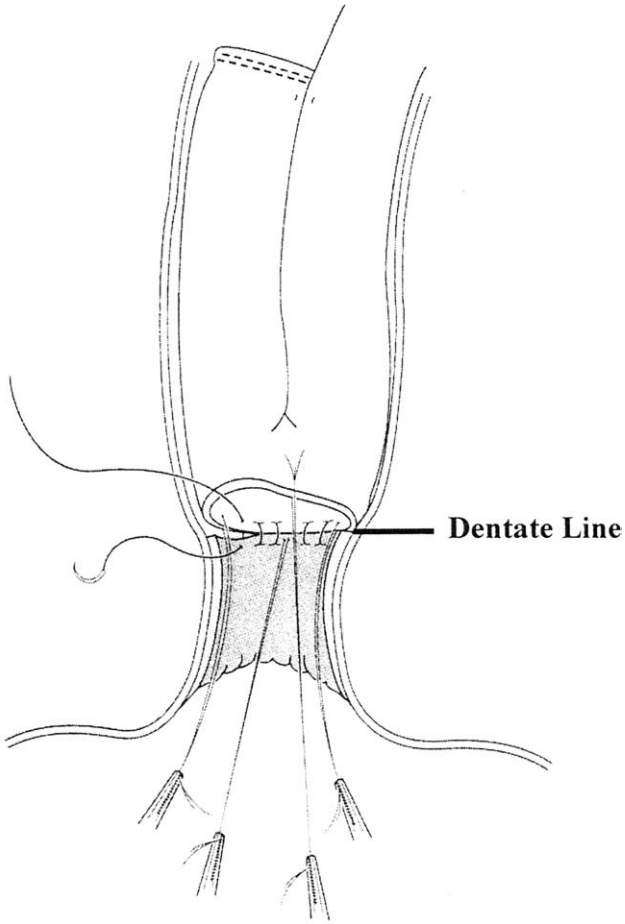

Fig. 8. Creating the ileal J-pouch–anal anastomosis. The ileal J-pouch is secured to the sphincter in each quadrant with a suture. The purse-string suture closing the enterotomy is cut to allow the apex of the pouch to open. An anastomosis is then created between the apex of the pouch and the anoderm with interrupted absorbable sutures. (Adapted from Becker JM, Stucchi AF. Ulcerative colitis. In Greenfield LJ, et al, eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

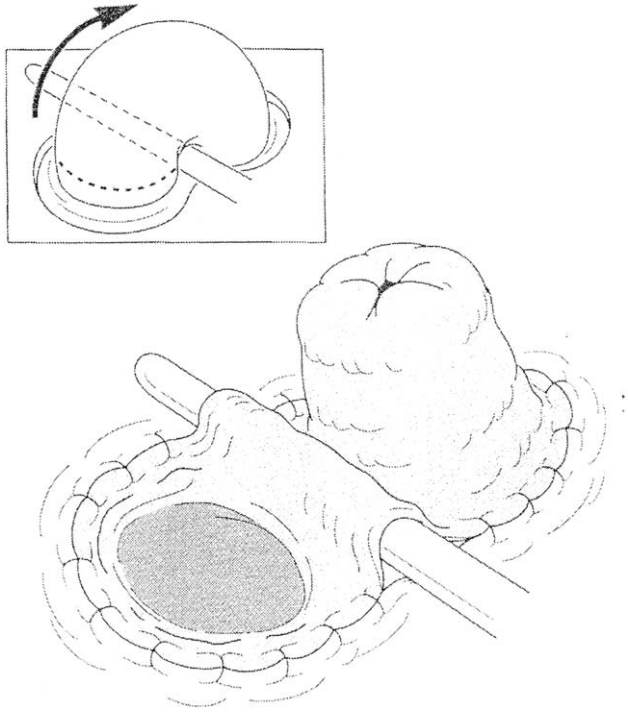

Fig. 9. A loop ileostomy is constructed 40 cm proximal to the ileal pouch and matured over a rod. (Adapted from Becker JM, Stucchi AF. Ulcerative colitis. In Greenfield LJ, et al, eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

have reliable follow-up data (Table 2) is comparable to that reported from major centers throughout the world.[17] Experience with IPAA supports the absence of mortality and low morbidity that can be achieved with this operation if it is performed frequently, carefully, and with a standard operative technique. No operative deaths have occurred in our series, and the overall operative morbidity after the IPAA portion of the operation is approximately 10%. The major operative morbidity is small bowel obstruction, undoubtedly due to the high rate of adhesion formation associated with IPAA.[18] We recently performed a meta-analysis of more than 17 major studies from around the world in which we surveyed complications and outcomes after IPAA,[14] and found similar rates of small bowel obstruction suggesting the need for more aggressive adhesion prevention.

The failure rate in our series, necessitating conversion to a permanent Brooke ileostomy, is approximately 2%, as compared to the pooled estimate of 6.2% that we found when we surveyed the literature. This is due in part not only to the fact that increased experience decreases the risk of postoperative and pouch-related complications and improves long-term outcome, but is also due to our continued effort to salvage failed pouches. Approximately 60% of the failed pouches in our series were successfully salvaged, thus avoiding permanent ileostomy.[19] These results suggest that a continued effort to salvage failed pouches, including the use of total reconstruction, is a viable alternative to permanent ileostomy.

In our own series, as throughout the literature, nonspecific idiopathic inflammation of the ileal pouch or pouchitis remains the most significant late, long-term complication that can overshadow the benefits of the operation, especially in patients experiencing chronic or recurring episodes. Pouchitis can present with any number of symptoms including increased

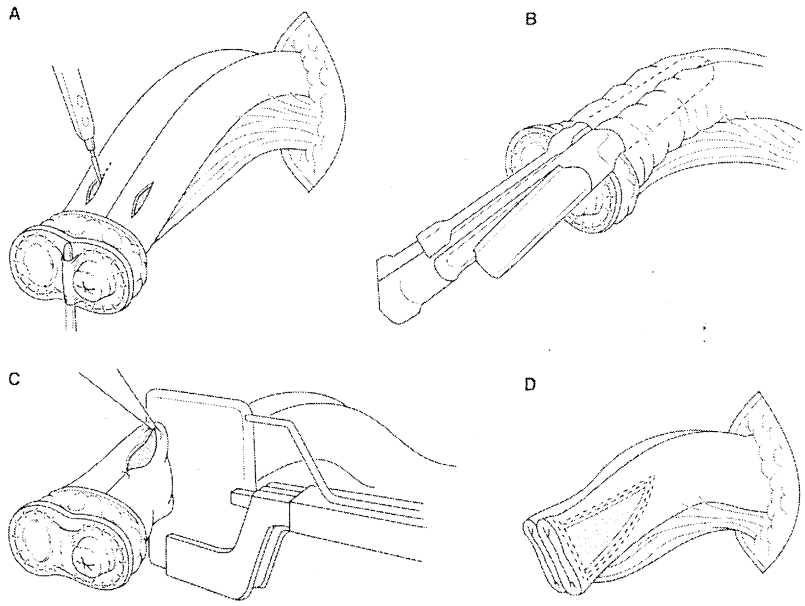

Fig. 10. Closure of loop ileostomy. **A**, A transverse elliptic incision is made around the stoma, and the limbs are dissected free. **B**, The antimesenteric surfaces of the limb are tacked together, and the jaws of an anastomosing stapler are passed through enterotomies and down into the lumen of each of the intestinal limbs. The stapler is then fired to create a side-to-side anastomosis between the afferent and efferent ileal limbs. **C**, A linear stapler is placed and fired below the former stoma and below the edges of the enterotomy. The stoma and distal limbs are amputated, and the stapler is released. **D**, The anastomosis is dropped back into the peritoneal cavity, and the peritoneum, fascia, and skin are closed. Alternatively, the stoma can be fully excised and a standard side-to-side functional end-to-end stapled anastomosis can be performed. (Adapted from Becker JM, Stucchi AF, Ulcerative colitis. In Greenfield LJ, et al, eds. Surgery Scientific Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, pp 1070–1089.)

stool frequency, watery diarrhea, fecal urgency, incontinence, rectal bleeding, abdominal cramping, fever, and malaise. Although the etiology of pouchitis is unknown, causes that have been investigated include undetected Crohn's disease, bacterial overgrowth or bacterial dysbiosis, either primary or secondary malabsorption, stasis, ischemia, and nutritional or immune deficiencies.[20,21] At present, pouchitis remains a clinically defined syndrome. Clinical, endoscopic, and histologic criteria have all been applied without clear controls or norms. Although a pouchitis disease activity index encompassing these diagnostic parameters and providing a simple, objective, and quantitative criteria for pouch inflammation has been proposed,[22] it is not widely used diagnostically. Pouchitis, which is common in patients receiving IPAA for CUC, is exceedingly rare in patients with FAP. There has only been one well-documented case in our own series. Fortunately, patients with suspected pouchitis respond well to a course or two of antibiotics such as ciprofloxacin and metronidazole; however, we have devised a treatment algorithm that has proved to be successful for even the most chronic cases.[23]

Table 1. Ileal pouch–anal anastomosis patient profile

Study period	August 1982 to December 2003
Total No. of patients	681
Diagnosis	
Chronic ulcerative colitis	605 (89%)
Familial adenomatous polyposis	76 (11%)
Age (yr)	
Mean	36
Range	11–76
Male: female ratio	378:303

IPAA remains an excellent option for most patients requiring colectomy for CUC, FAP, Gardner's syndrome, or in selected patients with hereditary nonpolyposis colorectal cancer. In our series, the overall outcome, morbidity, and functional results in patients who have received an IPAA for FAP have been significantly better when compared to those patients who have undergone the operation for CUC. Patients

Table 2. Ileal pouch complications

Complications	Percent (No. of patients)
Perineal complications	1.9% (n = 11)
Small bowel obstruction	17% (n = 97)
Requiring operation	6.7% (n = 38)
Pelvic abscess	6.7% (n = 38)
Diverting loop ileostomy reestablished	4.7% (n = 27)
Failed pouch with conversion to Brooke ileostomy	2.0% (n = 12)
Crohn's disease	0.9% (n = 5)
Sinus tract	1.0% (n = 6)
Other	0.1% (n = 1)
Pouchitis (overall)	22.2% (n = 128)
CUC – one episode	12.1% (n = 69)
CUC – chronic/recurrent	10.1% (n = 58)
FAP	0.2% (n = 1)
Total	570

CUC = chronic ulcerative colitis; FAP = familial adenomatous polyposis.

who have undergone IPAA for FAP have significantly fewer bowel movements per 24 hours than those operated on for ulcerative colitis, which averages approximately six bowel movements per day at 12 months after ileostomy closure. In our series, poor stool consistency, increased stool frequency, and nocturnal leakage are some of the more common postoperative complaints. In an effort to control stool output, patients have been placed on the antidiarrheal loperamide with supplementary fiber in the form of cellulose or psyllium mucilloid. In addition, patients are placed on a high-fiber diet and are counseled to consume a diet low in simple sugars and a high-fat nocturnal snack.

Even though the removal of all disease-bearing tissue by mucosal proctectomy eliminates the risk of recurrent disease and rectal cancer; most of the patients in my series undergo stringent follow-up, which includes surveillance pouchoscopies at 5-year intervals primarily to screen for pouch dysplasia and rectal cancer. Although recurrent disease and rectal cancer have been essentially nonexistent in our own series, we are encountering more patients with high-grade dysplasia and adenocarcinomas of the anal canal who have undergone IPAA but without a mucosal proctectomy. Although rectal mucosal resection was beneficial in our series, care must be taken as to the extent of anorectal smooth muscle resected at the time of mucosal proctectomy in order to preserve postoperative bowel and anal sphincter function.[24] A sagittal view of the ileal pouch showing the anastomosis to the anus at the dentate line following mucosectomy is depicted in Fig. 11.

As noted earlier, divergent points of view have arisen regarding this operative technique and its effect on anal physiology and function. Despite the potential increased risk of cancer, a number of centers that

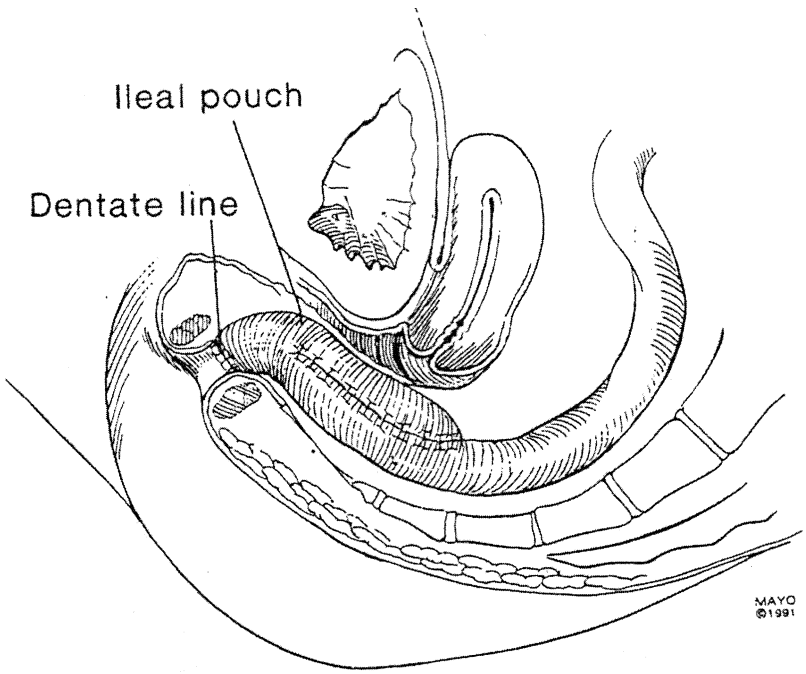

Fig. 11. A sagittal view of the ileal pouch–anal anastomosis with mucosectomy. (From Kelly KA. Anal sphincter-saving operations for chronic ulcerative colitis. Am J Surg 1992;163:5–11.)

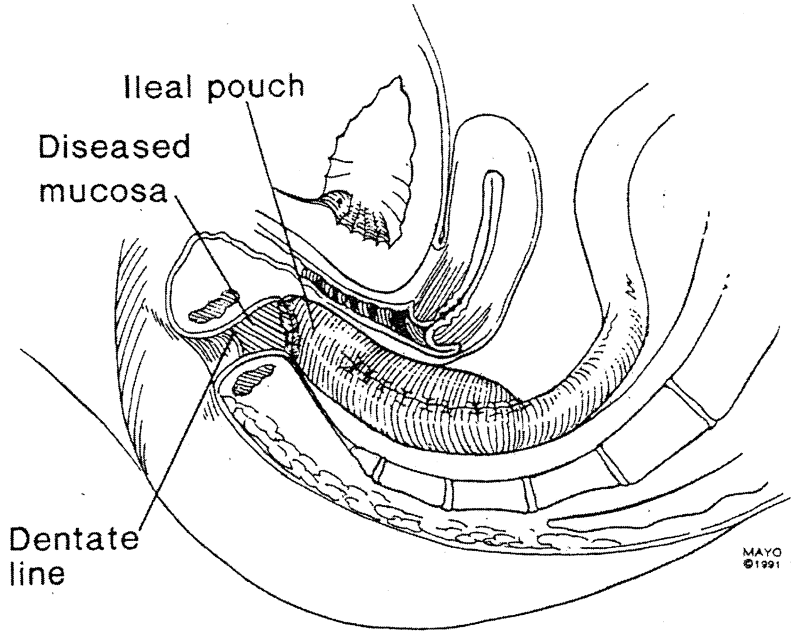

Fig. 12. A sagittal view of the ileal pouch-anal anastomosis without mucosectomy showing remaining disease-bearing tissue. (From Kelly KA. Anal sphincter-saving operations for chronic ulcerative colitis. Am J Surg 1992;163:5–11.)

perform IPAA have advocated an alternative approach that eliminates the mucosal proctectomy. A sagittal view of the ileal pouch showing the anastomosis to the anus above the dentate line with disease-bearing rectal mucosa remaining is depicted in Fig. 12. Instead, the distal rectum is divided with a stapler near the pelvic floor, leaving the anal canal largely intact. The ileal pouch is then stapled to the top of the anal canal with a circular stapling device.[25] Some surgeons believe that the preservation of the mucosa in the anal transition zone facilitates the maintenance of anatomic integrity of the anal canal and improves both daytime and night-time continence. Although resting pressures tend to be higher after a stapled IPAA,[26] this does not indicate significantly better long-term function. Those reports that show significantly higher rates of continence in patients who have undergone stapled IPAA were primarily observational studies,[27–29] and patients were not randomized by surgical technique, thus introducing a number of confounding factors. Advocates of this technique have not demonstrated in a randomized, prospective trial that stapled IPAA confers significantly better long-term functional results. In fact, in one of the only randomized, prospective studies to address this controversy, Reilly et al.[26] showed that the stapled IPAA conferred no apparent early advantage in frequency and continence compared with the hand-sewn IPAA.

Despite reports that the technically easier double-stapled technique for IPAA has fewer septic complications and results in fewer sepsis-related pouch excisions than the hand-sewn technique,[30] this is very much related to the surgeon's experience. The obvious concern is that, by leaving disease-bearing mucosa in the anal canal, patients are exposed to a lifelong risk of malignant transformation, which will require careful postoperative surveillance annually.[29] Thus we believe that mucosectomy should be recommended in all patients undergoing IPAA for CUC and FAP.

CONCLUSION

Ileoanal anastomosis has evolved through many phases before arriving at the highly successful procedure currently used at major centers. Interesting, in reviewing the world's literature, those series that report patient outcomes stratified by year show significant improvements in function and quality of life in patients who have received the operation more recently when compared with patients receiving the operation in the earlier years. Continued technical advances and greater surgeon experience can only further improve function, outcome, and patient satisfaction.

Despite some opposition,[31] under elective conditions, IPAA remains an excellent option for patients with CUC and FAP once the decision for surgery has been mutually reached by the patient and surgeon.[32] With technical modifications and with experience, mucosal proctectomy and IPAA can now be

performed with a low rate of complications, with good functional results and quality of life and excellent long-term outcome. As these patients, especially those with CUC, experience more frequent inflammatory episodes or become refractory to medical management, their medical and surgical management will require a closely coordinated effort by their gastroenterologists and their surgeons. Unless the colectomy is urgent, these patients typically tend to get referred earlier and therefore have more favorable outcomes. Optimal results are obtained by careful patient selection, appropriate preoperative management, meticulous standardized surgical technique, appropriate postoperative education, and rigorous follow-up.

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CT Diagnosis of Postoperative Intussusception After Penetrating Abdominal Trauma

Terry J. Chong, M.D., Gregory P. Victorino, M.D.

CASE REPORT

A 17-year-old male patient was seen in the emergency room after sustaining a gunshot wound to the right buttock. He complained of abdominal pain and had a tender abdomen on physical examination. The patient underwent an exploratory laparotomy, which revealed 10 small bowel perforating injuries. Four of the injuries were repaired primarily, whereas the remaining six injuries required two separate segmental resections and stapled end-to-end anastomoses.

On postoperative day 6, the patient's postoperative course was complicated by several episodes of emesis. Abdominal x-ray films showed dilated loops of small bowel consistent with a postoperative ileus. After several days of nasogastric decompression, the patient was noted to have flatus and bowel movements, but he continued to have nausea, vomiting, and abdominal pain. A CT scan revealed a small bowel obstruction secondary to an enteroenteric intussusception (Fig. 1).

On reexploration, a small bowel (jejunojejunal) intussusception was found consistent with the CT scan findings. After an attempt at reducing the intussusception was unsuccessful, an en bloc resection of the jejunojejunal intussusception was performed and an end-to-end anastomosis was completed. The patient did well postoperatively.

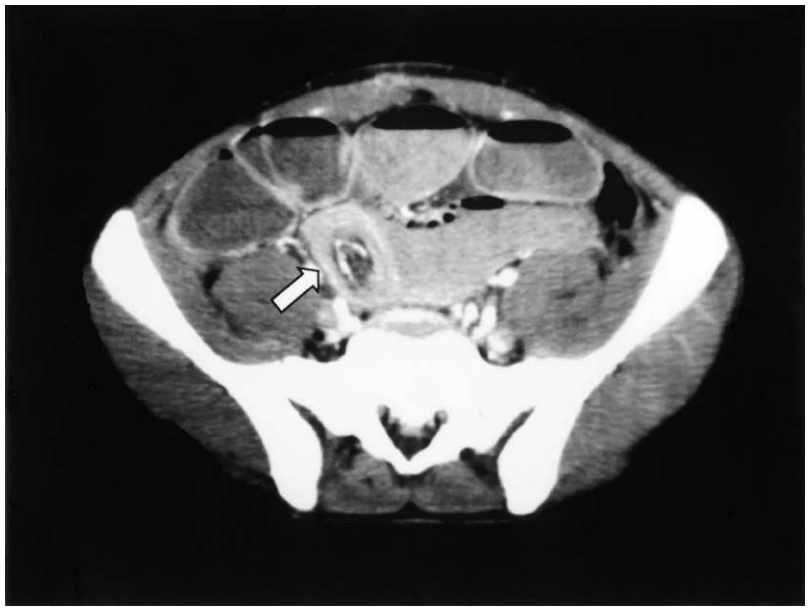

Fig. 1. CT scan demonstrating enteroenteric intussusception (arrow).

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DISCUSSION

The three classical signs of intussusception—acute abdominal pain, palpable abdominal mass, and lower gastrointestinal bleeding—are rarely seen in postoperative intussusception.[1,2] Most patients present insidiously with nausea, vomiting, and subacute abdominal pain.[1,2] The postoperative sequelae associated with surgery makes the diagnosis even more difficult. The surgical wound confounds the interpretation of postoperative abdominal pain and tenderness, and the use of postoperative pain medication adds to the confusion. Also, incisional pain and tenderness hinder adequate palpation of the abdomen. More commonly, patients are diagnosed with prolonged ileus or early bowel obstruction due to adhesions.[1,2]

A further impediment to the diagnosis of postoperative intussusception is the unreliability of radiographic studies. Plain roentgenograms of the abdomen usually show dilated loops of bowel that are consistent with postoperative ileus. Contrast studies of the upper gastrointestinal tract failed to diagnose intussusception in all but one case in a series of 25 patients with postoperative intussusception.[1] Barium enema is unreliable because most postoperative intussusceptions occur in the small bowel. The CT scan, however, appears to hold some promise. In a study of intussusception following abdominal trauma and exploratory laparotomy, one third of the patients were diagnosed by CT scans, even though that diagnosis could not be made based on the upper gastrointestinal series.[2] A CT scan was used in our patient to correctly diagnose postoperative intussusception (see Fig. 1). On the CT scan, the classic target sign of the intussuscepted bowel is indicated by the *arrow*.

Postoperative intussusception after penetrating trauma is rare and difficult to diagnose.[1,2] Results of physical examination are often unreliable, and plain x-ray films of the abdomen can be misleading. An abdominal CT scan may assist in earlier diagnosis of postoperative intussusception and potentially improve outcome.

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Controversies in Bariatric Surgery: Evidenced-Based Discussions

SYMPOSIUM CO-CHAIRS: *Daniel J. Deziel, M.D. and L. William Traverso, M.D.*

Summary Statement

The benefit of surgical treatment of obesity in properly selected patients is now well recognized by informed medical practitioners. Public interest in surgical weight reduction and the demand for bariatric operations have escalated enormously over several years driven by various forces, not the least of which are the shear number of obese persons, both in the United States and worldwide, and the developments in technology that have made more options available. The way to best incorporate these options into surgical practice, considering validated outcomes data and the challenging technical demands of various interventions, remains unsettled. We can generally agree that weight loss for obese patients improves defined comorbid conditions and that surgical methods of weight reduction almost always provide more effective long-term weight loss than nonsurgical methods. To date, however, consensus has been more elusive on issues such as which outcome measures are most important, which patients are best treated by which operations, and what are the human and economic costs over both the short and long term?

The invited speakers for this symposium were charged with addressing certain defined and emerging controversies in bariatric surgery in an evidenced-based fashion to the extent allowable by current data. The presentations, all by experts in the field, are summarized in the following pages. The symposium was formatted into four segments. The first three of these focused on the current controversies of open vs. laparoscopic approaches, laparoscopic gastric banding vs. laparoscopic gastric bypass, and gastric bypass vs. malabsorptive procedures. The fourth session presented electrical gastric stimulation as an emerging modality for weight loss, and also, with the use of video presentations, highlighted technical tips for several laparoscopic procedures.

Based on attendance and audience discussion at this symposium, it is evident that bariatric surgery is currently on the forefront of interest for many gastrointestinal surgeons. Although the audience discussion was predictably not "evidenced-based," it was certainly lively with enthusiastic proponents and opponents for various approaches. The discussion also brought out the common ground of certain difficult areas, in particular, the management of the patients in whom bariatric surgery has "failed."

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Open Roux-en-Y Gastric Bypass: Indications and Technique

Michael G. Sarr, M.D.

Roux-en-Y gastric bypass (RYGB) is currently the "gold standard" bariatric operation in the United States. Long-term data from more than 10 years are available in terms of outcome (weight loss, reversal of weight-related morbidity), and other newer procedures need to use RYGB outcomes as the benchmark.[1]

Development of minimally invasive techniques as adapted to allow laparoscopic RYGB (see below) have improved patient satisfaction and minimized certain types of postoperative morbidity (e.g., wound infection, incisional hernia) and length of hospitalization. However, laparoscopic RYGB is a technically challenging operation, requires special advanced expertise, and has a definite learning curve. Therefore it may not be an appropriate option for all surgeons. Relative or absolute contraindications to laparoscopic RYGB include previous gastric resection, hiatus herniorrhaphy, or transabdominal operations on the distal esophagus, known multiple adhesions, need for other non–minimally invasive intra-abdominal procedures, or most reoperative bariatric procedures. RYGB in very-short-stature patients (<5 feet or 153 cm tall) can prove to be very difficult. Moreover, even the most talented "laparologist" may need to convert from a laparoscopic to an open procedure; thus comfort with open RYGB is necessary.

TECHNIQUE

Open RYGB is accomplished through an upper midline incision.[2] Once the skin and dermis are incised, bilateral blunt traction allows the tissues to separate down to the midline with minimal bleeding. Careful incision of the fascia in the midline (linea alba) markedly facilitates later wound closure. I enter the peritoneal cavity not in the midline but rather 2 to 3 cm to the patient's left where the preperitoneal fat attaches to the posterior surface of the posterior rectus in an avascular plane. It is important to always look for an associated umbilical hernia (present in ~30% of patients).

A special bariatric abdominal wall retraction system, such as the Pilling Bariatric Retraction System (Pilling Co., Ft. Washington, PA), is almost essential. After thorough palpation of adnexa (in women), colon, and liver, my preference is to routinely carry out cholecystectomy (30% have stones, 30% will develop stones during intense weight loss, and risk of cholecystectomy is "getting there" and we are already "there"!).

Creation of Proximal Pouch

The first step involves creating a very small (<15 ml) proximal gastric pouch (of cardia, *not* fundus). The avascular window in the gastrohepatic ligament is opened, and the surgeon's left hand is inserted behind the body of the stomach staying caudal to the left gastric artery (Fig. 1, *A*). The fat pad overlying the cardia is elevated, exposing the left gastroesophageal junction. The index finger of the left and right hands will meet behind the cardia separated by an avascular veil of connective tissue, which is broken through bluntly. I place two Silastic 20 F tubes through this retrogastric tunnel via the rent in the gastrohepatic ligament. Because the neurovascular pedicle along the lesser curvature lies between these tubes and the gastric wall, the tubes are repositioned between the wall of the lesser curvature and the left aspect of this neurovascular pedicle, a maneuver that can usually be done without dividing any blood vessels or branches of vagus nerves (Fig. 1, *B*).

Using the Silastic tubes as guides, two 90 mm mechanical linear staplers are passed around the gastric cardia. By angling the stapler caudally, one can obtain more of the anterior wall of the cardia (to facilitate the cardiojejunostomy) while keeping the posterior anvil of the stapler near the posterior aspect of the gastroesophageal junction; this allows a very small–volume pouch of cardia. The staplers are fired and the cardia between transected, thereby anatomically separating the pouch from the bypassed remainder of stomach. Others prefer refiring the linear

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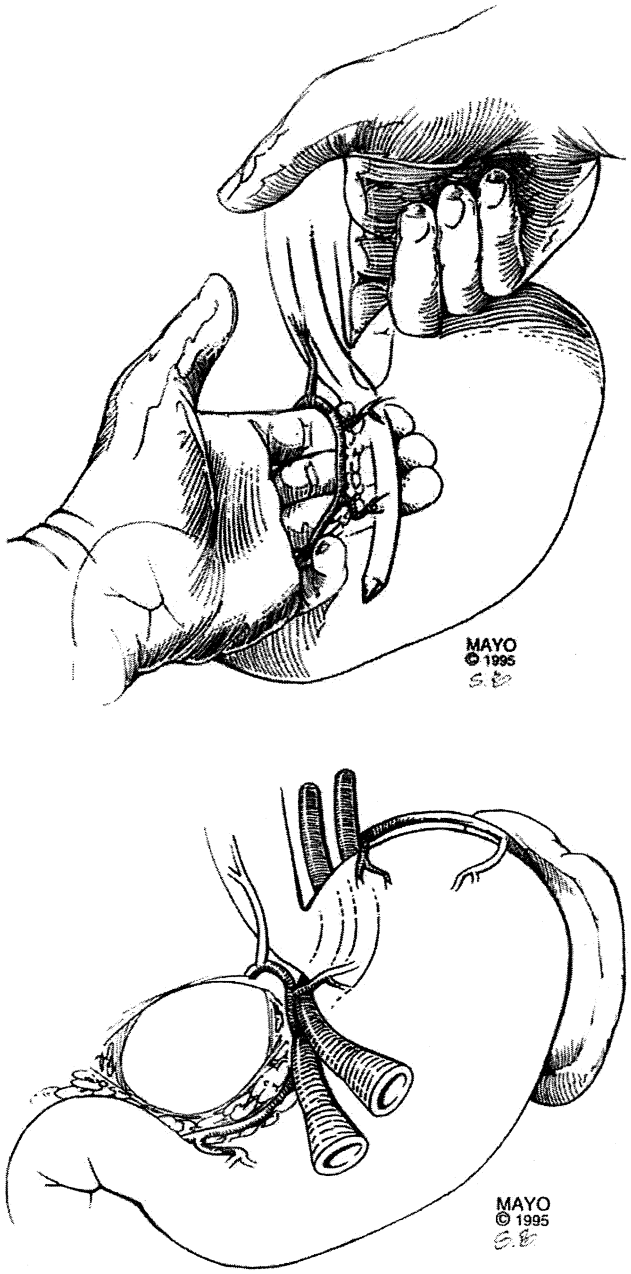

Fig. 1. Creation of pouch of cardia. **A**, Blunt mobilization of the retrogastric tunnel. **B**, Placement of Silastic 20 F tubes to guide passage of the linear staplers. (From Sarr MG. Vertical disconnected Roux-en-Y gastric bypass. Dig Surg 13:45–49, 1996. Reprinted by permission of the publisher.)

stapler three times in the same region without transecting the pouch from the bypassed stomach.

Creation of Roux-en-Y Limb

The proximal jejunum is transected approximately 50 to 100 cm distal to ligament of Treitz where branching of the jejunal mesenteric vessels allow both maintenance of the primary arterial and venous mesenteric supplying vessel and a more generously mobile Roux limb. This Roux limb, which I make 150 cm long (a so-called long-limb RYGB[3]), is then brought retrocolic, but ante*gastric*, just to the patient's left of the middle colic vessels through an avascular window in the mesocolon. Although the retro*gastric* plane may be 1 to 2 cm shorter than the *ante*gastric position, a stapled cardiojejunostomy is awkward with this positioning of the Roux limb (moreover, should the patient need reoperative reconstruction, it is much more difficult and hazardous to dissect out a retrogastric Roux limb). Others bring the Roux limb *ante*colic, but this distance can be up to 5 to 10 cm longer when the omentum is bulky, even if a pathway through the omentum is made.

Cardiojejunostomy

I prefer to use a No. 21 end-to-end mechanical stapler for this anastomosis (U.S. Surgical, Norwalk, CT). Via a very small anterior cardiotomy, the circular anvil head is placed in the proximal pouch with a purse-string 2-0 polypropylene suture to occlude the cardiotomy. The cartridge of the stapler is inserted through the end of the Roux limb (Fig. 2). The stem is extended through the highest point (marked previously by holding up Roux limb) on the antimesenteric surface of the Roux limb, and the stem is "docked" with the anvil. The stapler is carefully approximated being certain to not include any fat or tissue within the staple line. The stapler is fired, removed, and the tissue donuts are inspected; an incomplete donut usually requires transmural-reinforcing sutures at the site of the incomplete stapled anastomosis. At this point I place an additional layer of interrupted seromuscular sutures between the jejunum and cardia over the stapled anastomosis. The redundant end of the Roux limb is then transected and closed.

Closure of Internal Defects

Three mesenteric defects, not two, require obliteration. The first is at the site of the enteroenterostomy. The second, where the Roux limb passes through the transverse mesocolon, is obliterated after pulling a redundant supracolic Roux limb back down infracolically. Then the third defect, the so-called Petersen's hernia (Fig. 3), is the space posterior to the mobilized mesentery of the Roux limb (immediately infracolically) and anterior to the posterior peritoneum overlying the retroperitoneum. This is the internal hernia most often overlooked and misunderstood.[4]

Wound Closure

I close the fascia with a running No. 1 braided nylon suture; although many different techniques

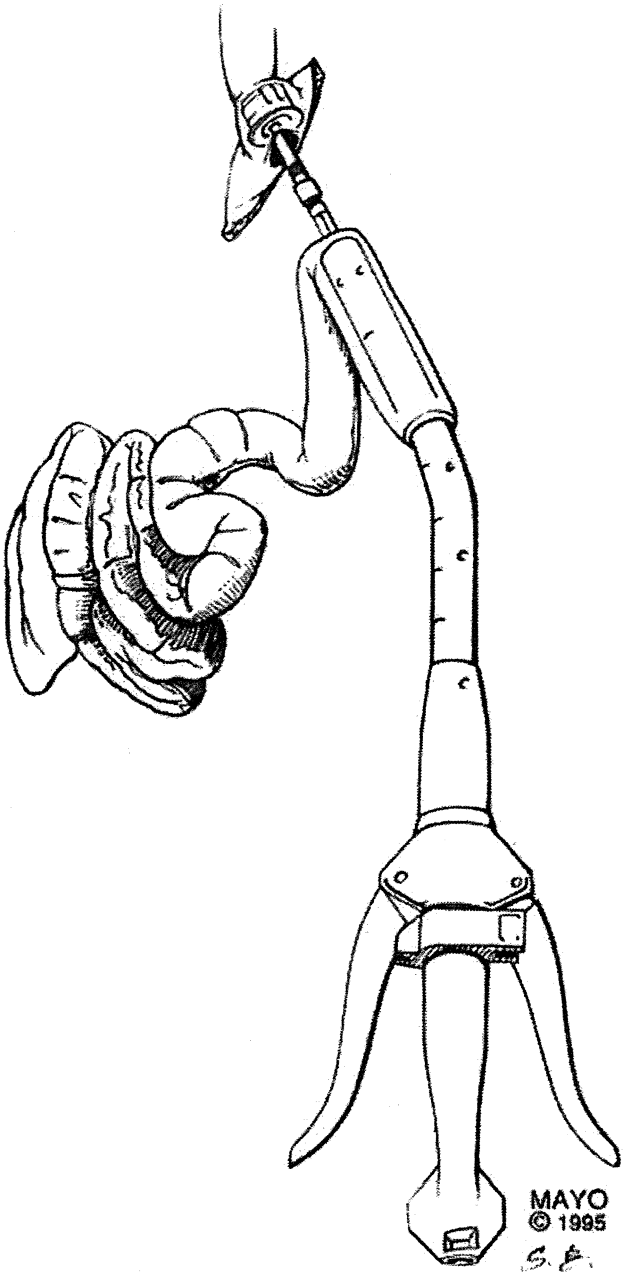

Fig. 2. Stapled cardiojejunostomy using an end-to-end 21 mm circumference stapler. (From Sarr MG. Vertical disconnected Roux-en-Y gastric bypass. Dig Surg 13:45–49, 1996. Reprinted by permission of the publisher.)

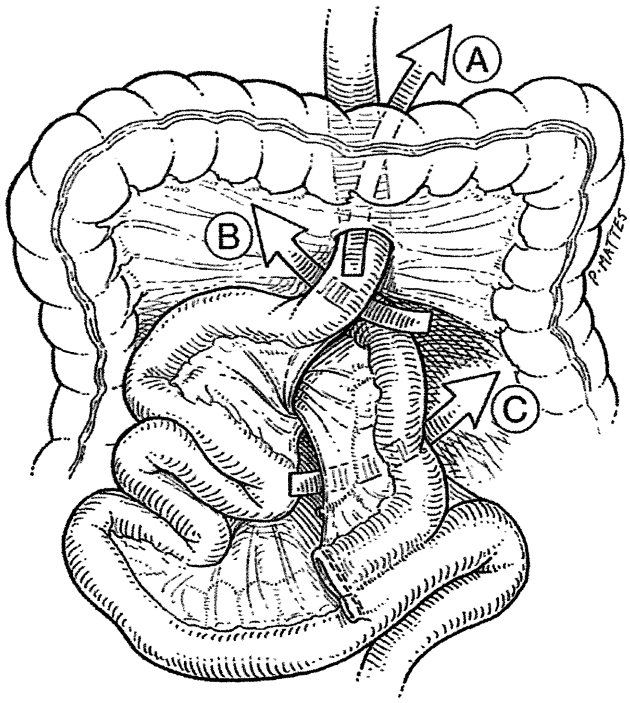

Fig. 3. Mesenteric defects. A: transverse mesocolon; B: Peterson's hernia, infracolic space posterior to Roux mesentery in front of posterior peritoneum; entero–enterostomy. C: jejunal mesenteric hernia. (From Schweitzer MA, DeMaria EJ, Broderick TJ, Sugerman HJ. Laparoscopic closure of mesenteric defects after Roux-en-Y gastric bypass. J Laparoendosc Adv Surg Tech [Part A] 10:173–175, 2000. Reprinted by permission of the publisher.)

have been described, incisional hernias occur (realistically) in 10% to 20% of patients (clearly a strong impetus for a minimal-access approach). Although tube gastrostomy is not required in the vast majority of patients, I usually use a gastrostomy in those in whom I perform a malabsorptive procedure. These patients are larger, have a higher rate of complications, and, if they require nutritional support, the malabsorptive anatomy prevents "hyper-" alimentation via an oral approach. Intragastric feeding uses the entire duodenum (with its digestive pancreatobiliary secretions), proximal jejunum, and distal ileum.

SUMMARY

Clearly, laparoscopic RYGB is a significant technologic advance. Nevertheless, there remains a role for open RYGB in many situations.

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Open vs. Laparoscopic Procedures in Bariatric Surgery

Ninh T. Nguyen, M.D.

BACKGROUND

With the introduction of laparoscopic bariatric surgery, there has been a recent increase in the demand for bariatric surgery. The public views laparoscopic bariatric surgery as a minimally invasive procedure with less postoperative pain, lower morbidity, and a faster recovery. The notion of improved outcomes with laparoscopic bariatric surgery was derived from the public's knowledge of the outcomes of laparoscopic cholecystectomy and other laparoscopic operations. However, can we infer that the clinical benefits observed in other laparoscopic operations will be the same for laparoscopic bariatric surgery? To answer this question, it is important to acknowledge that laparoscopic bariatric surgery is being performed in a different patient population (the morbidly obese) with more preexisting medical conditions, and the operation is often longer and technically more difficult than other commonly performed laparoscopic operations. Therefore the debate about laparoscopic vs. open bariatric surgery is very important inasmuch as the benefits observed after other laparoscopic operations do not necessarily apply to morbidly obese patients. Because Roux-en-Y gastric bypass (GBP) is the most commonly performed bariatric operation in the United States, this report will mainly emphasize the differences between laparoscopic and open approaches to GBP.

FUNDAMENTAL DIFFERENCES

It is important to understand the fundamental differences between laparoscopic and open approaches to bariatric surgery in order to understand the differences in clinical outcomes between the two operations. The primary differences between the two procedures are the method of access (length and number of abdominal incisions), the method of exposure, and the extent of operative trauma. Open GBP is commonly performed through an upper abdominal midline incision, whereas laparoscopic GBP is performed through five or six small abdominal incisions. The methods of exposure during open GBP are the use of abdominal wall retractors and mechanical retraction of the abdominal viscera. In contrast, the methods of exposure during laparoscopic GBP are the use of pneumoperitoneum to create a working space and gravity for displacement of the abdominal viscera. By reducing the length of the surgical incision and eliminating the need for mechanical retraction of the abdominal wall and viscera, we believe that the operative trauma after laparoscopic GBP is reduced compared to that of open GBP.

IMPORTANT MEASURES OF OUTCOME AND VALID COMPARISON

When comparing the outcomes of a single operation performed by two different techniques, it is crucial to understand which outcome measures are important for assessing clinical practice. With so many different clinical outcome measures, it is very important for an investigator to decipher what are poor and what are good measures of outcome, and how to measure these outcomes. Some of the commonly used measurements of outcome include operative time and length of hospital stay. A short operative time is always preferable, but operative time as a sole measure of outcome has never been shown to correlate with a better operative outcome. Similarly, the length of hospital stay can be misleading because it only represents the time of hospitalization that is considered to be safe before a patient is discharged. From the patient's perspective, better measures of outcome are the amount of postoperative pain and the duration of convalescence. In addition, to decide on the measures of outcomes, it is important to ensure a valid comparison. A valid comparison between laparoscopic and open bariatric surgery is only valid if (1) the principles of the laparoscopic operation

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are similar to those of the open operation and (2) the surgeon has passed the learning curve of the laparoscopic approach.

REDUCED SURGICAL INSULT IN LAPAROSCOPIC BARIATRIC SURGERY

The main premise of improved outcome after laparoscopic bariatric surgery is the reduced surgical insult to the host. We previously examined this question by indirect measurement of third-space fluid accumulation by measurement of the intra-abdominal pressure after laparoscopic and open GBP.[1] Surgical injury often results in accumulation of edema known as third-space fluid, and the degree of third-space fluid accumulation is often proportional to the extent of surgical trauma. We reported that intra-abdominal pressure after laparoscopic GBP was significantly lower than after open GBP on postoperative days 1, 2, and 3.[1] Another method of evaluating the extent of surgical injury is measurement of the systemic stress response. The magnitude of the systemic stress response has also been shown to be proportional to the degree of operative trauma. Interleukin-6 is a proinflammatory cytokine, and its level has been shown to correlate with the severity of operative injury. We previously reported that postoperative concentrations of interleukin-6 were significantly lower after laparoscopic GBP than after open GBP.[2] These findings suggested that the operative injury after laparoscopic GBP is less than after open GBP and substantiate the physiologic benefits of the laparoscopic approach.

CLINICAL OUTCOMES

Postoperative pain is an important measurement of outcome because it can be measured objectively. The degree of postoperative pain after open GBP is associated with the length of the surgical incision, the extent of operative dissection, and operative trauma. The results from our randomized trial comparing laparoscopic and open GBP demonstrated that patients undergoing laparoscopic GBP consumed significantly less intravenous morphine sulfate compared to patients undergoing open GBP on postoperative day 1 (46 ± 31 mg vs. 76 ± 39 mg, respectively).[3] Despite the higher amount of self-administered pain medication, patients undergoing open GBP still reported higher visual analog pain scores than patients undergoing laparoscopic GBP.[3]

Certain morbidities observed in open GBP are reduced in laparoscopic GBP. Initial reports of laparoscopic GBP suggested a higher rate of leaks after laparoscopic GBP than after open GBP. The higher leakage rate in these reports is likely related to the learning curve of the laparoscopic procedure. For example, Wittgrove and Clark[4] reported nine anastomotic leaks (3.0%) in their first 300 laparoscopic GBP procedures and only two leaks (1.0%) in their last 200 laparoscopic GBP procedures. The reduced incidence of wound infections after laparoscopic GBP is one of the easily recognized advantages of the laparoscopic approach.[5] Wound infection after open GBP is a complicated problem, because it often requires a prolonged course of wound care. Conversely, wound infection after laparoscopic GBP can be managed easily with opening of the trocar incision and a short course of local wound care. Another clinical advantage of laparoscopic GBP is the reduced incidence of a late incisional hernia. The incidence of a postoperative incisional hernia after open GBP can be as high as 20%. Most of these incisional hernias will require operative intervention, which will likely increase the costs associated with open GBP. By reducing the size of the surgical incision, the risk of anterior hernia after laparoscopic GBP is essentially eliminated.

Recovery is a very important outcome parameter and can be measured by questioning the patients' time to return to activities of daily living. We previously reported that laparoscopic GBP patients had a more rapid return to activities of daily living than open GBP patients.[5] Furthermore, we analyzed recovery based on the patients' ability to return to physical, social, and sexual functioning, and their perception of overall health. The SF-36 health survey and the Moorehead-Ardelt Quality-of-Life questionnaire were used as objective tools to evaluate these parameters. From the SF-36 survey, we learned that recovery based on physical and social functioning at 1 and 3 months postoperatively was significantly faster after laparoscopic GBP compared to open GBP.[5] In addition, patients undergoing laparoscopic surgery perceived their overall health to be better than that of open GBP patients when the survey was measured at 1 month postoperatively. From the Moorehead-Ardelt Quality-of-Life questionnaire, we learned that laparoscopic GBP patients had more sexual interest or resumed sexual activity earlier than open GBP patients at 3 months postoperatively, hence demonstrating a faster recovery.[5]

CONCLUSIONS

Laparoscopic GBP is a complex advanced laparoscopic operation that accomplishes the same objectives as open GBP but avoids a large upper midline abdominal incision. The differences between laparoscopic and open bariatric surgery are the method of

access and exposure. By reducing the size of the surgical incision and the operative trauma associated with the operative exposure, the surgical insult should be less after laparoscopic compared to open bariatric surgery. We reported a reduction in the surgical insult after laparoscopic GBP and believe that this is the physiologic basis for the observed clinical advantages of laparoscopic GBP. The important clinical advantages of laparoscopic GBP are not the reduced length of hospitalization but the reduction in postoperative pain, lower rate of wound-related complications, and faster recovery. Given the currently available evidence-based data, laparoscopic bariatric surgery should be considered the new standard for the treatment of morbid obesity as long as the surgeon has passed the learning curve of the laparoscopic approach.

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Controversies in Bariatric Surgery: Evidence-Based Discussions on Laparoscopic Adjustable Gastric Banding

Christine J. Ren, M.D.

Laparoscopic adjustable gastric banding (LAGB) is a surgical option that involves placing a silicone band circumferentially around the uppermost aspect of the stomach. The band creates a small proximal pouch that empties slowly resulting in early satiety and a decreased appetite. The band is attached to an access port that is secured to the rectus muscle and can be accessed percutaneously in the office with a needle. Injection of saline into the port results in tightening of the band. This is performed on an individual basis according to weight loss and appetite. Band adjustments are required approximately 5–6 times in the first year and 2–3 times in the second year. Weight loss is gradual, averaging 1–2 lb/week during the first 2 years after surgery. (J GASTROINTEST SURG 2004;8:396–397)

KEY WORDS: Laparoscopic gastric banding

INTRODUCTION

Laparoscopic adjustable gastric banding (LAGB) has been the most commonly performed operation for the treatment of morbid obesity in Australia and Europe since 1993. Its approval by the Food and Drug Administration (FDA) in 2001 has provided many patients with an alternative treatment to the Roux-en-Y gastric bypass (RYGB), which is presently the most commonly performed bariatric operation in the United States. The evaluation of LAGB as a surgical treatment option for morbid obesity requires the medical community to look at three questions: (1) what is the goal of surgery, (2) what is the cost or risk that the surgeon and the patient are willing to accept, and (3) what are the revisional options if the surgery results in suboptimal weight loss or weight regain.

GOALS OF BARIATRIC SURGERY AND LAGB

The benefits of bariatric surgery are not only the achievement of significant weight loss, but the durability of the weight loss. The amount of weight lost has been one of the indices used to judge the "success" of a bariatric operation in terms of percent excess weight loss (%EWL). However, the physician must not lose sight of the fact that morbid obesity is named such due to the fact that the severity of the obesity is causing or aggravating "morbidity." Therefore, it is the improvement or resolution of comorbidities related to obesity that should be the goal of bariatric surgery rather than the actual weight lost. In addition, improvement in quality of life and prolonging of life expectancy ensues after bariatric surgery. The amount of weight loss necessary to improve or resolve obesity-related comorbidities is moderate. A review of the literature suggests that a weight loss of 5%–10% results in improvement in Type II diabetes mellitus, hypertension, hypercholesterolemia, and obstructive sleep apnea.[1] In addition, a 5% decrease in body mass index (BMI) results in up to a 12% decrease in premature mortality.[1] A risk reduction of 51% for developing Type II diabetes mellitus can be achieved by a 15 lb weight loss, but is completely negated with weight regain.[2] Weight loss after LAGB ranges from 53%–64% up to 5 years in international studies and has been paralleled in the United States with up to 41% EWL at 1 year.[3] Comorbidities similarly decrease and/or resolve after LAGB with a complete resolution of Type II diabetes mellitus in up to 64%

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of patients with improvement in insulin sensitivity and beta-cell function.[4] Therefore, a weight loss of 60%–75% EWL, which has been quoted in some RYGB series, does not necessarily mean that it is better than 50% EWL if it is maintained long term.

SAFETY OF LAGB

Safety of an operation must be considered, particularly in bariatric surgery, which, although medically indicated, is elective and is performed on a high-risk population. LAGB is the safest bariatric operation with a mortality of 0.2%, 30-day morbidity of 5%, and delayed complication (gastric prolapse, erosion, port-tubing disconnection) rate of 12%.[3] This is compared with RYGB that has a mortality of 1.5% and 3% leak rate.[5] With 8 million Americans having BMI > 40, a difference in mortality from 0.2%–1.5% can mean a difference of 104,000 potential deaths.

No bariatric operation is a guarantee. Weight-loss failure and weight regain are to be expected from any operation with revisions required in 5%–7%. LAGB has the advantage of complete reversibility by laparoscopic explanation, preservation of anatomy, and ability to perform a RYGB or malabsorptive operation. Conversely, revision of RYGB poses a difficult challenge in terms of exactly what to do. Some surgeons have chosen to reinforce the stoma with nonadjustable silicone banding, whereas others have converted it into a malabsorptive operation by lengthening the Roux limb. The latter option places the patient at high risk for protein malnutrition because the 10–15 cc gastric pouch may not allow for adequate protein intake.

The Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S) is a subcommittee of the Royal Australasian College of Surgeons that has evaluated the LAGB against vertical banded gastroplasty (VBG) and RYGB in terms of safety and efficacy. Although there has been no prospective randomized trial, ASERNIP-S found LAGB to be safer than VBG and RYGB and to be effective up to 4 years after surgery. LAGB was found to result in less weight loss by 2 years as compared with RYGB, but with insufficient evidence to conclude that this was true after 2 years.

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Roux-en-Y Gastric Bypass Is the Operation of Choice for Bariatric Surgery

W. Scott Melvin, M.D.

KEY WORDS: Gastric bypass, vertical banded gastroplasty, laparoscopic gastric banding

INTRODUCTION

Morbid obesity is a recognized threat to the health of the developed world. Healthcare expenditures directly related to obesity continue to rise and represent a significant portion of dollars spent on healthcare in the United States. Since the National Institutes of Health Consensus (NIH) Conference convened in 1991, surgical approaches have been identified as the best course of treatment for patients with clinical severe obesity, with at least a body mass index of 35 and associated comorbid conditions. The NIH conference specifically identified Roux-en-Y gastric bypass (RGB) and vertical banded gastroplasty (VBG) as surgical options that provide significant benefits for patients with clinical severe obesity.[1]

LAPAROSCOPIC GASTRIC BANDING

In the last decade, multiple additional surgical options have become available to challenge the "gold standard" of RGB. These other options have become popularized during the time that the durability of VBG, horizontal stapled gastroplasty, and nonadjustable gastric banding were recognized as having poor long-term benefits and an unacceptable rate of long-term failure. Biliopancreatic diversion and the duodenal switch have been popularized especially through multiple works in Europe. Adjustable gastric banding has, in recent years, made a significant increase in the worldwide scope of bariatric surgery. The LapBand (INAMED Corp., Santa Barbara, CA) was approved for use in the United States by the Food and Drug Administration (FDA) in 2001. This followed years of experience in Europe with generally good results. The manufacturer of the device sponsored trials in the United States in an attempt to generate data for approval. The FDA multicenter trial accrued 292 patients in part A and 63 patients in part B. Two patients died secondary to the surgery. Most complications occurred early in the trial and the apparent incidences seemed to decrease with time and experience. Excess body weight loss (EBW) was 35% at 1 year (38% in part B) and 36% at 3 years (54% in part B).[2] Based largely on this data, and the preexisting European data, the FDA granted a controversial approval for sale of the LapBand device in the United States.

The data concerning the LapBand continues to accumulate. Recently, a group from Europe reported a prospective series of 500 patients with no mortality and a 10% incidence of reoperation. EBW was 43% at 1 year, 58% at 2 years, and 55% at 3 years.[3] Other reports like this one similarly demonstrate the safety and relative efficacy of the device. Short-term data issued for four United States centers was equally as enthusiastic and reported 115 patients with at least a 9-month follow-up, without mortality, and only 12 patients requiring reexploration. Two devices had to be removed during the course of this report. EBW was 42% loss at 12 months and 36% loss at 9 months.[2]

The early positive results have not been seen in longer-term studies from the United States. A total of 62 patients with different band types were reported from the University of Iowa in 2002. Thirty patients required intraabdominal reoperations and a total of 27 devices were removed in the 8-year follow-up. This report describes the experience of multiple different devices, however, the basic tenant being a foreign body restricting the proximal stomach was the same as the current devices. Other reports describing the experience of the LapBand have emerged. Thirty-seven patients originally entered in the FDA trial were reported separately. Fifteen of these patients required band removal and the EBW was unacceptably low at 38% for 3 years.[4] These reports, along with the growing concern of a long-term effect of a foreign body constricting the stomach with the potential of erosion and infections, have dampened early enthusiasm. Additional concerns have been raised

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over the creation of "pseudo-achalasia" resulting in a mega-esophagus. These esophageal side effects have not been well described or investigated and remain incompletely characterized.

COMPARISON OF GASTRIC BYPASS VS. VERTICAL BANDED GASTROPLASTY

The results of this new technology and these new procedures must be compared with existing procedures and results. Roux-en-Y gastric bypass has been well described and significant long-term data exists to validate its effectiveness. No strong data with a direct prospective comparison of RGB vs. adjustable gastric banding exists. The physiology of the LapBand is very similar to VBG, as it restricts the proximal stomach and reduces dietary intake. Good data comparing RGB with VBG does exist, so it is reasonable to use these comparisons to help surgeons guide their decisions regarding the choice of operation. Several series have studied this comparison and all have similar results. Roux-en-Y gastric bypass is associated with a longer hospital stay and a higher rate of complications.[5] The long-term follow-up confirms the effectiveness for durable lifelong loss. Most series continue to document that although VBG allows early weight loss, it is not a durable operation and therefore failure is seen in the long term.[6] Multiple reports as far back as 1987 have documented the difference between VGB and RGB and have demonstrated the superiority of RGB (see Table 1).

Roux-en-Y gastric bypass is, in fact, a well-studied and well-understood operation that is effective for the treatment of clinical severe obesity. Over 350 peer-reviewed articles are noted in the English literature since 1989 documenting the experience of RGB. A variety of different approaches and modifications have allowed incremental improvements without a quantum leap in changing the physiology of the operation, allowing significant improvement and demonstrating significant advantages of RGB over other operative approaches. Even before the recent modifications, Smith reported a series of 3855 patients who underwent surgery during a 7-year study. A mortality rate of 0.18% and a complication rate of 3.4% demonstrate that this operation was safe and predictable. Five-year weight loss was consistent and this was associated with good patient satisfaction and an improved quality of life.[11] The modern technique of laparoscopy has further improved outcomes in RGB. Schauer's initial report at the American Surgical Association demonstrated this advantage and these findings have been confirmed by many centers. He reported 275 patients with a mortality rate of 0.3% and a complication rate of 3.3% with a median hospital stay of 2 days. At 24 months EBW was 23%.[12] Our group at The Ohio State University has reported similar data with 304 patients undergoing a minimally invasive approach to RGB. There were no mortalities and a 5.6% complication rate with EBW of 56% at 1 year.[13] A plethora of good data after RGB also demonstrates the effectiveness of the procedures and the resolution of the pathologic sequelae of obesity.[14,15] The resolution of significant comorbid conditions validates the appropriateness of this type of surgery with most reports identifying complete resolution of diabetes, hypertension, gastroesophageal reflux disease (GERD), hypocholesterolemia, asthma, and depression with improvements noted in other comorbid conditions such as osteoarthritis, degenerative joint disease, and many other associated illnesses.[12] It is this type of data that confirms that the surgical approach, and specifically RGB, improves longevity and quality of life.

Table 1. Results of vertical banded gastroplasty (VBG) vs. Roux-en-Y gastric bypass (RYGB) for morbid obesity

Author	Year	No. of pts.	Follow-up	VBG	RYGB
Capella[7]	1996	952	5 yrs.	47	62%
Maclean[8]	1993	106	3 yrs.	39	83%
Hall[9]	1989	310	3 yrs.	48	64%
Sugerman[10]	1987	40	3 yrs.	37	64%

The psychological effect on the choice of the two different procedures is important and must be considered. The adjustable gastric band may be seen by many as less invasive, less costly, and less risky than other operations that are nonreversible. The advantages of reversibility, adjustability, and easy removal seem desirable. However, it is our observation that an adjustable gastric band is deliberately sought out by individuals who are not dedicated to significant lifestyle changes and subsequent weight loss. This pattern of behavior may lead to dissatisfied patients with a lower chance of good long-term weight loss and patient satisfaction. Fully informed and appropriately prepared patients for RGB understand that they are undergoing a life-changing event that is permanent and necessary to correct a life-threatening condition of morbid obesity. Patients who are so prepared enjoy a high quality of life and freedom from comorbid illness and can enjoy long-term effective weight loss without the need for frequent adjustments. Additionally, they do not have to be concerned about the long-term effects of a foreign body residing against a dynamic gastrointestinal tract.

CONCLUSION

The choice of surgical procedures for an individual patient must be made by a surgeon who has all of the tools available to them in their environment. Decisions need to be made depending on the individual clinical scenario. No single tool or procedure can be considered appropriate for all patients. Assimilation of the known data is necessary for the surgeon to offer the appropriate procedure to the appropriate patient. The well-informed and well-trained individual will recognize that the best choice for most patients seeking surgical treatment for clinical severe obesity is laparoscopic RGB.

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Is Gastric Bypass Superior for the Surgical Treatment of Obesity Compared With Malabsorptive Procedures?

Eric J. DeMaria, M.D.

KEY WORDS: Gastric bypass, biliopancreatic diversion

INTRODUCTION

When evaluating surgical interventions for morbid obesity, numerous end points could be considered valuable including quantity of weight lost, resolution of comorbid medical conditions, impact on quality of life, including social, cosmetic, and employment issues, cost effectiveness, and surgical risks. The complexity of bariatric surgery requires one to consider all these domains to some degree and it is most of all critical to look at long-term outcomes to determine the ability of a surgical procedure to provide a cure for the disease.

GASTRIC BYPASS

Gastric bypass surgery was first described over 30 years ago by Mason and gradually evolved over the course of time to include a small gastric pouch with a Roux-en-Y gastrojejunostomy anastomosis of small diameter. The gastric bypass procedure creates malabsorption by bypassing the distal stomach, duodenum, and a variable length of jejunum depending upon the surgical procedure chosen, which primarily creates a risk of malabsorption related to vitamin and nutrient deficiencies as compared with malabsorption of calorie intake. Although gastric bypass surgery is considered a "combination" restriction and malabsorption procedure, it might be better classified as an "altered absorption" procedure to distinguish it from true malabsorptive procedures that function by creating malabsorption of nutrition as compared with the vitamin malabsorption found with gastric bypass.

Most high-grade data from an evidence-based perspective regarding weight loss procedures involve open surgical procedures, and it is important to remember that the minimally invasive approach carries more technical challenges and modifications that could impact long-term outcomes; hence, the need for careful long-term follow-up studies. The original procedure in the malabsorptive category was the jejunal ileo bypass developed in the 1960s and 1970s, but subsequently discredited. Modern-day procedures involve intestinal bypass but with no stagnant bypass limb to create bacterial overgrowth and subsequent complications including liver disease. Modern-day procedures include the biliopancreatic diversion (BPD) procedure of Scopinaro as well as the biliopancreatic diversion with duodenal switch procedure (BPD/DS). The key to determining the degree of malabsorption with any procedure in this category is the length of the "common channel," which is the amount of small intestinal length distal to the small intestinal anastomosis between the Roux limb and the afferent or biliopancreatic limb. This represents the absorptive length wherein biliopancreatic secretions can mix with ingested foods for optimal absorption.

A review of the literature shows that all randomized and controlled trials that involve Roux-en-Y gastric bypass demonstrate a significantly greater long-term weight loss after this procedure compared with other procedures. Unfortunately, there is no grade A medical evidence comparing malabsorptive procedures to gastric bypass and the available literature essentially involves comparison of restrictive procedures such as vertical banded gastroplasty to gastric bypass. In a recent review by Buchwald, a number of collected studies with 1 year reported weight loss data suggested in nearly 3000 patients undergoing gastric bypass that the average reduction of excess weight was 69%. Long-term follow-up data is also available for gastric bypass, notably by Pories and associates in which 608 patients were followed up to 14 years with less than 3% lost to follow-up. Patients maintained 100 lb of weight loss on average up to 14 years after surgery and 83% of patients with non-insulin-dependent diabetes and 99% of patients with glucose impairment had normal glycosylated hemoglobin, glucose, and insulin values. Long-term follow-up data

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is also available from Sugerman and associates in which adolescent patients aged 12–17 years were followed up to 14 years. Although a decrease in excess weight loss was identified between 10 and 14 years (56% excess weight loss decreased to 33% excess weight loss), a closer examination of the data in this study demonstrates that there was a great deal of inhomogeneity within these patient groups. In other words, deleting 5 of 14 patients at 5- and 10-year follow-up and 1 of 6 patients at 14-year follow-up improved excess weight loss in the remaining patients to 75% and 61%, respectively. Thus, although some patients fail in the long-term after gastric bypass, it seems that the majority maintain quite adequate reductions in excess weight from their preoperative status.

Laparoscopic gastric bypass has been studied in comparison to open gastric bypass in a prospective randomized trial by Nguyen and associates in which longer operative time for the laparoscopic group were found but with less overall blood loss and shorter hospitalization. Higher operating room expenses were offset by lower hospital costs in laparoscopic patients, and a significant reduction in wound complications including hernia and wound infections were identified in the laparoscopic group. Our own case control data at the Medical College of Virginia suggests similar weight loss results between laparoscopic and open gastric bypass over 12 months of follow-up (unpublished). In terms of complications, the operative mortality for gastric bypass is in the range of 0.5%–1.0% in open and laparoscopic gastric bypass series. Long-term nutritional issues include a risk of iron deficiency anemia in menstruating women as well as the need for vitamin B12 supplementation. Protein calorie malnutrition is rare in gastric bypass patients.

BILIOPANCREATIC DIVERSION

BPD and BPD-DS procedures are suggested to create superior weight loss, particularly for superobese patients. In fact, a more accurate claim is superior weight loss maintenance. Some minor further improvement in resolution of comorbidities accompanies the weight loss of these procedures but at the added risk of protein calorie malnutrition for some patients. The previously cited review by Buchwald and associates collected nine series with nearly 4000 patients in which the average excess weight loss at 1 year was 69%. This number does not differ from the collected series reported by Buchwald for gastric bypass. The literature further cites operative mortality in a broad range of patients ranging from l.5% to as high as 6.5% in a series by Gagner and associates. The latter series with the highest mortality was for superobese patients (body mass index [BMI] $\geqslant$ 60) undergoing laparoscopic duodenal switch. Other potential complications include ulcers in 3%–10% of patients, diarrhea, malodorous flatulence, anemia in 5%–11% of patients, bone demineralization over long-term follow-up, and protein calorie malnutrition in 2%–5% of patients.

To lower the surgical risk of laparoscopic BPD-DS, Gagner and associates have proposed a two-stage procedure. In their initial small cohort of 18 patients with BMI greater than 60 undergoing two-stage laparoscopic DS procedure, mortality decreased from 6.5% in the prestudy population to zero with a reduction in complications from 23% to 5.6%. The initial surgical component for this two-stage approach is sleeve gastrectomy that interestingly provides significant weight loss in the order of 100 lb or more for some superobese patients. The overall recommendation at present is to complete the procedure with the delayed malabsorptive component after significant initial weight loss to prevent patients from regaining weight over time, similar to the phenomenon seen in purely restrictive procedures.

At the Medical College of Virginia, we have laparoscopically performed gastric bypass on 27 patients with BMI greater than 60 kg/m^2. Our data suggest feasibility of this approach with a detailed analysis showing no increase in surgical complications compared with patients with BMI less than 60 with an average of 148 lbs. lost at 1 year follow-up or 58% of excess weight and a range of 41%–85% of excess weight. Resolution of comorbidities was comparably high as well.

CONCLUSION

In summary, analysis of the literature with philosophical interpretation suggests that malabsorptive procedures for obesity should be reserved for high-risk patients with very severe obesity who are at risk for inadequate weight loss in the long-term after proximal gastric bypass. However, compliance and critical nutritional follow-up are mandatory for any population undergoing malabsorptive procedures. In terms of compliance issues, a paradox arises. Gastric bypass proponents believe that, because some morbidly obese patients are noncompliant, it is dangerous to perform malabsorptive procedures on them; in contrast, malabsorption proponents believe that, because all morbidly obese patients are noncompliant, they will eventually regain weight unless treated by malabsorptive procedures. This difference in basic philosophy of bariatric surgical treatment underlies much of the controversy in choice between the two procedures.

The data clearly favor Roux-en-Y gastric bypass as the gold standard therapy for bariatric surgery at this time with significant quality improvement using the laparoscopic approach by virtual elimination of wound and hernia complications seen so frequently after open gastric bypass. The gastric bypass procedure is a good procedure for weight loss with high resolution of comorbidities in all available studies and acceptable morbidity and mortality, particularly compared with malabsorptive procedures performed by a laparoscopic approach. One must continue to be very concerned about the long-term nutritional risk of malabsorptive procedures, particularly in noncompliant patients.

Summary Remarks

MODERATOR: *Bruce Schirmer, M.D., Stephen H. Watts Professor of Surgery*

This symposium focused on a debate as to which of two procedures should be used preferentially to perform bariatric surgery in the year 2003: laparoscopic adjustable gastric banding (LAGB) vs. laparoscopic Roux-en-Y gastric bypass (RYGB). At the start of the session, the audience was polled to determine how many of them perform these two procedures or a malabsorptive operation for the surgical treatment of morbid obesity. Approximately 65% of those in the audience perform gastric bypass, 30% LAGB, and approximately 15% a malabsorptive operation. The percentages are greater than 100% because some surgeons do more than one procedure.

Dr. Christine Ren, Associate Professor of Surgery at New York University, presented the case for LAGB as being the procedure of choice for treating severe obesity. Her arguments included the following main points:

1. The LAGB has a superior safety record in terms of deaths and severe complications after surgery compared to the RYGB.
2. The weight loss curves for RYGB and LAGB, based on data presented by Dr. Ren from selected series in the literature, are not significantly different after 3 years of follow-up following surgery. The RYGB patients tend to lose more weight during the first year, and then regain a small amount of weight on average. The LAGB patients tend to have small but incrementally significant continued weight loss at the 2- and 3-year marks postoperatively, such that both curves approximate a 55% excess weight loss after 3 years.
3. Dr. Ren showed patient preference for the three major types of bariatric procedures in her own practice, which offers all three. The trend over the past 2 years has been a definite shift toward patients requesting LAGB over either of the other two procedures, whereas years ago they requested primarily the laparoscopic RYGB.
4. LAGB causes no major metabolic abnormalities. One of the principal advantages of this is that if patients choose not to return for follow-up, their worst likely scenario would be poor weight loss and no metabolic consequences.
5. The improved speed, simplicity, and potential for the LAGB to eventually be an outpatient procedure was emphasized.

Dr. Scott Melvin, Professor of Surgery at Ohio State University, spoke in favor of the laparoscopic Roux-en-Y gastric bypass. He cited several important points:

1. The open RYGB has a long and proven track record of providing successful weight loss with acceptable morbidity and mortality after surgery. It is one of only two procedures endorsed by the National Institutes of Health Consensus Conference in 1991, and was given preferred status at that time. There have not been adequate data on the other operative approaches to warrant reconvening another Consensus Conference, at least in the opinion of many experts, and thus the RYGB remains the treatment of choice for the surgical treatment of severe obesity.
2. The practice patterns in the United States and the United States patient populations of morbidly obese patients differ from those in Europe, with a significantly higher percentage of the patients having a body mass index (BMI) greater than 50. The data for efficacy of the LAGB in this patient population is lacking. In addition, the data for the vertical banded gastroplasty, in the past, showed particularly poor results in the patient population with a BMI over 50 compared to patients with a lower preoperative BMI. Thus LAGB may not be a good operation for "superobese" patients.
3. The United States trial, supervised by experts in LAGB, produced very poor results for LAGB when it was first introduced in this country.
4. Patients who undergo LAGB are subjecting themselves to the vagaries of a foreign body

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placed near the gastroesophageal junction. The potential for erosion and problems, as demonstrated in the past by the Angelchick prosthesis, are of concern in these patients.

5. There have been troubling reports of esophageal dilatation in LAGB patients who have a slippage of the band and partial obstruction at the esophagogastric junction. If such patients choose not to return for follow-up despite symptoms, potential permanent damage to esophageal motility could occur.

Both speakers argued well in defense of the merits of their respective operations. Their points are appropriate and well founded. There is no question that since its approval for use in the United States by the FDA in June of 1999, the LAGB has grown in popularity in the United States. Its eventual role in the armamentarium of operations available for patients with morbid obesity is still undetermined. However, as the years go by since the first LAGB procedures were performed and longer follow-up data are available, the picture may become clearer.

There are some differences, although they are relatively minor, between the operations that would select out certain patients as being more favorable candidates for one type of operation over another. The RYGB has shown consistently superior results in reversing the comorbidities of type II diabetes and the symptoms of gastroesophageal reflux. LAGB may be a preferable operation for patients with a history of gastritis, nonsteroidal anti-inflammatory drug use, and significant degenerative joint disease likely requiring future nonsteroidal anti-inflammatory drugs or comparable medications. In a recent postgraduate course sponsored by the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) on bariatric surgery in adolescents, there was enthusiasm for using LAGB as perhaps the treatment of choice in this patient population, given its absence of metabolic complications and its potential for reversibility. However, currently the LAGB is FDA approved for use only in persons 18 years of age or over.

Although the FDA limitation on its approval of the use of the LAGB is one example of how regulations and health care policy can influence surgical therapy more profoundly than the surgeon's input itself, it is not the most profound one with respect to this operation. Currently, in the state of Virginia, where I perform bariatric surgery, there has not been one insurance company we have encountered in 18 months that will approve payment for a LAGB procedure. Their rationale is that the procedure is "experimental." The insurance companies maintain that because sufficient U.S. data has not yet been published, the procedure must be experimental. They ignore the 70,000 bands placed worldwide and the more than 500 articles in the surgical literature on the topic. By not approving the procedure, they obviously set up the ironic situation of potentially never having enough data to publish from a U.S. experience. This ostrich-like, "head in the sand" mentality and position is reprehensible for the greater process it represents—that is, finances, which are the business aspect of health care; this means that regulatory agencies may now dictate what operations, what type of care, and what access to health care is available for patients. This power has passed from the hands of surgeons and the medical community alike. It is indeed unfortunate that our patients do not have freedom of choice for data-driven and medically sound decisions, such as bariatric operations. The question is: who will speak up against this system? Will it be the physicians or is our political power too weak? Perhaps when enough patients think their care is dictated by business rather than medical concerns, such as the reaction to the managed care approach, this situation will be improved. Until such time, it behooves us as physicians to speak out for such change.

Biliopancreatic Diversion With Duodenal Switch vs. Gastric Bypass for Severe Obesity

Daniel M. Herron, M.D., F.A.C.S.

KEY WORDS: Biliopancreatic diversion, duodenal switch

INTRODUCTION

There are currently five different weight loss operations commonly performed in the United States: (1) Roux-en-Y gastric bypass (RNY-GB); (2) long-limb gastric bypass (LLRNYGB); (3) biliopancreatic diversion with or without duodenal switch (BPD-DS); (4) adjustable gastric banding (AGB); (5) vertical banded gastroplasty (VBG). The very existence of so many different procedures to treat the same disease refutes the position that there is one "best procedure" for all severely obese patients. The need for more than one bariatric procedure was succinctly summarized by Dr. Henry Buchwald in a recent article.[1] That is, there is no gold standard bariatric surgery procedure—there are several tested and effective operations for morbid obesity, the skilled bariatric surgeon should be able to perform more than one bariatric operation—whether by open or laparoscopic technique or both, and a given patient can be broadly matched with a given operation.

At present, several randomized prospective trials are underway in the United States and abroad comparing the outcomes of these procedures. However, until results from such studies are available, it is impossible to objectively declare one weight loss procedure superior to all others. In the interim, the choice of bariatric procedures must treat each patient as an individual and take into consideration the severity of the patient's obesity, comorbid conditions, lifestyle considerations, and ability to comply with long-term dietary supplementation and nutritional follow-up. Last, but certainly not least, this choice must acknowledge the wishes of the patient. With these considerations in mind, I believe that the BPD-DS holds an important place in the bariatric surgeon's armamentarium.

COMPARISON OF GASTRIC BYPASS VS. BPD-DS

Every bariatric procedure is intended to promote weight loss. However, each operation carries with it a unique set of risks and benefits with regard to both health status and lifestyle considerations. A full review of the pros and cons of each bariatric procedure is beyond the scope of this discussion; however, it is helpful to highlight some of the central differences between the RNY-GB and the BPD-DS.

Safety, Efficacy, and Generalized Acceptance

In the United States, RNY-GB is considered by many to be the "gold standard" bariatric procedure against which all others are measured. It is the most commonly performed bariatric operation in this country. The RNY-GB has been in existence since the 1960s and has been studied extensively and modified over time. It provides excellent long-term weight loss typically in the range of 49%–80% of initial excess body weight (IEBW) with an acceptably low rate of mortality (less than 1.5% in a recent series) and morbidity.[2]

The BPD and its variants have not yet achieved equivalent widespread acceptance in the United States. However, the BPD and the BPD-DS do possess a considerable track record. The BPD has been performed in Italy since the mid-1970s and BPD-DS in the United States since 1988.[3] Like the RNY-GB, the BPD-DS provides excellent weight loss ranging from 73%–80% of IEBW. The mortality rate is similar (0.5%–1.9%).[4,5]

Volume Restriction and Hunger

Despite its widespread acceptance, the RNY-GB results in some substantial lifestyle compromises that are often minimized by bariatric surgeons. First, the very small gastric pouch (1–2 oz or less) provides a severe amount of volume restriction. Many patients feel that their stomach pouch is so small as to preclude eating "normal" meals with their family or going out to a business lunch with clients. Some RNY-GB

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patients complain that, despite eating to the full physical capacity of their stomach pouch, they still have a residual feeling of hunger. This problem is widespread enough to have spawned an Internet newsgroup entitled "OSSG (Obesity Surgery Support Group)-hungry" with 1196 members at present.

The stomach pouch is substantially larger in the BPD-DS, providing far less volume restriction than the RNY-GB. This allows eating behavior far closer to the societal norm. In his study of 465 BPD-DS patients, Marceau[5] reported that 58% had no modification of their eating habits postoperatively and 89% suffered no vomiting.

Alteration in Types of Food Eaten

In addition to the substantial volume restriction imposed on them, RNY-GB patients suffer from restriction in the types of food they can eat as well. Whereas dumping syndrome is frequently cited as a desired consequence of RNY-GB, many patients are displeased by the idea that they may never again be able to eat a piece of cake on their birthday. Gastric bypass also places many restrictions on the texture of foods that patients may tolerate. Despite the fact that they are repeatedly encouraged to eat "healthy" foods, RNY-GB patients often avoid high-protein meats and vitamin-rich vegetables because of difficulty tolerating the texture. Many foods that are easily tolerated, like potato chips or crackers, represent poor dietary choices. These patients are faced with a long-term nutritional dilemma: the foods their surgeon suggests are frequently different from what their new stomach tolerates.

BPD-DS patients face dietary limitations as well, but these are generally far less severe than those of gastric bypass patients. The ingestion of fatty foods will typically result in loose bowel movements or excessive flatus. However, high-protein foods, such as lean meat and bulky vegetables, are far better tolerated by the BPD-DS patient. This may help explain why 83% of BPD-DS patients describe themselves as "satisfied" or "very satisfied" after their procedure.[5]

Endoscopic Access

In the RNY-GB, the gastric remnant is excluded from the alimentary path and cannot be accessed endoscopically. With the increasing performance of preoperative endoscopy to screen for H. pylori, gastritis, ulcers, and neoplasm, a growing subset of bariatric patients are being diagnosed preoperatively with intestinal metaplasia of the stomach. This lesion, although not precancerous, represents a risk factor for the subsequent development of gastric neoplasia. This is impossible to do in the excluded gastric remnant of the RNY-GB. In contrast, the BPD-DS does not result in an excluded portion of the stomach; the entire organ is accessible via upper endoscopy.

Long-Term Efficacy

Perhaps the true Achilles' heel of the RNY-GB is the issue of long-term success, particularly in the superobese patient (body mass index [BMI] >50 kg/m^2). Weight-loss success is typically defined as loss of greater than half of the initial excess body weight or postoperative BMI less than 35 kg/m^2. In MacLean's study of 5-year outcomes of 274 RNY-GB patients, 93% of those with a BMI less than 50 kg/m^2 enjoyed "good" or "excellent" weight loss. However, only 57% of superobese patients ultimately dropped their BMI to 35 kg/m^2 or less.[6] This is in stark contrast to the results of BPD-DS. Dr. Hess recently reviewed his results in 987 BPD-DS with a mean preoperative BMI of 51 kg/m^2. Follow-up ranged from 9 months to more than 10 years. Satisfactory weight loss, defined as 50% or more of IEBW, was obtained in 99.2% of patients.[7] These striking results are echoed in other series: in Dr. Marceau's subgroup analysis of 181 superobese patients undergoing BPD-DS, 97% lost 60% or more of their initial excess body weight.[5]

CONCLUSION

In the year 2003 there is no "one best bariatric operation" for every severely obese patient. The choice of operation must be tailored to each individual patient's needs and wishes. For the superobese patient, the patient diagnosed with intestinal metaplasia of the stomach, and for those patients who do not wish to undergo the severe dietary restrictions imposed by the RNY-GB, the BPD-DS is a valuable surgical option.

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Implantable Gastric Stimulation for Weight Loss

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With the epidemic of obesity worldwide, bariatric surgery has rapidly grown in popularity. Currently, a variety of surgical procedures are performed including Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, vertical banded gastroplasty, and biliopancreatic diversion. All of these procedures have been shown to succeed in achieving significant and sustainable weight loss for the majority of patients. However, these procedures also carry the potential for serious operative morbidity, altered gastrointestinal anatomy or function, or both. Electrical gastric stimulation via the implantable gastric stimulation (IGS) system is a relatively new and novel approach to treat obesity. The operative technique is relatively simple and the system does not alter gastrointestinal anatomy. Preliminary worldwide investigations have demonstrated safety and efficacy. This article will review the current experience with the IGS system. (J GASTROINTEST SURG 2004;8:408–412)

KEY WORDS: Gastric pacing, bariatric surgery

PHYSIOLOGIC BASIS FOR ELECTRICAL GASTRIC STIMULATION

Like the heart, the stomach has intrinsic myoelectrical activity and a native "pacemaker" located in the proximal stomach wall. This electrical conduction regulates gastric motility (contractile activity). Normal gastric myoelectrical activity consists of two components—slow waves and spike potentials.[1] The slow wave is omnipresent and occurs at regular intervals whether or not the stomach contracts. It originates in the proximal stomach and propagates distally toward the pylorus. The normal frequency of the gastric slow wave is about 3 cycles per minute (CPM) in humans. The gastric slow wave determines the maximum frequency, propagation velocity, and propagation direction of gastric contractions. When a spike potential (similar to an action potential) is superimposed on the gastric slow wave, a strong lumen-occluding contraction occurs.

Gastric dysrhythmias represent aberrations from the normal gastric myoelectrical activity. Similar to cardiac dysrhythmias, they include abnormally rapid contraction (tachygastria) and abnormally slow contraction (bradygastria). These abnormal waves may interfere with the normal slow wave propagation and possibly disrupt normal gastric contractions.

Gastric electrical stimulation (pacing) involves the application of an electrical current to the stomach to influence or change gastric myoelectrical activity. This may involve stimulating the stomach from proximal to distal (antegrade pacing) or from distal to proximal (retrograde pacing). Although it would be attractive to theorize that gastric pacing could influence gastric emptying, this has not been consistently demonstrated in humans. Antegrade stimulation might be expected to improve normal gastric emptying whereas retrograde stimulation would be used to retard or adversely impact normal gastric emptying. Thus, antegrade pacing may be potentially beneficial for patients with persistent gastric dysrhythmias and retrograde pacing may be of benefit for patients with abnormally rapid gastric emptying, such as those patients with dumping syndrome and the morbidly obese.[2] There is some evidence that antegrade gastric pacing can improve both symptoms and gastric emptying in a study of patients suffering from gastroparesis.[3]

THE DEVICE

The implantable gastric stimulator (IGS), a pacemaker-like device (Transcend, Transneuronix, Inc., Mt. Arlington, NJ), includes a battery-operated pulse

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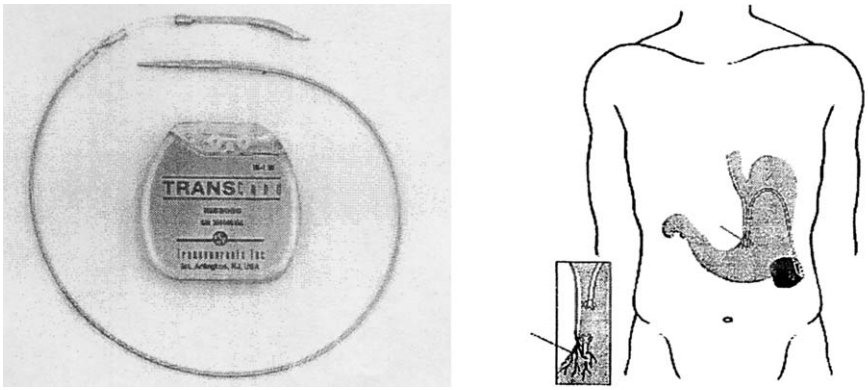

Fig. 1. The implantable gastric stimulation (IGS) device, lead, and depiction of its placement.

generator and a bipolar lead (Fig. 1). The generator is similar to a heart pacemaker and about the size of a pocket watch. It is implanted under the skin in the left upper quadrant. The system lead is laparoscopically inserted into the seromuscular layer of the anterior stomach wall. The programmer is a standard computer connected to a wand. The programmer communicates via the computer and wand with the implanted IGS using radio waves.

The IGS device sends electric current into the muscle of the stomach wall. The exact mechanism of action is still not completely known. It was originally postulated that the mechanism of action of retrograde gastric electrical stimulation was alterations of gastric emptying. This was based on the observation that obese individuals generally demonstrated more rapid gastric emptying than the nonobese. In a study of 77 human subjects composed of 46 obese and 31 age-, sex-, and race-matched nonobese individuals, obese subjects were found to have a more rapid emptying rate than nonobese subjects.[4] Obese men were found to empty much more rapidly than their nonobese counterparts. Whereas retrograde gastric electrical stimulation has been shown to slow emptying in animals, it has not been demonstrated in humans.

A more current theory that also has been supported by animal study is the effect of electrical stimulation on fundic relaxation. This relaxation is seen with postprandial gastric distention. Several studies have shown that gastric distention acts as a satiety signal to inhibit food intake.[5] However, the influence of electrical stimulation on hormonal production, cytokine release, and vagal stimulation has yet to be analyzed.

THE APPLICATION OF THE IGS SYSTEM TO TREAT OBESITY

In the late 1980s, a surgeon, Valerio Cigaina, first conceptualized the use of electrical gastric stimulation as a potential treatment modality for morbid obesity. Cigaina hypothesized that exogenous electrical impulses could be used to dysregulate normal gastric electromotor activity in obese patients, resulting in weight loss. Furthermore, the intention was to induce weight loss with minimal derangement of physiology and as few of the side effects as possible that are associated with conventional bariatric procedures.

Studies investigating the potential for gastric electrical stimulation to induce weight loss began in 1992 in a porcine model. The results showed that retrograde gastric electrical stimulation was both safe as well as effective in moderating weight gain in growing swine.[6] After 13 weeks of stimulation, animals subjected to high-frequency stimulation (100 Hz) decreased their feed intake relative to the control group and then their weight. After 8 months, the swine stimulated at 100 Hz weighed 10.5% less than the control animals. The overall feed intake in the group electrically stimulated was 12.8% lower than in the control group.

As a consequence of the animal study results, initial human studies were undertaken in 1995 by Cigaina and associates.[7] Four women with a BMI of 40 kg/m^2 or greater were implanted and followed for up to 40 months. All four patients were permitted food and drink ad libitum. At 40 months after implantation, one patient had lost 32 kg and a second had lost 62 kg. The other two patients did not lose weight. Evaluation revealed damage to the prototype leads, which was presumed to have occurred at the time of the surgical procedure. In addition to the success in achieving weight loss, chronic gastric electrical stimulation was also shown to be safe as no side effects were reported.

In 1998, a second study was then performed in 10 human subjects.[8] All patients had a BMI of more than 40 kg/m^2, a history of unsuccessful weight loss, and the absence of serious cardiac, respiratory, or psychiatric problems. After implant, all subjects were permitted food and drink ad libitum during three

regular meals but told not to eat between meals. Only sweet and alcoholic beverages were discouraged. Patients were followed at approximately monthly intervals. Data from these 10 patients is illustrated in Fig. 2. These patients continued to be followed and have maintained a mean of 23% excess weight loss after 4 years of follow-up. Note that the first device that they received had a battery longevity of only 1 year. All patients demonstrated weight gain while waiting for a replacement device (with longer battery longevity).

PRELIMINARY INTERNATIONAL INVESTIGATIONS

In the United States, a multicenter, randomized, controlled, double-blinded trial was developed to evaluate both the safety and efficacy of the IGS system. One-hundred and three patients were enrolled. One month after insertion, patients were randomized to device activation or had the devices kept in the "off" mode. After 7 months, the nonfunctioning devices were also activated. Device parameter settings were universal for all patients. Patients were clinically evaluated monthly for 24 months and carefully monitored for complications and weight loss. No dietary or behavioral counseling was provided.

There were no deaths or complications from implantation. Although none of the patients had experienced any untoward effects from this procedure, 17 of the first 41 leads were discovered to be dislodged from the stomach wall. This led to an alteration in technique to insure better lead security. However, lead dislodgement probably affected weight loss results. In addition, the lack of dietary and behavioral counseling and the inclusion of patients with binge eating disorders may have also affected the weight loss results. Interestingly, during the first 6 months, many patients admitted to have deliberately overeaten or experimented with their diets to discern whether or not their devices were activated. Despite these issues, after 1 year of stimulation 20% of the patients lost greater than 5% of their total body weight and the mean weight loss was 11%.

Simultaneously, several predominantly open-label trials were conducted in Europe and have consistently demonstrated approximately 25% excess weight loss results. These studies used suture sleeves to prevent lead dislodgement. Figure 3 depicts the data accumulated at eight European sites involving 77 patients.

The results of this first round of human trials assessing the electrical gastric stimulation for weight loss found that the device and the procedure were extremely safe to perform and caused negligible long-term consequences. However, a number of issues still remain to be addressed including patient selection criteria, the role of behavioral and dietary counseling, uniform vs. individualized parameter settings, and lead location and security.

CURRENT INVESTIGATIONS

A second round of investigations have recently been initiated in both the United States and Europe. In Europe, the Laparoscopic Obesity Stimulation Study (LOSS) currently includes 65 patients at eight clinical sites. This study is open label, but includes formalized behavioral modification. Thus far, the results are encouraging, as depicted in Fig. 4.

In the United States, the Dual-Lead Implantable Gastric Electrical Stimulation Trial (DIGEST), an

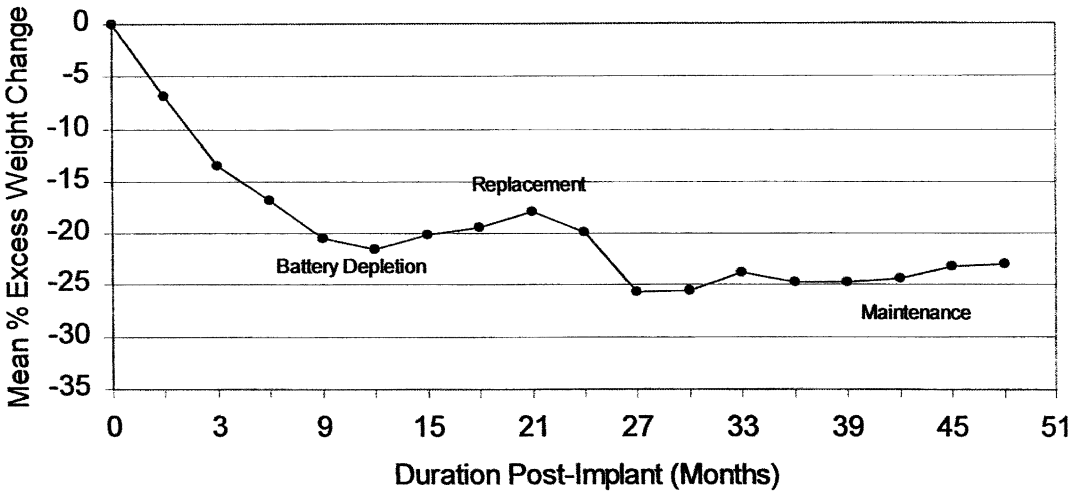

Fig. 2. Preliminary results from the first 10 patients.

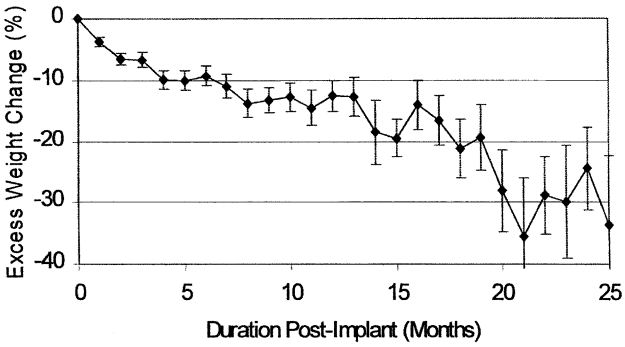

Fig. 3. Pooled results from eight European trials involving 77 patients.

open-label pilot trial, was initiated. It enrolled 30 patients at two clinical sites. This trial is unique for several reasons: First, binge eaters are excluded as they performed poorly in earlier trials. Second, behavioral support and dietary counseling are included. Third, the system includes two leads (four electrodes) that can be programmed separately or together. Finally, the device is programmed individually for each patient. A major clinical breakthrough was discovered early in this investigation. It was found that by programming high electrical outputs, most patients immediately developed symptoms of bloating, nausea, retching, and/or abdominal pain. This finding may be similar to the "capture" of cardiac rhythm during heart pacing. The output is then reduced slightly. Patients who experience symptoms have dramatic reductions in appetite and most have achieved weight loss. Thus far at our site we have achieved a mean excess weight loss of 21.3% at a mean follow-up of 7.3 months (range = 5−11 months). Eighty percent of patients have lost weight and 60% of patients have lost more than 10% of their excess weight (10%–89% excess weight loss).

As this technology continues to evolve, the results improve with each trial. Recently, a retrospective statistical analysis of the four large trials involving over 350 patients has discovered that a simple screening algorithm based on a questionnaire can identify responders and non-responders. Motivational factors seem to be most important. Applying this strategy retrospectively demonstrated that those patients who screened favorably for these motivational factors performed significantly better than those who screened unfavorably. This is demonstrated in Fig. 5 with the DIGEST trial. A prospective trial to validate this is currently being designed.

CONCLUSION

The implantable gastric stimulator offers a novel and exciting approach to surgical weight loss. Thus far, we know that it is easy to place and is safe. If the long-term weight loss results are as successful as hoped, this may represent a true breakthrough in the treatment of severe obesity. Refinements in patient selection, lead security, device settings, and postoperative behavioral and dietary support have resulted in steadily improving results.

This device will not likely replace the gastric bypass and other more radical weight loss procedures. However, it may offer bariatric treatment centers an additional option, especially for patients not appropriate

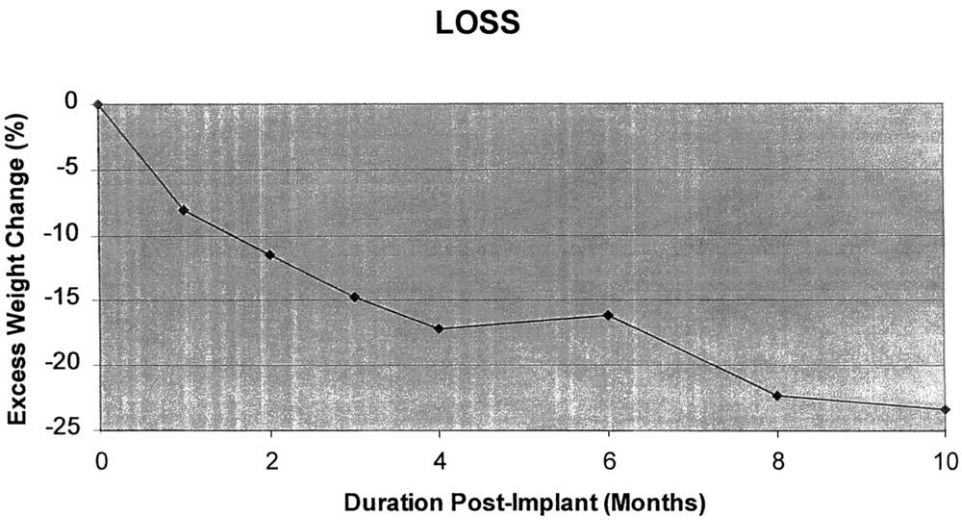

Fig. 4. The European Laparoscopic Obesity Stimulation Study (LOSS), which currently has included 65 patients at eight clinical sites.

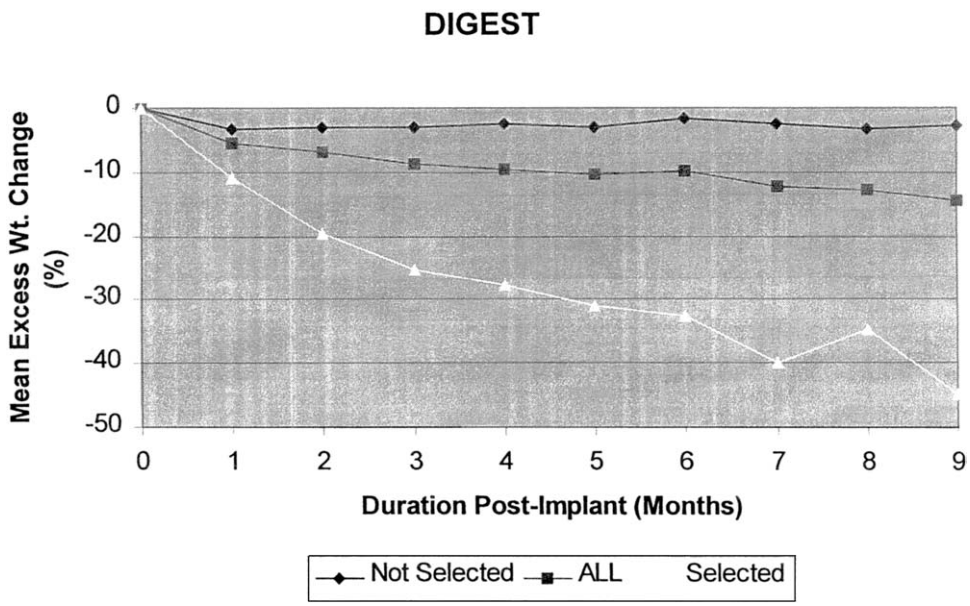

Fig. 5. Results from the United States Dual-Lead Implantable Gastric Electrical Stimulation Trial (DIGEST) investigation demonstrating the improved results achieved with preoperative screening.

or interested in the standard operations. In addition, it may find additional patient niches currently not served by conventional surgery or successfully treated by nonsurgical modalities. The IGS system is still a work in progress, but has the potential to be an effective option among the many current obesity treatment therapies.

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Role of Retinoid X Receptor mRNA Expression in Barrett's Esophagus

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The Barrett's multistage process is characterized histopathologically by progression from Barrett's intestinal metaplasia to Barrett's esophagus with dysplasia and ultimately adenocarcinoma. Understanding of the molecular alterations in this multistage process may contribute to improved diagnosis and treatment. Retinoid X receptors (RXR) play an important role in regulating the morphogenesis, development, growth, and differentiation of cells. Alterations in RXR expression have been observed in a variety of solid tumors; however, the role in Barrett's esophagus disease has yet to be determined. The aim of this study was to assess the prevalence and timing of RXR messenger RNA expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence and to investigate its role in the development and progression of this disease. We analyzed the mRNA expression of all three RXR subtypes (RXR-alpha, RXR-beta, and RXR-gamma) by using a quantitative real-time reverse transcription–polymerase chain reaction method in 108 specimens from 19 patients with Barrett's esophagus without carcinoma (BE group), 20 patients with Barrett's-associated adenocarcinoma (EA group), and a control group of 10 patients without evidence of gastroesophageal reflux disease (CG). RXR-α mRNA expression was significantly decreased ($P < 0.001$; Kruskal-Wallis test), and RXR-γ was significantly increased ($P < 0.001$) at higher stages in Barrett's esophagus. RXR-β expression was highest in Barrett's tissues and was significantly increased compared to normal squamous tissues ($P = 0.01$; Wilcoxon test) and adenocarinoma tissues ($P = 0.018$, Mann-Whitney test). RXR-α and RXR-β mRNA expression was significantly associated in normal squamous esophagus tissues ($r^2 = 0.49$; $P < 0.001$; Spearman test), Barrett's tissues ($r^2 = 0.63$; $P < 0.001$), and adenocarcinoma tissues ($r^2 = 0.68$; $P = 0.001$). There were significant differences in RXR-α ($P = 0.011$) and RXR-β ($P = 0.005$) mRNA expression in histopathologically normal squamous esophagus tissues in patients with cancer and the control group without evidence of gastroesophageal reflux disease. These findings suggest that alterations in the mRNA expression of all three RXR subtypes are frequent events in the development and progression of Barrett's esophagus and associated adenocarcinoma, that RXR mRNA expression levels may be useful biomarkers for this disease, and that a widespread "field-effect" is present in the normal esophagus of patients with esophageal adenocarcinoma. (J GASTROINTEST SURG 2004;8:413–422)

KEY WORDS: Barrett's esophagus, retinoids, retinoid X receptors, molecular markers, esophageal adenocarcinoma, gene expression

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Barrett's esophagus, the replacement of the normal stratified squamous epithelium of the esophagus by a metaplastic columnar lining, is a premalignant condition caused by chronic gastroesophageal reflux. This condition predisposes to the development of esophageal adenocarcinoma, the incidence of which has been increasing rapidly in the United States and other Western countries.[1] Patients with esophageal adenocarcinoma usually present at an advanced stage and undergo a rapidly fatal course, with 5-year survival rates of approximately 25% to 30%.[2] It is hoped that the identification of novel biomarkers associated with each stage of Barrett's disease and with an increased cancer risk will lead to earlier detection and improved survival for patients with this disease.

Retinoids exert their effects primarily through two subfamilies of steroid/hormone receptor superfamily: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). There are three types each of RARs (RAR-α, RAR-β, and RAR-γ) and RXRs (RXR-α, RXR-β, and RXR-γ), and all are nuclear, ligand dependent, DNA-binding transcriptional transactivator proteins.[3] The various RAR and RXR subtypes are encoded by different genes, are highly conserved in evolution, and display distinct spatiotemporal patterns of expression in early and adult stages of development, suggesting that each receptor has distinct physiologic functions.[3] Alterations in RAR and RXR gene expression have been reported in various cancers, including lung,[4,5] breast,[6] gastric,[7] and head and neck cancers,[8] which suggests a fundamental role in tumor development in these malignancies. Furthermore, alterations in RAR and RXR subtypes have been found to be of prognostic significance in non–small cell lung cancer.[9,10] Most retinoid-related research in esophageal cancer has been limited to RAR expression. RAR-β expression is frequently decreased during esophageal carcinogenesis,[11,12] and upregulation of RAR-α messenger RNA expression and downregulation of RAR-γ mRNA expression have been demonstrated in Barrett's esophagus and associated adenocarcinoma.[13] To date, however, there are no detailed studies on RXR mRNA expression in Barrett's esophagus and Barrett's-associated adenocarcinoma of the esophagus. The aim of the present study was to analyze the mRNA expression of all three RXR subtypes in the development and progression of Barrett's esophagus and associated adenocarcinoma, and to determine the potential usefulness of RXR mRNA quantitation in the clinical management of this disease.

MATERIAL AND METHODS

Tissue Samples for Reverse Transcription–Polymerase Chain Reaction

A total of 108 tissue samples obtained at endoscopy and operation from 19 patients with Barrett's esophagus without adenocarcinoma (BE group), 20 patients with Barrett's-associated esophageal adenocarcinoma (EA group), and 10 patients with no symptomatic, endoscopic or histopathologic evidence of Barrett's esophagus or chronic gastroesophageal reflux disease (control group, CG) were collected and immediately frozen in liquid nitrogen. There were 31 men and 18 women whose median age was 60.1 years (range 24 to 76 years). Endoscopic biopsies were obtained according to a protocol that required biopsy at 2 cm intervals from each quadrant (anterior, posterior, right lateral, and left lateral positions) of the visible length of Barrett's mucosa and an additional biopsy from the normal-appearing squamous mucosa of the esophagus. Normal biopsies of the esophagus were taken at least 4 cm proximal to the macroscopically abnormal epithelium. Part of the specimen or an adjacent specimen was fixed in formalin and paraffin for histopathologic examination.

Specimens were classified as intestinal metaplasia if intestinal metaplasia but no dysplasia or cancer was present. Specimens were classified as dysplastic if either low-grade dysplasia or high-grade dysplasia was present. Dysplastic tissues were not divided into low-grade or high-grade dysplasia groups because areas of low-grade dysplasia and high-grade dysplasia were commonly present in the same specimen. Using these criteria, the following tissues were analyzed for RXR mRNA expression: Barrett's intestinal metaplasia (n = 16), Barrett's dysplasia (n = 3) and matching normal squamous tissue (n = 19) in the BE group, Barrett's adenocarcinoma of the esophagus (n = 20), Barrett's intestinal metaplasia (n = 5), Barrett's dysplasia (n = 15), and matching normal squamous esophagus tissues (n = 20) in the EA group, and normal squamous esophagus tissues (n = 10) in the control group, for a total of 108 specimens.

RNA Extraction and cDNA Synthesis

Total RNA was isolated by a single-step guanidinium isothiocyanate method using the QuickPrep *Micro* mRNA Purification Kit (Amersham Pharmacia Biotech, Inc., Piscataway, NJ) according to the manufacturer's instructions, and cDNA samples were prepared as previously described.[14,15]

Polymerase Chain Reaction Quantification of mRNA Expression

Quantitation of RXRs cDNA and an internal reference cDNA (β-actin) was done using a fluorescence

detection method (ABI Prism 7700 Sequence Detection System [TaqMan]; Perkin Elmer Applied Biosystems, Foster City, CA), as previously described.[15–17]

The polymerase chain reaction (PCR) mixture consisted of 600 nmol/L of each primer, 200 nmol/L probe, 5 U AmpliTaq Gold Polymerase, 200 µmol/L each dATP, dCTP, dGTP, 400 µmol/L dUTP, 5.5 mmol/L $MgCl_2$, and 1 × TaqMan Buffer A containing a reference dye, to a final volume of 25 µl (all reagents from Perkin-Elmer Applied Biosystems). Cycling conditions were 50° C for 10 seconds, 95° C for 10 minutes followed by 46 cycles at 95° C for 15 seconds and 60° C for 1 minute. The primers and probes used are listed in Table 1.

Statistical Analysis

TaqMan analyses yield values that are expressed as ratios between two absolute measurements (gene of interest/internal reference gene). RXR expression levels in adenocarcinoma, Barrett's esophagus, and normal squamous esophagus tissues were compared using the Kruskal-Wallis test to identify significant differences in expressions among the histopathologic groups. The Kruskal-Wallis test was also used to compare the three groups of normal esophagus tissues. When the overall Kruskal-Wallis test (comparing 3 groups) was significant at the 0.05 level, pairwise comparisons were based on the Mann-Whitney test and the nominal *P* value was reported. The Wilcoxon signed-rank test was used for comparison of paired tissues. Spearman's test was used to test for bivariate correlations between RXR receptor expression. Statistical significance (with two-sided tests) was set at the 0.05 level.

Table 1. PCR primers and probes

Forward primer: RXR-αβγ
Sequence: 5′- *AAGGACCGGAACGAGAATGA* -3′
Reverse primer: RXR-α
Sequence: 5′- *ATCCTCTCCACCGGCATGT* -3′
TaqMan probe: RXR-α
Sequence: 6FAM 5′- *AGTCGACCAGCAGCGCCAACG* -3′TAMRA
Forward primer: RXR-β
Sequence: 5′- *CTCTGGATGATCAGGTCATATTGCT* -3′
Reverse primer: RXR-β
Sequence: 5′- *GCCATCTCGAACATCAATGGA* -3′
TaqMan probe: RXR-β
Sequence: 6FAM 5′- *ACTCCTCATTGCCTCCTTTTCACA CCG* -3′TAMRA
Forward primer: RXR-γ
Sequence: 5′- *GGGAAGCTGTGCAAGA AGAAA* -3′
Reverse primer: RXR-γ
Sequence: 5′- *TGGTAGCACATTCTGCCTCACT* -3′
TaqMan probe: RXR-γ
Sequence: 6FAM 5′- *TCAGCTCGCTCTCGGCTCCTCTG* -3′TAMRA
Forward primer: β-actin
Sequence: 5′-*TGAGCGCGGCTACAGCTT*-3′
Reverse primer: β-actin
Sequence: 5′-*TCCTTAATGTCACGCACGATTT*-3′
TaqMan probe: β-actin
Sequence: 6FAM5′- *ACCACCACGGCC GAGCGG* -3′TAMRA

RESULTS

RXR-α mRNA Expression in Barrett's Esophagus

RXRα mRNA expression was detectable by quantitative real-time PCR (TaqMan) in all 108 specimens (100%). Analyzed according to histopathologic group, the median RXR-α mRNA expression was highest in normal squamous esophagus tissues (median 2.64, range 0.9 to 9.9), intermediate in Barrett's esophagus (median 1.91, range 0.5 to 13.8), and lowest in Barrett's-associated adenocarcinoma of the esophagus (median 0.99, range 0.4 to 1.6; $P < 0.001$; Kruskal-Wallis test).

Eleven (57.9%) of 19 patients with the maximum diagnosis of Barrett's esophagus (BE group, n = 19) had lower RXR-α mRNA expression levels in Barrett's epithelium compared to matching normal squamous esophagus tissues. The median RXR-α mRNA expression in normal squamous esophagus tissue was 2.36 (range 1.4 to 9.7) and 2.51 in Barrett's esophagus (range 0.6 to 18.8; *P* = not significant; Wilcoxon test) (Fig. 1 and Table 2).

In the group of patients with Barrett's-associated adenocarcinoma (EA group, n = 20), 19 (95%) of 20 patients had lower RXR-α mRNA expression levels in cancerous tissue compared to matching normal esophagus tissues. The median RXR-α mRNA expression was 2.44 (range 0.9 to 9.9) in the normal esophagus, 1.67 (range 0.5 to 10.6) in Barrett's epithelium, and 0.99 (range 0.4 to 1.6) in Barrett's-associated adenocarcinoma ($P < 0.001$; Kruskal-Wallis test). Fig. 1 and Table 2 show that the median RXR-α mRNA expression was significantly lower in Barrett's-associated adenocarcinoma compared to matching normal esophagus tissues and Barrett's epithelium.

RXR-β mRNA Expression in Barrett's Esophagus

RXR-β mRNA expression was detectable by quantitative real-time PCR (TaqMan) in all 108 specimens (100%). Analyzed according to histopathologic group, the median RXR-β mRNA expression was highest in Barrett's esophagus tissues (median 1.01,

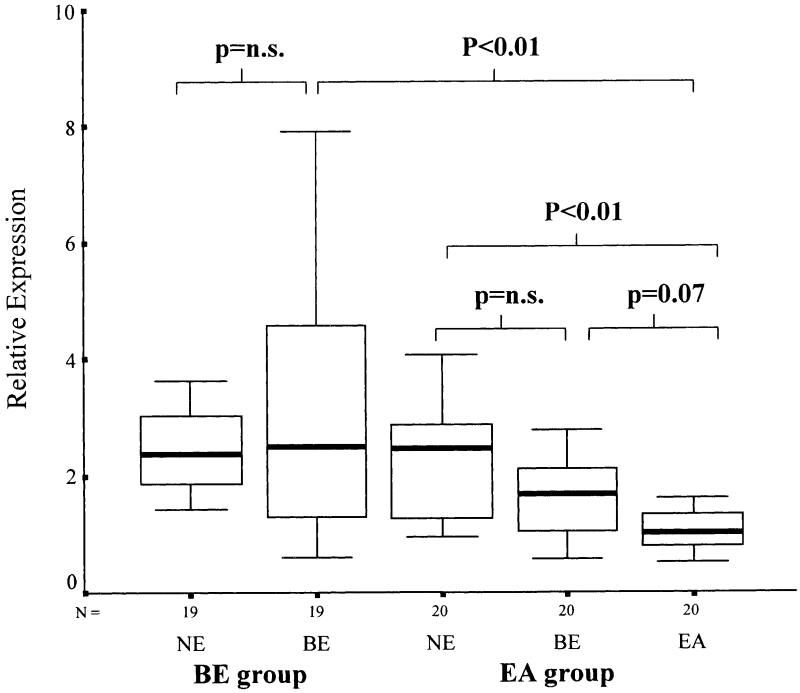

Fig. 1. Box and whisker plots of relative RXR-α mRNA expression levels for normal esophagus and Barrett's esophagus tissues from patients with the maximum diagnosis of Barrett's esophagus (*BE group*) and matching normal esophagus, Barrett's esophagus, and adenocarcinoma tissues from cancer patients (*EA group*). The boxes show the 25th and 75th percentile (interquartile) ranges. Median values are shown as a horizontal black bar within each box. The whiskers show levels outside the 25th and 75th percentiles.

range 0.4 to 3.2), intermediate in normal squamous esophagus (median 0.81, range 0.0.1 to 2.2), and lowest in Barrett's-associated adenocarcinoma of the esophagus (median 0.75, range 0.1 to 2.3; $P = 0.009$; Kruskal-Wallis test).

Twelve (63.2%) of 19 patients with the maximum diagnosis of Barrett's esophagus (BE group, n = 19) had higher RXR-β mRNA expression levels in Barrett's epithelium compared to matching normal squamous esophagus tissues. The median RXR-β mRNA expression in normal squamous esophagus tissues was 0.81 (range 0.4 to 1.3) and 1.04 in Barrett's esophagus (range 0.5 to 3.3; $P = 0.01$; Wilcoxon test) (Fig. 2 and Table 3).

In the group of patients with Barrett's-associated adenocarcinoma (EA group, n = 20), 10 (50%) of 20 patients had lower RXR-β mRNA expression levels in cancer tissues compared to matching normal esophagus tissues. The median RXR-β mRNA expression was 1.05 (range 0.0.1 to 2.3) in normal

Table 2. RXR-α mRNA expression in tissues from patients with adenocarcinoma and Barrett's esophagus

Pathology	n	RXRα expression		Interquartile range (25^{th}–75^{th} percentiles)	*P*
		Median	Range		
EA group	20				
Adenocarcinoma		0.99	0.5–1.6	0.7–1.3	<0.001
Barrett's mucosa		1.67	0.5–10.6	1.0–2.1	
Squamous esophagus		2.44	0.9–9.9	1.2–2.8	
BE group	19				
Barrett's mucosa		2.50	0.5–13.8	1.1–4.9	NS
Squamous esophagus		2.37	1.4–9.7	1.7–3.0	
CG group	10				
Squamous esophagus		4.39	2.6–7.4	3.1–5.4	

EA = adenocarcinoma group; BE = Barrett's esophagus group; CG = control group.

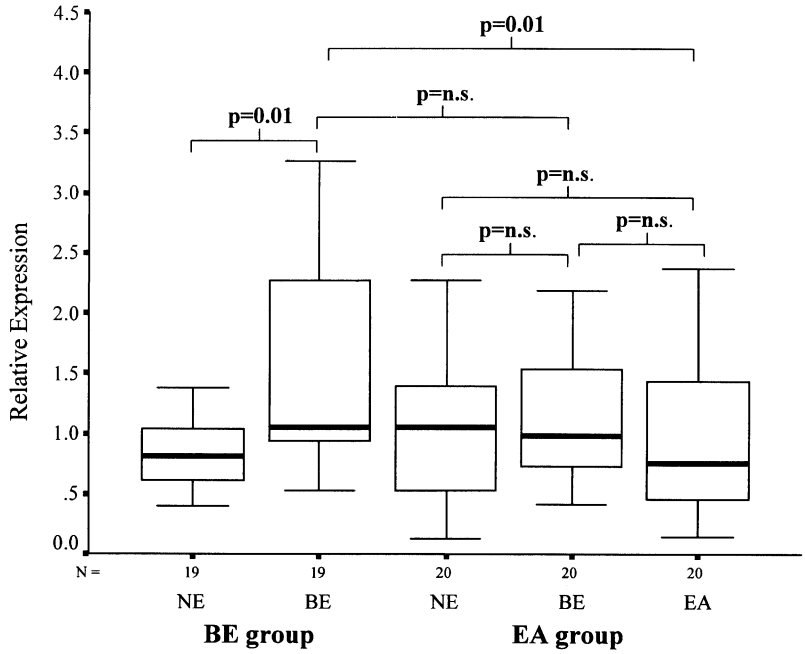

Fig. 2. Box and whisker plots of relative RXR-β mRNA expression levels for normal esophagus and Barrett's esophagus tissues from patients with the maximum diagnosis of Barrett's esophagus (*BE group*) and matching normal esophagus, Barrett's esophagus, and adenocarcinoma tissues from cancer patients (*EA group*). The boxes show the 25th and 75th percentile (interquartile) ranges.

esophagus, 0.98 (range 0.5 to 2.2) in Barrett's epithelium, and 0.76 (range 0.0.1 to 2.3) in Barrett's-associated adenocarcinoma (P = NS; Kruskal-Wallis test). Fig. 3 shows that the median RXR-β mRNA expression was significantly lower in Barrett's-associated adenocarcinoma compared to Barrett's epithelium from the BE group ($P = 0.01$; Mann-Whitney test).

RXR-γ mRNA Expression in Barrett's Esophagus

RXR-γ mRNA expression was detectable by quantitative real-time PCR (TaqMan) in 103 specimens (95.4%). Four normal squamous esophagus samples and one Barrett's esophagus were negative for RXR-γ mRNA expression. Analyzed according to histopathologic group, the median RXR-γ mRNA expression was lowest in normal squamous esophagus tissues (median 0.30, range 0 to 4.4), highest in Barrett's esophagus (median 2.49, range 0 to 17.1), and intermediate in Barrett's-associated adenocarcinoma of the esophagus (median 1.91, range 0.5 to 90.7; $P < 0.001$; Kruskal-Wallis test).

Nineteen (100%) of 19 patients with the maximum diagnosis of Barrett's esophagus (BE group, n = 19) had higher RXR-γ mRNA expression levels in Barrett's epithelium compared to matching normal squamous esophagus tissues. The median RXR-γ mRNA

Table 3. RXR-β mRNA expression in tissues from patients with adenocarcinoma and Barrett's esophagus

Pathology	n	RXR-β expression		Interquartile range (25^{th}–75^{th} percentiles)	*P*
		Median	Range		
EA group	20				
Adenocarcinoma		0.75	0.1–2.3	0.4–1.4	NS
Barrett's mucosa		0.98	0.4–2.1	0.6–1.5	
Squamous esophagus		1.05	0.1–2.2	0.5–1.3	
BE group	19				
Barrett's mucosa		1.04	0.5–3.2	0.9–2.6	0.01
Squamous esophagus		0.81	0.4–1.3	0.5–1.0	
CG group	10				
Squamous esophagus		0.44	0.1–1.1	0.3–0.6	

EA = adenocarcinoma group; BE = Barrett's esophagus group; CG = control group.

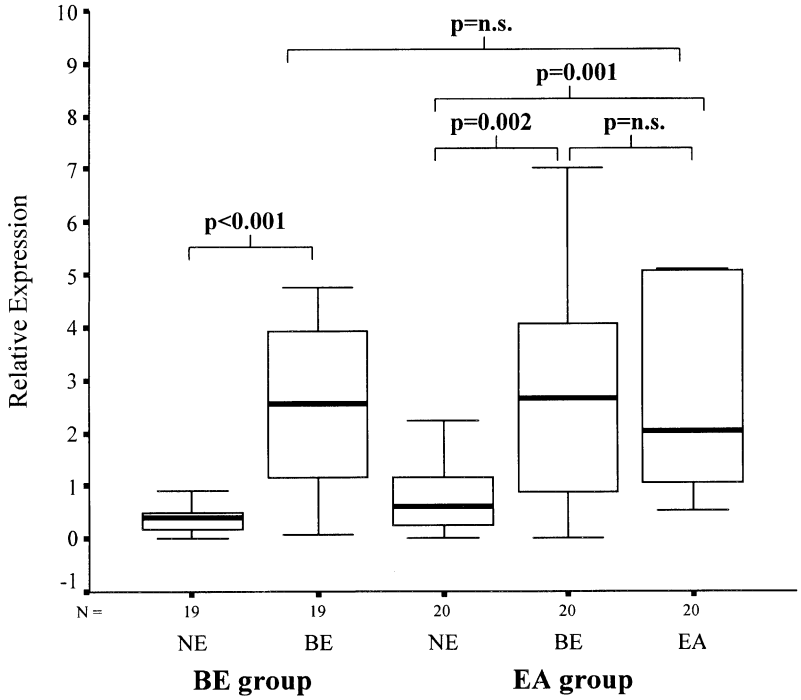

Fig. 3. Box and whisker plots of relative RXR-γ mRNA expression levels for normal esophagus and Barrett's esophagus tissues from patients with the maximum diagnosis of Barrett's esophagus (*BE group*) and matching normal esophagus, Barrett's esophagus, and adenocarcinoma tissues from cancer patients (*EA group*).

expression in normal squamous esophagus tissues was 0.27 (range 0 to 2.2) and 2.42 in Barrett's esophagus (range 0.1 to 17.1; $P < 0.001$; Wilcoxon test) (see Fig. 3 and Table 4).

In the group of patients with Barrett's-associated adenocarcinoma (EA group, n = 20), 17 (85%) of 20 patients had higher RXR-γ mRNA expression levels in cancer tissues compared to matching normal esophagus tissues. The median RXR-γ mRNA expression was 20.48 (range 0 to 4.4) in normal esophagus, 2.52 (range 0 to 10.0) in Barrett's epithelium, and 1.91 (range 0.5 to 90.7) in Barrett's-associated adenocarcinoma ($P < 0.001$; Kruskal-Wallis test) (see Fig. 3 and Table 4).

Expression of RXR Isoforms in Normal Squamous Esophagus Tissues From Patients With Adenocarcinoma, Barrett's Esopahgus, and Healthy Control Subjects

Overall, the three groups of normal esophagus tissue revealed substantial differences in RXR-α and RXR-β expression levels ($P = 0.01$; Kruskal-Wallis test). The median RXR-α mRNA expression in the

Table 4. RXR-γ mRNA expression in tissues from patients with adenocarcinoma and Barrett's esophagus

Pathology	n	RXR-γ expression		Interquartile range (25^{th}–75^{th} percentiles)	*P*
		Median	Range		
EA group	20				
Adenocarcinoma		1.91	0.5–90.7	1.0–5.1	<0.001
Barrett's mucosa		2.52	0–10.0	0.8–4.0	
Squamous esophagus		0.48	0–4.4	0.2–1.1	
BE group	19				
Barrett's mucosa		2.42	0.1–17.1	0.9–4.1	<0.001
Squamous esophagus		0.27	0–2.2	0.1–0.5	
CG group	10				
Squamous esophagus		0.27	0.1–0.7	0.2–0.3	

EA = adenocarcinoma group; BE = Barrett's esophagus group; CG = control group.

group of histologically normal squamous esophagus tissues from the healthy control group (median 4.39, range 2.6 to 7.4) was significantly higher than the median RXR-α expression found in normal squamous esophagus tissues from patients with Barrett's esophagus only (median 2.37, range 1.4 to 9.7; $P = 0.01$; Mann-Whitney test) and normal squamous esophagus tissues obtained from patients with adenocarcinoma of the esophagus (median 2.44, range 0.9 to 9.9; $P = 0.01$; Mann-Whitney test) (Fig. 4).

Again, the three groups of normal esophagus tissue revealed substantial differences in RXR-β expression levels ($P = 0.008$, Kruskal-Wallis test). The median RXR-β mRNA expression in the group of histologically normal squamous esophagus tissues from the healthy control group (median 0.44, range 0.1 to 1.1) was significantly lower than the median RXR-β expression found in normal squamous esophagus tissues from patients with Barrett's esophagus only (median 0.81, range 0.4 to 1.3; $P = 0.011$; Mann-Whitney test) and normal squamous esophagus tissues obtained from patients with adenocarcinoma of the esophagus (median 1.05, range 0.1 to 2.2; $P = 0.005$; Mann-Whitney test) (Fig. 5). The three groups of normal esophagus tissue revealed no significant differences in RXR-γ expression levels (P = NS; Kruskal-Wallis test).

Associations Between RXR Subtype Expression Levels in Barretts's Tissues

Table 5 shows the associations between RXR subtype expression levels in different Barrett's tissues. RXR-α and RXR-β mRNA expression were significantly associated in normal squamous esophagus tissues ($r^2 = 0.49$; $P < 0.001$; Spearman's test), Barrett's tissues ($r^2 = 0.63$; $P < 0.001$), and adenocarcinoma tissues ($r^2 = 0.68$; $P = 0.001$).

DISCUSSION

The main risk factor for the development of esophageal adenocarcinoma is the presence of Barrett's esophagus. The mechanisms underlying the increased development of cancer in this tissue are not fully understood, but substantial evidence exists that progression to Barrett's carcinoma is associated with a variety of genetic and epigenetic alterations.[18–20] This study demonstrates that RXR subtype mRNA expression levels are altered in Barrett's esophagus and Barrett's-associated esophageal adenocarcinomas. RXR-α expression was decreased and RXR-γ was increased in Barrett's tissues, indicating that alterations in the expression of these genes is an early event in

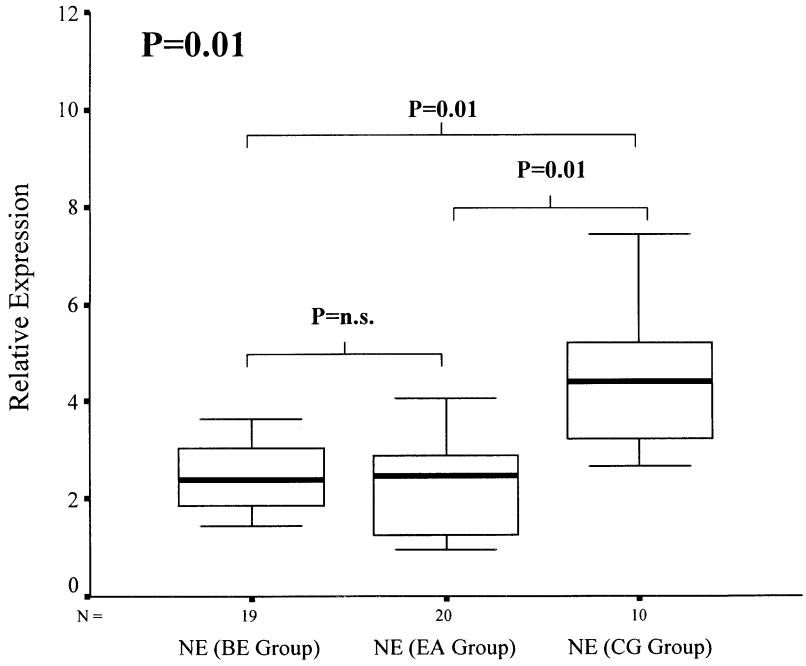

Fig. 4. Box and whisker plots of relative RXR-α mRNA expression levels for normal squamous esophagus tissues from a control group (*CG*) without evidence of Barrett's esophagus or chronic gastroesophageal reflux, and patients with Barrett's esophagus (*BE group*), and patients with adenocarcinoma of the esophagus (*EA group*).

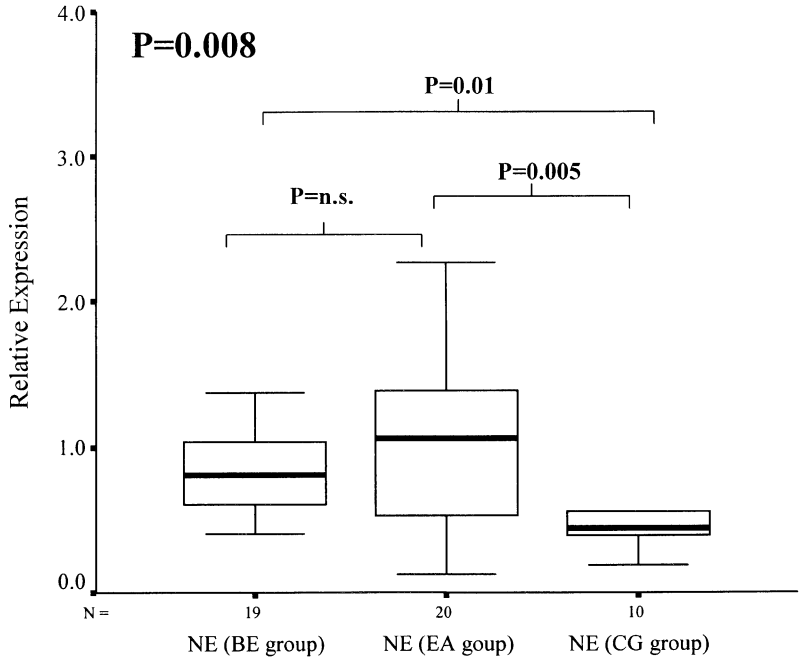

Fig. 5. Box and whisker plots of relative RXR-β mRNA expression levels for normal squamous esophagus tissues from a control group (*CG*) without evidence of Barrett's esophagus or chronic gastroesophageal reflux, and patients with Barrett's esophagus (*BE group*), and patients with adenocarcinoma of the esophagus (*EA group*).

the progression from Barrett's esophagus to adenocarcinoma. Our findings complement the results of previous studies that reported alterations in RAR and RXR expression in various human cancers. Alterations in RAR and RXR gene expression have been reported in lung,[4,5] breast,[6] gastric,[7] and head and neck cancer,[8] suggesting a fundamental role in tumor development in these malignancies. These results suggest that inappropriate RXR subtype expression is a somewhat specific effect that contributes to tumor development and is not simply a function of generalized inflammation in Barrett's esophagus.

Our results suggest that quantitation of RXR subtypes of mRNA expression offers promise as biomarkers for following disease progression in patients with Barrett's esophagus. It seems plausible that patients with Barrett's esophagus with a more abnormal RXR expression profile are at greater risk of progression to more advanced disease stages because of an increased capacity for invasion and proliferation, but this needs to be demonstrated in studies of sequential biopsies in individual patients. It is likely that molecular diagnosis and staging of Barrett's esophagus will require the assessment of a panel of gene expressions. Results of studies from this institution and elsewhere suggest that many genes have significantly different expressions or mutation frequencies at different Barrett's stages.[13,15,20–24]

The mechanism leading to inappropriate RXR expression in tumorigenesis, and whether the effects of RXRs on invasion and proliferation are induced by mechanisms that are linked or mutually exclusive, is

Table 5. Associations between RXR expression in Barrett's tissues

	NE			BE			EA				
Subtypes	**RXR alpha**	**RXR beta**	**RXR gamma**	**RXR alpha**	**RXR beta**	**RXR gamma**	**RXR alpha**	**RXR beta**	**RXR gamma**		
RXR alpha	1.000	0.496 <0.001	−0.113 NS	1.000	0.633 <0.001	0.295 0.068	1.000	0.689 0.001	−0.202 NS	r^{2*}	$P^{\dagger}$
RXR beta		1.000	0.92 NS		1.000	0.402 0.011		1.000	−0.433 NS	r^{2*}	$P^{\dagger}$
RXR gamma			1.000			1.000			1.000	r^{2*}	$P^{\dagger}$

NE = normal esophagus; BE = Barrett's esophagus; EA = adenocarcinoma.
*Correlation coefficient.
†Spearman test; NS = not significant.

not yet known and was not the focus of this investigation. RARs can form heterodimers with RXRs and recognize retinoid acid response elements that can activate transcription. RXRs can also form homodimers and activate retinoid X response elements or form heterodimers with other members of the steroid receptor family, thus providing opportunities for cross-talk among different signaling pathways.[3] Our observation of widely coregulated RXRα and RXRβ mRNA expression levels in different Barrett's tissues suggests combined alteration of different RXR subtype expression during progression of Barrett's disease. Further studies are warranted to determine the underlying mechanisms leading to altered RXR expression in this disease.

Expression levels were significantly different in normal squamous esophagus tissues from patients with cancer compared to patients with the maximum diagnosis of Barrett's esophagus and the control group without evidence of Barrett's esophagus or chronic gastroesophageal reflux for RXR-α and RXR-β. We and others have found similar evidence of the presence of a widespread oncogenic "field effect" in the normal esophagus of patients with cancer in studies of gene expression and DNA methylation analysis.[13,15,21–25] One explanation for this field change is that because of an injurious environmental agent, for example, the gastroesophageal refluxate, some of the early events of tumorigenesis have already occurred. These early events might predispose the apparently normal squamous esophagus tissue to undergo further genetic changes leading ultimately to the development of Barrett's esophagus and adenocarcinoma. An alternative explanation is that clones of abnormal cells, in the presence of cancer, have expanded widely throughout the mucosa to replace previously normal cells. In either case it is apparent that genetic changes can precede the appearance of morphologic changes in this disease.

In summary, these data suggest that alterations of RXR mRNA expression are an early event in Barrett's multistage disease, which already occurs at the level of Barrett's metaplasia and further increases during progression to cancer. The presence of esophageal adenocarcinoma seems associated with an "oncogenic" field effect on the normal squamous esophagus mucosa. Quantitation of RXR mRNA subtype expression might serve as novel biomarkers for the detection of cancer in patients with Barrett's esophagus.

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GSTP1, GSTM1, and GSTT1 Genetic Polymorphisms in Patients With Cryptogenic Liver Cirrhosis

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We investigated glutathione S–transferase (GST) P1 Ile (105) Val, T1, and M1 polymorphisms in 45 patients with documented cryptogenic cirrhosis and 56 healthy control subjects. Polymerase chain reaction–based procedures were performed in the studied populations to confirm the genotypes of GSTT1, M1, and P1. Ile/Val and Val/Val GSTP1 genotypes were more frequent in the patients with cirrhosis (n = 39, 87%) than in the control subjects (n = 10; 18%) (odds ratio [OR] 34.04; 95% confidence interval [CI] 10.70 to 108.31, $P < 0.001$). Among these patients with cirrhosis, 16 were heterozygous and 23 were homozygous, whereas only one person in the control group was homozygous. The GSTM1 null genotype was also more prevalent in cirrhotic patients than in healthy control subjects (OR 6.83, 95% CI 2.53 to 18.42, $P < 0.001$). The rate of GSTT1 deletion did not show a significant difference between the two groups (OR 2.35, 95% CI 0.76 to 7.28, $P = 0.111$). To our knowledge, this is the first evidence that GSTP1 and GSTM1 polymorphisms may be related to the development of cirrhosis by unknown mechanisms. The significant association of cryptogenic cirrhosis with Val/Val GSTP1 genotype encoding a low detoxification activity protein implicates this polymorphism as a risk factor for the occurrence of the disease. (J GASTROINTEST SURG 2004;8:423–427)

KEY WORDS: Glutathione S–transferase genotype, cryptogenic cirrhosis

Progression of hepatitis to cirrhosis and the response to therapy are variable among individuals. This variability is due to the primary cause of disease and interindividual differences in target proteins and drug metabolism.[1] Genetic polymorphisms may affect gene expression or the function of the various enzymes involved.[2] Five percent to 15% of cases of cirrhosis are found to be caused by an unidentified abnormality with a diagnosis of cryptogenic cirrhosis.[3] Liver cell damage and replacement by scar tissue in the course of cirrhosis may result in liver failure that is often caused by the altered activities of liver enzymes deactivating toxic compounds and carcinogens.[4] Among liver detoxifying enzymes, the glutathione S–transferases (GSTs) play a key role in the protection against oxidative stress because oxidative injury contributes to the development of liver disease.[5] We hypothesized that two members of the GST superfamily, GSTM1 and GSTP1, which are expressed in the biliary epithelium, could influence the hepatic status in patients with cryptogenic cirrhosis. GSTs, the enzymes involved in phase II of detoxification reactions, have been shown to be widely expressed in human tissues and to be overexpressed in several types of tumors.[6] Polymorphisms have been found in several GST genes, some of which were associated with cancer susceptibility. The frequency of the GST genotypes and the activity of corresponding enzymes vary among different ethnic groups.[7,8] Therefore the possible relationship between GST polymorphism and increased risk of various diseases

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has been examined in numerous molecular epidemiology studies.[9–11] However, few published data are available that evaluate the ability of known GST polymorphisms to contribute to the development of cryptogenic cirrhosis. In this study, we analyzed the frequency of GSTP1 polymorphism at codon 105 and deletions in GSTM1 and GSTT1 in a group of patients with cryptogenic cirrhosis compared to control subjects.

PATIENTS AND METHODS

Study Subjects and Data Collection

Cases of cryptogenic cirrhosis were identified through blood transfusion organizations in Tehran and Gastroenterology Clinics at Taleghani Hospital, Shahid Beheshti University of Medical Sciences, between June 2002 and December 2002. After informed consent was obtained, a total of 45 patients (30 males and 15 females) with documented cryptogenic cirrhosis and 56 control subjects were enrolled in the study. Blood samples were collected from these individuals and used for genomic DNA isolation. Medical and pathology records from each patient were reviewed to confirm the diagnosis, which was based on history and/or clinical signs of liver damage requiring medical therapy. None of the patients had a history of liver-targeting viral infections, occupational exposure to hepatitis B or C virus, drug treatment, or metabolic or autoimmune liver disease. Nonviral hepatitis B and hepatitis C status was confirmed by retesting hepatitis B and hepatitis C virus RNA in plasma. Subjects who had the preceding viral nucleic acids in their plasma were excluded from this study.

The 56 control subjects (33 males and 23 females) studied were persons who were attending general medical clinics and blood donors. Control subjects had to have no evidence of liver disease and had to be demographically similar to patients in the experimental group; they also had the same baseline cigarette smoking status (current, former, never) among patients who provided a blood specimens. Control subjects who had a history of gastrointestinal disease or a previous diagnosis of cancer were excluded from this study. All study subjects gave informed consent to participate in this research under a protocol approved by the Committee for Studies on Human Subjects at Shahid Beheshti University of Medical Sciences.

Genomic DNA for the present study was isolated and processed from buffy coats using the salting-out protocol modified from Miller et al.[12] DNA samples from patients and control subjects were further analyzed in a blinded manner with regard to name and case status of each sample.

Glutathione S–Transferase Genotyping

To detect the deletions of GSTM1 and GSTT1, a triplex polymerase chain reaction (PCR) was used including primers directed at β-globin gene for a control of DNA integrity (Fig. 1). In order to detect variants of codon 105 of GSTP1, PCR-restriction fragment length polymorphism (RLFP) analysis was employed (Fig. 2).

The testing was performed in the following protocols. The complete gene deletions at GSTM1 and GSTT1 were determined by using a PCR-based assay. Isolated DNA (30 to 50 ng) was amplified in a 25 μl reaction containing 30 pmol of each of the following: GSTM1 primers of 5′-TTC TGG ATT GTA GCA GAT CA – 3′, 5′-CGC CAT CTT GTG CTA CAT TGC CCG-3,′ and GSTT1 primers of 5′-TTC CTT ACT GGT CCT CAC ATC TC-3′, 5′-TCA CCG GAT CAT GGC CAG CA-3′. As a positive internal control, β-globin gene was coamplified using the primers 5′-CAA CTT CAT CCA CGT TCA CC-3′ and 5′-GAA GAG CCA AGG ACA GGT AC-3′ in the presence of 200 μmol/L dNTP, PCR buffer, 1.5 mmol/L $MgCl_2$, and 2 U Taq DNA polymerase (Roche Diagnostics Ltd., Penzberg, Germany). The thermocycling performed in a Personal Thermocycler (Eppendorf, Hamburg, Germany) consisted of an initial denaturation for 5 minutes at 94° C followed by 35 cycles of 1 minute at 94° C, 1 minute at 58° C, and 1 minute at 72° C, and

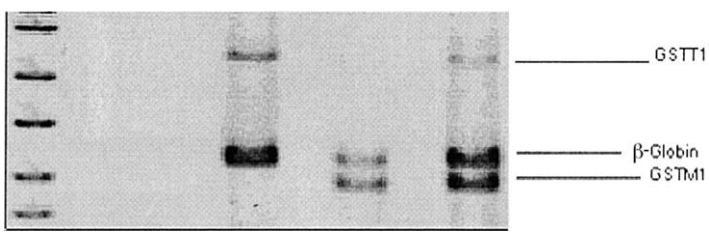

Fig. 1. Agarose gel electrophoresis of GSTM1, GSTT1, and β-globin PCR product. Lane 1, DNA ladder (difference in each band is 100 bp); lane 2, null GSTM1; lane 3, null GSTT1; lane 4, wild type.

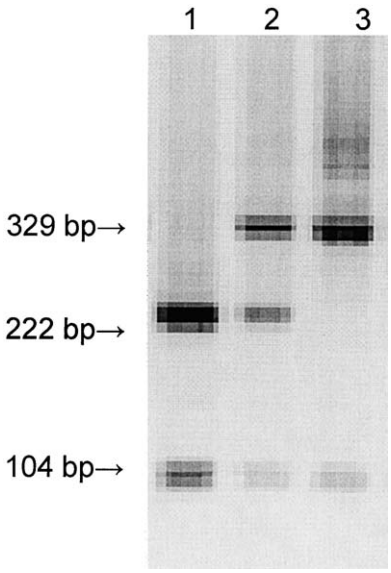

Fig. 2. Agarose gel electrophoresis of GSTP1 (105) PCR-RFLP product. Lane 1, homozygous mutant; lane 2, heterozygote; lane 3, homozygous wild type.

ended with an elongation step 10 minutes at 72° C. The PCR products were then analyzed electrophoretically on a 2% agarose gel containing ethidium bromide (see Fig. 1).

In order to detect the variants of codon 105 of GSTP1, PCR-RLFP analysis was employed. In PCR reactions, 11 pmol of each primers PiF2306 (5′-GTA GTT TGC CCA AGG TCA AG-3′) and PiR3800 (5′-AGC CAC CTG AGG GGT AAG-3′) specific for exon 5 were used to amplify 100 ng DNA in a PCR mixture for a total reaction volume of 25 µl. An elevated annealing temperature was applied in the first 15 cycles of PCR to prevent nonspecific priming. After an initial denaturation step 12 minutes at 95° C, 15 cycles of PCR were performed (denaturation 30 seconds at 95° C, annealing 30 seconds at 58° C, elongation 60 seconds at 72° C), followed by 25 cycles of amplification (denaturation at 30 seconds 95° C, annealing 30 seconds at 55° C, elongation 60 seconds at 72° C) and one cycle of elongation 5 minutes at 72° C yielding a PCR product of 433 bp. Ten microliters of the PCR product was digested with 2.5 U BsmA1 (Fermentas, Litva) in a total volume of 12 µl. The digested fragments were separated on a 2% agarose gel stained with ethidium bromide to visualize the bands (see Fig. 2).

Statistical Analysis

Associations between specific genotypes, other potential confounders, and the incidence of cryptogenic cirrhosis were examined by use of logistic regression to calculate the odds ratios (OR) and 95% confidence intervals (CI). The SPSS for Windows (version 11.0) statistical package was used for all statistical comparisons. The chi-square statistic was calculated to test the distribution trend of each index by genotype. Relative risk was calculated by logistic regression analysis. The data obtained were analyzed with the SPSS for Windows (release 6.1). A value of $P = 0.05$ was considered significant.

RESULTS

The patient group consisted of 45 subjects (30 males and 15 females; mean age 44 years [range 20 to 72 years]). The control group included 56 subjects (33males and 23 females; mean age 47 years [range 14 to 74 years]). Among the genetic polymorphisms tested, we found that GSTM1 and GSTP1 Val/Val polymorphisms were significantly associated with the development of cirrhosis. In the subsequent multivariate analysis of these two genes, the relative risk of dying increased two to three times for patients who lacked the beneficial genotype in one or more genes ($P < 0.001$).

The relative frequencies of the GSTP1, GSTT1, and GSTM1 genotypes are shown in Table 1. The patient group and control group were not significantly different with respect to age and sex distribution. Analysis of the genotype data revealed that Ile/Val or Val/Val GSTP1 genotype was more prevalent among the patients (n = 39; 88%) than among control subjects (n = 10, 18%) (OR = 34.9; 95% CI = 11.19–108.86). Among those patients, there were 16 heterozygotes compared to nine heterozygotes in the control group (OR = 3.5; 95% CI = 1.2 to 8.3) and 23 homozygotes compared to one homozygote in the control group (OR = 50.7; 95% CI 6.46 to 398.9).

Although the GSTM1 gene deletion was frequent in control subjects, it was found to be more frequent among patients (n = 27; 60%) than healthy individuals (n = 16; 28.6%) (OR = 3.7; 95% CI = 1.63 to 8.4). GSTT1 deletions did not show any significant difference between the two groups (OR = 2; 95% CI 0.86 to 6.28).

The present study provides the first demonstration of a significant association between GSTP1 and GSTM1 gene polymorphisms and development of chronic liver disease. It is possible to regard the Val/Val GSTP1 genotype as a significant risk factor for the occurrence of this type of liver disease.

DISCUSSION

Numerous recent studies have shown the particular GST alleles to be associated with altered risk or

Table 1. Glutathione S–transferase genotypes in patients and control subjects

GSTP1 polymorphism	Patients (n = 45)	Control subjects (n = 56)	Odds ratio (95% CI)
Val/Val	23 (53%)	1 (2%)	50.7 (6.46–398.9)
Ile/Val	16 (35%)	9 (16%)	3.5 (1.2–8.3)
Ile/Val & Val/Val	39 (88%)	10 (18%)	34.9 (11.19–108.86)
GSTM1 polymorphism null	27 (60%)	16 (28.6%)	3.7 (1.63–8.4)
GSTT1 polymorphism null	12 (27%)	8 (14%)	2 (0.86–6.28)

outcome of various diseases including malignancies.[13] Our data provide the first evidence of a significant association between GSTP1 and GSTM1 expression and the course of chronic liver disease. Indeed, we found that individuals with GSTP1 Ile/Ile alleles are less prone to develop cryptogenic cirrhosis; however, both GSTP1 val/val (that displayed the most different distribution between control and case groups) and val/Ile genotypes, as well as GSTM1 deletions, had a higher risk of liver disease progression. This association persisted after adjusting for potential confounding variables that might have independently influenced hepatic status in patients.

In the liver, the GSTM1 accounts for more than half of the cytosolic GST activity, and it is expressed at high levels in hepatocytes and lower levels in biliary epithelial cells.[14–16] GSTP1 expression is predominant in biliary epithelial cells.[17] Both GSTP1 and GSTM1 polymorphic variants are associated with altered catalytic function of the enzyme. In vitro studies in human tissues revealed that val/val genotype is associated with a lower enzyme activity compared to that of the heterozygous and Ile/Ile genotype. Therefore patients who are genetically predisposed to produce a less active and less specific enzyme might be more prone to develop cryptogenic cirrhosis.

Cirrhosis is the morphologic result of multiple lesions of parenchyma in the liver. It may progress by several mechanisms resulting in injury directed to hepatocytes and adjacent small vessels. Molecular pathogenesis of hepatic fibrosis has been recently attributed to the activation and proliferation of hepatic stellate cells mediated by the products of oxidative stress.[18,19] The mechanism for this is not precisely known, but it is probably associated with an increased production of reactive oxygen species resulting in lipid peroxidation and activation of stellate cells. Therefore their activation into myofibroblasts can be triggered by lipid peroxidation. The GSTs increase the efficiency of glutathione-dependent detoxification of electrophilic xenobiotics and the byproducts of oxidative stress that are critical to cellular homeostasis.[20,21] One can postulate that, depending on GSTP1 and GSTM1 genotypes, activated hepatic stellate cells have different abilities to detoxify lipid peroxidation. It suggests a link between GSTP1, GSTM1 genotype, and the antioxidant status that could contribute to liver disease, a link worthy of further investigation.

GSTP1 is also able to bind, nonenzymatically, a variety of other compounds including steroid and thyroid hormones, bile acids, bilirubin, heme, fatty acids, and c-Jun NH2 terminal kinase.[22–24] Both the in vitro and in vivo data support the idea that GSTP1 influences cell proliferation, most likely as a consequence of its role in regulating cellular kinase activities.[25] Recent studies identified the association of GSTP1 with JNK activity. This implies a noncatalytic function for GSTP1 that may be related to liver protection.

Considering the high frequency of GSTP1 and GSTM1 polymorphisms, it is entirely possible to regard them as a risk factor for the occurrence of cryptogenic cirrhosis. The results of this study may be of particular relevance to clinical practice: GSTP1 and GSTM1 testing can be used as a screening tool for finding those patients who are vulnerable to development of cryptogenic cirrhosis. Although we discover no significant correlation between GSTT1 genotypes and cryptogenic cirrhosis, our findings further support the role of GSTs in hepatic cytoprotection and raise the possibility that an alteration in their activity may compromise detoxification and antioxidant defense in the injured liver. Identification of GSTP1 and GSTM1 polymorphism, especially val/val genotype, may have prognostic value in high-risk population and may help to direct more targeted therapy toward persons with an increased risk of liver disease.

CONCLUSION

Our data suggest that the progression of liver disease is associated with particular GSTP1 and M1 genotypes coding for lower activity enzymes. Both GSTP1 polymorphism and M1 null genotype were significantly more prevalent in patients with cryptogenic cirrhosis. Hence, we assume that a decrease in

GSTs activity may contribute to the development in hepatic disease in cryptogenic cirrhosis.

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Postoperative Jejunal Feeding and Outcome of Pancreaticoduodenectomy

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Complications following pancreaticoduodenectomy are common, partly because of nutritional debilitation. The aim of this study was to evaluate the impact of early postoperative tube feeding on outcome of pancreaticoduodenectomy and determine the best method for delivering enteral feeding. A retrospective review of 180 consecutive patients undergoing Whipple operations from 1994 to 2000 was performed. Two nonrandomized patient groups were retrospectively studied: those with early postoperative tube feeding vs. those with no planned feeding. Ninety-eight patients (54%) received postoperative jejunal feeding, whereas 82 patients (46%) did not. Jejunal feeding was delivered via a bridled nasojejunal tube in 55 patients (56%) and a gastrojejunal tube in 43 (44%). Vomiting (10% vs. 29%; $P = 0.002$) and use of total parenteral nutrition (6% vs. 27%; $P < 0.0001$) were less in the jejunal feeding group as well as rates of readmission (12% vs. 27%; $P = 0.022$), early (52% vs. 62%; $P = 0.223$) and late (12% vs. 31%, $P = 0.005$) complications, and infections (13% vs. 20%, $P = 0.014$). Tube-related complications occurred in 6 of 98 patients, all of which were associated with gastrojejunal tubes ($P = 0.021$). Early postoperative tube feeding after pancreaticoduodenectomy is associated with significantly less use of total parenteral nutrition and lower rates of readmission and complications. A bridled nasojejunal feeding tube appears to be a safe and reliable method of short-term enteral feeding. (J GASTROINTEST SURG 2004;8:428–433)

KEY WORDS: Pancreaticoduodenectomy, nasojejunal feeding, enteral nutrition, postoperative complications, delayed gastric emptying

Pancreaticoduodenectomy is associated with a high incidence of postoperative complications, even when performed at high-volume centers. An overall morbidity rate of 48% can be anticipated at major centers, whereas these centers maintain a mortality rate of less than 2%.[1,2] The high rate of complications is likely multifactorial but may include overall nutritional debilitation in that most patients with periampullary tumors present with a significant weight loss.[3] Previous studies have not shown a benefit from perioperative total parenteral nutrition (TPN) in these patients. Paradoxically the use of TPN significantly increases postoperative complications, especially those associated with infections.[4]

The aim of this study was to evaluate the impact of early postoperative enteral tube feeding on the outcome of patients undergoing pancreaticoduodenectomy (Whipple operation) and determine the optimal method for delivering enteral feeding.

METHODS

A retrospective review of patients who underwent a Whipple operation at the Cleveland Clinic Foundation from January 1994 through December 2000 was performed. The type of resection, pylorus-sparing

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vs. standard pancreaticoduodenectomy, depended on the location and extent of the disease, as well as the surgeon's preference. The technique of pylorus-preserving pancreaticoduodenectomy has been well described and was similarly performed in all cases.[5]

Patients were compared on the basis of whether or not early postoperative jejunal feeding was used. The decision to use enteral feeding and the type of feeding tube were based solely on the surgeon's preference. There were principally three surgeons performing these procedures: one never used a feeding tube, one always used a feeding tube, and the third selectively used a tube. One group of patients received early enteral feeding through a secured nasojejunal tube or a surgical gastrostomy with jejunal extension placed into the jejunal limb beyond the enteroenteric anastomosis. The nasojejunal tubes were 10 F (43-inch polyurethane tubes (Corpak MedSystems, Wheeling, IL) secured to the nose by a 3.2 mm umbilical tape looped around the nasal septum and vomer as described by Popovich et al.[6] The gastrojejunal tubes were 18 F 18-inch silicone tubes (Moss Tubes, West Sand Lake, NY). Enteral feeding was begun on postoperative day 2 (using Isocal HN (Mead Johnson, Evansville, IN) at a rate of 30 ml/hr and increased by 10 ml daily to a goal determined by the Harris-Benedict equation.[7] The time required to achieve the goal calories was unpredictable, with effort directed at achieving goal in those patients who had delayed gastric emptying. Enteral feedings were continued until the patient tolerated a regular diet, whether this occurred before or after discharge from the hospital. Immune-modulating enteral formulas are unavailable for use at our hospital and were not considered for use. The second group of patients had the same surgical procedure without the provision for enteral access. In both groups, nasogastric tubes were removed after the return of gastric function, and diet was advanced as tolerated. Delayed gastric emptying was defined as requiring nasogastric decompression beyond postoperative day 5 because of high gastric residual. Prokinetic agents routinely used for delayed gastric emptying included metoclopramide, 10 mg intravenously every 6 hours, and erythromycin, 125 mg intravenously every 6 hours. There was no uniform postoperative algorithm for the use of prokinetic agents or any other parameters. TPN was given to patients with delayed gastric emptying, if enteral feeding was not planned or could not be achieved. TPN was delivered through a central venous catheter and continued until the patient tolerated a regular diet. A hyperalimentation team determined the amount of calories and TPN composition based on the Harris-Benedict equation. Patients receiving TPN required an additional complete blood count and metabolic panel three times a week. Data reviewed included age at operation, sex, diagnosis, preoperative albumin and hemoglobin levels, type of procedure, delayed gastric emptying, duration of nasogastric decompression, incidence of vomiting after nasogastric tube removal, use of prokinetic agents, operative time, need for blood transfusion, length of hospitalization, intensive care unit (ICU) stay, use of TPN, early and late complications, and readmissions within 30 days of discharge. Operative time was measured starting from the skin incision until the application of the wound dressing. The retrospective nature of this study did not allow for additional preoperative nutritional assessment such as body mass index.

An early complication was defined as occurring within 30 days of surgery and included death, wound infection requiring drainage, intra-abdominal collection, pancreatic fistula, enterocutaneous fistula, intra-abdominal bleeding, gastrointestinal bleeding, deep venous thrombosis, pulmonary embolism, pneumonia, respiratory failure requiring endotracheal intubation, pancreatitis, renal failure, myocardial infarction, urinary tract infection, facial dehiscence, arrhythmias, line sepsis, and pseudomembranous colitis.

A late complication was defined as occurring after 30 days of surgery and included diabetes, pancreatic fistula, anterior hernia, cholangitis, small bowel obstruction, gastric outlet obstruction, deep venous thrombosis, stroke, hepatic abscess, and myocardial infarction. Organ failure was defined according to the University of Michigan Surgical Intensive Care Unit criteria.[8] The two-tailed Student's t test was used to compare the continuous variables, while the chi-square test was used for the nominal data. A P value < 0.05 was considered significant.

RESULTS

A total of 180 consecutive patients underwent a pancreaticoduodenectomy between January 1994 and December 2000. Group 1 included 98 patients (54%) who received early postoperative enteral feeding, whereas group 2 (82 patients; 46%) did not. Although this was not a randomized study, both groups were comparable in terms of sex (59% vs. 60%; $P = 0.941$ males), diagnosis (42% vs. 56%; $P = 0.079$ pancreatic adenocarcinoma), preoperative albumin level (3.7 ± 0.6 g/dl vs. 3.7 ± 0.7 g/dl; $P = 0.965$), preoperative hematocrit level ($38.7 \pm 5.0\%$ vs. $39.0 \pm 5.1\%$; $P = 0.706$), and type of procedure (84% vs. 85%; $P = 0.916$ pylorus sparing). Although this was not statistically significant, there tended to be more patients with ampullary carcinoma in group 1. Patients

Table 1. Patient demographic data

Demographic data	Group 1	Group 2	*P* value
Number of patients	98 (54%)	82 (46%)	
Mean age ± SD (yrs)	66.2 ± 11.0	60.1 ± 15.1	0.003*
No. of males	58 (59%)	49 (60%)	0.941
Preoperative hematocrit (%)	38.7 ± 5.0	39.0 ± 5.1	0.706
Mean preoperative albumin ± SD (g/dl)	3.7 ± 0.6	3.7 ± 0.7	0.965
Pylorus-preserving pancreaticoduodenectomy	82 (84%)	70 (85%)	0.916
Diagnosis			
Pancreatic adenocarcinoma	41 (42%)	46 (56%)	0.079
Ampullary adenocarcinoma	24 (24%)	11 (13%)	0.093
Duodenal adenocarcinoma	10 (10%)	8 (10%)	0.880
Cholangiocarcinoma	11 (11%)	9 (11%)	0.853
Pancreatic cystic neoplasm	4 (4%)	4 (5%)	0.916
Other tumor†	3 (3%)	3 (4%)	0.846
Pancreatitis	5 (5%)	1 (1%)	0.304

SD = standard deviation.
*$P < 0.05$.
†Islet cell tumors, primitive neuroectodermal tumors and renal cell carcinoma metastases.

in the enteral feeding group were significantly older (66.2 ± 11.0 years vs. 60.1 ± 15.1 years; $P = 0.003$) (Table 1). The mean operative time (401 ± 76 minutes vs. 362 ± 81 minutes; $P = 0.0012$) and the incidence of blood transfusion (44% vs. 18%; $P < 0.0001$) were higher in the enteral feeding group. Intraoperative complications were similar (1% vs. 1%; $P = 0.557$) and included one intraoperative myocardial infarction in group 1 and one superior mesenteric artery injury in group 2.

Enteral feeding was delivered via a nasojejunal tube in 55 patients (56%) and gastrojejunal tube in 43 patients (44%). Enteral feeding lasted a mean of 10.5 ± 16.2 days in the hospital and 12.4 ± 71.3 days after discharge and supplied a mean of 1250 Kcal/day. Twenty-one (21%) of 98 patients in group 1 were discharged with home tube feeding. The duration of nasogastric tube decompression (mean 6.3 ± 6.2 days vs. 6.2 ± 4.9 days; $P = 0.956$), use of prokinetic agents (55% vs. 51%; $P = 0.816$), and time when a regular diet was started (postoperative day 10.3 ± 9.7 vs. postoperative day 10.5 ± 7.7; $P = 0.880$) were similar in both groups. The incidence of vomiting after nasogastric tube removal was significantly lower in the enteral feeding group (10% vs. 29%; $P = 0.002$) (Table 2). Both groups had a similar length of hospitalization (mean 13.9 ± 9.5 days vs. 14.8 ± 8.8 days; $P = 0.499$) and ICU stay (mean 1.3 ± 4.2 days vs. 1.0 ± 2.1 days; $P = 0.592$). The incidence of ICU readmissions (6% vs. 10%; $P = 0.499$) and the mean length of extended stay due to delayed gastric empting (1.5 ± 4.2 days vs. 2.3 ± 4.9 days; $P = 0.214$) were less, although not significant, in the enteral feeding group (see Table 2). ICU readmissions were due to

Table 2. Patient outcomes

Variables	Group 1 (n = 98)	Group 2 (n = 82)	*P* value
Mean length of hospitalization ± SD (days)	13.9 ± 9.5	14.8 ± 8.8	0.499
Mean ICU stay ± SD (days)	1.3 ± 4.2	1.0 ± 2.1	0.592
No. of ICU readmissions	6 (6%)	8 (10%)	0.38
Mean length of stay due to delayed gastric emptying ± SD (days)	1.5 ± 4.2	2.3 ± 4.9	0.214
TPN use	6 (6%)	22 (27%)	<0.0001*
Mean TPN duration ± SD (days)	1.9 ± 9.5	3.7 ± 7.9	0.156
Vomiting	10 (10%)	24 (29%)	0.002*
Readmission within 30 days of discharge	12 (12%)	22 (27%)	0.022*
Early complications	52 (52%)	51 (62%)	0.223
Late complications	12 (12%)	25 (31%)	0.005*

SD = standard deviation; ICU = intensive care unit; TPN = total parenteral nutrition.
*$P < 0.05$.

respiratory failure (7% vs. 5%; $P = 0.749$), cardiac failure (0% vs. 1%; $P = 0.900$), intra-abdominal bleeding (3% vs. 1%; $P = 0.744$), sepsis (1% vs. 4%; $P = 0.491$), and stroke (0% vs. 1%; $P = 0.744$). There was a significantly lower incidence of TPN use in the enteral feeding group (6% vs. 27%; $P < 0.0001$). Six (6%) of 98 patients in group 1 required postoperative TPN because of feeding tube occlusion in four patients or accidental removal in two patients, and all of these were in gastrojejunal feeding tubes ($P = 0.021$). In addition, patients in group 1 received TPN for a shorter period of time (mean 1.9 ± 9.5 days vs. 3.7 ± 7.9 days; $P = 0.156$) (see Table 2). Patients in group 1 were discharged to home (89 patients; 91%) or a skilled nursing facility (8 patients; 8%), whereas one patient (1%) died of multiorgan system failure following a pancreatic leak. Patients in group 2 were discharged to home (79 patients; 96%) or a skilled nursing facility (3 patients; 4%). There was a significantly lower rate of readmission within 30 days of discharge in the enteral feeding group (12% vs. 27%; $P = 0.022$) (see Table 2). The rate of early complications was lower in group 1 (52% vs. 62%; $P = 0.223$). Moreover, patients in group 1 had a significantly lower incidence of late complications (12% vs. 31%; $P = 0.003$) (see Table 2). The total incidence of early infectious complications was significantly lower in the enteral feeding group (13% vs. 20%; $P = 0.014$) and included wound infection (10% vs. 18%), pneumonia (1% vs. 2%), urinary tract infection (0% vs. 4%), line sepsis (0% vs. 2%), and pseudomembranous colitis (2% each). The early and late complications are summarized in Table 3.

Table 3. Early and late complications

	Group 1 (n = 98)	Group 2 (n = 82)	*P* value
Early complications			
Infections	13 (13%)	24 (20%)	0.014*
Intra-abdominal collection	13 (13%)	12 (15%)	0.962
Pancreatic or enterocutaneous fistula	3 (3%)	2 (2%)	0.842
Bleeding	5 (5%)	4 (4%)	0.784
Mortality	1 (1%)	0 (0%)	0.900
Others†	17 (17%)	9 (7%)	0.318
Total	52 (52%)	51 (62%)	0.223
Late complications			
Diabetes	1 (1%)	2 (2%)	0.876
Pancreatic fistula	1 (1%)	0 (0%)	0.900
Ventral hernia	4 (4%)	6 (7%)	0.537
Cholangitis	1 (1%)	1 (1%)	0.557
Small bowel obstruction	1 (1%)	3 (4%)	0.491
Gastric outlet obstruction	4 (4%)	9 (11%)	0.136
Deep venous thrombosis	0 (0%)	1 (1%)	0.900
Stroke	0 (0%)	1 (1%)	0.900
Hepatic abscess	0 (0%)	1 (1%)	0.900
Myocardial infarction	0 (0%)	1 (1%)	0.900
Total	12 (12%)	25 (31%)	0.005*

*$P < 0.05$.
†Includes deep venous thrombosis, pulmonary embolism, arrhythmia, facial dehiscence, pancreatitis, pulmonary, and renal failure.

DISCUSSION

Pancreaticoduodenectomy is an operation with high morbidity. When performed at high-volume centers, the mortality rate can be reduced to less than 4%,[1,9–11] yet the incidence of postoperative complications continues to range from 35% to 50% in most series.[2,12–14] Most patients with periampullary tumors present with significant weight loss due to anorexia and malabsorption,[3] and are expected to have a period of inadequate oral intake for up to 10 days after surgery.[15] In addition, investigators concluded that the catabolic response to surgery is mainly related to inadequate food intake and not operative stress exclusively.[16] Perioperative enteral nutrition can be beneficial in these patients in that it may reduce mortality, morbidity, and the length of hospital stay.[17,18] Routine postoperative TPN is not recommended for most patients undergoing pancreaticoduodenectomy and can significantly increase the infectious complications.[4] Early enteral feeding, however, had been shown to decrease the postoperative septic complications in a meta-analysis of eight prospective randomized trials,[19] and improve glucose tolerance,[20] protein kinetics, and wound healing.[21] Furthermore, enteral nutrition is safer and less expensive than parenteral nutrition.[22] Delayed gastric emptying remains a frequent and vexing complication after pancreaticoduodenectomy, even when the pylorus-preserving Whipple procedure is performed. The incidence ranges from 19% to 23% and leads to prolonged hospitalization.[14,23] The presence of a feeding jejunostomy tube allows nutritional support during this time and facilitates hospital discharge in patients with delayed gastric emptying.

Our results also show an interesting benefit of enteral feeding with fewer readmissions and secondary complications. This interesting outcome might be unrelated to the enteral feeding, per se, or it could represent an overall diminished capacity to recover from this degree of surgical stress over a prolonged time period, demonstrating that even modest early nutritional support may be globally beneficial.

There are several methods for delivery of enteral nutrition after pancreaticoduodenectomy. These include gastrojejunal tubes, feeding jejunostomy, and

nasojejunal tubes. Nasojejunal tubes provide a cost-effective and desirable method of enteral nutrition[24,25] without the morbidity from an additional enterotomy. There are, however, several studies that reported a 35% to 100% rate of nasojejunal tube dislodgment and occlusion.[26,27] Bridling to the nasal septum prevents tube dislodgment and accidental removal. This method is safe and is not associated with bleeding, infection, sinusitis, or nasal septal necrosis.[6] There were no tube-related complications in the 55 patients receiving nasojejunal feeding in this study. Tube occlusion can be prevented by the use of polyurethane feeding tubes, irrigation with 20 ml water every 8 hours, and after giving medications.[28,29] Although tube diameter has not been found to increase the occlusion rate,[28] we have now begun to use 12 F tubes.

Combined gastrojejunostomy tubes have the advantage of concomitant gastric decompression and jejunal feeding.[30] Theoretically these tubes would be suitable for delayed gastric emptying after pancreaticoduodenectomy; however, they are associated with a higher rate of complications. Complication rates reported in the literature range from 13% to 57%,[31–34] and include bleeding at the gastrostomy site, wound infections, intraperitoneal leaks, skin irritation, erosion through the abdominal wall, occlusion, and distal migration with bowel obstruction. Six (14%) of our 43 patients who received enteral feeding via a gastrojejunal tube had tube-related complications. Four patients had tube occlusion and two had accidental tube removal. As a result, these six patients received postoperative total parenteral nutrition.

Feeding jejunostomy tubes were not used in this study because of surgeon preference, since any unnecessary enterotomy is a potential source of complications. Reported complications, which ranged from 6% to 19%, included dislodgment, cellulitis, occlusion, bowel perforation, volvulus, intraperitoneal leaks, and skin necrosis.[35–38] On balance, our nonrandomized review supports the use of bridled, nasojejunal feeding tubes.

There are several potential limitations to this study. It is retrospective, nonrandomized, and reflects the preference of surgeons at our institution to avoid surgical feeding jejunostomies that may not represent the experience of other centers. The sample size might suggest that our findings do not represent outcome results due to the surgeon's experience alone. In addition, postoperative management was not standardized among patients undergoing pancreaticoduodenectomy, and the study lacked an objective definition of delayed gastric emptying. Despite not being randomized, both groups were comparable in terms of sex, preoperative albumin and hematocrit levels, pathologic diagnosis, and type of resection. The age and operative time were higher in the enteral feeding group that had less parenteral nutrition and fewer septic complications and readmissions. This correlates with previous studies that showed an increased rate of infectious complications with parenteral nutrition.

Whether a different, more immunonutritional formula could have produced an even more pronounced difference in outcomes is controversial and associated with increased cost.[39] The results of numerous trials are mixed, with most outcome measures positively affected including infection rates and length of hospital stay.[40,41] Two studies specifically involving patients undergoing pancreatic resections showed no specific benefit.[42,43]

CONCLUSION

Early postoperative jejunal tube feeding is beneficial in patients undergoing pancreaticoduodenectomy. It is associated with a significantly lower incidence of TPN use, readmission, early infectious complications, and overall late complications. A bridled nasojejunal tube is our preferred route for early enteral feeding after pancreaticoduodenectomy because it can also address nutritional needs in the event of delayed gastric emptying.

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Adenocarcinoma Appearing Very Late After Antireflux Surgery for Barrett's Esophagus: Long-Term Follow-Up, Review of the Literature, and Addition of Six Patients

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Antireflux surgery is supposed to prevent the development of adenocarcinoma in patients with Barrett's esophagus. The purpose of this study was to determine the prevalence of adenocarcinoma late after antireflux surgery. A total of 161 patients with long-segment Barrett's esophagus had antireflux surgery and were followed for a mean of 148 months (range 54 to 268 months) Clinical, endoscopic, histologic, and functional studies were performed. Of the original 161 patients, 147(91.3%) completed long-term follow-up. Six patients (4.1%) developed adenocarcinoma 4,5,6,9,17, and 18 years, respectively, after surgery. Five were men. Two of them were asymptomatic for 12 and 17 years. Three of them had extra-long–segment Barrett's esophagus. Five underwent manometric evaluation with only one showing an incompetent lower esophageal sphincter. In two cases, 24-hour pH studies showed massive acid reflux. Two patients had early adenocarcinoma, whereas four had advanced carcinoma. Adenocarcinoma in long-segment Barrett's esophagus seems to develop mainly in patients with recurrence of pathologic reflux, especially among men. A review of the English language literature during the last 23 years found 25 articles dealing with Barrett's esophagus and antireflux surgery. Most of these reports had only a few patients with short-term follow-up (<60 months). To determine the true prevalence of this complication, a long-term objective follow-up is necessary. (J GASTROINTEST SURG 2004;8:434–441)

KEY WORDS: Barrett's esophagus, autoreflux surgery, adenocarcinoma

Esophageal adenocarcinoma is probably the cancer that has increased the most rapidly over the past decades, much more so than any other type of carcinoma.[1] Gastroesophageal reflux is a very common condition among adults both in the United States[2] and in other countries such as Chile.[3] Barrett's esophagus is a severe and acquired complication of gastroesophageal reflux disease, and is characterized by the presence of intestinal metaplasia in the mucosa lining the distal esophagus.[4] It is well known that chronic gastroesophageal reflux disease[5] and the presence of Barrett's esophagus[6,7] are the two most important factors in the development of adenocarcinoma.[8] It is postulated that antireflux surgery could reverse the progression of Barrett's esophagus-dysplasia-adenocarcinoma by decreasing or eliminating reflux of gastric and duodenal contents into the esophagus and, by restoring the function of the lower esophageal sphincter.[9] It is hypothesized that a properly formulated antireflux procedure could stop the continual irritation to the metaplastic mucosa and would allow the cells to become quiescent.[4]

The purpose of this article was to report on six patients with adenocarcinoma that appeared late after antireflux surgery for Barrett's esophagus and to review the literature concerning this particular aspect.

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PATIENTS

Material and Methods

This prospective study was begun in March 1978 and ended in December 2002, with a mean actual follow-up of 148 months (range 84 to 268 months). Detailed features of this group have been published elsewhere.[10–12] However, among the original four cases reported,[10,12] since the end of the previous study, two more patients have presented with adenocarcinoma at late follow-up. All patients included in the original investigation had long-segment Barrett's esophagus (>3 cm) with intestinal metaplasia. There was a single case of short-segment Barrett's esophagus. Among the 161 patients included in the complete follow-up, six (3.7%) developed adenocarcinoma. If 14 patients are excluded (1 patient died after the operation and 13 patients were lost to follow-up this implies that six (14.1%) of 147 patients represent the true prevalence.

A careful clinical assessment was performed in all six patients, and they were questioned about the presence of gastroesophageal reflux symptoms. In the present study, these patients were classified as either symptomatic or asymptomatic.

All endoscopic studies were performed by two of us (A.C. and I.B.) using an Olympus GIFXQ-20 endoscope (Tokyo, Japan). The details have been published elsewhere.[10,12]

Histologic Analysis

In all patients, four biopsy samples were taken 5 mm distal to the squamo-columnar junction; then two samples of 2 cm each along the length or the columnar epithelium. Details regarding the type of cells present in the metaplastic mucosa have been described previously.[10–13] After surgery, specimens were carefully examined with respect to the size of the lesions, the depth of infiltration of the esophageal wall, and the presence of lymph node metastasis.

Functional Studies

In five patients, manometric studies were performed when the adenocarcinoma was diagnosed; in addition, 24-hour pH studies were carried out in two of them. These procedures have been previously reported in detail.[10–13]

Surgical Procedure

Two patients underwent transhiatal esophagectomy and gastric pullup with cervical anastomosis. In three patients, a right colon interposition was performed after either transthoracic (n = 2) or transhiatal (n = 1) esophagectomy. One patient refused the operation.

RESULTS

Among the original 147 patients followed for a mean of 148 months, 52 (35.3%) were asymptomatic (Visick grades I and II) late after surgery. Ninety-five (64.7%) had a clinical recurrence. The mean time to recurrence was 6 years for 72 patients who had nondysplastic changes, 8.2 years for 17 patients who developed low-grade dysplasia, and 9.8 years for patients with adenocarcinoma. The complete results of clinical, endoscopic, histologic, and functional studies in patients with and without recurrence and in patients with low-grade dysplasia have been published in detail elsewhere,[11,12] and it is not the purpose of the present study to repeat them.

Table 1 presents a summary of clinical and pathologic findings in the six patients who had adenocarcinoma after classic antireflux surgery. These five men and one woman had mean age of 54 years (range 21 to 76 years). The time of the appearance of adenocarcinoma after surgery varied from 4 to 18 years. Two patients developed carcinoma 17 and 18 years, respectively, after surgery. These two patients had been asymptomatic for up to 12 and 17 years after surgery, whereas the other four had symptoms 1 to 2 years after surgery. Only one patient had a low-grade dysplasia at the time of surgery, which progressed to adenocarcinoma 4 years after laparoscopic Nissen fundoplication. Three patients had long-segment Barrett's esophagus (length 30 to 99 mm), and three (50%) had an extra-long segment, that is, 100 mm or more in length. Manometry performed in five of them at the time of diagnosis of adenocarcinoma showed a hypotensive lower esophageal sphincter in only one of the five patients. However, 24-hour pH studies performed in two patients demonstrated massive pathologic acid reflux. Two patients (33%) had an early adenocarcinoma infiltrating up to the submucosa without lymph node metastasis. Three patients had advanced carcinoma, with two of them having lymph node metastasis. One patient (no. 4) with advanced carcinoma, who was 76 years of age, refused to have surgery and died 8 months after the diagnosis. One patient (no. 2) with early carcinoma is alive 16 years after resection. The other patient (no. 6) with early carcinoma died of massive intravascular coagulation with diffuse bleeding after surgery. Another two patients with advanced adenocarcinoma (nos. 1 and 2) died of disseminated disease 4 and 8 months

Table 1. Clinical and pathologic findings in six patients who developed adenocarcinoma after classic antireflux surgery

	Patient					
	1	2	3	4	5	6
Age (y)	21	50	50	76	58	69
Sex	M	M	M	F	M	M
Date of antireflux surgery	1980	1984	1980	1994	1984	1985
Type of surgery	Hill	Hill	Hill	Nissen	Hill	Nissen
Time after surgery before appearance of adenocarcinoma (y)	5	6	9	4	18	17
Symptoms of GERD postoperatively (yr)	+3	+4	+6	+3	17	12
Preoperative histologic findings	IM	IM	IM	IM + LGD	IM	IM
Length of BE (mm)	100	65	60	50	150	120
LESP (mm Hg)	12(5 yr)	8(5 yr)	12(5 yr)	8(3 yr)	—	5(5 yr)
24 hour pH (% time pH < 4)	—	—	—	50(3 yr)	—	30(15 yr)
Postoperative pathologic findings	Advanced	Early	Advanced	Advanced	Advanced	Early
Lymph node metastasis	(+)	(−)	(+)	?	(−)	(−)

GERD = gastroesophageal reflux disease; BE = Barrett's esophagus; IM = intestinal metaplasia; LESP = lower esophageal sphincter pressure; LGD = low-grade dysplasia.

after surgery. One patient (no. 5) is alive well 18 months after surgery.

DISCUSSION

It is a commonly held belief that antireflux surgery can prevent the development of adenocarcinoma in patients with Barrett's esophagus. This seems to hold true when medical treatment is compared to the surgical option, if retrospective or nonrandomized studies are performed. McCallum et al.[14] followed 152 patients receiving medical treatment and 29 patients after antireflux surgery. Dysplasia and adenocarcinoma occurred in 19.7% of the medically treated group, whereas dysplasia only one appeared in 3.4% of the surgically treated group with no adenocarcinoma. McEntee et al.[15] compared 23 patients treated medically with 21 patients undergoing antireflux surgery. After 2 years of follow-up three new cases of dysplasia appeared after medical treatment, whereas four of 10 patients with dysplasia who had surgery showed regression of low-grade dysplasia. No cancer was found in either group. Katz et al.[16] compared 82 patients treated with medication to 17 patients treated with antireflux surgery for a follow-up period of 4.8 years. Approximately 8% of the medically treated group developed high-grade dysplasia, whereas none of the surgically treated group showed this progression. None had adenocarcinoma. It should be noted that in these last two papers, there is no mention of the presence of adenocarcinoma—only dysplasia. In a prospective nonrandomized study[17] 29 patients treated with medication were compared with 19 patients undergoing antireflux surgery. At 3 years, one patient in each group developed adenocarcinoma, thus showing that antireflux surgery offered no protection. Three prospective randomized studies comparing medical and surgical treatment in patients with Barrett's esophagus have been published. Ortiz et al.[18] compared nearly 30 patients in each group who were followed for 5 years. Dysplasia developed in five patients who received medical treatment and in one patient after surgery. The only patient who developed adenocarcinoma belonged to the surgically treated group. These same investigators[19] recently reported their long-term results in a larger group of patients, including 43 who were treated with medication and 58 who had fundoplication. The mean follow-up was 6 years in the surgically treated group. High-grade dysplasia was found in two (5%) of these 43 patients in the medically treated group and in two (3.4%) of the 58 patients treated with surgery. These two patients had adenocarcinoma. However, the authors concluded that these patients had recurrence of reflux after surgery and no adenocarcinoma was found after successful antireflux surgery. Spechler et al.,[20,21] in a randomized study with a follow-up of 10 years, reported four cases of adenocarcinomas appearing after medical treatment (2%) and one case (1.2%) after surgical treatment, with no significant differences.

We have reviewed the English literature with regard to results of antireflux surgery in patients with Barrett's esophagus between 1980 and 2003.

During this period of observation, we found six reports that mentioned only isolated patients with Barrett's esophagus who had antireflux surgery combined with a much larger number of patients without Barrett's esophagus.[22–27], Thor et al.[22] treated one patient with Barrett's esophagus with a Nissen procedure and three patients with a Toupet fundoplication, without reporting any special results. Loustarrinen,[23] in 105 patients who underwent fundoplication and were followed for 10 years, mentioned the presence of only six patients with Barrett's esophagus before operation, with no special mention at the late control. Rantanen et al.,[24] who also performed late follow-up of patients undergoing antireflux surgery, mentioned only five patients with Barrett's esophagus before surgery and none at the late control. Johansson et al.,[25] reporting the outcome at 5 years after fundoplication, mention only two patients with Barrett's esophagus before surgery. DeMeester et al.,[26] reporting the results of 160 patients who underwent fundoplication, mention only four patients with Barrett's esophagus before operation. Finally, Lundell et al.,[27] in an elegant prospective randomized study comparing omeprazole with antireflux surgery, mention only that the prevalence of Barrett's esophagus did not change during follow-up, with no special report on objective data. In contrast, we have found 25 reports dealing specifically with antireflux surgery in patients with Barrett's esophagus. Table 2 lists 14 reports in which no mention is made of the appearance of adenocarcinoma.[14,15,28–39]

Table 2. Absence of adenocarcinoma after antireflux surgery in patients with Barrett's esophagus (N = 14)

Reference	n	Criteria for BE	Mean follow-up (mo)	% Good results
Ranson et al.[28] 1982	10	>3 cm	36	66
Skinner et al.[30] 1983	10	>3 cm	48	90
Lascone et al.[29] 1983	13	>3 cm	36	85
DeMeester et al.[31] 1990	35	IM	36	77
McEntee et al.[15] 1991	21	IM	22	90
McCallum et al.[14] 1991	29	IM	60	?
DeMeester et al.[32] 1998	45	IM	24	?
Low et al.[33] 1999	14	IM	24	90
Patti et al.[34] 1999	38	IM	24	92
Farrell et al.[35] 1999	20	IM	24	90
Chen et al.[36] 1999	45	IM	36	93
Hofstetter et al.[37] 2001	85	IM	60	74
Bamehriz et al.[38] 2002	21	IM	39	2
Mabrit et al.[39] 2003	13	IM	46	77
TOTAL	399		36.7	84.0

BE = Barrett's esophagus; IM = intestinal metaplasia.

In this table the criteria used for diagnosis of Barrett's esophagus are shown, demonstrating that most of the histologic criteria were used. The mean number of patients followed as low, and the follow-up in all reports is 60 months or less. None reported a follow-up of longer than 5 years, with the mean being 3 years of follow-up. Clinical success varied from 66% to 93% with a mean of 84%.

Table 3 presents similar values, but the 11 publications listed reported the appearance of adenocarcinoma after classic antireflux surgery.[10,12,17–21,39–45]. In the majority, histologic criteria were employed. The mean follow-up was 5 years, with five reports of more than 60 months of follow-up. Good clinical results were reported in 38% to 91%, with a mean of 71%. Twenty-three patients had adenocarcinoma that appeared after antireflux surgery (3.7%), with an incidence ranging from 1.6% to 13%. In 13 of these patients (57%), adenocarcinoma appeared before 5 years of follow-up, whereas 10 patients (43%) had adenocarcinoma between 6 and 18 years after surgery. Only seven reports deal clearly with the presence or absence of symptoms of recurrent reflux after surgery. Brand et al.[40] reported that one adenocarcinoma appearing 4 years after surgery had been *symptomatic*. Starnes et al.[41] mentioned that the only patient who developed adenocarcinoma was *asymptomatic*. Williamson et al.[42] reported three patients who developed adenocarcinoma 1, 6, and 10 years after surgery, all of whom were *asymptomatic*. Sagar et al.[43] found one patient with adenocarcinoma 9 years after surgery *with no symptoms*. McDonald et al.[44] reported the development of adenocarcinoma in three patients, all of whom were *asymptomatic*. Ortiz et al.[18] described one patient who developed adenocarcinoma 7 years after surgery as being *symptomatic*. Parrilla et al.[19] reported two *symptomatic* patients who developed adenocarcinoma among patients with recurrence of pathologic acid reflux, but none among patients who had successful antireflux surgery. Finally, four of our six patients were clearly *symptomatic* after surgery, whereas two patients remained *asymptomatic* for 12 and 17 *years*, *respectively*. Therefore, with the available data concerning presence of symptoms, 10 patients who developed adenocarcinoma were *asymptomatic* before the appearance of this tumor, whereas eight were symptomatic. However, it seems more important to perform objective studies in order to evaluate the recurrence of pathologic acid reflux. Only two reports mention this assessment (reference 19 and the present study). The excellent article by Parrilla et al.[19] suggests that adenocarcinoma can appear in patients with recurrence of reflux, and successful antireflux surgery seems to guard against its appearance.

Table 3. Adenocarcinoma appearing after antireflux surgery in patients with Barrett's esophagus (N = 11)

Reference	n	Criteria for BE	Mean follow-up (mo)	% Good results	Adenocarcinoma	Years after operation
Brand et al.[40] 1980	9	IM	60	40	1(10%)	4 *symptomatic*
Starnes et al.[41] 1984	8	>3 cm	26	75	1(13%)	2 mean *asymptomatic*
Williamson et al.[42] 1996	37	IM	60	81	3(8%)	1-6-10 a*symptomatic* Adequate antireflux
Attwood et al.[17] 1992	19	IM	36	79	1(5%)	3
Sagar et al.[43] 1995	56	>3 cm	66	75	1(1.8%)	9 *asymptomatic (men)*
Ortiz et al.[18] 1996	28	IM	60	90	1(3%)	7 *symptomatic*
McDonald et al.[44] 1996	112	IM	66	82	3(2.7%)	1-2-3 *asymptomatic*
Yau et al.[45] 2000	75	IM	24	84	3(4.3%)	2–4
Spechler et al.[20,21] 1992–2001	38	IM	108	38	1(2.6%)	7
Csendes et al.[10–12] 1998–2002	161	IM	108	42	6(4%)	4-5-6-9-17-18 4 *symptomatic (5 men)* 2 *asymptomatic* (1 women)
Parrilla et al.[19] 2003	58	IM	72	91	2(3%)	4-6 *symptomatic* 2 men
TOTAL	622		61	70.6	21/3.7%	

BE = Barrett's esophagus; IM = intestinal metaplasia.

Among our six patients, acid reflux studies were performed in two and both showed a pathologic reflux. Table 4 summarizes these 25 publications on the appearance of adenocarcinoma after classic antireflux surgery. It can be clearly seen that in the "absent" group there are two serious concerns from our point of view: (1) The mean number of patients followed is low, almost half, compared to the group in whom carcinoma was present; and (2) follow-up is too short (36 months), compared to the group in whom adenocarcinoma was present (61 months). In addition, only in this latter group did 45% of the reports have a follow-up longer than 61 months.

Therefore we question the real validity of the reports in the "absent" group. Is the scientific evidence adequate to conclude with certainty, after a short follow-up of 3 years after surgery, that surgery guards against the development of adenocarcinoma in patients with Barrett's esophagus? What will happen to all these patients 10 to 15 years after surgery? We were impressed with a short commentary by Richter,[46] who urged us to "let the truth be told concerning antireflux surgery and adenocarcinoma." As can be seen in the reports presented and from our own experience, antireflux surgery as well as medical treatment do not predictably cause Barrett's metaplasia to regress, nor do they protect patients from the subsequent development of adenocarcinoma of the esophagus.[46] However, perhaps the most important point is whether or not there is recurrence of pathologic reflux in these patients. It seems that if no recurrence of reflux is present, successful antireflux surgery could possibly prevent the appearance of adenocarcinoma. In contrast, recurrence of reflux is an important factor for the possible development of adenocarcinoma, as shown by Parrilla et al.[19] and the present study. The key point is that we as surgeons do not know which patients will develop recurrence of reflux, and that is why we stress the importance of objective surveillance for a long period of time in all operated patients. Absence of symptoms does not necessarily mean absence of reflux. In our experience, 5% of patients who had a recurrence were asymptomatic.[12] We challenge all other surgical groups to report their very late objective results after antireflux surgery. In our large group of patients with Barrett's esophagus who had surgery,[10] up to 4 years after surgery no adenocarcinoma appeared and if we would have reported our results at a follow-up of 48 months (longer

Table 4. Results in 25 publications concerning appearance of adenocarcinoma after classic antireflux surgery

	Absent	Present	Total
No. of publication	14	11	25
No. of patients operated	399	622	1021
Mean follow-up (mo)	36.7	61	47
>61 mo	0/14	5/11(45%)	5/25(20%)
% Good results	84	70.6	77
Development of adenocarcinoma	0	23 patient 1/165 patient-years	1/208 patient-years
Mean number of patients/publication	29.7	56.5	40.8

than publications with "absent" carcinoma), we too would not have found a single positive case. A recent very important publication from Sweden,[8] reporting on a retrospective analysis of a population-based cohort study, included 6046 men and 4671 women who underwent antireflux surgery. No distinction was made with respect to the prevalence of Barrett's esophagus in this population. They were followed for 96 months. Among these patients, during 1 to 32 years of observation, a clear risk for developing adenocarcinoma was demonstrated, which remained elevated with time after surgery; there were 16 cases among men, compared to 1.1 expected cases based on incidence rates for the general population. None of the female patients developed esophageal adenocarcinoma. One of the possible explanations is that the critical carcinogenic events have already occurred before surgery, which tends to be the treatment of last resort, as postulated by DeMeester.[14] He postulates that cellular and genetic alterations leading to the development of high-grade dysplasia have already occurred at the time of the operations, and it could take up to 6 years for adenocarcinoma to develop in patients with Barrett's esophagus with low-grade dysplasia. This could be true for those 13 patients reported to have adenocarcinoma earlier than 5 years after surgery. However, in 10 patients with a follow-up of 6 to 18 years, carcinoma appeared 9.8 years after surgery.

The mechanisms responsible for the development of adenocarcinoma after antireflux surgery in patients with Barrett's esophagus are not clearly understood. We have demonstrated by means of functional studies performed 8 to 10 years after antireflux surgery[10,12] that small amounts of pathologic acid reflux and duodenal reflux can occur even in patients who are asymptomatic (Visick grade I or II). In recent experimental and clinical studies, it has been shown that acid and bile salts are synergetic in the development of Barrett's esophagus and may induce carcinogenesis.[47]

In several elegant studies, a number of investigators[48–51] have shown that bile salts, independent of acid, may contribute to proliferative alterations in Barrett's esophagus mucosa, also in a dynamic fashion, but may have a complex effect when they interact with acid reflux. These experimental data together with our clinical study,[10] which is the only publication evaluating the results of Bilitec testing 10 years after antireflux surgery, suggest that variations in acid and bile exposure of the distal esophagus may contribute to the proliferative changes in Barrett's esophagus mucosa and therefore may play an important role in the development of cancer.

Therefore we conclude, on the basis of our own experience and based on 25 articles on this subject, that we have found no clear and convincing evidence of a protective effect of antireflux surgery on the development of adenocarcinoma of the esophagus, this is similar to what was stated by Richter.[46] However, it seems that with successful antireflux surgery there is a much lower probability that adenocarcinoma will develop compared to patients with recurrence of reflux. Besides, follow-up is still too short for a definitive conclusion. The rate of development of adenocarcinoma, which is one patient each for 165 patient-years among the group with adenocarcinoma, or a rate of one each for 208 patient-years among the entire group of 1021 patients undergoing surgery, is an important and high value and is similar to the individual risk of a patient with Barrett's esophagus treated with medication, which is one cancer per 150 persons per year.[52] However, we again stress the need for long-term (10 years or more) studies with objective evaluations (several endoscopic studies, multiple biopsy specimens, and 24-hour pH and Bilitec studies), in order to report very clearly and honestly the real final late results. Reports based on telephone calls to determine patients' status with few or no endoscopic and histologic evaluations should not be accepted as "proof" of the beneficial effects of antireflux surgery in preventing the development of adenocarcinoma among patients with Barrett's esophagus. There is another important aspect that should be emphasized. Barrett's adenocarcinoma occurs mainly among men. Despite of this, only three reports clearly mention the sex of patients with adenocarcinoma.[19,41,43] All four of those patients were men. In the present study, five of six patients were men and it is therefore important to stress the need for closer surveillance, especially among men with objective recurrence of pathologic reflux.

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Mechanical Consequences of Short Gastric Vessel Division at the Time of Laparoscopic Total Fundoplication

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Laparoscopic Nissen fundoplication is currently the most commonly practiced antireflux operation. Some adverse consequences of the operation remain in the form of mechanical side effects, labeled postfundoplication complaints, of which dysphagia and gas bloat seem to predominate. Measures have been suggested to counteract some of these and one frequently advocated has been division of the short gastric vessels to create a short-floppy wrap. The advantages of this are still debated, particularly in the long-term perspective. The aim of the present study was to evaluate the mechanical consequences of dividing all short gastric vessels at the time of a laparoscopic total fundoplication. Ninety-nine patients with chronic gastroesophageal reflux disease (GERD) were originally allocated on a random basis to have either all short gastric vessels divided or left intact at the time of a laparoscopic total fundoplication. A subsample of these patients, again selected at random, were recruited for a comprehensive manometric investigation 1 year after the operation. In this cohort, 12 patients had all short gastrics divided and in 12 patients, the wrap was done with intact vessels by use of the anterior portion of the fundus. Manometry was carried out by the use of a sleeve sensor to straddle the lower esophageal sphincter (LES), and gastric distension (750 ml air) was used to trigger transient LES relaxations (TLESR). The basal LES tone was similar in the two groups (14.2 ± 2.4 and 18.8 ± 4.3, mean ± SE), respectively. Accordingly, all other relevant manometric variables were equal when the two groups were compared, except for the total number of TLESRs (triggered by gastric distension by air) that were significantly higher ($p < 0.02$) in patients having their short gastric vessels intact. Consequently, numerically more common cavities were recorded in the latter group. Very similar outcomes in terms of motor function of the LES and esophageal body were observed after a total fundoplication irrespective of whether a complete division of all gastric vessels had been carried out or not. However, after gastric distension with air, more TLESRs were recorded in the latter group suggesting a better maintained ability to vent air from the stomach. (J GASTROINTEST SURG 2004;8:442–447)

KEY WORDS: Laparoscopic fundoplication, LES tone, nadir pressure, transient LES relaxation, peristaltic pressure

INTRODUCTION

A total fundoplication, as introduced by Rudolf Nissen[1] in 1956 and later modified by Rossetti and Hell,[2] has become the most frequently used antireflux operation within most surgical institutions. The total fundic wrap effectively controls reflux, but mechanical side effects resulting in dysphagia, gas bloat, and inability to belch are commonly reported.[3–5] A variety of measures have therefore been introduced to counteract some of these drawbacks. One is to mobilize the fundic part of the stomach by complete division of the short gastric vessels to secure the construction of a short floppy and tension-free wrap.[6,7] However, recent randomized clinical trials have been unable to demonstrate any significant advantages of one procedure over another when the functional outcomes were evaluated during the first postoperative year.[8–10] The present study aimed to evaluate the mechanical consequences of similar operations using sophisticated manometric technology to elucidate subtle differences,

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which may be of importance for our understanding of the mechanisms behind, and prediction of, the long-term outcome of these operations.

MATERIAL AND METHODS

A total of 24 patients were recruited at random from a cohort of 99 patients with chronic gastroesophageal reflux disease and enrolled into a controlled, randomized clinical trial.[10] These subjects also agreed to undergo a complete study program at the time of the 1 year postoperative follow-up after the original operation. All patients had previously undergone a complete preoperative evaluation including esophageal manometry, 24-hour pH monitoring, endoscopy, and symptom assessments (Table 1). Relevant demographic information has previously been described for the entire study population.[10] Twelve patients were originally given a total fundoplication incorporating division of the short gastric vessels whereas 12 patients had these vessels left intact. The operative procedures were performed using standard laparoscopic operative techniques and all operations were performed by two experienced surgeons. The technical details of each procedure has been given in detail elsewhere.[10] A posterior crural repair was performed with the use of nonabsorbable sutures in all patients. The short gastric vessel division also included dissection of all tissues between the posterior portion of the stomach and the left crus starting at the level of the inferior pole of the spleen and progressing in a cephalitic direction along the greater curvature of the stomach until complete mobilization of the fundus had been achieved.

Table 1. Preoperative patient evaluations (esophageal manometry, 24-hour pH monitoring, endoscopy, and symptom assessments)

	Divided	Intact
Gender (females)	5	5
Age (mean ranges)	52.0 (38.0–65.0)	50.2 (26.0–68.5)
Hiatus hernia	10	9
Comorbidities	0	0
Preop grade of esophagitis		
0	4	2
1	3	4
2	3	5
3	2	1
Barrett's esophagus	1	1
24 h pH measure	8.5 ± 1.5	10.8 ± 2.4
% time pH< 4	(n = 10)	(n = 11)

In patients randomized to the intact short-gastric vessels, the anterior wall of the gastric fundus was pulled behind the esophagus for construction of the fundoplication. To ensure that the completed fundoplication was free of tension, a 52 Fr bougie was inserted into the esophagus during the construction of the wrap. The wrap was sutured by three interrupted polyester sutures and made approximately 1.5 cm long.

The perioperative and postoperative courses were uneventful in both study groups with similar morbidity spectrum and length of the postoperative hospital stay, respectively.[10] Complete control of reflux disease, as assessed by the level of symptom control and the ambulatory 24-hour pH monitoring, was achieved in all study patients at the 1 year postoperative follow-up.

Manometry was performed by use of a water-perfused multi-lumen pressure catheter with side holes positioned at 5 cm intervals that had a sleeve sensor attached to its distal end.[11] The catheter was introduced into the esophagus through one nostril and the sleeve sensor was positioned to straddle the gastroesophageal junction. The side hole distal to the sleeve measured the intragastric pressure continuously. Each portion of the catheter assembly was connected to a pressure transducer and constantly perfused with water (0.5 ml/minute) with a low compliance capillary system (Arndorfer System, Arndorfer Medical Specialities, Greendale, WI). The recording system was calibrated to atmospheric pressure and to standardized hydrostatic pressures before and after each examination. The intraluminal end-expiratory esophageal body motor events and gastric pressure served as a reference for the lower esophageal sphincter (LES) tone. LES pressure was recorded at 1-minute intervals in a period of a stable pressure level with no interference from swallows. Recording of LES tone was continued for 30 minutes after the air insufflation as well.

The patients were investigated after an overnight fast. During the investigation they were kept recumbent in the right lateral decubitus position for 30 minutes. The patients were then placed in a sitting position for a 10-minute stabilization period. Air (750 ml) was then insufflated into the stomach, with LES pressure measurements taken during the subsequent 30 minutes.

Each manometric recording in the recumbent and sitting positions was initiated by ten swallows, each containing 5 ml of room-temperature water and when every swallow was separated by an interval of at least 15 seconds. The mean contraction amplitude of the peristaltic wave induced by the ten water swallows was calculated in the distal third of the esophageal

body. When we estimated the duration of each contraction, we defined the intercept points of the steep up-and-down strokes of the contraction in relation as LES relaxed and then compared them to the baseline intraluminal pressure on each tracing. The length of time between these interrupts was measured in seconds.

A complete transient LES relaxation was defined as an abrupt (⩾1 mm Hg/s) fall in the LES pressure exceeding 5 mm Hg to a level of 2 mm Hg or less above intragastric pressure with a duration of at least 5 seconds.[12] No swallows were allowed during the 5 seconds preceding the onset of a LES relaxation. Post-swallowing transient LES relaxations were, however, included in the analysis. The completeness of a transient LES relaxation was also assessed in relation to the nadir pressure during repeated water swallows. This is of particular importance after fundoplication, which exposes the LES to external compressing effect by the fundic cuff. The recordings were also analyzed for the occurrence of gas reflux as indicated by the presence of common esophagogastric cavities. For the purpose of this study a common cavity was characterized as an abrupt increase in the esophageal pressure to intragastric pressure levels concomitantly occurring in at least two esophageal recording sites.

To assess the intraabdominal length as well as the total length of the high-pressure zone in the LES area, a station pull-through technique was performed when using the side hole proximal to the sleeve. The probe was withdrawn in 0.5 cm increments and kept at each level for at least 30 seconds or until the recordings stabilized. The length of the intraabdominal part of the high pressure zone was calculated as the distance from the point of the first stable pressure rise above the fundus pressure to the first point of negative pressure to occurring on inspiration.

Ramp pressure, in this context identical to the intrabolus pressure, was assessed in the distal third of the esophagus just proximal to the sleeve sensor. It was defined as the plateau pressure (⩾2 mm Hg) above the intraluminal baseline pressure, which was established immediately before the steep up stroke of the peristaltic contraction. The ramp pressure was calculated as the mean pressure level above intraluminal pressure occurring during ten consecutive water swallows.

The frequency of failed primary peristalsis was determined and was characterized as either an absence of propulsive peristaltic activity, disappearance of the corresponding motor event through the aboral transmission through the esophagus, or an amplitude reaching a level of less than 10 mm Hg in the distal esophagus. The investigator (CE) performing the analysis of the manometric recordings was blinded for the type of surgery that each patient had undergone.

STATISTICS AND ETHICS

The local ethics committee had approved the study protocol and informed consent to participate in the study was obtained from each patient. Statistical analyses were carried out with the χ^2 test, the Student's t test, and nonparametric tests (Fisher's nonparametric exact test). Data are presented as mean and SE when appropriate assessments had been performed on the normal distribution of respective data sets.

RESULTS

The basal LES tone varied only slightly between the two study groups, with a mean pressure of 16 mm Hg (14.2–18.8) in both study groups. The total (3.8 ± 0.3, 3.6 ± 0.3 cm) as well as the intraabdominal lengths (2.6 ± 0 .4, 2.2 ± 0.4 cm) of the high pressure zone did not differ between patients having all short gastric vessels divided or left intact (NS). Furthermore, we were unable to demonstrate any intergroup differences regarding the ability of the LES to relax on proper stimulation (Fig. 1). Very few transient LES relaxations were recorded in basal state as well as after instillation of 750 ml of air into the stomach (Fig. 2). However, more transient lower esophageal sphincter relaxations (TLESRs) were observed (0.7 ± 0.3 vs. 2.1 ± 0.5) in patients with intact short gastric vessels ($p < 0.02$), but very few common cavities with no difference between the two groups.

The manometric findings reflecting the motor characteristics of the esophageal body are summarized in Table 2. Almost identical values were recorded in the two study groups, including the intrabolus (ramp) pressures, which were calculated to be 7.2 ± 2.0 and 7.5 ± 1.6 mm Hg in those submitted to a completely mobilized fundus as opposed to those having intact short gastric vessels, respectively.

DISCUSSION

The efficacy of total fundoplications in the treatment of chronic, symptomatic gastroesophageal reflux disease (GERD), even many years postoperatively, is well established.[11,12] Another well-accepted fact is that the division of the short gastric vessels to secure a fully mobilized fundus to construct a floppy wrap does not enhance the potency of the antireflux barrier.[8–10] Two important mechanical side effects are associated with a Nissen fundoplication: dysphagia

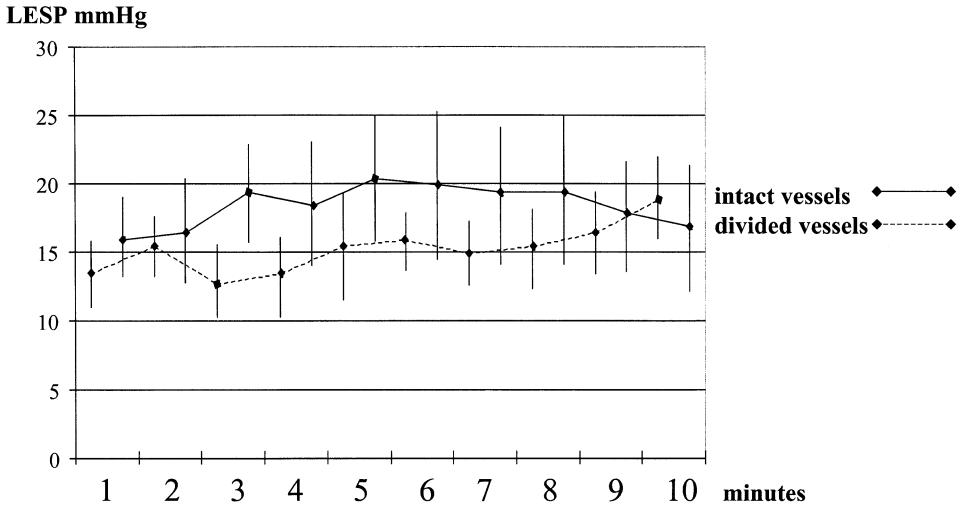

Fig. 1. Variation over time in basal lower esophageal sphincter (LES) tone (mm Hg) as assessed in patients after total fundoplication with or without division of the short gastric vessels (the mean and SE are given).

and the inability to vent air from the stomach. Some controversy still exists regarding the question of whether laparoscopic total fundoplications are followed by more mechanical obstructive complaints than when performed by an open technique.[13–18] A widely held view is that a total wrap should not only be floppy but also short to prevent side effects.[19] The scientific data to support the importance of similar details in the design of a total fundoplication are still incomplete.[20,21] Overall, dysphagia is a transient postoperative phenomenon where there seems to be a relationship between the recorded basal LES tone and the magnitude of similar complaints.[17,11,14,22] Both of these events seem to diminish with growing experience of the operator.[23] We, like others, have been unable to show any differences in dysphagia scores when a total fundoplication has been created with or without division of the short gastric vessels.

In this context it has to be recognized that we recorded not only a high basal tone of the LES in both study groups, but also a nadir pressure after water swallows, emphasizing incomplete relaxation of the high pressure zone. Some investigations have reported quite a substantial nadir pressure after a total fundoplication resembling a pseudoachalsia situation—a phenomenon that seems to decline with increasing experience.[23] In fact, the presence of a ramp pressure (reflecting intrabolus pressure) in the distal third of the esophagus preceding the steep rise of the peristaltic pressure suggests a relative outflow obstruction in the gastroesophageal junction.[16,17] It is, however, important to note that we were unable

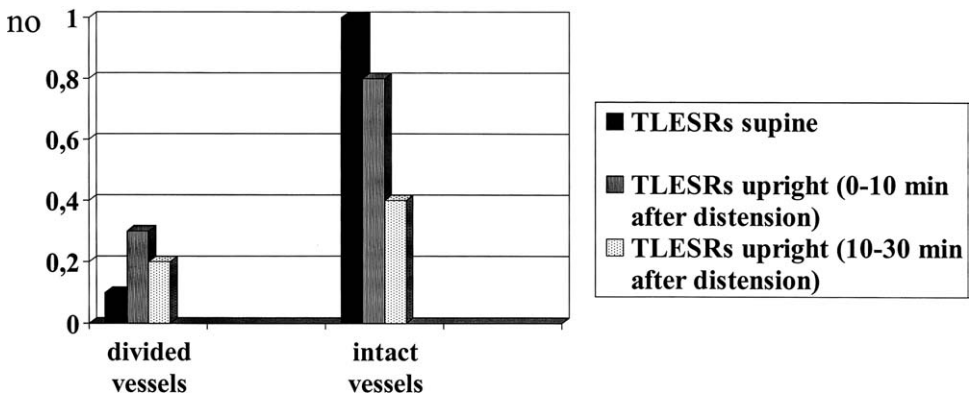

Fig. 2. Transient lower esophageal sphincter relaxations (TLESRs) in the basal state and 30 minutes of gastric distension by 750 ml of air in patients after a total fundoplication with or without division of the short gastric vessels (the mean and SE are given).

Table 2. Manometric findings reflecting the motor characteristics of the esophageal body

	Divided	Intact
Ramp pressure (mm Hg)	7.2 ± 2.0	7.5 ± 1.6
LES basal tone (mm Hg)	14.2 ± 2.4	18.8 ± 4.7
LES nadir pressure (mm Hg)	3.5 ± 1.3	3.8 ± 1.0
Total LES length (cm)	3.8 ± 0.3	3.6 ± 0.3
Abdominal LES length (cm)	2.6 ± 0.4	2.2 ± 0.4

LES = lower esophageal sphincter.

to demonstrate any differences between patients having a total fundoplication with or without the short gastric vessels divided. These manometric observations therefore co-vary with the equality of the short-term outcome results after similar operative interventions.[8–10] We were unable to demonstrate any differences between our two study groups in basal LES tones, the sizes of the total and intraabdominal portions of the high pressure zone, the nadir pressures, and the intrabolus pressures.

Another indirect estimate of the level of obstruction in the gastroesophageal junction can be measured by the magnitude of the peristaltic pressure wave in the distal esophagus.[24] We again did not notice a significant difference between the two samples, reinforcing the conclusion that the static mechanical effects of a total fundoplication are the same irrespective of whether complete divisions of all short gastric vessels have been performed or not.

It has repeatedly been reported that fundoplication operations dramatically reduce the number of transient lower esophageal sphincter relaxations occurring both in the basal state as well as after artificial gastric distension or meal ingestion.[25–27] This effect after antireflux operations is essential, further verifying the pathogenetic role of these lower esophageal sphincter relaxations for the genesis and perpetuation of reflux disease.[28–30] Although the neuronal mechanisms for the control of transient lower esophageal sphincter relaxations have not been fully elucidated, it can be concluded that they are triggered by distension of mechano-receptors in the proximal part of the stomach. As a consequence of these receptor activations, long vagal reflex arcs are activated with subsequent adjustment of LES tone.[30,31] Aside from the reflux controlling function of transient lower esophageal sphincter relaxations, sphincter events—specifically transient realizations—control our ability to belch and effectively vent air from the stomach.[32] Postoperative observations have suggested that important mechanical and functional differences may exist between partial vs. total fundoplication and these differences may translate into fewer complaints of abdominal fullness.[12,26,27,33,34]

As expected, we observed very few transient lower esophageal sphincter relaxations in the basal state as well as after gastric distension in our study groups, but we recorded significantly more TLESRs in patients having their short gastric vessels intact after a laparoscopic total fundoplication. One possible explanation behind this finding may be found in the unavoidable partial denervation of the proximal stomach area when mobilizing the fundus completely. In animal experiments this operative procedure has been shown to affect the triggering of the mechano-receptors of that area, thus interfering with the mentioned neuronal reflex arc.[35] A recently presented long-term follow-up of patients operated with laparoscopic total fundoplication, with or without their short gastric vessels divided, suggested an interesting difference in terms of less gas bloat-like complaints in the latter group.[36] Although these long-term follow-up results have to be confirmed, our observation would offer a functional explanation behind these reported clinical outcome differences.

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Epidermal Growth Factor Receptor Expression Correlates With Histologic Grade in Resected Esophageal Adenocarcinoma

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Activation of the epidermal growth factor receptor (EGFR) has a role in oncogenesis and may correlate with prognosis. The aim of this study was to examine EGFR expression in esophageal adenocarcinoma and correlate EGFR status with pathologic and clinical prognostic features. An exploratory retrospective review of 38 patients with surgically resected esophageal adenocarcinoma was performed. All patients underwent an esophagogastrectomy with regional lymphadenectomy; 24 patients underwent primary resection and 14 patients had surgery after preoperative chemoradiation therapy. Immunohistochemical analysis was performed on paraffin-embedded tissue samples using an EGFR monoclonal antibody. Low- and moderate-grade tumors were positive for EGFR expression in 2 of 15 patients; poorly differentiated tumors were positive for EGFR expression in 13 of 23 patients ($p = 0.02$). The median survival was 35 months (confidence interval [CI]: 29–40) for EGFR negative patients (n = 23) and 16 months (CI: 10–22) for EGFR positive patients (n = 13) ($p = 0.10$). Disease recurred in 3 of 21 EGFR negative patients and 6 of 13 EGFR positive patients ($p = 0.06$). Poorly differentiated adenocarcinomas of the esophagus demonstrated higher EGFR expression compared to low-grade tumors based upon immunohistochemical analysis. A trend toward improved disease-free and overall survival was seen in EGFR negative patients. (J GASTROINTEST SURG 2004;8:448–453)

KEY WORDS: Esophageal adenocarcinoma, epidermal growth factor receptor, tyrosine kinase receptors, immunohistochemical analysis

INTRODUCTION

The epidermal growth factor receptor (EGFR) and its homologues (HER2, HER3, and HER4) are glycoproteins that consist of an extracellular domain for binding ligands, a short lipophilic transmembrane domain, and an intracellular domain (with the exception of HER3) that has tyrosine kinase activity.[1–3] The 170-kDa transmembrane receptor contains an external ligand binding domain for epidermal growth factor as well as transforming growth factor α. The receptors are activated by dimerization between identical receptors (homodimerization) or between different members of the same family (heterodimerization).[4] Activation of the EGFR is thought to play a role in various cellular functions including proliferation, differentiation, and oncogenesis.[5] How the various receptor ligand interactions affect tumor biology is important, but still poorly understood.

Cell proliferation is the predominant response of normal cells to EGFR activation and many solid tumors overexpress the EGFR including bladder, head and neck, breast, gastric, and colorectal cancers.[6,7] At present, the relationship between increased EGFR and tumor growth remains unknown. The prognostic and therapeutic value of this molecular marker has come under intense study with the development of EGFR modulating drugs.[8] New EGFR targeted therapies are being developed and tested for a variety of solid organ malignancies.[9,10]

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There have been numerous reports identifying expression of EGFR in biopsies taken from the normal esophagus and Barrett's esophagus. Some have suggested that EGFR expression may play a role in carcinogenesis and have prognostic significance.[11–17] Reflux esophagitis causes chronic epithelial injury to normal squamous mucosa and has been strongly implicated in the histogenesis of Barrett's esophagitis. How chronic acid and bile reflux relates to the development of adenocarcinoma of the esophagus and if the EGFR pathway is involved in this process remains speculative at this point.[18–20] The goals of this study were to evaluate the expression of EGFR in resected esophageal adenocarcinoma, to correlate EGFR expression with standard pathological features, and to evaluate the prognostic use of EGFR.

MATERIALS AND METHODS

Study Population

Institutional Review Board (IRB) approval was obtained before conducting the review. This exploratory retrospective study included 38 patients with locoregional esophageal adenocarcinoma who underwent surgical resection at Roswell Park Cancer Institute (RPCI) between December 1995 and November 2002. The median follow-up for the entire group was 15 months (range 0.5–76 months). Patient and tumor characteristics regarding sex, age, associated Barrett's esophagus, tumor location, histology, grade, lymph node status, and preoperative chemoradiation were entered into a database. Only cases that contained adequate specimen blocks for immunohistochemical (IHC) analysis were included in the study. Many cases with preoperative treatment had minimal tumor available for analysis and, therefore, tumors that demonstrated a complete or near complete pathologic response to therapy were excluded from this study. All patients were followed per institutional guidelines. There was one postoperative death that was included in the pathologic and IHC analysis, but not included in survival analysis.

Tissue Processing

All of the surgical specimens underwent standard pathological processing including fixation in 10% formalin and embedding in paraffin wax. To perform immunohistochemical staining, the slides were deparaffinized and rehydrated in distilled water. Slides were then immersed in 3% hydrogen peroxide for 15 minutes to block endogenous peroxidase activity and were washed in phosphate-buffered saline (PBS) for 5 minutes. The sections were pretreated with Proteinase K (20 μg/ml) (Invitrogen Corp., Carlsbad, CA) for 14 minutes, washed in PBS for 5 minutes, and blocked with 0.03% casein for 30 minutes. Antimouse EGFR monoclonal antibody (Zymed Laboratories Inc., San Francisco, CA) was applied to tissue sections at a concentration of 1 μg/ml and incubated for 1 hour at room temperature. After two 5 minute rinses in PBS, secondary goat antimouse antibody (Jackson ImmunoResearch, West Grove, PA) was applied to tissue sections at a dilution of 1:200 for 30 minutes at room temperature. The slides were washed twice in PBS for 5 minutes and incubated with Streptavidin (1:20 dilution) (Zymed Laboratories Inc., San Francisco, CA) for 30 minutes at room temperature. After additional washing in PBS (2 times for 5 minutes), the chromogen diaminobenzidine (DAB) (DAKO Corp., Carpentiera, CA) was applied to the sections for 5 minutes. The slides were rinsed in tap water for 3 minutes and then in distilled water. Tissue sections were counterstained with Hematoxylin for 2 minutes, dehydrated through a graded series of alcohols, cleared in Histoclear, mounted with Permount, and analyzed. The specificity of immunoreaction was verified by the use of known negative and positive controls.

Results of EGFR immunohistochemical staining were reported as positive only when membrane staining was observed. The intensity of EGFR membrane staining was graded on a scale from 0 (negative staining) to 2+ (maximum intensity of staining). Tumors with weak or focally strong membrane staining were scored as 1+. A squamous cell carcinoma line, A431, served as a positive external control.

Statistical Analysis

All analyses were of an exploratory nature. EGFR status was expressed as either positive or negative. Comparisons between the distribution of EGFR status and patient characteristics were done using the Fisher exact test. Disease-free and overall survival were calculated using the Kaplan–Meier method; differences were evaluated with the Wilcoxon (Gehan) test. Patients with persistent disease were excluded from the disease-free analyses. No adjustments were made for multiple comparisons.

RESULTS

A total of 38 patients met the study criteria. All had esophageal or gastroesophageal junction adenocarcinomas that were amenable to surgical resection. The majority of patients underwent an Ivor–Lewis esophagectomy with two-field lymphadenectomy, although 3 patients underwent transabdominal esophagogastrectomy for distal lesions. These three cases

had either early stage disease or had undergone preoperative therapy. The majority had lower primary esophageal tumors arising in Barrett's esophagus or a preexisting history of Barrett's esophagus (n = 20). All had surgically resected adenocarcinoma of the esophagus and adequate tumor samples were available for pathologic study. Fourteen of the 38 patients underwent preoperative chemoradiation therapy using a 5-FU and platinum-based regimen in combination with radiation (4500–5040 cGy).

Tumor grades were separated into a favorable histology (n = 15) (well and moderately differentiated) and an unfavorable histology (n = 23) (poorly differentiated and signet ring). The number of patients by group were as follows: well differentiated (n = 2), moderately differentiated (n = 13), poorly differentiated (n = 19), and signet ring cell tumors (n = 4). Lymph node analysis was standardized to either celiac node dissection (n = 2) or two field node dissection (n = 36). The average number of lymph nodes analyzed was 27. Twenty patients had node negative disease and 18 had nodal metastasis. Preoperative chemoradiation therapy was used in 14 of the 38 patients. A high proportion of these cases had poorly differentiated tumors (10/14) and node positive disease (7/14) (Table 1).

Table 1. Clinical and pathologic features of 38 resected esophageal carcinomas

Patient features	n = 38	%
Sex		
Male	34	89%
Female	4	11%
Age		
<65	20	53%
>65	18	47%
Location		
Middle	3	8%
Lower	28	74%
GE junction	7	18%
Barrett's associated	20	53%
Histology		
Adenocarcinoma	34	89%
Signet ring adenocarcinoma	4	11%
Squamous	0	0%
Grade		
Well differentiated	2	5%
Moderately differentiated	13	34%
Poorly differentiated (Signet ring cell n = 4)	23	61%
Lymph node involvement		
Negative	20	53%
Positive	18	47%
Primary surgery	24	63%
Preoperative chemoradiation	14	37%

Immunohistochemical Staining

EGFR membrane staining (+1 and +2) was present in 15 patients and absent in 23 patients. Tumor grade correlated with EGFR expression. Well and moderately differentiated tumors expressed EGFR infrequently (2 of 15), whereas poorly differentiated tumors expressed EGFR more often (13 of 23) ($p = 0.02$) (Table 2). Patients who underwent preoperative chemoradiation therapy demonstrated EGFR expression in half of the cases (7 of 14). Those taken directly to surgery demonstrated EGFR expression less frequently (8 of 24), but this difference was not statistically significant ($p = 0.49$). There were no significant differences in the distribution of EGFR expression and lymph node status or pathologic stage (Table 2).

There was a notable heterogeneity of the EGFR expression between individual glands within a given malignant tumor (Fig. 1). In subset analysis of poorly differentiated tumors, EGFR expression was more uniformly distributed and of a greater intensity compared to moderately and well-differentiated tumors. Neoplastic cells in the deepest regions of tumor invasion had the strongest EGFR membrane staining.

Survival

Examining all patients (primary surgery and preoperative chemoradiation therapy), the median survival for EGFR negative patients (n = 23) was 35 months

Table 2. Epidermal growth factor receptor (EGFR) expression distribution by esophageal cancer staging and treatment criteria

EGFR staining				
Total		n		
EGFR negative		23 60%		
EGFR positive		15 40%		
Histologic grade				
Favorable		Unfavorable		$p = 0.02$
EGFR negative	13	EGFR negative	10	
EGFR positive	2	EGFR positive	13	
Lymph node status				
Negative		Positive		$p = 0.32$
EGFR negative	14	EGFR negative	9	
EGFR positive	6	EGFR positive	9	
Preoperative therapy				
No		Yes		$p = 0.49$
EGFR negative	16	EGFR negative	7	
EGFR positive	8	EGFR positive	7	
Pathologic stage				
I & II		III & IV		$p = 0.22$
EGFR negative	13	EGFR negative	5	
EGFR positive	4	EGFR positive	5	

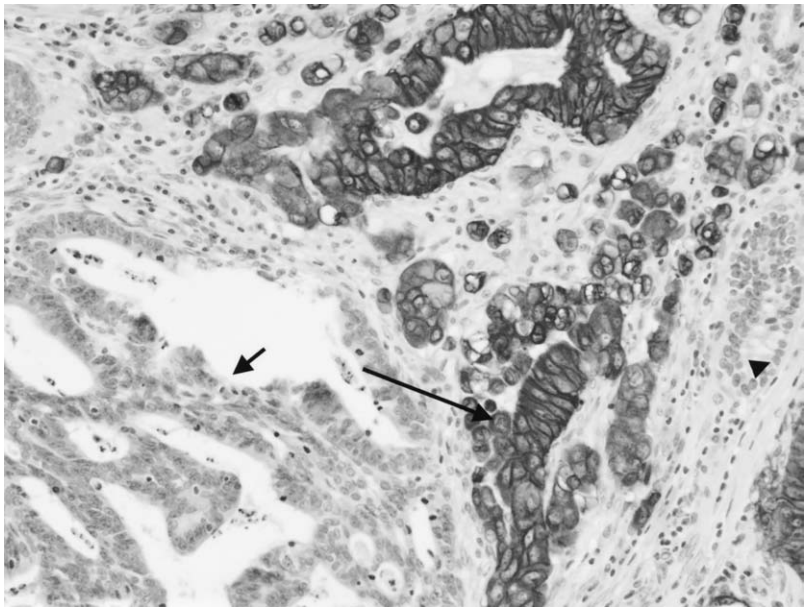

Fig. 1. Focal heterogeneous epidermal growth factor receptor (EGFR) expression is seen within the glandular elements of the primary resected tumor. Staining (*long arrow*) and nonstaining glands (*short arrow*) coexist within a single visual field. Adjacent Barrett's esophagus is present at the periphery (benign nonstaining glands) (*arrow head*).

(95% confidence interval [CI]: 29–40) and 16 months (95% CI: 10–22) for EGFR positive patients (n = 13) ($p = 0.10$). The median disease-free survival in the EGFR negative patients (n = 21) was 35 months (95% CI: 21–48) and 16 months (95% CI: 9–24) for EGFR positive patients (n = 13) ($p = 0.07$). Overall, disease recurred in 3 of 21 EGFR negative patients and 6 of 13 EGFR positive patients ($p = 0.06$). In the patients treated with primary surgery (n = 24), the median survival for EGFR negative patients (n = 16) was 35 months (95% CI: 25–44 months) and 16 months (95% CI: 6–26) for EGFR positive patients (n = 8) ($p = 0.30$). The median disease-free survival for patients treated with primary surgery (n = 24) was 35 months (95% CI: 21–48) for the EGFR negative patients (n = 14) and 16 months (95% CI: 8–24) for EGFR positive patients (n = 8) ($p = 0.48$). In patients treated with primary surgery, disease recurred in 3 of 14 EGFR negative patients and 4 of 8 EGFR positive patients ($p = 0.34$). A trend toward an improved outcome was observed in EGFR negative patients although no comparison reached statistical significance using the Wilcoxon (Gehan) test.

DISCUSSION

In 2003, 13,900 new cases of esophageal cancer will be diagnosed and 13,000 deaths will occur in the United States alone.[21] The prevalence of squamous cell carcinoma has fallen rapidly whereas adenocarcinoma is rising at 10% per year. Reflux esophagitis causes chronic epithelial injury to normal squamous mucosa and has been strongly implicated in the histogenesis of Barrett's esophagitis. There have been numerous reports identifying the expression of EGFR in biopsies taken from areas of Barrett's esophagus and some have suggested that EGFR expression may play a role in esophageal carcinogenesis.[11–20]

In squamous cell esophageal carcinoma the expression of EGFR has been reported,[22] yet the incidence of surgically resectable squamous cell tumors has dropped dramatically in Western countries. At this time, the majority of newly diagnosed esophageal cancers are adenocarcinomas in the United States. Therefore, we sought to examine the expression of EGFR in patients presenting with esophageal adenocarcinoma. We included patients who received preoperative therapy because most patients with advanced poorly differentiated tumors underwent this form of treatment at our institution in recent years.

In this study, EGFR expression was seen in over half of the poorly differentiated tumors, but rarely seen in well and moderately differentiated cases. In the group who underwent preoperative chemoradiation therapy, half expressed EGFR and all of these cases were thought to have the more advanced poorly differentiated tumors before initiating therapy. In patients who had a complete or near complete response

to preoperative chemoradiation, tumor for analysis did not exist; therefore, there may be a selection bias in this study with possible inclusion of chemorefractory patients. Historically, only 25% of patients have a complete pathologic response after chemoradiation based upon long-term survival analysis.[23] Unfortunately, minimal residual disease also precluded analysis in this study and the actual number of cases not analyzed was higher than 25%. During the same timeframe at RPCI, 28 cases of esophageal adenocarcinoma were treated with preoperative chemoradiation therapy, yet only 14 were analyzed for EGFR. Therefore, we estimate that approximately one-half of the patients treated with preoperative chemoradiation therapy had minimal residual disease and these cases were excluded from this EGFR analysis. Despite a trend toward a favorable prognosis in the EGFR negative subset, the small study size and relatively high proportion receiving preoperative chemoradiation may have been confounding factors.

Expression of EGFR in Barrett's esophagus varies in the literature (30%[11]; 74%[14]; 100%[13]) and at present it seems that there is little association between expression and progression to adenocarcinoma. Expression of EGFR has been suggested as a significant prognostic indicator for squamous cell esophageal carcinoma and also for gastric carcinoma.[22,24,25] In gastric carcinoma, overexpression of EGFR may play an important role in tumor progression.[26] Only small retrospective studies exist that examine EGFR expression and esophageal adenocarcinoma. Al-Kasspooles and associates[11] and Yacoub and associates[14] reported that EGFR overexpression is seen in 33% (3/10) and 64% (16/25), respectively, of esophageal adenocarcinomas based on IHC. We report overexpression of EGFR in 39% (15/38) of resected esophageal adenocarcinomas. EGFR is overexpressed in 13% (2 of 15) of well and moderately differentiated tumors compared to 56% (13 of 23) of poorly differentiated tumors ($p = 0.02$).

In this study, EGFR expression varied within the tumor and within individual neoplastic glands. This variation within glandular units requires further study. Focal heterogeneous EGFR expression has implications for tissue processing whereby positive and negative regions could easily be combined or missed depending on sample analysis such as in the case of endoscopic biopsy or gene array. Examination of metastatic lesions needs to be explored to determine if the variable glandular pattern is reproduced and/or determine which cells (EGFR positive or negative) have a higher propensity to metastasize to nodal and distant sites. A better understanding of EGFR in this disease is required to evaluate new EGFR modulators in patients with premalignant lesions such as Barrett's esophagus and advanced adenocarcinomas of the esophagus.

The early results of clinical trials of tyrosine kinase inhibitors indicate that these agents possess antitumor activity in certain malignancies.[9,10,27] Interruption of the EGFR receptor signaling with antibodies or small molecule inhibitors of the tyrosine kinase pathway results in inhibition of proliferation and viability in vitro and in vivo.[28] Identification of tumors with EGFR up-regulation, the association of EGFR overexpression with poor patient prognosis, and the lack of the obvious physiologic role of EGFR in the normal esophagus suggest that EGFR may be a rational molecular target for antitumor strategies.

In conclusion, this study demonstrates that EGFR expression occurs primarily in poorly differentiated esophageal adenocarcinomas, but is rarely seen in well and moderately differentiated tumors. Patients presenting with advanced poorly differentiated adenocarcinoma of the esophagus have a poor prognosis and new treatment modalities are needed. Patients with EGFR expression may benefit from biologically directed agents such as tyrosine kinase inhibitors.

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Cytoreductive Surgery With Intraperitoneal Hyperthermic Chemotherapy for Advanced Gastric Cancer

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Peritoneal carcinomatosis is a common and universally fatal sequelae of gastric carcinoma. Treatment of peritoneal carcinomatosis from appendiceal and colorectal sources with intraperitoneal hyperthermic chemotherapy (IPHC) combined with aggressive cytoreductive surgery has been shown to be effective. There are few data on this treatment modality for carcinoma of the stomach. This study evaluates cytoreductive surgery and IPHC with peritoneal carcinomatosis from gastric carcinoma. Thirty-four patients with peritoneal carcinomatosis due to gastric carcinoma underwent gastric resection with cytoreductive surgery followed by IPHC with mitomycin C. A control group consisting of 40 contemporaneous patients, who underwent radical gastrectomy without extended nodal resection, was identified through the tumor registry. Despite more advanced disease in the IPHC group compared to the control group ($P < 0.001$), overall survival in the two groups was similar. Proportional-hazards regression analysis shows that only resection status is significantly correlated with improved survival ($P = 0.0068$). Within the IPHC group, patients who underwent an R0/R1 resection had increased survival times (11.2 vs. 3.3 months, $P = 0.015$) vs. those who underwent R2 resection. The group who had an R0/R1 resection had 1- and 2-year survival rates of 45% and 45% compared to 16% and 8%, respectively, in the R2 group. Cytoreductive surgery and IPHC is a modality with limited potential for the treatment of peritoneal carcinomatosis from gastric carcinoma. Careful patient selection for this procedure is imperative, and patients in whom an R0/R1 resection can be achieved are the best candidates.
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KEY WORDS: Surgery, peritoneal carcinomatosis, malignant ascites, gastric cancer, chemotherapy

Peritoneal carcinomatosis is a common cause of death in patients with gastric carcinoma, as well as other gastrointestinal malignancies.[1–4] Its development is invariably fatal.[4–8] Advanced disease is often present at the time the primary tumor is diagnosed[6,9,10]; even when curative gastrectomy is performed, peritoneal recurrence develops in nearly 50% of patients.[2,3,9,11] The median survival in this patient population ranges from 2.2 to 8.8 months,[1] with a 5-year survival of 0%.[4,5]

Peritoneal carcinomatosis may occur after curative resection of any intra-abdominal malignancy.[5,7–9,11,12] The sloughing of cells from the surface of tumors that have invaded the serosa of intra-abdominal organs is thought to account for most peritoneal metastasis.[1,9,11] It has been shown that the area of serosal tumor invasion is positively correlated with the detection rate of intraperitoneal free cancer cells.[12] Intraoperative spread of tumor cells stemming from disruption of lymphatic channels is also thought to contribute to seeding of the peritoneum and the subsequent development of carcinomatosis.[11] It is doubtful whether this can be routinely prevented during the extensive dissection requisite in the resection of gastric carcinoma. Further, irrigation with saline solution has been shown to be ineffective in removing

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any neoplastic cells that may have contaminated the peritoneal cavity during the course of cytoreductive surgery (CS).[5]

Current options for the treatment of peritoneal recurrences are limited. In large randomized trials, neither intravenous chemotherapy nor radiation has been shown to improve survival from this disease.[9] Systemic chemotherapy is largely ineffective against metastatic gastric cancer in general, and peritoneal carcinomatosis in particular. This may be the result of poor penetration of intravenously administered antineoplastic agents into the peritoneal cavity[1,4,13] or limited neovascularization of the peritoneum.[1,5] One recent Japanese study suggested that a combination of intravenous methotrexate and 5-fluorouracil was effective in alleviating the sequelae of peritoneal carcinomatosis; however, the median survival time (9.2 months) was not substantially improved.[14]

Intraperitoneal instillation of chemotherapy has been shown to prevent the development of peritoneal carcinomatosis after implantation of neoplastic cells in an animal model.[11] When it is instilled directly into the peritoneal cavity, peak tissue concentrations of agent are much higher than those attained through the intravenous route.[13] The addition of hyperthermia to a chemotherapeutic agent acts synergistically with selected agents (such as mitomycin C) to increase the cell kill by a given dose of drug.[3,8,15] Hyperthermia also increases the depth of penetration of these drugs into tumor tissue, and alone has some cytotoxic effect on neoplastic cells.[7]

Intraperitoneal hyperthermic chemotherapy (IPHC) has been extensively studied in Japan.[4,9,13,15] A recent prospective randomized Japanese trial suggested that IPHC is effective in preventing peritoneal recurrences of advanced gastric carcinoma and conveyed a significant survival advantage to patients treated with this modality in addition to CS.[16] Further, we have reported that the combination of CS and IPHC can immediately ameliorate symptoms of malignant ascites and improve the patient's quality of life.[17] This study reviews our experience with CS and IHPC for adenocarcinoma of the stomach.

METHODS

The study protocol was reviewed and approved by the institutional review board of the Wake Forest University School of Medicine. Patients undergoing IPHC were accrued between December 1991 and June 2001. A group of contemporaneous patients undergoing resection for adenocarcinoma without known distant metastasis was identified through the Wake Forest University/Baptist Medical Center tumor registry and served as a control group. Patients undergoing gastrectomy for carcinoid disease, lymphoma, and gastrointestinal stromal tumors were excluded. The IPHC protocol was open to patients with peritoneal carcinomatosis from both gastrointestinal and nongastrointestinal primary lesions. Patients with malignant ascites were included. Patients in the control group did not have clear evidence of peritoneal carcinomatosis on preoperative imaging, whereas most patients in the IPHC group did. Patients with full-thickness disease of the gastric wall were eligible for IPHC.

Patients being considered for IPHC were required to have normal organ function (serum creatinine <2 mg/dl or creatinine clearance ≥ 60 ml/min; alkaline phosphatase and serum glutamic oxaloacetic transaminase [aspartate transaminase] or serum glutamate pyruvate transaminase [alanine transaminase] <3 times the upper limit of normal), white blood count $\geq 4{,}000/mm^3$, and platelet count $\geq 100{,}000/mm^3$. The diagnosis of gastric cancer was confirmed by histologic examination before CS and IPHC. Patients were required to be at least 18 years of age and could not be pregnant. Patients were not eligible if they had uncontrolled or severe cardiovascular disease, including recent (<3 months) myocardial infarction, congestive heart failure, angina (symptomatic despite optimal medical management), cardiac arrhythmia requiring medical therapy, or uncontrolled hypertension. Patients were also ineligible if they had active bacterial, viral, or fungal infection, active peptic ulcer disease, uncontrolled diabetes mellitus, or severe obstructive or restrictive pulmonary disease. Patients with extra-abdominal or hepatic metastases were not eligible for inclusion in the study protocol.

All patients who underwent CS and IHPC were operated on by one of two surgeons (E.A.L. or B.W.L.). The general surgery staff of the Wake Forest University School of Medicine operated on all patients in the control group. Control patients underwent radical gastrectomy (D1 dissections) without extended nodal dissection. CS consisted of radical resection of the stomach and all gross tumor with involved organs, peritoneum, or tissue that was deemed technically feasible and safe for the patient. Any tumor adherent or invasive to vital structures that could not be removed was cytoreduced using the Cavitron ultrasonic surgical aspiration device (Valleylab, Boulder, CO). If bowel resection was performed, any anastomoses or ostomies were completed after the IPHC portion of the procedure was completed. Extensive peritoniectomy procedures were not performed.

Patients were cooled to a core temperature of approximately 34 to 35C by passive measures (i.e., not warming airway gases or intravenous solutions and

cooling the room). After CS was completed, peritoneal perfusion catheters were placed percutaneously. Two inflow catheters (22 F) were directed beneath the left and right hemidiaphragms. Outflow catheters (32 F) were placed in both the true and false pelvis. Temperature probes were placed on the inflow and outflow catheter tips. The abdominal skin incision was closed temporarily with a running suture to prevent leakage of peritoneal perfusate. A perfusion circuit was established with approximately 3 liters of Ringer's lactate. Flow rates of approximately 800 to 900 ml/min were maintained using a roller pump managed by the pump technician. The pelvic catheters drained to a standard cardiotomy reservoir containing a coarse filter for debris and to reduce foaming. The circuit continued through a single roller pump, through a heat exchanger, and then to the patient. Heated water was pumped to the heat exchanger device from a Blanketrol (Cincinnati Sub-Zero Products, Inc., Cincinnati, OH) heating/cooling blanket reservoir. The temperature of the fluid in the patient-return and patient-directed tubing was monitored using stainless steel couplers with temperature probe connectors and needle probes at the tips of one inflow and one outflow cannula. The abdomen was gently massaged throughout the perfusion to improve drug distribution to all peritoneal surfaces.

Constant temperature monitoring of all temperature probes was carried out. Once inflow temperatures exceeded 38.5C, 30 mg of mitomycin C was added to the perfusate, and at 60 minutes an additional 10 mg of mitomycin C was added to the perfusate to maintain the mitomycin C perfusate concentrations above 10 μg/ml. A maximum inflow temperature of 41.0C was realized during the perfusion. The target outflow temperature was 40C. The total perfusion time after the initial addition of mitomycin C was 120 minutes.

Following the perfusion, the peritoneum was washed out with 2 liters of Ringer's lactate. The skin was opened, and the cannulae were removed under direct vision. The abdomen was inspected, and requisite anastomoses or ostomies were created. The fascia and skin were then closed in a standard fashion with running monofilament sutures. The patient was transferred to the postanesthesia care unit for aftercare and then to the intensive care unit. After clinical stabilization, patients were transferred to a regular hospital room and discharged from the hospital when it was clinically appropriate.

The resection status of patients was estimated following CS on the basis of the following classification: R0, complete removal of all visible tumor and negative cytologic findings or negative microscopic margins; R1, complete removal of all visible tumor and positive cytology or microscopic margins; R2a, minimal residual tumor, nodule(s) $\leq$0.5 cm; R2b, gross residual tumor, nodule $>$0.5 cm but $\leq$2 cm; and R2c, extensive disease remaining, nodules $>$2 cm.

Clinical follow-up occurred at 1 month and every 6 months thereafter for up to 5 years. After 5 years, follow-up examinations were carried out annually. Abdominal and pelvic CT scans were obtained at all follow-up visits except at 1 month, or when clinically indicated. Some patients received systemic chemotherapy after referral back to their medical oncologists.

All data from the IHPC group were collected prospectively, with data on the control group collected retrospectively. Chi-square tests and *t*-tests were used to compare the distribution of patient characteristics between treatment groups. Overall survival was calculated from the date of surgery to the last recorded date of follow-up or death. Kaplan-Meier methods were used to estimate the survival distributions stratified by pertinent clinical and pathologic variables. Unadjusted group comparisons of overall and disease-free survival data were done using the log-rank test. Cox's proportional hazards regression model was used to perform multivariate analysis of clinicopathologic factors to determine the joint predictors of survival and to assess the difference in treatment groups after adjustment for patient characteristics. For the purposes of this report, a value of $P < 0.05$ was considered significant.

RESULTS

A total of 74 patients with advanced gastric cancer were studied. Thirty-four of these patients underwent CS and IPHC to treat their disease (IPHC group), whereas 40 underwent standard curative surgery alone (control group). Patients in the control group were slightly but significantly older than those in the IPHC group (Table 1). Patients in the control group were significantly less likely to have metastasis compared to those in the IPHC group. Patients in the IPHC group were significantly more likely to have stage IV disease, as well as an R2 resection (see Table 1).

Estimates of the median survival and survival at 1, 2, and 5 years are provided in Table 2, overall and by resection status and extent of disease. For all patients, the median survival was 8.0 months; 36% were alive at 1 year and 26% at 2 years. For patients with an R0 resection, median survival was 23.3 months. This compares to 11.2 months for those with an R0/R1 resection and 4.6 months for those with an R2 resection ($P = 0.0068$). Median survival was 11.9 months

Table 1. Patient demographics and baseline data

Variable	Control (n = 40)	CS and IPHC (n = 34)	*P* value
Age (yr)	67.2 (12.1 SD)	54.5 (14.0 SD)	<0.001
Sex			0.30
Male	27 (68%)	19 (56%)	
Female	13 (32%)	15 (44%)	
Extent of disease			<0.001
Stage 1–3	28 (76%)	5 (15%)	
Stage 4	9 (24%)	29 (85%)	
Unknown	3 (—)		
Resection status			0.0177
R0	20 (58%)	7 (21%)	
R1	5 (14%)	5 (15%)	
R2	11 (31%)	19 (56%)	
Unknown	4 (—)	3 (—)	

CS = cytoreduction surgery; IPHC = intraperitoneal hyperthermic chemotherapy.

for patients with stage I to III disease compared to 7.7 months for those with stage IV disease ($P = 0.0667$).

Kaplan-Meier survival estimates are presented in Fig. 1 for both groups of patients. The control group had a median survival of 7.8 months compared to a median survival of 8.0 months for patients undergoing CS and IPHC ($P = 0.29$). Survival estimates are broken down by resection status and extent of residual disease for each group of patients in Tables 2 and 3, and are plotted in Figs. 2 to 5. More complete resection and lower stage disease were associated with increased survival in both groups, although the differences were not always statistically significant because of the small numbers in each group. In patients for whom an R0/R1 resection status was possible in conjunction with IPHC, the median survival time was 11.2 months. This was significantly increased over the median survival of 3.3 months in patients who received an R2 resection along with IPHC ($P = 0.015$). The group receiving an R0/R1 resection had a 1- and 2-year survival of 45% and 45%, respectively, compared to 16% and 8% for the R2 group. The longest survivor of the R2 subgroup survived 39 months.

Table 2. Overall survival data by extent of disease and resection status

	N	Median (mo)	1 yr (%)	2 yr (%)	5 yr (%)	*P* value
Total	74	8.0	36	26	12	
Resection status						0.0068
R0	27	23.3	58	47	21	
R1	10	11.2	26	13	—	
R2	30	4.6	21	10	—	
Extent of disease						0.067
Stage 1–3	33	11.9	48	31	16	
Stage 4	38	7.7	24	20	6	

Patients receiving CS and IPHC who had an R0/R1 resection had a longer median survival time when compared to control subjects with less than stage IV disease. However, the 3-month increase (from 8.6 months to 11.2 months) was not statistically significant. Patients with less than stage IV disease (but with full-thickness wall invasion) who were treated with CS and IPHC had an increased median survival time when compared to those patients with less than stage IV disease who underwent curative surgery alone (36 months vs. 8 months, respectively). This survival advantage was, however, not statistically significant ($P = 0.66$), perhaps because of the small number of patients in this group. Patients with stage IV disease treated with conventional surgery had a median survival of 7.7 months; those with stage IV disease who were treated with CS and IPHC had a median survival of 8.0 months. As was the case with the control and IPHC groups in general, this survival difference was not statistically significant ($P = 0.9$). However, most of the patients in the control group were found to have low-volume metastatic disease at laparotomy, whereas most of those in the IPHC group had obvious metastatic disease found on preoperative imaging or previous exploration.

There was no significant difference in survival advantage conferred to patients based on sex, age, or surgeon performing the procedures.

A proportional-hazards regression analysis was performed with respect to age, sex, procedure performed, resection status, and stage of disease at diagnosis to determine whether these factors may have a joint impact on survival. This analysis of both control and experimental patient groups revealed that, taken as a whole, neither conventional surgery nor combined CS and IPHC was associated with improved survival. Resection status was the only variable that was positively correlated with improved survival in both groups ($P = 0.018$, see Table 3). Analysis of the CS and IPHC groups showed that female sex was also positively correlated with improved survival when compared to male sex ($P = 0.038$). No other variable was identified in this group that correlated with improved survival. There was no significant difference in the median length of stay between the control group (10 days; range 4 to 110 days) and the CS and IPHC group (11 days; range 5 to 105; $P = 0.51$).

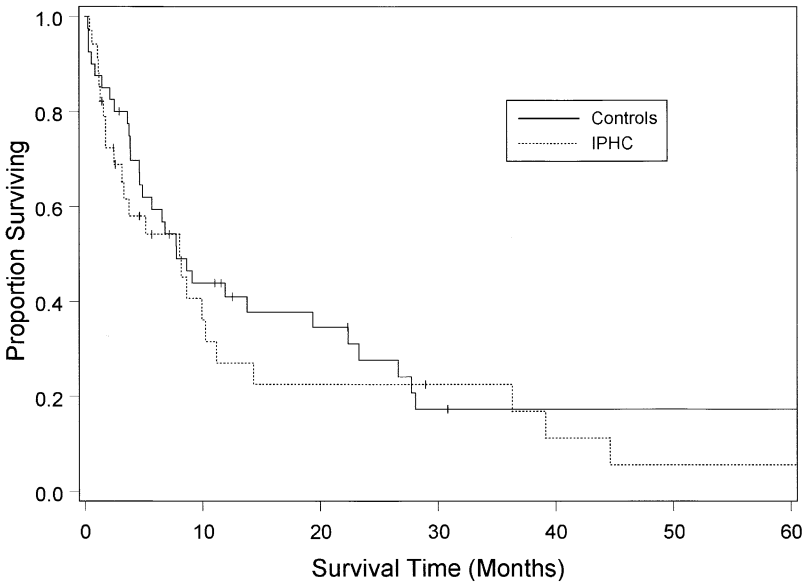

Fig. 1. Kaplan-Meier survival curve: Intraperitoneal hyperthermic chemotherapy (*IPHC*) and control groups.

The control group, who underwent conventional surgery alone, had a perioperative morbidity rate of 17.5% (7 of 40). Perioperative mortality (defined as death within 30 days of surgery) was 15% (6 of 40) in this group. The IPHC group had a perioperative morbidity of 35% (12 of 34), with a mortality rate of 0%. However, one patient in the IPHC group died after 30 days without leaving the hospital. Complications arising from each study group are described in Table 4. The IPHC group did have twice the morbidity rate (35% vs. 17.5%) of the control group, and many of these complications were life-threatening. The morbidity and mortality in this study were similar to recently published results.[29]

DISCUSSION

The diagnosis of peritoneal carcinomatosis due to gastric carcinoma has a dismal prognosis. Resection alone has been shown to yield poor outcomes for patients with advanced gastric cancer.[18,19] Recently, however, there have been a number of encouraging reports published regarding the efficacy of CS and

Table 3. Survival data by extent of disease and resection status for each group

	Control group					IPHC group				
	N	**Median (mo)**	**1 yr (%)**	**2 yr (%)**	**5 yr (%)**	**N**	**Median (mo)**	**1 yr (%)**	**2 yr (%)**	**5 yr (%)**
Total	40	7.8	41	28	17	34	8.0	27	23	6
Extent of disease										
Stage 1–3	29	8.6	44	25	20	5	36.3	75	75	—
Stage 4	9	7.7	33	33	—	29	8.0	20	15	8
Resection status										
R0	20	23.3	59	45	30	7	36.3*	56	56	—
R1	5	6.8	20	—	—	5	11.2*	33	33	—
R2	11	6.5	27	14	—	19	3.3*	17	8	—
R0 and R1	25	19.4	50	34	23	12	11.2†	45	45	—
R2	11	6.5	27	14	—	19	3.3†	17	8	—

IPHC = intraperitoneal hyperthermic chemotherapy.
*P value for survival comparisons = 0.05.
†P value for survival comparisons = 0.015.

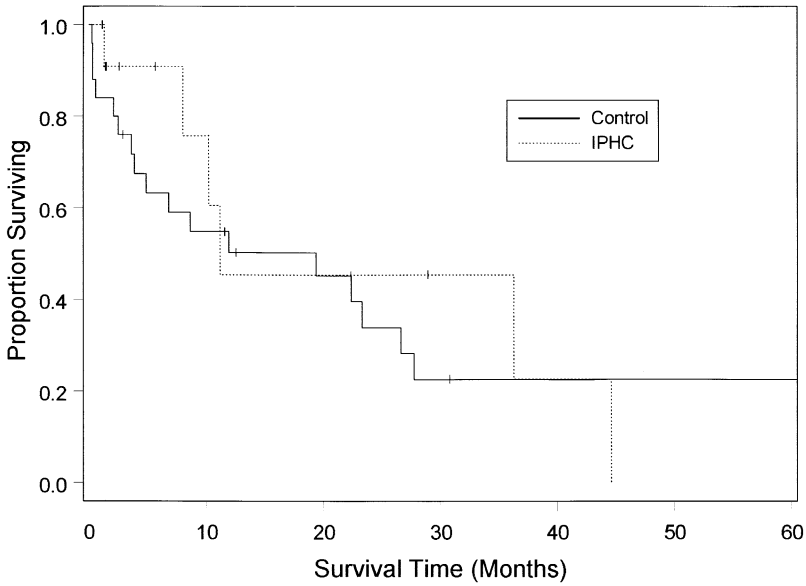

Fig. 2. Kaplan-Meier survival curve for R0/R1 patients: Intraperitoneal hyperthermic chemotherapy (*IPHC*) and control groups.

IPHC in the treatment of various disseminated intra-abdominal malignancies.[13,16,20,21] A prospective randomized trial of CS and IPHC has shown a statistically significant doubling of survival for peritoneal carcinomatosis from colorectal cancer when compared to systemic chemotherapy alone.[22] This has led to an opinion that care may be possible for selected patients with carcinomatosis with CS and IPHC.[23]

Peritoneal carcinomatosis from gastric cancer is likely to be multifactorial in etiology. There are a number of investigators who suggest that gastric cancers penetrating the serosa slough neoplastic cells into the peritoneal cavity,[1,9,11] and that it is these cells that are a nidus for future carcinomatosis. In 1959, Fisher et al.[24] suggested that patients with gastrointestinal malignancies harbor high numbers of

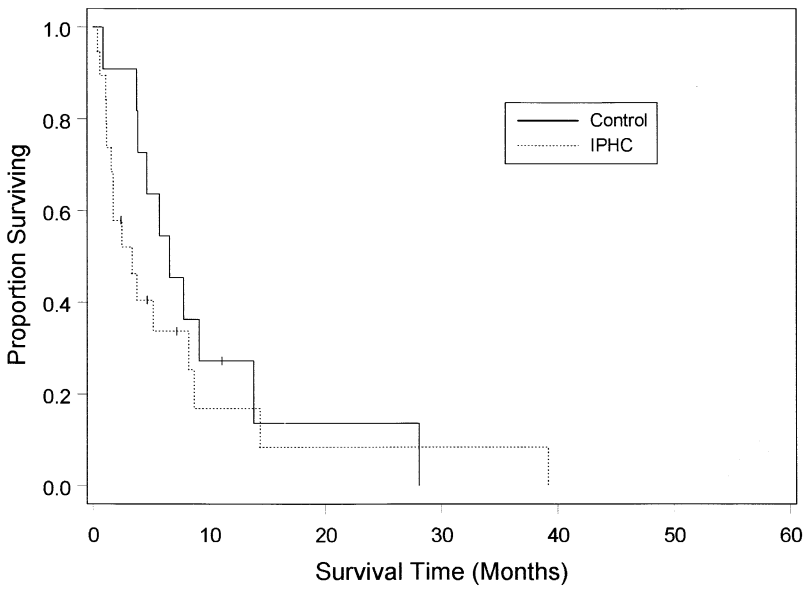

Fig. 3. Kaplan-Meier survival curves for R2 patients: Intraperitoneal hyperthermic chemotherapy (*IPHC*) and control groups.

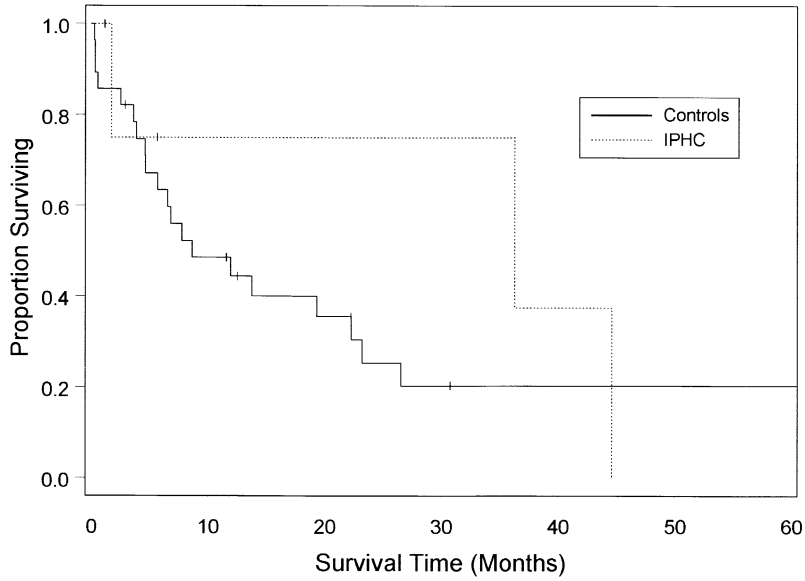

Fig. 4. Kaplan-Meier survival curves for stage I-III patients: Intraperitoneal hyperthermic chemotherapy (*IPHC*) and control groups.

tumor cells within the portal blood. The lymphatic and vascular spaces may also be a source of neoplastic cells that escape into the peritoneal cavity at the time of surgery. The expression of adhesion molecules, such as integrins, on the surface of the neoplastic cells allows cells to adhere to extracellular matrix proteins on the raw exposed surfaces of viscera and the peritoneal cavity during surgery.[21,22,25,26] Despite the fact that this is a common clinical problem, there is a paucity of work evaluating the molecular basis of peritoneal metastasis.

Systemic chemotherapy is a poor treatment for peritoneal metastasis,[1,4, 5,13] although a small survival advantage has been reported for gastric cancer patients with carcinomatosis who are undergoing systemic chemotherapy.[14] Shortly after surgery, a significant host inflammatory response occurs, potentially encasing any tumor cells in a protective fibrotic

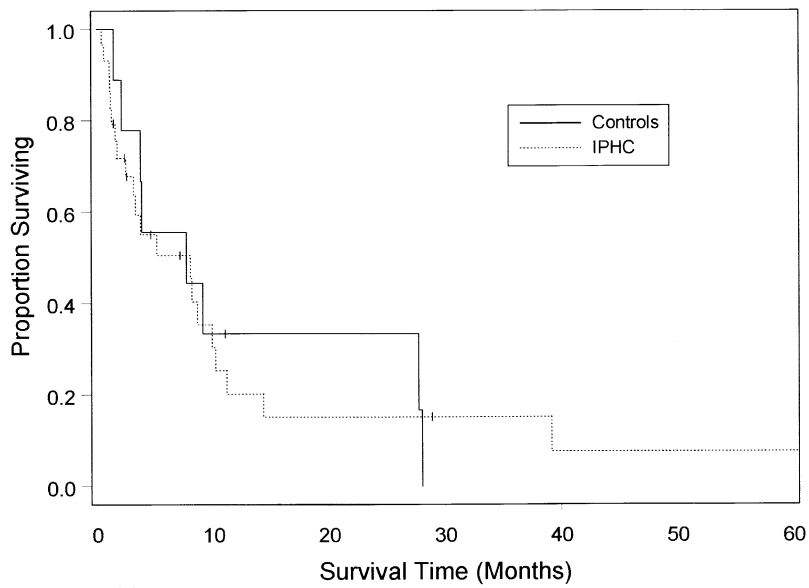

Fig. 5. Kaplan-Meier survival curves for stage IV patients: Intraperitoneal hyperthermic chemotherapy (*IPHC*) and control groups.

Table 4. Complications in each group

Complication	Control (n = 40)	IPHC (n = 34)
Anastomotic leak	3	4
Sepsis	3	5
Wound infection	0	3
Leukopenia	0	3
Myocardial infarction	0	1
Pulmonary embolism	0	1
Atrial fibrillation	0	1
Prolonged ventilator dependence	1	0

shell, with limited neovascularization, potentially protecting them from the antineoplastic effects of postoperative chemotherapy.[1,5,9,21,25] Intraoperative intraperitoneal chemotherapy has the advantage of bathing the entire peritoneal cavity prior to such fibrosis. An additional advantage to intraperitoneal chemotherapy is a far greater local drug concentration than can be achieved using systemic means.[26,27] Hyperthermia increases the depth of penetration of these drugs and has some intrinsic cytotoxic effect alone.[7] A number of investigators have shown that there is some survival advantage conferred to patients with gastric cancer in conjunction with IPHC.[3,4,13,28] For these reasons, IPHC was proposed to prevent the occurrence of peritoneal metastases following resection of gastric cancer. Further, agents with greater activity against gastric cancer than mitomycin C could make IPHC more efficacious.

In this study it is important to note that the patients in the CS and IPHC group had more extensive disease than those patients who underwent conventional resection alone (control group). This is demonstrated by the rate of R0/R1 resections in the control group, which is twice as high as that in the IPHC group, despite aggressive efforts at cytoreduction. The data presented here reinforce a potential role of IPHC in the treatment of intra-abdominal malignancy. Specifically, a survival advantage could be conferred on patients in whom a total or near-total resection of disease is possible (R0/R1), regardless of the stage of disease at the time of surgery. To minimize the risk of a peritoneal recurrence, we suggest IPHC in combination with resection of all macroscopic disease (R0/R1 resections). If adequate cytoreduction is achieved, the intraperitoneal chemotherapeutic agents should act on the both neoplastic cells that may have contaminated the peritoneal cavity as well as any residual microscopic disease.

We and others have shown that CS and IPHC can and does produce long-term survivors among patients with peritoneal carcinomatosis.[3–5,13,20–23,28] This study supports the previous findings that resection status is the key prognostic indicator for this procedure.[5,20,28] It must be emphasized that the patients in the CS and IPHC arm of this study had significantly more advanced disease than those in the control group ($P < 0.001$). This suggests that survival in the IPHC group may be better when compared to a group more closely matched than those patients in the conventional surgery group. Further, had IPHC not been attempted in patients undergoing the procedure, an outcome similar to that in patients undergoing an R2 resection would be anticipated, with a median survival of approximately 5 months. Although the differences in survival times do not reach statistical significance, the limited number of cases makes the possibility of a type II error substantial. Therefore this suggests that there may be a potential benefit of CS and IPHC for patients undergoing procedures in which an R0/R1 resection is possible. Further, our limited findings in patients without peritoneal carcinomatosis who underwent IPHC (see Fig. 4) seem to support the survival advantage seen in the recent Japanese prospective randomized trial.[9] Whether systemic therapy would improve the outcomes of patients undergoing complete cytoreduction remains to be seen.

Although the results of this study indicate that there may be a role for IPHC in the setting of advanced gastric carcinoma, it is clearly not the treatment modality of choice for most patients who carry this diagnosis. We selected patients without known hepatic or pulmonary metastases and adequate cardiopulmonary and renal function. A selection bias is suggested by the average age in our IPHC group, which was more than 10 years younger than the control group. Our data do show that IPHC in combination with CS can produce prolonged survival in patients who can undergo complete resection of all gross disease. However, this procedure is not without its drawbacks. The morbidity in the IPHC group was twice that seen in the control group. The mortality and morbidity from the combined procedure are reported to be 3% to 10% and 10% to 55%, respectively,[5,7,9,21,29] and hospital stays average 10 days. For patients who have complications from this procedure, hospital stays can be prolonged. However, the hospital stays in this study were similar in patients undergoing gastrectomy and gastrectomy with IPHC. In looking at the subset of patients in our series who survived for more than 3 years, the need for reexploration and further tumor debulking was present in all of them. Only one of these had an initial R0 resection. Of those without R0 resections, the disease progression seemed slower than expected for typical gastric cancer; whether or not this was due to the IPHC is

unknown and could be a focus of future clinical trials. The longest survivor in the series underwent an R0 resection with IPHC and survived for almost 4 years free of disease; this patient eventually died of cardiopulmonary disease. Therefore the results of this study are promising, particularly in the adjuvant setting.

The patient population that would be most likely to benefit from this treatment modality has yet to be precisely determined. The procedure itself is lengthy, and the postoperative period is fraught with potential complications ranging from anastomotic leaks to neutropenic sepsis and death. Although long-term quality of life has been shown to improve in patients undergoing IPHC,[17] this outcome has not been studied in this particular cohort of patients. The financial costs to the patient are also substantial. It is not uncommon for patients undergoing this procedure and who have a complicated course to have hospital bills exceeding $50,000. When dealing with potential candidates, it is imperative to keep in mind that CS and IPHC is essentially an aggressive palliative procedure.

Consequently, based on our experience, we recommend that patients be carefully selected for this procedure. Our current criteria include otherwise healthy patients with good preoperative functional status and no evidence of extraperitoneal or hepatic metastasis. Further, imaging should suggest that an R0 resection might be achieved. Patients with full-thickness gastric wall resections without evidence of peritoneal carcinomatosis are also potential candidates. If an R1 resection cannot be achieved, one must have engaged in a discussion with the patient prior to surgery as to the patient's wishes at this point. We do not recommend this procedure for patients in whom resection of all gross disease cannot be achieved. Although palliative resection in selected patients with stage IV disease has been suggested to be of value, this is a decision that we believe is best made when both physician and patient understand both the limitations and implications of such procedures. A confirmatory prospective, randomized trial comparing resection with adjuvant IPHC vs. curative resection alone for less advanced gastric carcinoma (stages II and III) is needed to more fully evaluate this method of treatment for patients presenting with gastric cancer.

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Aggressive Surgical Treatment for T4 Gastric Cancer

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Surgical treatment for locally advanced gastric cancer remains controversial, and many still question the benefits of extended resection. The aim of this study was to evaluate the effectiveness of combined resection of the involved organs with regard to survival in patients with gastric cancer. Between 1993 and 2000, among the 1638 patients with gastric cancer who underwent gastrectomy, 82 were found to have evidence of adjacent organ spread at laparotomy. A retrospective analysis of these patients was performed. Curative resections were carried out in 50 patients, whereas noncurative resections were performed in 32 patients. The 5-year survival rate in the group undergoing curative resection was 36.9%. The survival rate in the R0 group was significantly higher than the survival rate for patients undergoing noncurative resections. There was no significant difference in survival rates between patients with pT3 cancer and those with pT4 cancer. Seventy-one patients were pathologically proved to have lymph node metastasis, and the survival rate for patients with a lymph node ratio greater than 0.2 was lower than that in other groups. In multivariate analysis, peritoneal dissemination, lymph node ratio, and histologic findings were the predictors of survival. Patients with T4 gastric carcinoma, even with lymph node metastasis, might have benefited from aggressive surgery with curative intent. (J GASTROINTEST SURG 2004;8:464–470)

KEY WORDS: Gastric cancer, locally advanced, T4, surgery

The surgical technique of gastrectomy for gastric cancer has become more widely established and has been shown to achieve good results. However, surgical management of locally advanced (T4) gastric cancer remains controversial. It is also unclear whether the postoperative survival rate can be improved by combined resection of involved organs with extended lymph node dissection. This study was designed to investigate the survival benefits of aggressive surgery in patients with T4 gastric cancer.

PATIENTS AND METHODS

Between 1993 and 2000, a total of 1638 patients with primary gastric cancer were treated with surgery at the National Cancer Center Hospital East Japan. Among these 1638 patients, 82 were proved to have direct invasion to the adjacent organs macroscopically at laparotomy. Combined resection with curative intent was indicated for those patients with visible tumor invasion of the adjacent organs who had no evidence of liver metastasis or peritoneal dissemination. Some palliative resections were also performed. D2 lymph node dissection was performed as standard radical gastrectomy. D3 (extended) lymph node dissection was also performed, if necessary, for curative resection. The lymph node ratio (i.e., the ratio of the number of positive lymph nodes to the number of negative lymph nodes) was calculated.

Various clinicopathologic factors that were presumed to influence survival and postoperative complications in these 82 patients were reviewed. Clinical and histologic classification followed the TNM classification of malignant tumors.[1] The median length of follow-up was 23.1 months (range 1 to 93 months).

A standard data collection format was constructed through the researchers' common efforts. When data were insufficient, clinical records were referenced. Follow-up information was obtained at clinical outpatient visits or from mailed questionnaires. Disease-specific survival was calculated from the day

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of surgical treatment according to the Kaplan-Meier method. The log-rank test was used to assess statistical significance between groups. Significance was determined by chi-square analysis. Cox proportional hazards analysis was performed for patient-related parameters. $P < 0.05$ was considered statistically significant.

RESULTS

Details concerning the clinicopathologic factors are shown in Table 1. The patients were divided into two groups on the basis of the pT factor. There was no significant difference between the two groups in patient characteristics. Overall, curative resections (R0) were carried out in 50 patients (R0 group), whereas noncurative resections (R1 and R2) were performed in 32 patients. Reasons for noncurative resections included peritoneal dissemination, liver metastasis, and distant lymph node metastasis.

The overall survival rate for all patients with T4 gastric cancer was 59.8% at 1 year, 40.9% at 3 years, and 31.1% at 5 years (Fig. 1). The survival rate for the R0 group was significantly higher than that for the R1 and R2 groups ($P = 0.004$). Survival curves for patients with pT3 and pT4 cancer are shown in Fig. 2. There was no significant difference in survival between patients with pT3 cancer and those with pT4 cancer.

Seventy-one patients were pathologically proved to have lymph node metastasis, and the survival rate for patients with a lymph node ratio greater than 0.2 was lower than that for the other patients (Fig. 3). There was no significant difference in the survival rate between stage IV and other stages (Fig. 4).

Operations for combined resection are listed in Table 2. The organs that were invaded macroscopically included the pancreas (36 patients), transverse

Table 1. Clinical features of 82 cases

Patient characteristics	pT3 (n = 42)	pT4 (n = 40)	*P*
Age (yr)	64 (range 26–84)	64 (range 27–79)	NS
Sex (M/F)	29/13	29/11	NS
Tumor size (cm)	10.8 ± 4.8	9.0 ± 3.3	NS
Operative procedure			NS
Total gastrectomy	30	20	
Subtotal gastrectomy	12	20	
Complications			NS
Preoperative	13	19	
Postoperative	11	12	
Lymph node status			NS
pN0	6	5	
pN1	14	9	
pN2	10	14	
pN3	12	12	
Resectability			NS
R0	26	24	
R1	1	1	
R2	14	14	

NS = not significant.

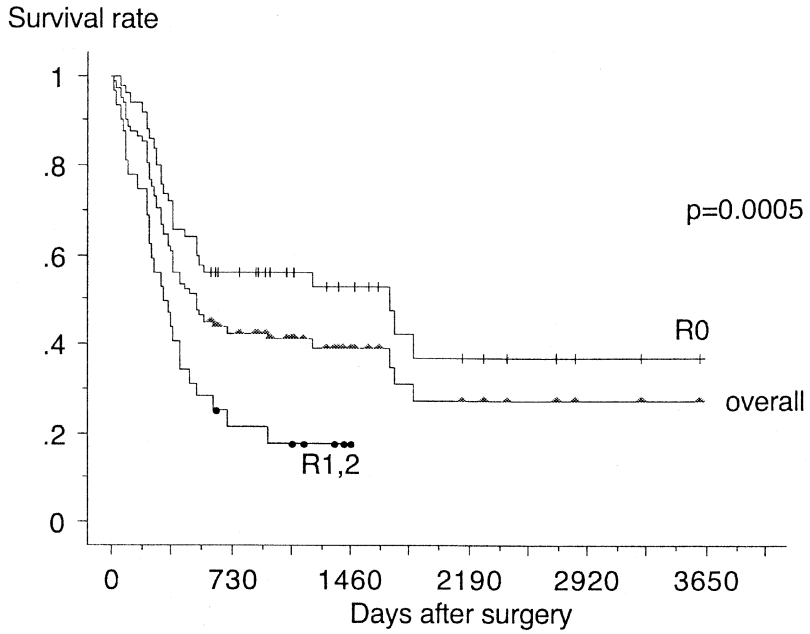

Fig. 1. Survival curves of patients grouped according to different types of treatment modalities. Patient survival was significantly worse in the palliative treatment group (*R1,2*) compared to the curative group (*R0*).

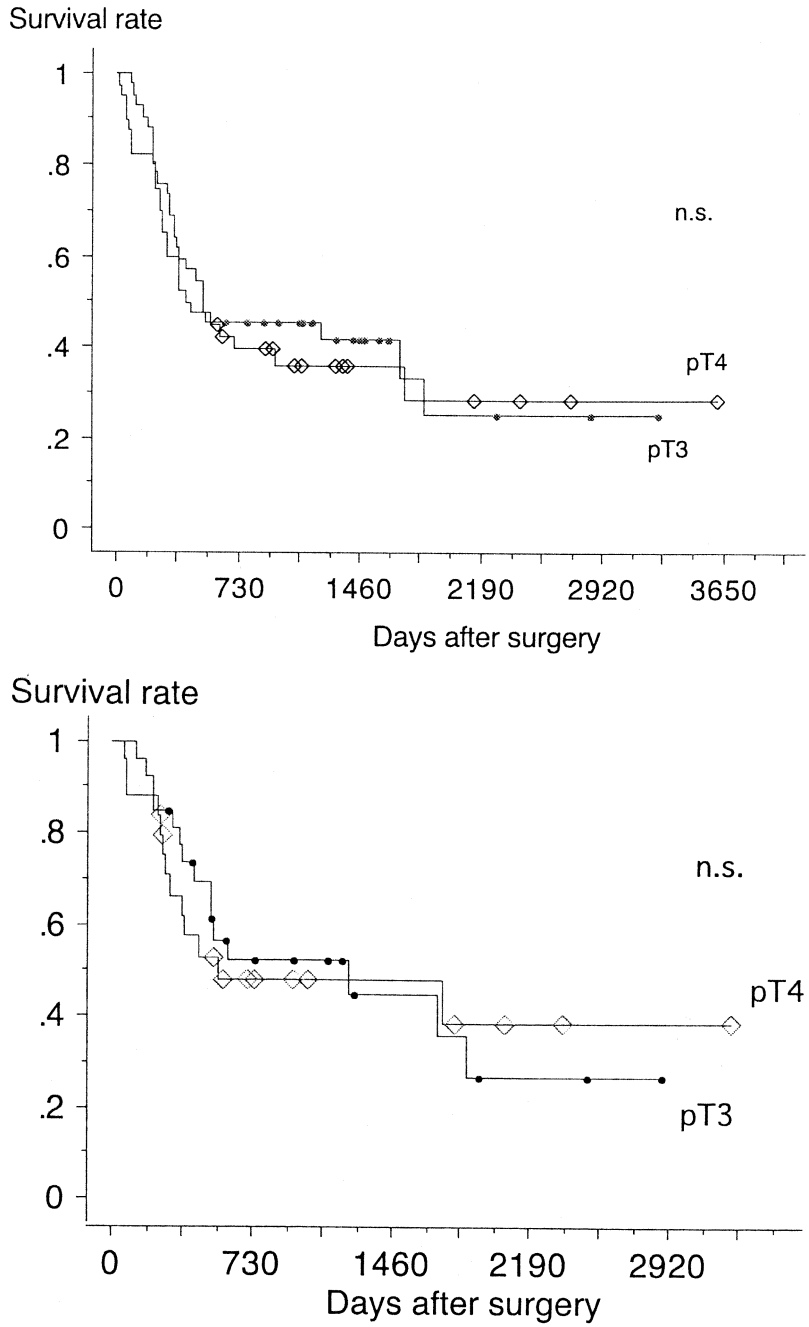

Fig. 2. *A*, Survival curves of patients who had undergone surgery stratified by pT factor. There was no significant difference in survival rates between patients with pT3 cancer and those with pT4 cancer. n.s. = no significant difference. *B*, Survival curves of patients who had undergone curative surgery (R0) stratified by pT factor. There was no significant difference in survival rates between patients with pT3 cancer and those with pT4 cancer. n.s. = no significant difference.

colon (35 patients), liver (10 patients), adrenal gland (7 patients), diaphragm (6 patients), abdominal wall (2 patients), and spleen (2 patients) (Table 3). There was no correlation between survival rate and which organ was invaded (data not shown).

Other prognostic factors were also evaluated (Table 4). Peritoneal dissemination, tumor histology, and extensive vascular and lymph vessel invasion were all associated with patient survival according to univariate analysis. Multivariate analysis demonstrated

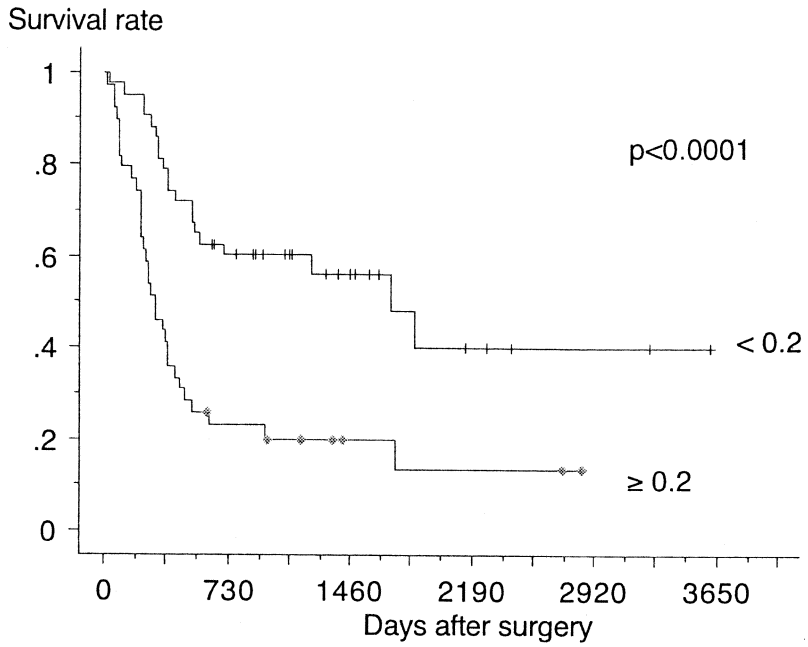

Fig. 3. Survival curves of patients who had undergone surgery stratified by lymph node ratio. Survival rate in patients a with lymph node ratio greater than 0.2 was lower than that in patients with other cancers ($P < 0.0001$).

that peritoneal dissemination, lymph node ratio, and tumor histology were predictors of survival (Table 5).

Postoperative complications occurred in 23 patients (28.0%) (Table 6). There was one operative death (1.2%).

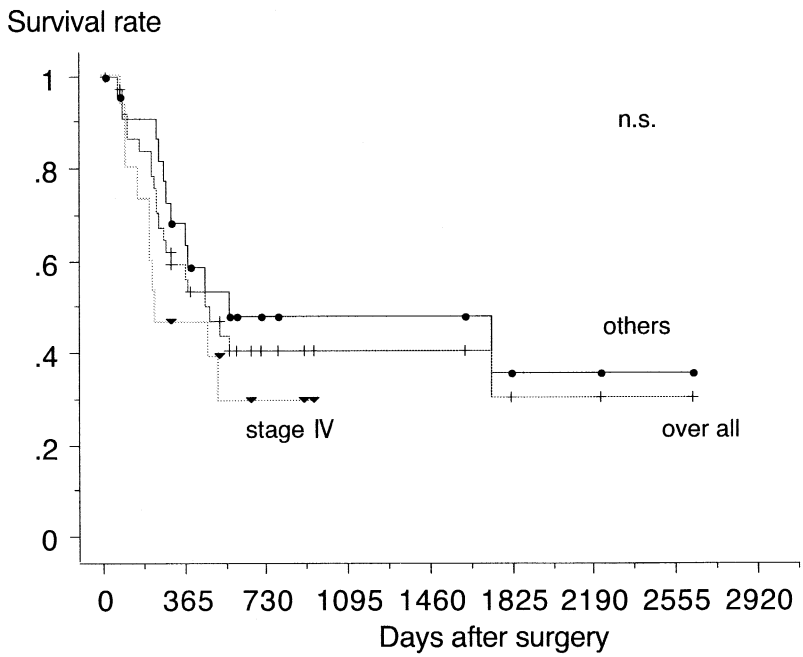

Fig. 4. Survival curves of patients who had undergone surgery stratified by TNM stage. There was no significant difference in the survival rate between stage IV and other cancers.

Table 2. Combined resection

Operation	No.
Distal pancreatectomy + splenectomy	36
Transverse colectomy	35
Liver resection	
Lateral segmentectomy	3
Partial hepatectomy	7
Splenectomy	9
Adrenalectomy	7
Partial resection	
Diaphragm	6
Abdominal wall	2

DISCUSSION

Gastric cancer is one of the most common cancers in Japan. With early detection and a standardized surgical protocol, the prognosis for patients with gastric cancer has been improving. A survival advantage has been reported for the removal of the primary tumor over noncurable operations. However, the prognosis for patients with advanced gastric cancer is still poor, and the surgical management of locally advanced gastric cancer remains controversial.[2]

Accurate preoperative and perioperative staging of gastric cancer is a difficult problem. Although improvements in various imaging methodologies seem to enhance the preoperative staging accuracy, this has not yet been established. Endoscopic ultrasound imaging is the standard technology that is used to characterize the degree of invasion. Its accuracy in staging T3 and T4 tumors is reported to be approximatly 90% and 80%, respectively.[3–5] However, we are often, and unexpectedly, faced with macroscopic cancer invasion to adjacent organs at laparotomy.

According to the Union Internationale Contre le Cancer classification,[1] stage IV gastric cancer contains T4, N3, and M1. The 5-year survival rate in patients with stage IV gastric cancer is reported to be 0 to 9.0%.[6,7] Although our analysis contained only surgically treated patients, we obtained a good survival rate in patients with stage IV cancer, regardless of the invasion site; the 5-year survival rate was 31.3%. In addition, our data showed that pT factor did not affect prognosis. These results suggested that we could manage the T factor by aggressive surgical resection.

Siewert et al.[8] report relevant prognostic factors in 1182 patients with gastric cancer undergoing R0 resection. They noted that lymph node ratio and lymph node status were the most important prognostic factors in patients with resected gastric cancer. They also suggest that radical lymph node removal may be associated with improvement in long-term survival, particularly in patients with incipient lymph node metastases. However, some randomized trials have shown that extended lymphadenectomy increases the postsurgical morbidity and mortality and

Table 3. Organs showing tumor invasion

Organs	Macroscopic invasion	Microscopic invasion
Pancreas	36	18
Transverse colon	35	22
Liver	10	4
Adrenal gland	7	4
Diaphragm	6	2
Abdominal wall	2	0
Spleen	2	1

Table 4. Univariate analysis of prognostic factors in patients with T4 gastric cancer (n = 82)

Parameters	Survival rate (%) 1 yr	3 yr	*P*
Age			0.210
>60 yr	54.0	37.6	
≤60 yr	65.6	46.2	
Tumor size			0.441
>10 cm	58.3	38.9	
≤10 cm	64.7	43.7	
Operative procedure			0.128
Total gastrectomy	54.0	36.0	
Subtotal gastrectomy	71.9	49.3	
Histology			0.012
Well, moderately differentiated	77.4	57.7	
Other	51.0	30.8	
Vascular invasion			0.025
Extensive	56.6	31.8	
Not extensive	69.0	57.9	
Lymph vessel invasion			0.036
Extensive	50.0	28.8	
Not extensive	73.7	55.0	
Liver metastasis			0.064
+	40.0	20.0	
−	63.9	43.8	
Peritoneal dissemination			0.0031
+	36.8	21.1	
−	68.3	46.8	
Complications			
Preoperative			0.853
Yes	55.6	38.7	
No	65.2	43.0	
Postoperative			0.957
Yes	56.5	47.4	
No	62.7	38.4	

Table 5. Multivariate analysis of prognostic factors in patients with T4 gastric cancer (n = 82)

Parameters	Category	Relative risk	95% CI	*P* value
Age	>60 yr	1.421	0.76–2.64	0.269
Tumor size	>10 cm	0.921	0.50–1.71	0.794
Histology				0.012
Well, moderately differentiated	No	2.400	1.21–4.75	
Vascular invasion	Extensive	1.140	0.54–2.41	0.732
Lymph vessel invasion	Extensive	1.244	0.63–2.45	0.527
Lymph node ratio	⩾0.2	2.035	1.01–4.12	0.048
Preoperative complication	Yes	0.827	0.46–1.49	0.527
Peritoneal dissemination	Yes	2.222	1.11–4.46	0.024
Liver metastasis	Yes	2.196	0.88–5.47	0.091
Depth of invasion	pT4	0.935	0.53–1.67	0.827

CI = confidence interval.

does not improve the survival benefit in patients with gastric cancer.[9–13] Kitamura et al.[14] and Saito et al.[15] report that resection of the involved organs in combination with gastrectomy should be performed when lymph node metastasis is not evident. On the contrary, our data showed that we could expect a good survival even in node-positive patients, except those with a lymph node ratio greater than 0.2, when extended lymph node dissection was performed. Therefore it was thought that node-positive patients were also candidates for combined resection.

Postoperative morbidity and mortality rates for patients with gastric cancer who undergo gastrectomy are reported to range from 17.8% to 33.0% and 2.0% to 11.9%, respectively [16–19] In our patients, pancreatic fistula was the most common postoperative complication (19.5%). It was probably due to the extended lymph node dissection and distal pancreatic resection. Ikeguchi et al.[16] reported that existence of preoperative complications and combined resection of other organs are found to be important risk factors for postoperative morbidity, but the extent of lymph node dissection is not a significant risk factor. They also reported that during noncurative operations in patients with advanced gastric cancer, unnecessary lymph node dissection or combined resection should be avoided because of the associated higher mortality. The present study demonstrated that gastrectomy with additional organ resection for locally advanced gastric cancer could be achieved with acceptable operative morbidity (28%) and minimal mortality (2.0%). Long-term survival could be achieved in patients with T4 gastric cancer, with a 5-year survival rate of 31.1%. Lymph node ratio, tumor histology, and peritoneal dissemination were the predictors of poor survival.

Table 6. Postoperative complications

Reason	No.
Pancreatic fistula	16
Anastomotic leak	5
Abdominal abscess	4
Pneumonia	4
Ileus	2
Stenosis	1
Morbidity rate (%)	28.0

CONCLUSION

Combined resection of involved organs with extended lymph node dissection in patients with clinical T4 gastric cancer can be performed with acceptable morbidity and minimal mortality, and has been shown to improve outcomes. Although the extent of lymph node metastasis is a predictor of survival, node-positive patients should also be considered as possible candidates for combined resection.

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1990–2001 U.S. General Surgery Chief Resident Gastric Surgery Operative Experience: Analysis of Paradigm Shift

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The almost complete disappearance of benign gastric ulcer disease has led to the perception that there may be an insufficient gastric surgery experience for surgery residents. This study analyzed resident-reported gastric procedure experience by chief residents from U.S. programs. The Resident Statistic Summaries (Report C) for 1990–2001 were compiled and analyzed. Results are expressed as the average number of operations performed per resident, standard deviation (SD), and the percentage (%) of total gastric operative cases. For all gastric-related surgery, the average reported cases per chief resident ranged from 9.8–12.4 with a peak in 1990 and a nadir in 1999; in 2001 the reported case average was 11.3 (SD ranged from 6–8). Over the same interval, vagotomy decreased from 24% in 1990 to 7% in 2001, whereas gastric-reduction operations increased from 5%–34%. Total gastrectomy remained a constant less than 1.0 per chief resident (range 0.6–0.8), whereas partial gastric resection (PGR) was unchanged. The percentage of all types of gastric resections slightly diminished from 34% in 1990 to 29% in 2001. U.S. surgical chief residents report a widely variable experience in gastric surgery over the period analyzed. However, their overall experience has not significantly diminished since 1990 although specific procedural volume has varied. (J GASTROINTEST SURG 2004;8:471–478)

KEY WORDS: Gastric surgery, surgical education, general surgery residency

INTRODUCTION

"Where have gastric surgery cases gone" has been a common question asked across medical centers in the United States. However, given an annual incidence of less than 15,000 cases, procedures for gastric malignancy were never commonplace in the United States, thus the question really should be "where have benign gastric surgery cases gone." The answer to that question, at least in part, is related to the significant developments in the nonoperative management of benign gastric ulcer and associated complications. The almost ubiquitous use of gastric acid inhibitor therapies (H2 antagonists or proton pump inhibitors) and the therapeutic/prophylactic treatment of gastric *H. pylori* disease can be credited with the relative disappearance of benign gastric ulcer disease.[1–3]

Another more recent development has been the rapid penetration of laparoscopic surgical procedures into community practice and subsequently into academic training centers, which has further and significantly reduced the opportunity for general surgery residents to obtain "open" gastric surgical experience. This combination of medical nonoperative management of ulcer disease and the conversion of standard open gastric procedures to laparoscopic procedures has led to the perception that current surgical residents in training do not have adequate exposure to gastric surgery with potential significant impact on their ability to care for patients in need of such services.

To separate perception from reality, we sought objective data on actual case-reported experience for U.S. general surgical residents. We hypothesized that given the above described conditions, the number of gastric-related operative procedures had decreased over the preceding decade and that the number of

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procedures per individual resident had similarly diminished.

MATERIALS AND METHODS

The Surgical Operative Log is a computerized national database that collects the total operative experience of all finishing surgical residents. Created by the Residency Review Committee for Surgery in 1986, it contains several reports including the Resident National Data, the Program National Data, and the Resident Statistical Summary (Report C).

The Resident Statistical Summaries (Report C) from 1990–2001 were obtained from the Residency Review Committee for Surgery. Report C lists the resident operative experience under 16 surgical categories. The reported gastric operative experience for all U.S. surgical chief residents was compiled and then analyzed. The data in these reports is organized by the indexed procedure (Table 1). Results are expressed as the average number and range of operations performed per chief resident and the percentage (%) of total gastric operative cases.

RESULTS

It is important to note that the total number of chief residents has slightly increased whereas the number of U.S. general surgery residency programs has decreased over the last 10 years resulting in an increase in the average number of chief residents being trained per program (Fig. 1). Also, it is not until the year 1994 that laparoscopic cases were recorded by the Resident Statistical Summaries (Report C).

Table 1. The current list of U.S. surgical chief resident index procedures under Report C gastric surgical category

Chief resident index procedures
Gastrostomy—open
Gastrostomy—laparoscopic
Gastric resection—partial, open
Gastric resection—partial, laparoscopic
Gastric resection—total
Vagotomy—open
Vagotomy—laparoscopic
Proximal vagotomy—open
Proximal vagotomy—laparoscopic
Repair of perforation—gastric disease
Gastric reduction procedure—morbid obesity
Other major gastric procedure

Over the interval reviewed, the average reported gastric index cases reported per chief resident ranged from 9.8–12.5 with a peak in 1990 and a nadir in 1999; in 2001 the reported case average was 11.3 (Fig. 2). The 12-year average gastric cases per resident was 10.8. Table 2 displays the relative contribution of each separate index case category to the overall average number of gastric cases performed by chief residents for each year. Gastrostomy averaged 1.7 (range 1.2–2.2) whereas the laparoscopic gastrostomy case average was 0.25 with a range from 0.2–0.3. Gastrostomy procedures remained relatively constant at 17% of all index cases from 1990–2001 (Fig. 3). Partial gastric resection (PGR) was unchanged at an average of 3.0 per chief resident (range 2.7–3.4); laparoscopic PGR was less than 0.1 per chief resident (range 0–0.3).

Laparoscopic PGR accounted for 10% of the procedures performed in 2001. The percentage of all types of gastric resections slightly diminished from 34% in 1990 to 29% in 2001. Total gastrectomy remained a constant at less than 1.0 per chief resident (range 0.6–0.8) (Fig. 4). Vagotomy averaged 1.9 (range 1–3) and laparoscopic vagotomy averaged less than 1.0 per chief resident with a range of 0–0.1. Interestingly, the percentage of all index gastric cases that were vagotomy-gastric procedures (open and laparoscopic) decreased from 24% in 1990 to 7% in 2001 (Fig. 5). Gastric reduction operations averaged 1.5 cases per chief resident with a range of 0.6–3.8 cases per chief resident. The percentage of gastric-reduction operations increased dramatically from 5%–34% of all index cases over the interval (Fig. 6).

DISCUSSION

U.S. surgical chief residents report a widely variable experience in gastric surgery over the period analyzed. The variability in operative experience is likely a function of individual training program strengths and referral patterns. The average of all index cases reported by a chief resident caseload suggests that overall gastric surgical experience has remained relatively constant over the 12 years studied. Hence, the first tenet of our hypothesis that a significant reduction in gastric procedures had occurred over the period examined was incorrect. Unfortunately, data for the preceding decade (1980–1990) is not available. The impact of medical therapies in the treatment of benign gastric disease requiring operation (ulcers) would most likely have been apparent several years after the introduction of H2 receptor inhibitors and identification of *H. pylori* as a causative pathogen, that is, the late 1970s and mid-1980s,

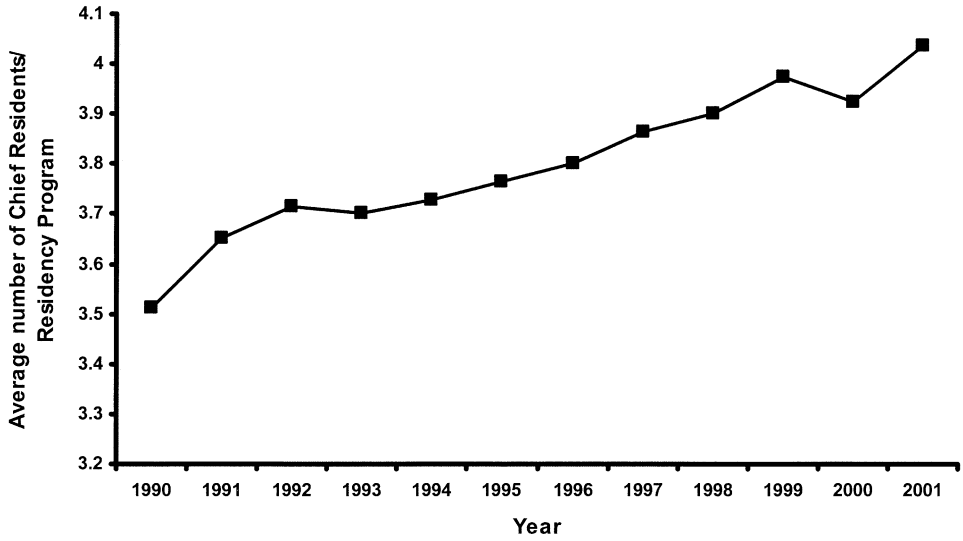

Fig. 1. The average number of U.S. surgical chief residents being trained per program for each year from 1990–2001.

respectively.[4,5] When a chief resident's case experience is evaluated by method (open vs. laparoscopic), it is notable that during the interval reviewed, laparoscopic gastric resection procedures were not a contributory component of the chief resident's case experience.

Gastrostomy is one of the fundamental surgical procedures, but over the decade reviewed, the average chief resident only reported approximately 2.0 gastrostomy procedures. The laparoscopic gastrostomy technique does not seem to have had a significant impact on this case experience, because the average laparoscopic caseload reported was less than 0.3 cases. This is a notable issue on its own because gastric access is perceived as a common procedure and it is likely that the emergence and rapid adoption of percutaneous endoscopic gastrostomy (PEG) and other percutaneous-type gastrostomy techniques had already supplanted the surgical approach by 1990. The introduction of the PEG-tube procedure introduced by Gauderer occurred in 1980[6] and to validate our assumption that endoscopic procedures altered resident case experience would similarly require unavailable data from the previous decade.

The authors recognize that the inherent limitations of this study likely precluded the potential

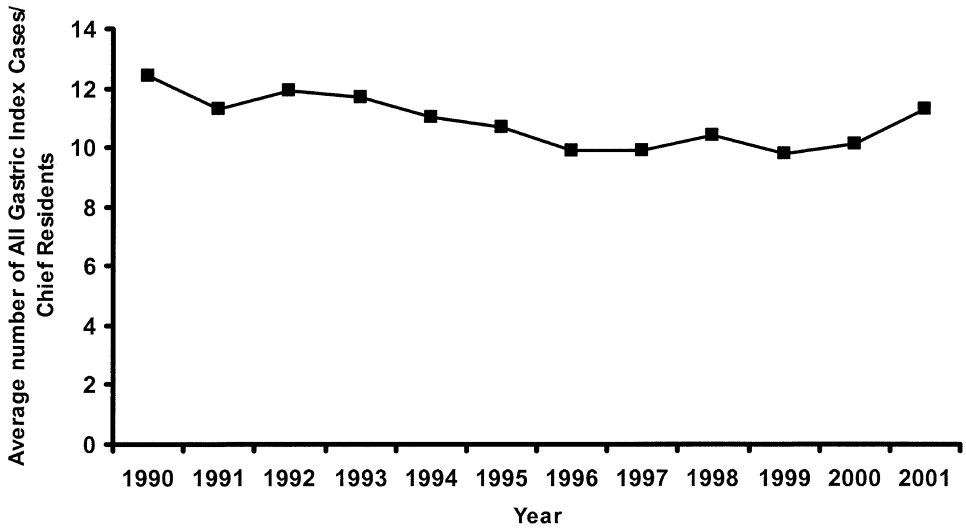

Fig. 2. The average reported gastric index cases reported per chief residents for each year from 1990–2001.

Table 2. The reported U.S. surgical chief resident operative experience of each separate index case category performed for each year from 1990–2001

	Average number of cases per chief resident											
Chief resident index procedure	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Gastrostomy—open	2.2	1.9	2.1	2.1	1.7	1.5	1.5	1.6	1.6	1.3	1.3	1.2
Gastrostomy—laparoscopic					0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3
Gastric resection—partial, open	3.4	3	3.3	3.3	3.1	3.3	2.9	2.9	2.9	2.7	2.6	2.7
Gastric resection—partial, laparoscopic					0	0	0.1	0.1	0	0.1	0.1	0.3
Gastric resection—total	0.8	0.8	0.9	0.9	0.8	0.8	0.8	0.7	0.6	0.6	0.6	0.6
Vagotomy—open	3	2.8	2.6	2.7	2.4	2.2	1.7	1.5	1.2	1	0.9	0.8
Vagotomy—laparoscopic					0	0	0.1	0	0	0	0	0
Proximal vagotomy—open	0.5	0.4	0.4	0.3	0.3	0.3	0.2	0.1	0	0.1	0.1	0
Proximal vagotomy—laparoscopic					0	0	0	0	0	0	0	0
Repair of perforation—gastric disease	0.8	0.8	0.9	0.9	0.9	0.9	0.9	1	0.9	0.7	0.7	0.7
Gastric reduction procedure	0.6	0.6	0.7	0.8	0.9	1	1.1	1.2	1.9	2.3	2.8	3.8

identification of a marked and significant reduction in gastric surgery experience for chief residents. These limitations are in great part associated with the noted developments in patient care (i.e., medical nonsurgical management of gastric ulcer and endoscopic facilitated gastric access procedures) as well as the unavailability of the residency review committee (RRC) statistical data before the interval was analyzed.

The average number of partial gastrectomies reported by chief residents was relatively unchanged over the interval studied and laparoscopy accounted for less than 0.5 cases per chief resident in the years 1994–2001. Although gastric malignancy has remained a persistent problem in the U.S., with specific patient populations actually demonstrating an increased incidence, the chief resident's experience with total gastrectomy has remained relatively constant and low.

Perhaps most notable from this evaluation was the observation that vagotomy in all its forms (proximal or selective, open or laparoscopic) has, in essence, ceased to be an operation performed by chief residents. Interestingly, evidence to suggest that this present trend in resident experience might occur was noted

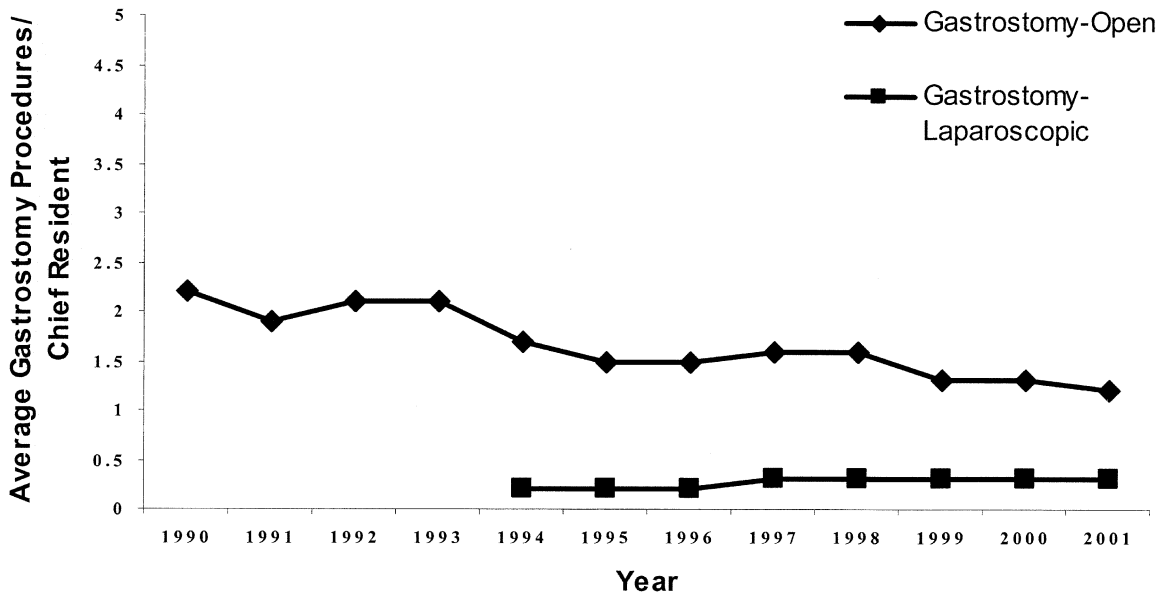

Fig. 3. The average reported number of gastrostomy procedures performed by U.S. surgical chief residents for each year from 1990–2001.

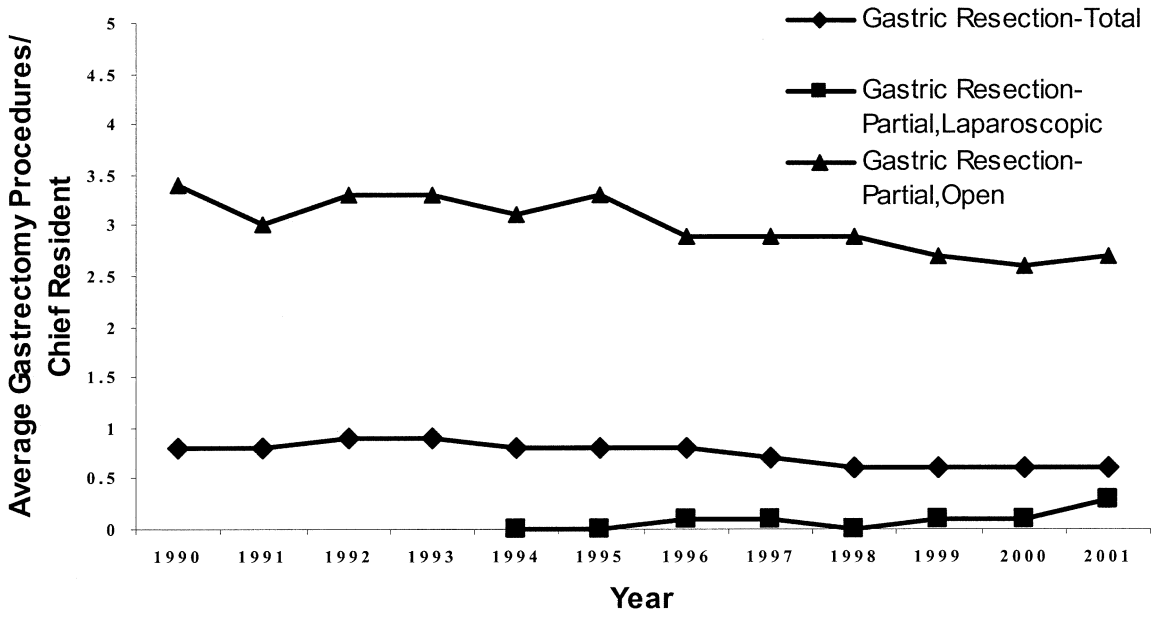

Fig. 4. The average reported number of gastrectomy procedures performed by U.S. surgical chief residents for each year from 1990–2001.

several years ago.[7] At present, there are no defined criteria by which to measure the technical competence of graduating residents at performing any specific procedure. Resident experience is presented in the annual RRC report as individual resident cases, percentile rank by comparison to other residents in the same residency program, and to a national statistical experience. Although this method is useful for descriptive comparative review, for specific procedures, such as gastrectomy, where the program and national resident experience may be minimal, the only conclusions that can be inferred are how exposed

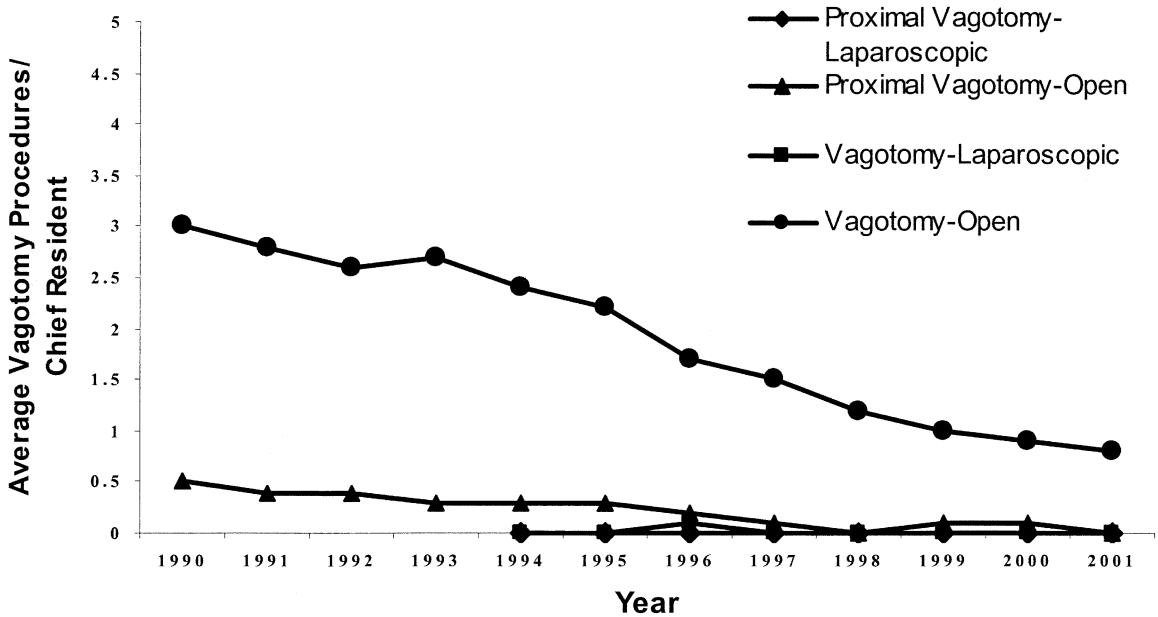

Fig. 5. The average reported number of vagotomy procedures performed by U.S. surgical chief residents for each year from 1990–2001.

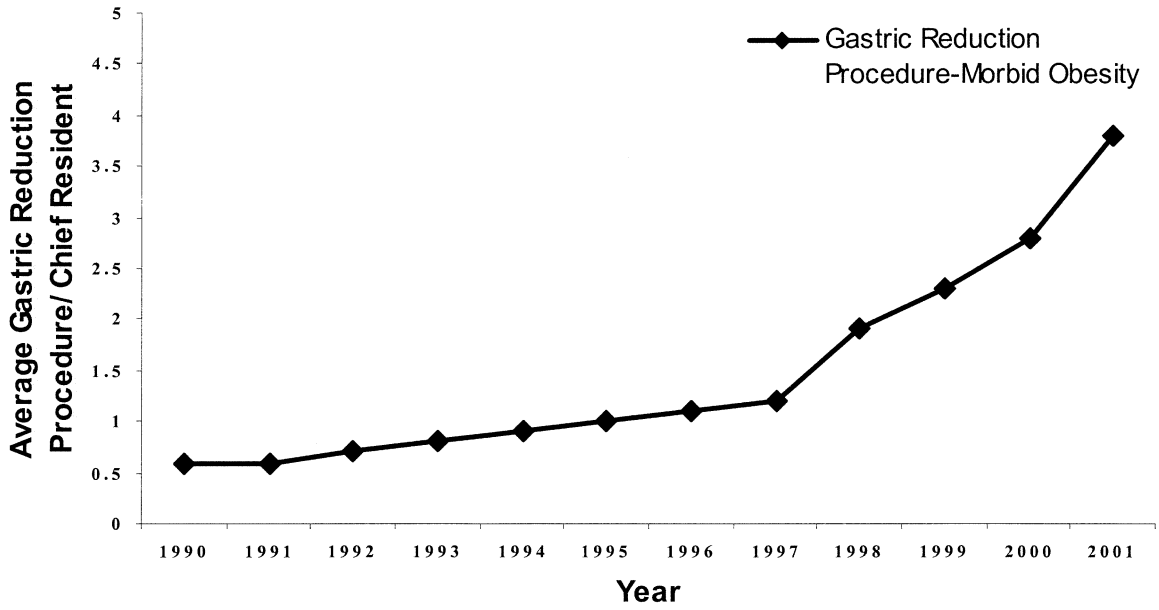

Fig. 6. The average reported number of gastric reduction operations performed by U.S. surgical chief residents for each year from 1990–2001.

any resident or any group of residents are relative to some annual benchmark. Factual competence is measured by the written "qualifying" portion (part 1) of the American Board of Surgery (ABS) exam and "judgment" competence is assessed by the "oral" portion (part 2) of the ABS exam.

Within this context, the data from the present report can be employed to describe the patterns of the surgical chief residents' procedural experience and to highlight where future deficits may arise for general residency programs, which are potentially a factor of significantly less procedural volume with a specific type of procedure. In sharp contradistinction to the disappearance of vagotomy there has been an explosive increase in the number of gastric-reduction procedures. Gastric reduction for morbid obesity had, in the past, been performed by specialized centers with surgeons having a specific interest in this disease. However, market forces and rapidly developing instrumentation that allow for this procedure to be performed laparoscopically[8] have likely been fundamental in the noted dramatic increase of this procedure in the chief residents' experience.

It is important to clarify that the data herein presented and our analysis of these data do not imply or support any equivalence for the replacement of gastrectomy procedures by gastric reduction/bypass procedures in the training of general surgery residents. The fundamental observation to be made is that whereas specific procedures (i.e., vagotomy) have all but disappeared, different operations have replaced this component of resident operative volume. This substitution of a set of procedures by another is likely a reflection of changing clinical disease patterns and population demands.

In the last quarter century, several nonoperative treatment strategies seem to have contributed to the reduction in gastric operations, most notably for the treatment of benign gastric ulcer disease. These findings have significant potential future impact on the care of patients because surgical intervention will still be necessary, albeit with reduced frequency.[9] Specifically affected may be patients with gastric ulcer disease unrelated to either *H. pylori* and acid secretion,[10] those with ulcer-related gastric strictures,[11] patients with refractory acid production for whom vagotomy procedures may be necessary,[12] and those for whom an initial operation has been unsuccessful.[13] Thus, an important component for preparing current residents during residency training will require that we recognize that experience in specific gastric procedures is diminishing and that during residency training, specific attention is placed on providing operative opportunities to emphasize different anatomic and technical facets of gastric surgical procedures.

As presented, the noted increase in resident-reported gastric-reduction procedures, driven by rapidly improving instrumentation and patient demands for this approach, would suggest that residents would be adequately trained during residency for these laparoscopic gastric procedures. However, at the present time, significant numbers of graduating residents

pursue additional training in laparoscopic or foregut surgery and the demand for additional post-residency training has led to a substantial increase in the number of laparoscopic fellowships available in the last 5 years. Despite the increased number of fellowships available, this past year an average of 20 applicants vied for each available fellowship position.

There is no data to support an objective difference in the technical acuity necessary to perform open gastric surgery compared with laparoscopic gastric surgery. Similar to the historical appreciation (albeit arbitrarily) that a partial gastrectomy was a technically less complex procedure than total gastrectomy—a description loosely based on parameters such as length of procedure, potential complications, etc.—the more frequently performed laparoscopic procedures in the present day have been classified as laparoscopic and "advanced laparoscopic." Examples of laparoscopic procedures would include appendectomy or cholecystectomy, whereas advanced laparoscopic procedures represent operations such as laparoscopic gastric bypass, Heller myotomies, and adrenalectomy, for example.

A general observation that can be made about who performs these advanced procedures within residency training programs is that they are being performed by "attending level" physicians and their specialty fellows, in essence, "stealing" the actual case experience from chief residents and essentially relegating the chief residents to perioperative care of the patient. There is no data to specifically support this hypothesis, however, the stringent qualifying credentials beyond general surgical residency training needed to obtain clinical privileges to perform these operations requires demonstrated experience or fellowship training, leaving a potential void for the nonspecialty fellow resident physician.

Public and hospital demands for improved surgical outcomes are thought to be a contributing factor for the rapid explosion in surgical specialty fellowship positions presently available. However, whereas the volume of procedures performed at institutions with fellowship training slots is likely to increase in coming years, for the above summarized observations, it is unlikely that graduating chief residents will increase their operative experience.

Again, we must clarify that these added requirements are not limited to laparoscopy. In fact, several surgeon hospital volume/outcome studies have suggested that complex operations (e.g., pancreaticoduodenectomy or hepatectomy) require specific surgeon and institution experience to optimize patient outcome. The implications for this can be appreciated by the recent formation of the American Hepato-Pancreato-Biliary Association (AHPBA), the Society for Surgery of the Alimentary Tract (SSAT), and the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) initiative to standardize specialty training in "foregut surgery." With further expanding fellowship opportunities, particularly those based at institutions with general surgery residencies, the experience for the resident would be expected to be negatively impacted.

These observations and many more outside the scope of the present report have been cited as fundamental evidence for the need to "track" residents into career training slots early in their residency to maximize operative experience for those pursuing a general surgical career and provide residents pursuing other specialty careers a similar option. This concept has met with divided opinion among American surgical leadership.

We further recognize that these observations are within the context of another significant new force, that is, the mandated 80-hour work week for residents—the effects of which will be unknown for several years. As we have outlined, the types of gastric surgery that will continue to prevail in the nonoperative era of benign gastric ulcer disease will be of an urgent nature, likely presenting as emergencies. Thus, an already limited experience may become even further diluted by the "luck of the draw" as to which resident participates in said operative procedures.

CONCLUSIONS

Surgical resident operative experience is a dynamic process changing in concert with the needs of the population. Continuous analysis of these data is necessary for training programs to define the requirements and structure of general surgery training.

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Prospective Evaluation of Biliopancreatic Diversion With Roux-en-Y Gastric Bypass in the Super Obese

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The aim of this study was to determine prospectively the efficacy and safety of the biliopancreatic diversion with Roux-en-Y gastric bypass (BPD with RYGBP) procedure used as the primary bariatric procedure in super obese patients. The main characteristics of the BPD with RYGBP procedure were a gastric pouch of 15 ± 5 ml, biliopancreatic limb of 200 cm, common limb of 100 cm, and alimentary limb of the remainder of the small intestine. From June 1994 through July 2003, 132 super obese patients (body mass index [BMI]: 57 ± 7), with an incidence of comorbidities 6 ± 2 per patient, underwent BPD with RYGBP and subsequent follow-up. Mean follow-up time was 29 ± 14 months. Maximum weight loss was achieved at 18 months postoperative with average excess weight loss (EWL) 65%, average initial weight loss (IWL) 39%, and average BMI 35 kg/m^2. Thereafter, a decline was observed with EWL stabilizing at around 50%, IWL at around 30%, and BMI at around 40 kg/m^2, respectively, by the end of the study period. The majority of preexisting comorbidities were permanently resolved by the 6-month follow-up visit. Early mortality was 1% and early morbidity was 11%. Late morbidity was 27%, half of which was due to incisional hernia. Deficiencies of microelements were mild and successfully treated with additional oral supplementation. The incidence of hypoalbuminemia was 3% and there were no hepatic complications. We conclude that BPD with RYGBP is a safe and effective procedure for the super obese with few metabolic complications. (J GASTROINTEST SURG 2004;8:479–488)

KEY WORDS: Morbid obesity, super obesity, biliopancreatic diversion, distal gastric bypass, malabsorption

INTRODUCTION

Surgical treatment remains the only effective approach for the long-term management of morbid obesity.[1] Bariatric operations have been defined as restrictive, malabsorptive, or a combination of both.[2] Super obesity has a more complicated clinical course following surgery, attributable to increased comorbidity, and a significant long-term failure rate associated with restrictive bariatric operations.[3] Many investigators suggest that surgical procedures in which malabsorption is the main component will result in better maintenance of weight loss and increased rate of success.[4,5]

It is generally accepted that biliopancreatic diversion (BPD) refers to a pathophysiological change based on an anatomic arrangement within the gastrointestinal (GI) tract that diverts bile and pancreatic secretions from their usual anatomic paths and not to a specific operation, thus BPD can be achieved in different ways.[4] Weight loss maintenance after these operations is primarily due to intestinal malabsorption.[5] In fact, the long-term weight loss results are remarkable; however, this is at the expense of a considerably high rate of metabolic complications.[6,7] The main representatives of malabsorptive procedures are the Scopinaro type BPD[6] and the duodenal switch modification described by Hess.[8] In addition, several forms of "distal gastric bypass" have been described. Actually, these procedures are modifications of the standard Roux-en-Y gastric bypass, where the mixing of bile and pancreatic juice with food takes place more distally in the jejunum or the terminal ileum with various lengths of intestinal limbs.[5,7,9–11].

A particular type of BPD procedure is performed at our institution in an attempt to achieve acceptable weight loss results and resolution of comorbidities

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without the high rate of metabolic complications reported for other types of biliopancreatic diversion. The aim of this study is to report the effectiveness, complications, and long-term results of this surgical approach specifically in the super obese patient population.

MATERIALS AND METHODS

From June 1994, when the Morbid Obesity Clinic of the Department of Surgery was established at the University Hospital of Patras, through July 2003, 353 morbidly obese patients have undergone various bariatric procedures at our institution. In this study we present our experience with the use of biliopancreatic diversion with Roux-en-Y gastric bypass (BPD with RYGBP) in a super obese population.[12] From our bariatric database, the prospectively collected follow-up data of 132 super obese patients (BMI $\geqslant$ 50) who underwent biliopancreatic diversion with Roux-en-Y gastric bypass (BPD with RYGBP) were selected and studied. The patients' preoperative characteristics are shown in Table 1. Whenever a revision bariatric procedure was performed, follow-up results from these patients were not included thereafter in the study. A multidisciplinary team, including the surgeon, an endocrinologist, a cardiologist, a pneumonologist, a psychologist, and a nutritionist-dietitian, evaluated all patients preoperatively and postoperatively to assess and optimize their physical condition.

Surgical Technique

The main characteristics of the BPD with RYGBP procedure were a gastric pouch of 15 $\pm$ 5 ml, a biliopancreatic limb of 200 cm, a common limb of 100 cm, and an alimentary limb of the remainder of the small intestine. A detailed presentation of the procedure is as follows: under general and epidural anesthesia the abdomen was entered via a midline abdominal incision from the xiphoid process to just below the umbilicus. The small intestine was divided 200 cm distal to the ligament of Treitz with a linear stapler gastrointestinal anastomosis (GIA) (Tyco Healthcare, USSC, Norwalk, CT) using a 2.5-mm stapling cartridge thus forming the biliopancreatic limb. The jejuno–ileal enteroenterostomy was constructed 100 cm from the ileocecal valve with a linear stapler GIA in a side-to-side fashion creating a common channel of 100 cm. The mesenteric window was closed with 2-0 absorbable sutures. After mobilization of the gastroesophageal junction, a vertical 4-cm long pouch of 15 $\pm$ 5 ml was created at the lesser curvature of the stomach using a twice-fired TA90B (Tyco Healthcare) superimposed without complete anatomic separation from the bypassed gastric remnant.

Before the stapler was fired, the capacity of the pouch was measured by infusing 15 ml saline solution into it at a pressure of 70 cm H_2O. By the end of the first year, 5 of the first 69 patients had developed partial staple dehiscence (7%), thus creating a gastro–gastric fistula. For this reason, in the remaining 63 patients of the present study, and in all patients thereafter, the gastric pouch was transected from the bypassed distal stomach with the use of EndoGIA staplers (Tyco Healthcare) and the Roux-Y limb interposed between the pouch and the bypassed stomach. In these patients the volume of the gastric pouch was visually estimated. The Roux-Y jejunal limb was brought through an opening in the transverse mesocolon, positioned in a retrogastric location, and an end-to-side anastomosis was performed between the gastric pouch and the jejunum using a single layer of running absorbable sutures polydioxanone (PDS) 3-0, creating an internal stoma of 1.5 cm. The defect in the transverse mesocolon was closed with a running 2-0 absorbable suture. A silastic round site marker was placed on the anterior wall of the gastric remnant and secured on the anterior abdominal wall (Fig. 1). A closed-suction drain was positioned near the gastro–jejunal anastomosis.

Cholecystectomy was always added to the main procedure. Appendectomy was also routinely performed at the time of the main procedure to exclude the possibility in the future of confusing right-quadrant colicky pain due to lipid malabsorption with appendicitis. Furthermore, because fatty liver and nonalcoholic steatohepatitis are common in the super obese, liver biopsy was routinely performed to assess preoperative liver histopathology to be used as a baseline for comparison if a problem in hepatic function should arise in the future. The fascia of the abdominal wall was closed using continuous running double-stranded PDS-1 suture starting at both ends of the

Table 1. Preoperative patient characteristics

	BPD with RYGBP
Number of patients	132
Sex (male/female)	34/98
Age (years)	36 $\pm$ 10
Height (cm)	164 $\pm$ 9
Weight (kg)	156 $\pm$ 25
Excess weight (kg)	95 $\pm$ 21
BMI (kg/m^2)	57 $\pm$ 7 (range: 50–85)

BMI = body mass index.

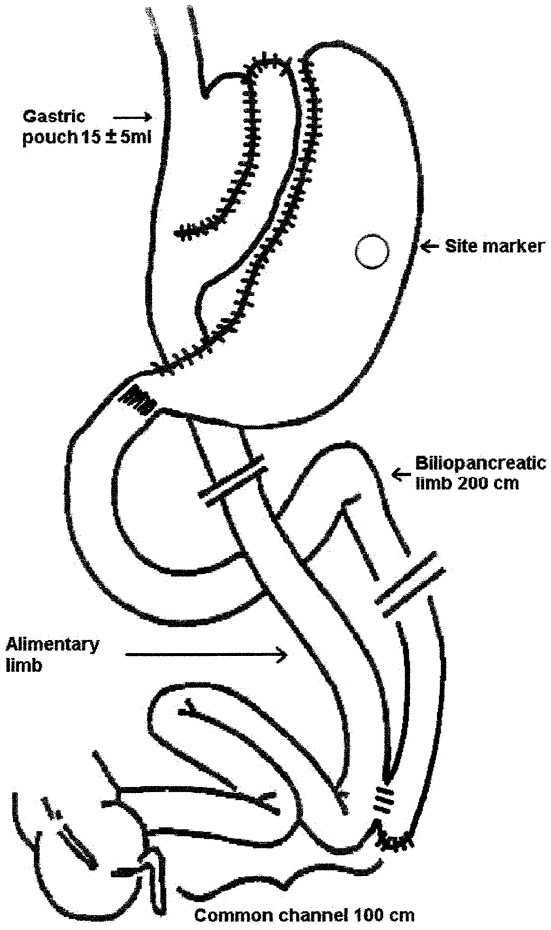


Fig. 1. Diagram of biliopancreatic diversion with Roux-en-Y gastric bypass procedure.

wound and tied in the middle. Nonsubcutaneous sutures or drains were used. The skin was closed with staplers. Perioperatively, a second-generation cephalosporine and metronidazole were prescribed. Low molecular weight heparin (nadroparin 9500 IU anti-Xa) was administered subcutaneously daily and sequential compression devices were used perioperatively.[13]

Postoperative Dietary Management

All patients underwent extensive nutritional counseling by our team's dietitian and followed a specific dietary protocol. On the fourth postoperative day, after uneventful upper GI radiologic evaluation, a liquid diet was started which was progressively increased to include blenderized foods before hospital discharge. Over the next 4–6 weeks, patients were gradually advanced to a more varied soft diet until regular foods were tolerated. During this time, all patients received high-protein dietary supplements. After surgery all patients also received a daily multivitamin and mineral supplement and two grams of calcium. No additional fat-soluble vitamin supplementation was given other than that included in the multivitamin supplement prescribed to all patients which contained 4000 IU of vitamin A, 400 IU of vitamin D, and 10 mg of vitamin E. An oral iron supplement was prescribed for all premenopausal women at a dose of 80 mg/day. Starting at 6 months postoperatively, vitamin B_{12} supplementation was given intramuscularly (IM) at a dose of 1000–3000 μg, as necessary, depending on measured values.[14]

Postoperative Follow-up and Evaluation

Complete postoperative evaluation was performed at 1, 3, 6, 12, 18, and 24 months and yearly thereafter. Each follow-up visit included personal nutritional and medical evaluation by the team members and complete labs and evaluation by other medical personnel as necessary. In addition, at the first year follow-up visit a routine x-ray examination for staple-line disruption was performed in all patients and interim x-ray examinations were performed as necessary whenever there was clinical suspicion of disruption such as sudden unexplained weight gain.

STATISTICAL ANALYSIS

All the values presented are expressed as mean ± standard deviation, unless otherwise stated. Comparisons of observed values at various time periods during the study for cholesterol (CHOL), triglycerides (TRIG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose (GLU), and parathormone (PTH) were performed using one-way analysis of variance (ANOVA). When statistically significant differences were observed, the Tukey post-test was used for determination of the specific time points that contributed to this significance. All reported p values are two-sided and significant at a level of $p \leqslant 0.05$.

RESULTS

For all patients, except for two who had undergone adjustable gastric band (AGB) in the past, BPD with RYGBP was their first bariatric operation. During the procedure 204 additional abdominal procedures took place, the majority of them cholecystectomies (59%). The mean operative time was 205 ± 41 minutes. Two patients were admitted to the intensive care unit (ICU) postoperatively (2%), one for a 2-day period for application of continuous positive airway

pressure (CPAP) to treat hypoventilation syndrome and the other for 35 days due to multiple organ dysfunction after peritonitis due to leakage of the gastric remnant. The mean postoperative hospitalization time was 9 ± 6 days. The mean follow-up time was 29 ± 14 months. The rate of successful follow-up was 99% at 12 months, 99% at 18 months, 96% at 24 months, 93% at 36 months, 92% at 48 months, and 83% at 60 months. It should be emphasized that only 1 patient was lost completely to follow-up and that another patient, who lives permanently in Australia, had irregular follow-up. In four patients (3%) a revision bariatric procedure was performed and, in agreement with the study design, their subsequent follow-up results were not included in the analysis.

Weight Loss

Weight loss results at each time period expressed as actual weight, BMI, percentage of excess weight loss (EWL %), and percentage of initial weight loss (IWL %) are presented in Table 2. Maximum weight loss was achieved at 18 months postoperative with average EWL 65%, average IWL 39%, and average BMI 35 kg/m^2. Thereafter a decline was observed with EWL % stabilizing at around 50%, IWL % at around 30%, and BMI at around 40 kg/m^2. Further analysis of the distribution of EWL % and IWL % is illustrated in Fig. 2 *A*, *B*, respectively.

Comorbidities

The incidence of preexisting comorbidities was 6 ± 2 per patient. The majority of these were permanently resolved by the first 6 months postoperatively with the remaining showing significant improvement. The preoperative prevalence and postoperative percentage of resolution and improvement of clinically significant comorbidities are presented in Table 3.

Hypercholesterolemia (cholesterol > 200 mg/dl) was present in 59 patients preoperatively. In these patients mean preoperative cholesterol levels (243 ± 26 mg/dl) had decreased significantly ($p < 0.001$) by the first postoperative month (156 ± 26 mg/dl) and remained normal thereafter. Similarly, hypertriglyceridemia (triglycerides > 160 mg/dl) was present in the 36 patients preoperatively (226 ± 79 mg/dl). From the first postoperative month triglyceride levels in these patients were significantly lower than preoperative levels (161 ± 51 mg/dl, $p < 0.001$) and by the third month the mean value reached normal levels (128 ± 46 mg/dl). Also of interest is that mean HDL levels in all patients were significantly less than preoperative values up until 6 months postoperatively ($p < 0.001$), after which time they gradually increased reaching preoperative levels at 1 year and increasing progressively thereafter. This increase, however, did not reach statistical significance when compared to preoperative HDL levels.

There were 23 patients with diabetes (blood glucose >125 mg/dl) preoperatively. Of these patients, 18 were not on any type of medication either because they were unaware of the problem or because they were on conservative management with diet alone. Five patients were being treated with oral hypoglycemic agents (for a period of <5 years) and none were insulin dependent. Postoperatively, blood glucose levels had returned to normal in all patients by the first postoperative month and by the third month all 5 patients on oral hypoglycemic agents were able to discontinue treatment.

Complications

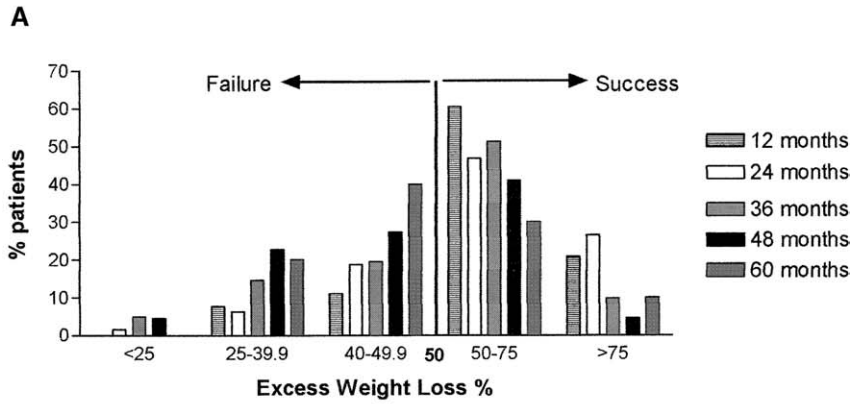
Intraoperative Complications. The only observed intraoperative complication that occurred was splenectomy, which was performed in, seven patients (5%) when conservative attempts to control hemorrhage from intraoperative injury to the spleen failed.

Early Mortality and Morbidity. There was one death that occurred in the early postoperative period (1%) in a patient who presented with peritonitis due to leakage of the gastric remnant on the second postoperative day. The patient died 35 days later in the ICU from multiple organ failure after three reoperations for abdominal sepsis.

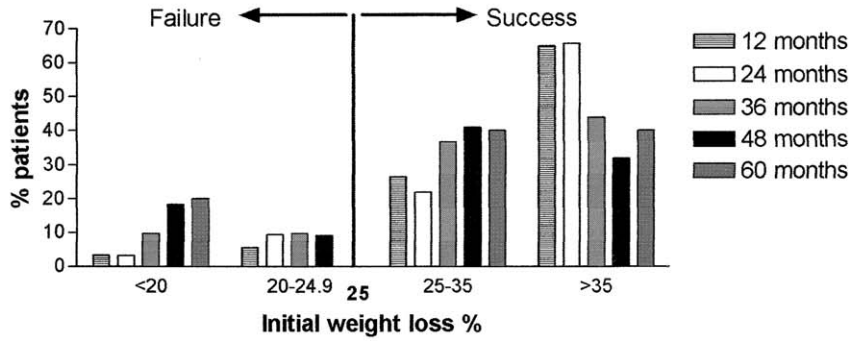
Table 2. Weight loss results

		Postoperative years (followed-up patients)				
	Preoperative	**1 (91)**	**2 (64)**	**3 (41)**	**4 (22)**	**5 (10)**
Weight	155 ± 25	95 ± 18	94 ± 16	99 ± 14	107 ± 15	111 ± 20
BMI	57 ± 7	35 ± 7	35 ± 6	37 ± 6	41 ± 7	43 ± 9
IWL %	—	38 ± 9	38 ± 10	33 ± 11	30 ± 10	32 ± 12
EWL %	—	63 ± 16	63 ± 16	57 ± 17	49 ± 16	50 ± 19
Patients (%) with ⩾ 50% EWL	—	81	73	61	45	40

BMI = body mass index; EWL = excess weight loss; IWL = initial weight loss.



Months	12	24	36	48	60
Patients (n)	91	64	41	22	10
EWL%			% patients		
<25	0	1	5	4	0
25-39.9	8	6	15	23	20
40-49.9	11	19	19	27	40
50-75	60	47	51	41	30
>75	21	27	10	5	10



Months	12	24	36	48	60
Patients (n)	91	64	41	22	10
IWL%			% patients		
<20	3	3	10	18	20
20-24.9	6	9	10	9	0
25-35	26	22	36	41	40
>35	65	66	44	32	40

Fig. 2. Graphs representing analytical distribution of (**A**) excess weight loss % (EWL %) and (**B**) initial weight loss % (IWL %). The values in the tables below the graphs represent the percentages of followed-up patients in each weight loss category at each study period.

The overall rate of early morbidity (<30 days postoperative) was 11% and is presented in Table 4. The most serious complications were the two cases of anastomotic leakage, associated with the gastrojejunal anastomosis, which were treated conservatively without need for reoperation. The subhepatic abscess, drained percutaneously under CT guidance, developed as a result of bile accumulation due to an accessory bile duct at the gallbladder bed not recognized at the time of surgery, which also included a cholecystectomy. Major postoperative lung atelectasis, which presented in four patients, was resolved bronchoscopically.

Late Mortality and Morbidity. No deaths occurred during the late postoperative follow-up period. The overall rate of late morbidity was 27% and the details are shown in Table 4. More than half of

Table 3. Incidence of comorbidities and their evolution postoperatively

Comorbidity	Incidence (% of the total)	Follow-up time period	Resolved (% of the diseased)	Improved (% of the diseased)	Without change (% of the diseased)
Hypertension	48 (63/132)	24 months	68	28	4
Diabetes mellitus	17 (23/132)	3 months	100		
Glucose intolerance	17 (22/132)	1 month	100		
Hypercholesterolemia	45 (59/132)	1 month	100		
Hypertriglyceridemia	27 (36/132)	3 months	100		
Sleep apnea	15 (20/132)	1 month		100	
Hypoventilation syndrome	4 (5/132)	1 month		100	
Pickwick Syndrome	4 (5/132)	1 month		100	
Obstructive pulmonary disease	22 (29/132)	3 months	97		3
Hyperuricemia	24 (32/132)	6 months	100		
Osteoarthritis	36 (48/132)	6 months		100	
Depression	9 (12/132)	12 months	20	40	40

these late complications were incisional hernias, which almost always occurred during the first postoperative year. The six patients who presented with small bowel obstruction all underwent surgical exploration. Of these, three were treated with adhesiolysis, two were treated with enterotomy and removal of food bezoars, and the last was treated with enterectomy of 80 cm of small intestine, which was necessary because of necrosis of the obstructed portion of the intestine. Disruption of the gastric partition with formation of a gastro–gastric fistula occurred in five patients. In three of these patients the stoma of the gastro–gastric fistula was smaller than 1 cm and they were treated conservatively. Two of the patients continued to have favorable weight loss results. The third, despite unfavorable weight loss results, did not opt for revision surgery. In the other two patients a fistula stoma of greater than 1 cm was discovered at 12 and 36 months postoperative, respectively. Both had ineffective weight reduction and both underwent conversion to a modified Scopinaro BPD. Another patient also underwent conversion to a modified Scopinaro BPD after resection of a stenotic Roux-Y limb, which was thought to have been caused by poor vascular perfusion. The two patients with stenosis of the gastrojejunal anastomosis were treated successfully with endoscopic dilatation. Diarrhea, defined as four or more loose stools per day, was not a major problem for most patients and there was a diminishing trend over the years. At the 12-month follow-up visit 8% of patients presented with diarrhea periodically and only 2% frequently. After this time there were no further complaints of frequent episodes of diarrhea. Fourteen patients (11%) presented anorectal complications during the entire follow-up period.

Table 4. Incidence of nonmetabolic postoperative complications

Complications	No. of patients	% of the total
Early (≤30 days)		
Anastomotic leakage	2	1.5
Subhepatic abscess	1	0.8
Evisceration	2	1.5
Incisional seroma	2	1.5
Pneumonia	4	3
Lung atelectasis (clinically significant)	4	3
Total	15	11
Late (>30 days)		
Incisional hernia	22	16.7
Small bowel obstruction	6	4.6
Gastro–gastric fistula	5	3.8
Stenosis of gastro–jejunal stoma	2	1.5
Stenosis of Roux-Y limb	1	0.8
Total	36	27

Metabolic Effects

Anemia. The mean rate of postoperative anemia (hemoglobin: men < 13.5 mg/dl, women <12.5 mg/dl) was 33%. For parameters correlated with anemia, the mean rates of postoperative deficiency were 13% for iron (<35 μg%) and 25% for vitamin B_{12} (<200 pg/ml). Additionally, the incidence of low ferritin levels (<9 ng/ml) was 20%. Folate deficiency did not occur at any time period during the study. The deficiencies were clinically mild, did not require transfusion, and were treated successfully with additional oral supplementation.

Calcium–Phosphorus Metabolism. Levels of calcium, phosphorus, and alkaline phosphatase (ALP)

remained within the normal range throughout the study, whereas parathormone (PTH) values, after an initial drop immediately after surgery, steadily increased. Starting at the 2-year follow-up period, mean values of PTH surpassed preoperative values and continued to increase over the years without, however, reaching statistical significance. The percentage of patients presenting with postoperative PTH values greater than 90 ng/l was 15% and oral supplementation with 1α-OH–D_3 was initiated at this time. No spontaneous bone fractures occurred during the course of the study nor were there any signs and symptoms of metabolic bone disease based on clinical observation and the parameters studied.

Hypoalbuminemia. The occurrence of hypoalbuminemia was evaluated at every time period during the study. Mean serum albumin levels were always in the upper range of normal. Only 4 patients (3%) presented with a serum albumin level below 3 g/dl at some time during follow-up. In 1 patient this occurred during the second postoperative year and was attributed to a very low dietary protein intake combined with an increased intake of fat causing diarrhea and therefore further protein malabsorption. The patient was hospitalized and received total parenteral nutrition for a three-week period and after further instruction and increased dietary protein intake there were no further complications or recurrence of the problem. Another patient experienced two episodes of hypoalbuminemia during the first and second postoperative year, both of which were treated successfully with a 3-week course of total parenteral nutrition. However, during the third postoperative year there was a recurrence of hypoalbuminemia and the decision was made to perform revision surgery with elongation of the common channel to 250 cm at the expense of biliopancreatic limb. This was the only case where revision surgery was necessary because of hypoalbuminemia, an occurrence rate of 1%. In the remaining two patients hypoalbuminemia occurred during the first postoperative months as a result of total patient noncompliance resulting in an extremely low dietary protein intake. Both patients were hospitalized and underwent placement of tube gastrostomy through the silastic site-marker under CT guidance and the hypoalbuminemia was resolved by the administration of high-protein enteral nutrition supplements.

DISCUSSION

Surgery is the only therapeutic option that offers permanent weight loss results in most morbidly obese patients.[15] Because of the high rate of weight loss failure following gastric restrictive operations,[3,9] malabsorptive procedures are increasingly being performed all over the world.[16] Weight loss maintenance after procedures such as biliopancreatic diversion and the duodenal switch is primarily due to intestinal malabsorption.[6,8,17]

Similarly it has been reported that standard RYGB does not provide sufficient long-term weight loss in many super obese patients.[3,18] Adding malabsorption of macronutrients by elongating the Roux limb has proven satisfactory in weight control in this particular subgroup of patients.[5,7,9–11] There are only a small number of reports available in the literature regarding the use of different limb lengths in an attempt to increase the success rate in these patients.[5,7,9–11] To the best of our knowledge, the present study is one of the largest series to date of super obese patients treated with the same malabsorptive bariatric procedure with a thorough and very successful follow-up, which is greater than 80% throughout the 5-year study period.

Three digestive components contribute to weight loss in malabsorptive procedures: the volume of the functional stomach, the length of the common channel, and the length of the alimentary limb.[19,20] Fat is essentially absorbed in the common channel, but the digestion/absorption of protein and complex starch depends mainly on the total intestinal length from the gastroenteroanastomosis to the ileocecal valve. Alterations in functional gastric volume and intestinal limbs correlate with weight loss, its maintenance over time, and the occurrence of metabolic complications.[17,19,20] This study presents our experience in an exclusively super obese population using the particular biliopancreatic diversion procedure described above. This bariatric procedure is a malabsorptive procedure as a portion of the gastrointestinal tract—the 200 cm biliopancreatic limb—is excluded from digestion. Early weight loss is initiated by the small gastric pouch, which causes early satiety and anorexia.[21] Simultaneously, the entrance of nutrients directly into the jejunum, in addition to causing activation of the dumping effect, further promotes satiety and anorexia via chemical and mechanical receptors of the small intestine[21] and alterations in the secretion of gastrointestinal hormones.[21–23] After the first 6 postoperative months anorexia subsides, the dumping effect essentially disappears, and patients no longer experience significant limitations in food intake. From this time on, malabsorption becomes the main component of further weight loss and weight loss maintenance, although a relative increase in resting energy expenditure may also play an adjuvant role.[19,21,24] Generally, patients are able to eat a regular diet in desired

amounts with special attention paid to avoiding fibrous foods, which can lead to the formation of food bezoars and small bowel obstruction. Patients are also advised to avoid simple sugars and alcohol consumption as these calorie-rich non-nutritive substances are completely absorbed and may lead to a less successful outcome in terms of weight loss. However, the weight loss is still sufficient to achieve long-term improvement in preexisting comorbidities.

The construction of the small gastric pouch, initially measured to be 15 ± 5 ml, is based on that described in previous reports.[12] Transection of the gastric pouch from the bypassed stomach, the volume of which from that time on was visually estimated, and the interposition of the Roux-Y limb between the pouch and the gastric remnant are also performed as previously described.[25,26] This resulted in elimination of the problem of gastro–gastric fistula. The avoidance of distal gastrectomy, which has its potential complications, makes the operation reversible. The addition of the silastic site-marker on the gastric remnant[26] makes it possible to perform an upper GI radiologic or endoscopic investigation or to create a gastrostomy for nutritional support, as was needed in 2 patients with refractory hypoalbuminemia. Because a small gastric pouch with small common channel and alimentary limb has been reported to result in significant mortality and morbidity,[7,27] we decided to combine a small gastric pouch with a longer common channel and alimentary limb in an attempt to decrease metabolic sequelae even though this would mean a compromise in terms of weight loss.

As shown in Table 3, the mean percentage of excess weight loss (EWL %) was maintained at around 50% through the fifth postoperative year, whereas the mean percentage of initial weight loss (IWL %) was always greater than 30%. Upon closer analysis of EWL %, as shown in Fig. 2, it can be seen that although a large number of patients were below 50% and would therefore be considered failures, the majority of them were able to maintain EWL % greater than 40%, which may be acceptable in this patient population. Superior weight loss results have been reported following biliopancreatic diversion with distal gastrectomy and duodenal switch; however, the published reports contain mixed populations of both the morbidly and super obese.[6,17,28,29] Therefore, results are difficult to interpret. Studies reporting exclusively on super obese patients are few. In one such study, Hess et al.[8] presented very good long-term weight loss results following BPD with duodenal switch in a super obese subpopulation. Other authors have reported similar or even better weight loss results in the super obese following other malabsorptive procedures.[5,7,10,11] However, the results are hard to evaluate because the procedures are different in terms of common channel, alimentary, and biliopancreatic limb lengths. Furthermore, the number of patients in these series is smaller than in the present study and the follow-up is inadequate and often not carried out on a personal basis.[7,10]

It is well known that super obesity, due to increased comorbidity, has a more complicated clinical course than morbid obesity.[9] In our study as well as in others, the incidence of preexisting comorbidities is very high in this patient population and the primary goal of bariatric surgery in the super obese should be the resolution or improvement of comorbidities rather than the achievement of normal body weight.[30] It has been reported that a reduction of 10–20% of initial weight is sufficient for the resolution of comorbidities.[31,32] It has also been proposed that a more realistic goal of bariatric surgery in this population may be the long-term maintenance of 50% EWL or 25% IWL, which will ensure the resolution of most comorbidities without serious metabolic complications.[30] Based on the above observations, it is our opinion that the weight loss provided by our procedure can be considered acceptable in the super obese population. In agreement with results described by others,[8,17,19] in our patients the majority of preexisting comorbidities were permanently resolved or improved by the sixth postoperative month. As with other malabsorptive bariatric procedures, hypercholesteremia and hypertriglyceridemia, as well as glucose intolerance, were resolved from the first postoperative months, even though significant weight loss had not yet been achieved.[6,8] The potential of gastric bypass and biliopancreatic diversion in the treatment of diabetes mellitus type II has been described in detail in recent papers.[32–35]

Early mortality and morbidity were low and comparable to that found in other series.[5,10,17] Late morbidity was also comparable to that reported by others,[5,10,17,19] most of which was due to incisional hernia (17%). An interesting feature of our procedure was the absence of stoma ulcers in contrast to results reported by others.[5,6,36] The explanation for this may be the absence of acid-producing cells in the small gastric pouch near the esophago–gastric junction, which could also be the reason for the greater deficiency of vitamin B_{12} observed in our study as compared to others.[5] In general, metabolic deficiencies are common after malabsorptive procedures; however, the percentage of metabolic deficiencies in our study was much smaller than that following biliopancreatic diversion with distal gastrectomy[19] or duodenal switch.[8,17] Metabolic deficiencies encountered in our study were more similar to those seen following

various types of "distal gastric bypass"[5,10] and, based on our own experience, similar to those found after the standard RYGBP.[14] All of the deficiencies encountered were mild and easily corrected with additional oral supplementation. Calcium deficiency, which has been stated in other reports,[5,8,17,19] did not occur, whereas postoperative measurements of calcium, phosphorus, and alkaline phosphatase were always within the normal range. Starting at the 2-year follow-up period, mean values of PTH surpassed preoperative values and continued to increase over the years. However, the increase when compared to preoperative values did not reach statistical significance. Oral supplementation with 1α-OH–D_3 was prescribed for the patients who presented postoperative PTH values greater than 90 ng/l. It must be noted that levels of fat-soluble vitamins were not measured and, therefore, comments cannot be made based on the present study. However, no clinical symptoms of deficiency were observed and despite the fact that vitamin K is not contained in the multivitamin supplement prescribed, no patients presented with increased prothrombin time. Diarrhea was also not a major problem. It occurred in a smaller percentage of patients than has been reported by others[6,7] and was always resolved by the first postoperative year. The incidence of hypoalbuminemia was also very low in our series (3%). Furthermore, in only one patient (1%) was it necessary to perform revision surgery due to refractory hypoalbuminemia. This is in contrast to higher percentages reported for other types of BPD procedures.[7,10,19,27] The longer total alimentary limb and the lower incidence of diarrhea could explain this difference. Finally, in contrast to the reports of others,[7,27] no patient experienced liver failure or cirrhosis.

Overall, metabolic complications were relatively rare in our patients, therefore justifying the less impressive weight loss results. It is our opinion that weight loss should not be viewed as the ultimate measure of success, but only as a part of the total picture with the main focus on reduction in morbidity and mortality and improvement in quality of life.[37] On the other hand, the risk of metabolic complications after this type of malabsorptive bariatric procedure does exist, and, therefore, close medical and nutritional follow-up, as well as full patient compliance are essential to its overall success.

CONCLUSION

Biliopancreatic diversion with Roux-en-Y gastric bypass as performed at our institution is an effective and safe surgical procedure for the treatment of super obese patients. Constructing a biliopancreatic limb of 200 cm and a common channel of 100 cm of the terminal ileum combined with a very small gastric pouch achieves acceptable weight loss maintenance, resolution of comorbidities, and significant improvement in quality of life without significant metabolic or nutritional complications. We recommend BPD with RYGBP as a primary procedure for super obese patients (BMI $\geqslant$ 50) with severe preexisting comorbidities and as a revision procedure for failed previous restrictive operations provided that the patients are well-educated and informed regarding the need for lifetime medical follow-up.

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Pneumoperitoneum From Gas Gangrene of the Pancreas: Three Unusual Findings in a Single Case

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A 62-year-old man was first seen with acute pancreatitis with diffuse intrapancreatic gas and pneumoperitoneum. An immediate exploratory operation revealed diffuse pancreatic necrosis but no perforated viscus; postoperatively, the patient rapidly died. This case represents a constellation of extremely rare findings: *Clostridium perfringens* infection of the pancreas, pancreatic emphysema or "gas gangrene," and pneumoperitoneum without a perforated viscus. (J GASTROINTEST SURG 2004;8:489–492)

KEY WORDS: Pancreatitis, acute necrotising, pneumoperitoneum, retropneumoperitoneum, *clostridium perfringens*, gas gangrene

CASE REPORT

A 62-year-old man was initially seen with a 2-day history of worsening abdominal pain. His serum amylase and lipase levels were 1549 IU/L and 3791 IU/L, respectively. Four of five early Ranson's criteria[1] were present on admission (age >55 years, serum glucose >200 mg/dl, lactate dehydrogenase >350 IU/L, and aspartate transaminase >250 IU/liter). The patient had undergone a cholecystectomy and right nephrectomy in the remote past. CT revealed both intrahepatic and portal vein gas (Fig. 1). Gas was also present throughout the entire pancreas and retroperitoneum (Fig. 2). The CT severity index was the maximum score of 10 (predicted complication rate 92%).[2] Because pneumoperitoneum was seen (see Figs. 1 and 2), the patient was assumed to have a perforated viscus and was taken to the operating room for laparotomy. A total abdominal colectomy for ischemia from mesenteric venous thrombosis and pancreatic necrosectomy was performed. However, no perforated viscus or fistula was found after an extensive exploratory operation. This was confirmed in the resection specimen on surgical pathologic examination. Within 24 hours of presentation, the patient had developed acute renal failure, acute liver failure, and acute respiratory distress syndrome. The patient had four of six late Ranson's criteria (PaO_2 <60 mm Hg, serum calcium <8 mg/dl, hematocrit drop >10%, and base deficit >4 mmol/L), bringing his total Ranson's criteria to 8 of 11 with a predicted mortality of 100%.[1] He died on postoperative day 1. Cultures of the necrotic pancreas obtained intraoperatively later grew *Clostridium perfringens*.

DISCUSSION

The diagnosis of acute, necrotizing pancreatitis has been well described. The decision as to whether or when to operate remains problematic, with medical management generally recommended initially unless the necrotic pancreas is infected.[3,4] Neither the presence nor the extent of pancreatic necrosis is an absolute indication for debridement,[4] although morbidity and mortality increase with the extent of necrosis.[2] In this case there was whole-organ involvement, with gas ("emphysema") throughout. This patient's course was fulminant, infected, and fatal. The case reported here is therefore noteworthy for the following three reasons: pancreatitis associated with *C. perfringens*; the presence of retroperitoneal and intrapancreatic gas (i.e., "gas gangrene of the pancreas" or emphysematous pancreatitis); and pneumoperitoneum without perforation of a hollow viscus.

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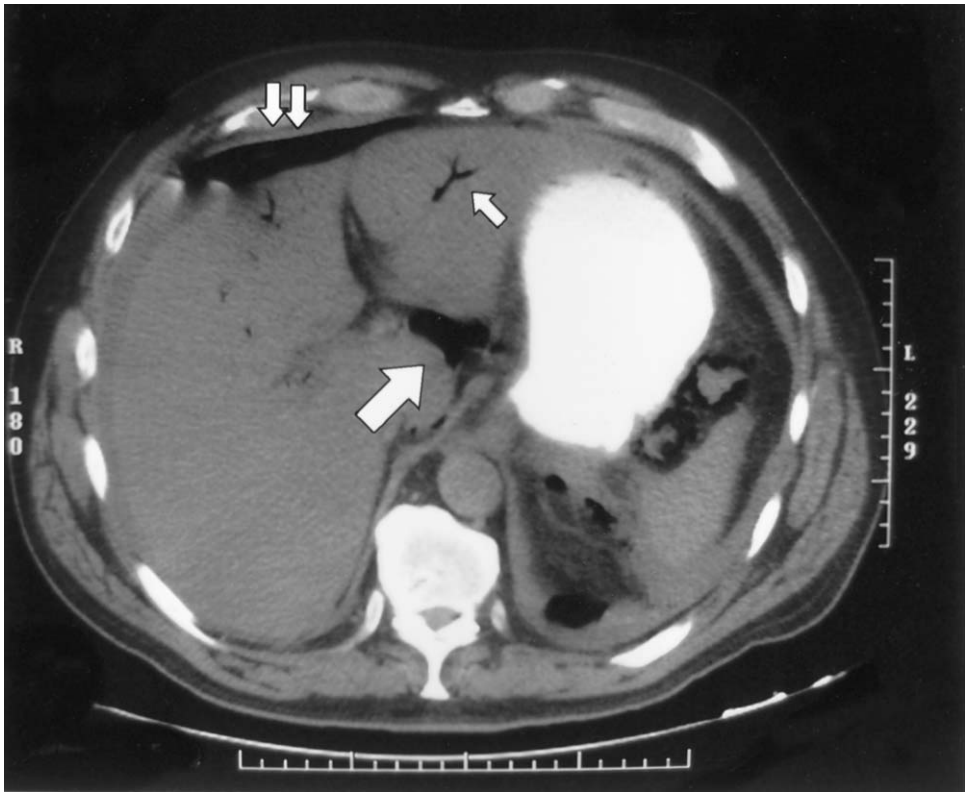

Fig. 1. CT scan of the abdomen showing portal vein gas (*large arrow*) and intrahepatic gas (*small arrow*), and pneumoperitoneum (*double arrow*).

The role of *C. perfringens* in soft tissue infections is legendary and needs no discussion here. On the other hand, it is a common bowel commensal, it can be found in the bile of up to 18% of patients undergoing biliary surgery, and it is rarely associated with significant intra-abdominal infection,[5] although it has been reported to produce gas gangrene of the liver after cholecystectomy.[6] A review of the literature identified seven previous cases of pancreatitis associated with *C. perfringens* (or *C. welchii*, as it was formerly known). Of these, two cases occurred after pancreatic biopsies,[7,8] two were associated with gallstone pancreatitis,[9,10] one occurred in "hemorrhagic pancreatitis" without gas being present,[11] and two occurred without prior instrumentation or other underlying etiologies (i.e., as "primary" or "spontaneous" infections), with gas in the pancreas.[12,13] Our case would therefore represent the third reported case of true gas gangrene of the pancreas (i.e., pancreatic gas with *C. perfringens* infection), and the eighth report of *C. perfringens* infection of the pancreas. Among the seven cases with known outcomes, there were four deaths (57%).

Pneumoretroperitoneum around the left kidney from pancreatic necrosis has been described,[14] similar to the left "renal halo" sign on plain radiographs denoting edema from peripancreatic inflammation.[15] The report by Chaudhary et al.[16] of a series of 17 patients with complications of pancreatic necrosis included two patients with pneumoperitoneum on chest radiographs, but one had jejunal perforation and the other had erosion of the lateral duodenal wall, and 14 were referred from elsewhere after 26 to 53 days. Ours may therefore represent the first or second case of pneumoperitoneum without perforation from necrotizing pancreatitis reported in the literature, with that finding prompting exploration on presentation.

Bowel perforation from necrotizing pancreatitis is a recognized phenomenon; reports of perforation of the stomach, duodenum, jejunum, colon, and biliary tract have even been reported from the same series.[16] Colon involvement has been reported in 2% of cases of acute pancreatitis, with the transverse colon being the site usually involved, presumably because of its proximity and poor collateral blood supply.[16] In our patient, most of the colon was nonviable because of venous thrombosis, but it was without perforation.

However, the presence of free air has been suggested as a means to differentiate pancreatic necrosis

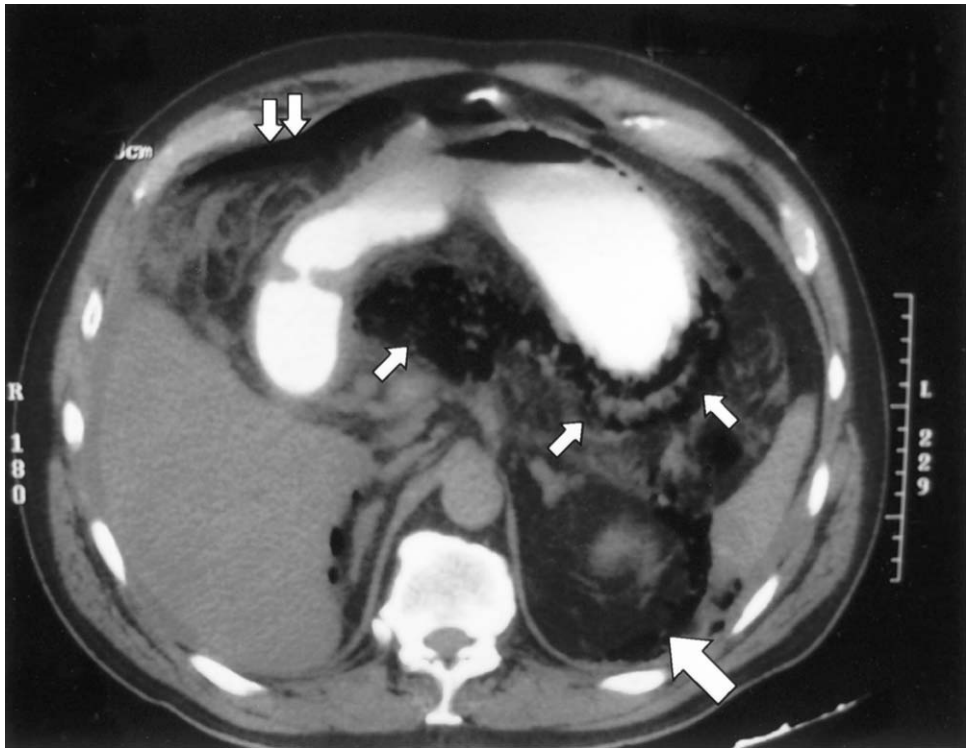

Fig. 2. CT scan of the abdomen showing gas throughout the pancreas (*small arrows*) and retroperitoneum, including around the left kidney (*large arrow*). "Free air" within the peritoneal cavity is again seen (*double arrows*).

from the retroperitoneal gas seen with posterior perforation of peptic ulcer[17]; in other words, that pancreatic necrosis without perforation will not produce free air. This was incorrect in our patient, although in retrospect exploration was still indicated as the pancreas was infected. Thus the surgical truism of pneumoperitoneum mandating laparotomy remains intact.

In summary, we present a truly unusual case: primary "gas gangrene" of the pancreas (pancreatic emphysema from *C. perfringens* infection) with pneumoperitoneum but without perforation.

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Laparoscopic Distal Pancreatectomy Combined With Preservation of the Spleen for Cystic Neoplasms of the Pancreas

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The precise role of laparoscopy in the resection of cystic neoplasms of the pancreas (CyNP) remains unknown. In addition, the question of spleen-preserving distal pancreatectomy is controversial. This report evaluates the feasibility and outcome of laparoscopic spleen-preserving distal pancreatectomy (LapSPDP) in 19 patients (17 women and 2 men) with CyNP. A prospective comparison was made between 11 consecutive patients (group I) with splenic vessel preservation (SVP) and 8 patients (group II) without SVP (Warshaw technique). This study used color-Doppler ultrasound (CDUS) as a tool to identify patients at high risk for postoperative splenic complications. The mean tumor size was, in both groups, 5 cm. In group I, with an intent-to-treat basis of SVP, only in 54.5% of patients the spleen was preserved with an intact splenic artery and vein; in the remainder, conversion to the Warshaw technique was required for intraoperative bleeding. Evaluation of intraoperative factors showed that the mean operative time was significantly shorter (165 vs. 222 minutes) and the mean blood loss significantly lower (225 vs. 495 mL) in the group of LapSPDP with the Warshaw technique. No patients required blood transfusion in both groups. The overall conversion rate was 0%. The overall rate of pancreatic fistula was 15% and it was classified as biochemical leak (no clinical symptomatology). Overall splenic complications were observed in 16.6% of patients but occurred only in three patients undergoing LapSPDP with the Warshaw technique; CDUS showed in 2 patients a focal splenic infarct; the third patient had an initial hospital stay of 5 days, was readmitted 2 days later for a massive splenic necrosis, and splenectomy was performed. The overall hospital stay was 5.7 days. At mean follow up of 22 months (range 6–42), there have been no local recurrences. (J GASTROINTEST SURG 2004;8:493–501)

KEY WORDS: Cystic neoplasms of the pancreas, laparoscopic pancreatic resection, spleen salvage

INTRODUCTION

In recent years, cystic neoplasms of the pancreas (CyNP) are diagnosed much more frequently and the treatment varies with the type of CyNP.[1] In patients with serous cystic neoplasms resection should probably be reserved for mass related symptoms or when differentiation from mucinous cystic neoplasms cannot be made confidently. However, mucinous cystic neoplasms of the pancreas should be considered premalignant or overtly malignant and, whenever safe, resected. For CyNP in the body or tail of the pancreas, a classical distal pancreatectomy with splenectomy may be the best treatment.[1] Nevertheless, splenic preservation has been described in conjunction with distal pancreatectomy.[2] Warshaw[3] described a technique of distal pancreatectomy with splenic preservation in which splenic vessels are ligated but preserve the short gastric and left gastroepiploic vessels. Others have described the technique of preserving both the splenic artery and vein.[4] Both strategies work, and each has its place.

Laparoscopic pancreatic procedures are still at the stage of evaluation with regard to their indications and the technical variations used. Laparoscopic pancreatic surgery is currently used for staging malignant pancreatic tumors,[5] for occasional management

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of inflammatory disorders of the pancreas,[6,7] and for the resection of benign pancreatic tumors.[8–16]

The use of laparoscopic ultrasonography and the advent of technological refinements in laparoscopic instruments have led some groups, including our own, to explore the role of laparoscopic surgery in patients with cystic neoplasms of the pancreas (CyNP). This report evaluates the feasibility and outcome of laparoscopic spleen-preserving distal pancreatectomy (LapSPDP) in patients with CyNP and provides information on the indications and limitations of the procedure.

PATIENTS AND METHODS

In January 1999, a prospective study was initiated using the laparoscopic approach in patients with CyNP. The group included 19 patients—17 women and 2 men with a mean age of 55 years (range 34–70 years). Abdominal or back pain was the most common complaint. The tumors were characterized by CT. On average, the size was 5.2 cms (range 4–8 cms) and they were located in the body-tail of the pancreas.

In all patients a laparoscopic spleen-preserving distal pancreatectomy (LapSPDP) was planned. In a subgroup of 11 consecutive patients, an intent-to-treat basis with splenic vessels preservation was performed. In this subgroup of patients, the mean tumor size was 5.3 cm. In another subgroup of 8 consecutive patients, a LapSPDP without splenic vessels preservation, after the Warshaw technique,[3] was performed. In this latter group, the spleen was kept vascularized by preserving the short gastric vessels and the left gastroepiploic vessels. In this subgroup of patients the mean tumor size was 5.1 cms.

Laparoscopic Surgery

Using our approach, the patient is placed in the half-lateral position with the left side up. The surgeon and assistant stand on the left side of the patient and the camera person and scrub nurse stand on the opposite side. Four 10- to 12-mm trocars are inserted in the abdominal wall 3–4 cm above the umbilicus on the xiphoid area, subcostal on the midaxillary line, and subcostal to the midclavicular line. Two monitors were used. CO_2 pneumoperitoneum was used. Abdominal pressure was monitored and maintained at less than 14 mmHg. A 30º scope was used. The liver was explored visually and by laparoscopic ultrasonography (LapUS) (7.5 MHz probe, 10 mm diameter; B-K Medical, Gentolfe, Denmark).

The first step is to start with sectioning the lienorenal ligament and dissecting the subjacent fascia lateral to the spleen. The splenocolic ligament is divided using Harmonic Scalpel. The splenic flexure of the colon is mobilized downward. The gastrocolic momentum is widely opened up to the level of the mesenteric vessels and the body-tail of the pancreas is then visualized. The anterior aspect of the pancreas is exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. Care must be taken to preserve the short gastric and the left gastroepiploic vessels. The inferior border of the pancreas is dissected and the body and tail of the pancreas are completely detached from the retroperitoneum. This mobilization of the left pancreas allows visualization of the posterior wall of the gland where the splenic vein is easily identified. The splenic vein is pushed away from the posterior pancreatic wall with gentle blunt dissection. Visual magnification through the laparoscope permits excellent control of the small pancreatic veins, which are coagulated using the LigaSure device, the Harmonic scalpel, or clipped with titanium clips. A tunnel is created between the splenic vein and the pancreas. The splenic artery is identified through this space using blunt careful dissection with a curve dissector. The pancreas is then transected with a 30 mm endoscopic linear stapler. Usually two stapler applications are necessary. The tail of the pancreas is then grasped and retracted anteriorly with 5 mm forceps and traction is applied to expose the small branches of the splenic artery and vein, which are coagulated using the LigaSure device. The dissection is continued laterally until the splenic hilum (Fig. 1). All specimens are extracted within an endoscopic plastic bag.

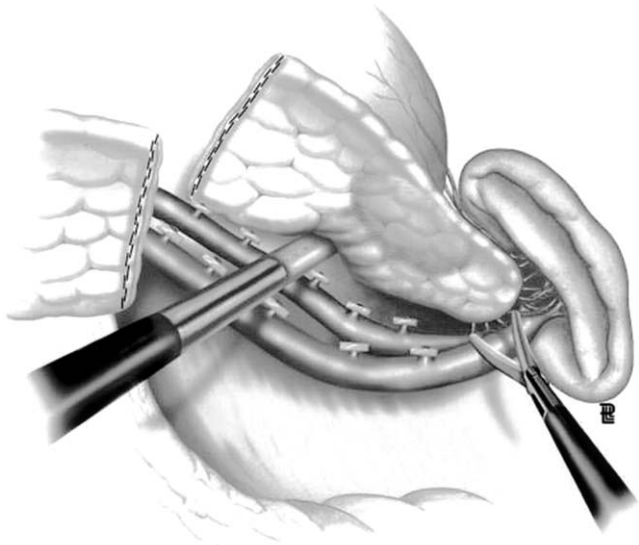

Fig. 1. Laparoscopic spleen-preserving distal pancreatectomy with splenic vessels preservation.

The technique of SPDP without splenic vessels preservation follows the same surgical steps as described above. At this point the splenic vein is divided between clips. The use of LapUS demarcates the line of pancreatic transection 2 cm from the tumor. After pancreatic transection the splenic artery is divided between clips. The left pancreas is then lifted up and mobilized posteriorly with the splenic artery and vein. The latter are clipped and divided as they emerge from the pancreatic tail to enter the hilum of the spleen. The spleen is kept vascularized solely from the short gastric vessels and the left gastroepiploic vessels (Fig. 2). All specimens are extracted in an endoscopic plastic bag. A silicon drain is left in the pancreatic bed close to the pancreatic stump.

Evaluation criteria included operative factors such as estimated blood loss, operative time, and intraoperative complications. Evaluated postoperative data included length of hospital stay and postoperative complications with a specific focus on pancreatic leak, intra-abdominal abscess, splenic complications, and other major infectious complications (i.e., pneumonia, wound infection). Postoperative pancreatic leaks were defined as a drain amylase level (measured after the third postoperative day) more than three times the upper limit of the normal serum amylase level in the absence of clinical sequelae. A clinical leak was defined as a biochemical leak in the presence of clinical sequelae such as fever or elevated white blood cell count, intra-abdominal abscess, or the need for percutaneous drainage or reoperation. Color Doppler ultrasound (CDUS) studies were performed with a Toshiba Powervision (Toshiba, Nasu, Japan) or a Sequoia 512 (Siemens-Acuson, Mountain View, CA) with a multifrequency 2–4 MHz transducer. CDUS studies were carried out in the postoperative period in all patients undergoing LapSPDP without splenic vessels preservation and when clinically indicated: unexplained fever, abdominal pain, or elevated white cell count. The CDUS study included a complete abdominal examination: liver, bile ducts, portal vein patency, kidneys, pancreatic area, spleen, and search of intra-abdominal fluid collections. The spleen evaluation included size, echostructure, and the presence of fluid collections, which were evaluated by real-time ultrasonography. The Doppler study (pulsed and color) was done at hiliar and parenchimal levels just at the point in which the branches enter into the spleen. The arterial waveform was quantified by the resistive index (RI = peak systolic velocity–end diastolic velocity/peak systolic velocity). Doppler parameters were adjusted to optimize the detection of low blood flow velocities.

Statistical analysis was performed using the Sigma Plot software package for Windows (SPSS Inc., Chicago, IL). Data were expressed as means ± standard deviation (SD). The Kruskal–Wallis test and the Student *t* test were applicable. A p value less than 0.05 was considered significant.

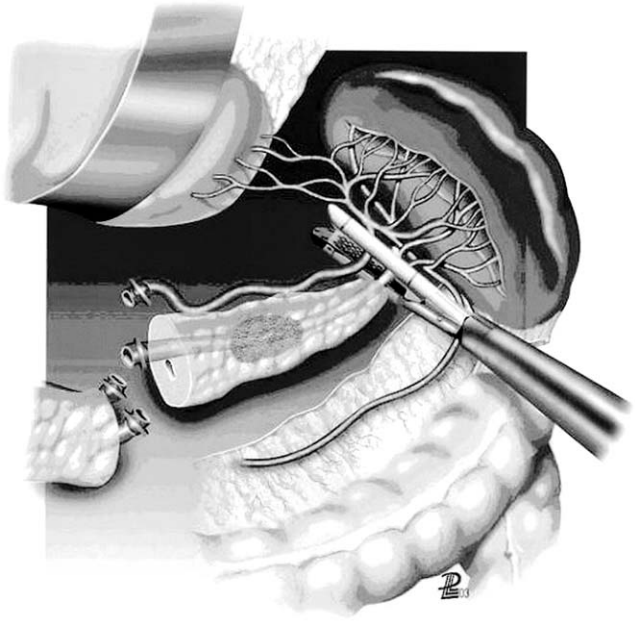

Fig. 2. Laparoscopic spleen-preserving distal pancreatectomy without splenic vessels preservation. The spleen is kept vascularized by the short gastric and left gastroepiploic vessels.

RESULTS

In the subgroup of 11 patients undergoing LapSPDP, the splenic vessels preservation was feasible in six patients, but in five patients intraoperative bleeding occurred at the time of pancreatic transection (2 patients) and during dissection of the splenic vessels when separating the tumor from the pancreas (3 patients). As a result, in three patients the splenic artery was ligated using four clips and then divided so that two clips were left in the remnant, but the splenic vein remained intact. In one patient the splenic vessels were divided using endoscopic staplers. Another patient with a tumor of 8 cm in diameter, after stapling the splenic vessels, was converted to a hand-assisted technique and en block resection that included the spleen because the tumor was densely adherent to the splenic hilum (Table 1). The mean operative time of the whole group with an intent-to-treat basis of splenic vessels preservation was 222.7 ± 65.2 minutes (range 180–400 min) and intraoperative blood loss 495 ± 228.5 mL (range 200–850 mL). No patients required blood transfusion. In the

Table 1. Outcome of spleen-preserving distal pancreatectomy for cystic neoplasms of the pancreas

Patients	Tumor size (cm)	Intraoperative complications	Operative time (min.)	Blood loss (mL)	Postoperative complications	Hospital stay (days)
Patients in an intent-to-treat basis of splenic vessels preservation						
1	4	—	180	400	—	5
2	4.5	—	180	300	—	5
3	5	—	180	400	—	5
4	6	bleeding (splenic artery secured by clips)	220	400	pancreatic fistula	7
5	5	bleeding (splenic artery and vein secured by endoscopic linear stapling)	400	800	splenic infarct	5
6	5.5	—	240	300	—	5
7	4.5	bleeding (splenic artery secured by clips)	200	600	pancreatic fistula	8
8	6	—	190	400	—	5
9	5.5	bleeding (splenic artery secured by clips)	200	800	—	5
10	4.5	—	190	200	—	5
11	8	bleeding* (splenic artery and vein secured by endoscopic linear stapling)	270	850	—	5
Mean	5.3		222.7	495.5		5.45
Patients in an intent-to-treat basis of division of splenic vessels (Warshaw technique)						
12	5	—	150	200	—	5
13	6	—	180	300	focal splenic infarct	6
14	5	—	190	450	pancreatic fistula	7
15	4,5	—	170	300	—	5
16	5	—	180	300	focal splenic infarct	7
17	6	—	150	200	—	5
18	6	—	150	250	—	5
19	4	—	150	200	—	5
Mean	5.1		165	275		5.63

*Hand-assisted surgery. Pancreatic body-and-tail "en block" resection with splenectomy.

subgroup of eight patients undergoing LapSPDP without splenic vessels preservation after the Warshaw technique the mean operative time was 165 ± 16.9 minutes (range 150–190 min) and the mean blood loss of 275 ± 84.5 mL (range 200–450 mL). No patient required blood transfusion (Table 1).

A comparative study between the two subgroups showed that the mean operative time was significantly shorter ($p = 0.002$) and the mean blood loss was significantly lower ($p = 0.017$) in the subgroup with LapSPDP with the Warshaw technique.

Overall postoperative complications (31.6%) were observed in six patients after LapSPDP. Pancreatic fistulas of low volume (<100 ml) and a drain amylase greater than 5000 UI/L developed postoperatively in two patients after LapSPDP and splenic vessels preservation and in one patient after LapSPDP without splenic vessels preservation, but without clinical symptomatology. These patients had a hospital stay of 5 days, but they were discharged home with the drain "in situ" based upon persistent drain output. The drain was discontinued 2 weeks after surgery.

The evaluation of the vascularity of the spleen by the Doppler parameters, quantified by the resistive index (RI), showed an RI between 0.44 and 0.52 in the patients undergoing LapSPDP without splenic vessel preservation. Splenic complications occurred in three patients (RI of 0.44, 0.46, and 0.48, respectively). One patient, in whom splenic vessels division was performed for intraoperative bleeding, was discharged home 5 days after surgery; however, 2 days later he presented fever (38C) and clinical sepsis. The patient was rehospitalized and splenectomy was performed for massive necrosis of the spleen. Two other patients in the group of LapSPDP without splenic vessels preservation presented early in the postoperative period pain in the left upper quadrant of the abdomen. CDUS showed a focal splenic infarct of 3 and 4 cm, respectively (Fig. 3). Both patients were treated with antibiotics to prevent abscess formation in the splenic infarct.

The mean length of a postoperative hospital stay (LHS) was 5.7 days (range 5–8 days). In patients who had an uncomplicated course, the mean LHS was 5 days and patients with complications had a mean LHS of 6.6 days. This difference was statistically significant ($p = 0.01$). There were no late postoperative complications and no deaths within 30 days of operation. The majority of patients returned to previous activities 3 weeks after the operation. Final pathological report showed mucinous cystoadenoma in 17 patients, mucinous cystic tumor borderline in one patient, and mucinous cystadenocarcinoma in another patient. The mean follow up was 22 months (range 6–42 months). No tumor recurrences were observed.

DISCUSSION

The use of laparoscopy for managing benign pancreatic tumors has still not been defined. With the introduction of each new laparoscopic technique, there have been predictable cycles characterized by an introductory phase (in which the surgical technique is developed), a definition phase (with exploration of technical variations and classification of the operative indications), and an educational phase. The definition phase is currently underway for laparoscopic pancreatic surgery.

Laparoscopic pancreatic surgery must be considered an advanced laparoscopic procedure and should be performed only in institutions with expertise in pancreatic surgery by a team with advanced

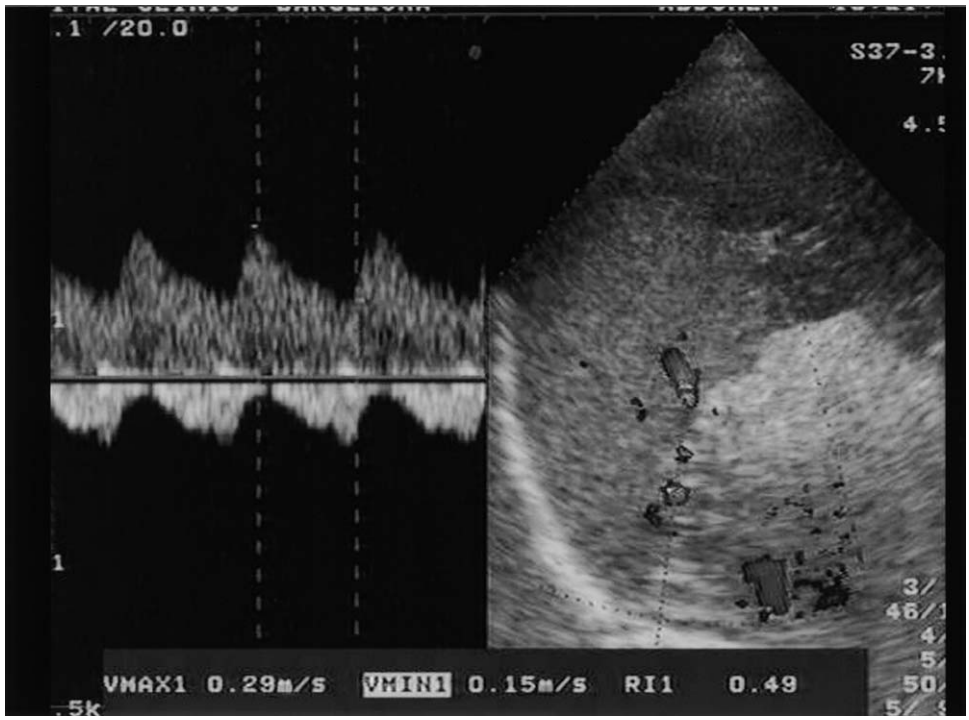

Fig. 3. Color-Doppler ultrasound shows a hypoechoic/heterogeneous area that involves the caudal part of the spleen. In the Doppler study, low-resistance arterial waveforms (infrared [IR] = 0.49) are obtained in the preserved spleen, which shows a homogeneous echostructure.

laparoscopic skills. Most published reports on laparoscopic pancreatic surgery resections are on single cases or limited series of patients.[5–16] Moreover, the follow-up is short, and therefore little is known about the long-term results. Three factors should be considered for the indications of this new procedure—the proper patient, the proper procedure, and the proper performance.

Proper Patient

The appropriate treatment for CyNPs varies considerably, based on the specific type of neoplasm.[1] Serous cystoadenoma of the pancreas affects predominantly women with an average age of 50 years (range 35–84 years). Most patients experience vague abdominal pain and symptoms seemingly related to the mass effect of the tumor. Serous cystoadenoma can often be distinguished quite reliably by their characteristics: multiple small (<2 cm) cystic areas often resembling a honeycomb both grossly and on imaging tests. Occasionally they have a starburst appearance, with a centrally located calcified scar. These neoplasms are universally benign, although there have been unusually reported patients with histologically documented malignant serous cystoadenocarcinomas.[1] Surgical treatment is indicated in symptomatic patients. Mucinous cystic neoplasms are the most frequently encountered cystic tumors of the pancreas accounting for 45%. These neoplasms predominate in women with an average age of 53 (range 19–82). The most common symptoms seem to be related to a local mass effect. These neoplasms, more common in the body or tail of the pancreas (70%), are composed of cystic areas filled with viscous mucous material and the cyst walls are dense and fibrous with occasional calcification. Pathognomonic findings on CT include the presence of thin or thick papillary fronds or septae on the individual cysts. A detailed clinicopathologic correlation has been proposed by Sarr et al.,[17] separating these tumors into three groups: (1) mucinous cystoadenomas comprising 65% of mucinous tumors; (2) proliferative cystic mucinous neoplasms (30% of mucinous neoplasms) composed of varying degrees of atypia, dysplasia, and even changes of carcinoma in situ but without tissue invasion; and (3) mucinous cystadenocarcinomas (<10% of all mucinous cystic neoplasms) with frank stromal invasion beyond the epithelium. The latter group behaves like ductal adenocarcinoma of the pancreas. However, according to the Mayo Clinic experience, there were no recurrences in patients with either cystoadenoma or proliferative mucinous cystic neoplasms on follow-up of up to 30 years.[17] However, two recent series of mucinous cystic neoplasms describe invasive carcinoma in 36% (47/130)[18] and 29% (16/56).[19]

We believe that serous cystoadenomas and mucinous cystic neoplasms are suitable for the laparoscopic approach based on the frequent location of these tumors in the body and tail of the pancreas and the high frequency of these neoplasms being benign or premalignant lesions.[17,18] The laparoscopic approach is probably unsuitable for large tumors with evidence of malignancy.

Proper Procedure

The aim here is to reproduce the technique used for open pancreatic surgery and the application of the principles of oncological surgery. Enucleation or pancreatic resection have been advocated in open surgery to manage these tumors.[20,21] Enucleation of pancreatic cystic tumors offers the possibility of complete tumor removal without loss of pancreatic parenchyma, possible diabetes, and splenectomy. Enucleation can be safely performed laparoscopically and has been proposed as the technique of choice in patients with insulinoma.[13] However, enucleation seems to be a debatable procedure in patients with CyNP. Tumor enucleation does not address the malignant potential of these tumors and should be used (in selected cases) with caution to avoid inadequate tumor margins. In addition, the incidence of pancreatic fistulas after tumor enucleation was reported to be 30%[21] to 50%,[20] leading to a long hospital stay (19.5 days in the John Hopkins' series).[21]

In the literature, when the tumor was located in the body or tail of the pancreas, the technique most frequently used was distal pancreatectomy with en block resection that included the spleen. Talamini et al.[21] reported that 74% of patients with mucinous cystoadenomas undergoing distal pancreatectomy had splenectomy. One late septic death occurred in this group. Nevertheless, distal pancreatectomy with splenic preservation has been advocated by a number of others.[2] The question of spleen preserving distal pancreatectomy is controversial. Recently, Lillemoe et al.[22] have reported the largest single-institution experience with distal pancreatectomy (235 patients) for a variety of pancreatic disorders including chronic pancreatitis and benign and malignant pancreatic tumors, and only 16% of patients had splenic preservation. In another series of 71 patients reported by Fernández-del Castillo et al.,[23] the incidence of spleen preservation was 20%. It could be suspected that for patients in whom distal pancreatectomy is considered appropriate, simultaneous splenectomy is routine because of its technical simplicity. However, because it became apparent that the incidence of post-splenectomy sepsis is about 0.28%–1.9% with a mortality rate of 2.2%, the significance of preservation of the spleen has come to be widely recognized.[24]

Published data from two retrospective reviews comparing patients who had surgery mainly for trauma or pancreatitis, undergoing distal pancreatectomy with and without splenectomy, had shown no differences in complication rates between groups concluding that splenectomy should not be a routine part of distal pancreatic resection.[25,26] On the other hand, Benoist et al.[27] analyzed 40 patients undergoing distal pancreatectomy for other indications than chronic pancreatitis. Fifteen patients underwent distal pancreatectomy with spleen conservation and 25 had splenectomy. Pancreatic left resection with splenectomy turned out to have a lower morbidity rate, as pancreatic complications such as fistula or subphrenic abscess occurred more frequently in patients after spleen-conserving surgery. More recently, Shoup et al.[2] reported the series from the Memorial Sloan-Kettering Cancer Center including 211 patients undergoing distal pancreatectomy. Splenectomy was performed in 79 patients (63%) and splenic preservation in 46 (37%). The most common histopathologic conditions were neuroendocrine tumors (n = 45) and benign cystic tumors (n = 44). Perioperative complications occurred in 49% after splenectomy and in 39% after splenic preservation. Perioperative infectious complications and severe complications were significantly higher in the splenectomy group (28% and 11%), compared with the splenic preservation group (9% and 2%). The length of hospital stay was 9 days post-splenectomy and 7 days post-splenic preservation.

We encourage laparoscopic spleen-preserving pancreatectomy to prevent the potential long- and short-term complications associated with splenectomy. The question is whether it should be performed with or without splenic vessel preservation. The latter technique, in which the short gastric and gastroepiploic arteries are the only blood supply to the spleen, was described by Warshaw.[3] Splenomegaly is a contraindication for this means of spleen conservation because the increased mass is insufficiently nourished by the short gastric vessels. There is no doubt that by preserving the splenic artery and vein, the blood supply to the spleen is well maintained and the danger of splenic necrosis and abscess formation is reduced. On the other hand, distal pancreatectomy with conservation of the splenic artery and vein is both time- and labor-consuming. Dissecting the splenic vessels from the pancreas may be difficult to perform in the presence of tumors distorting and compressing the course of the vessels.

In this report we conducted a prospective study to evaluate the feasibility and outcome of laparoscopic spleen-preserving distal pancreatectomy with and without splenic vessels preservation. In this series the mean tumor diameter was 5.2 cm. In 11 patients, an intent-to-treat basis of splenic vessels preservation was performed. Only in 6 patients (54.5%) was the spleen preserved with an intact splenic artery and vein. In the remainder, intraoperative bleeding due to injury of splenic vessels needed the sacrifice of the splenic artery (but the splenic vein remained intact) or the splenic artery and vein and the spleen was kept vascularized by the short gastric and the left gastroepiploic vessels. Our results indicate that the preservation of the splenic vessels is not always possible when dealing with large tumors. In eight consecutive patients, the splenic artery and vein were secured by clips and the short gastric and gastroepiploic collaterals were preserved to nourish the spleen. The comparison between the groups with splenic vessels preservation and the Warshaw technique demonstrates a statistically significant difference in the parameters of operative time and intraoperative blood loss in favor of division of the splenic vessels.

We advocate, in all circumstances, laparoscopic spleen-preserving distal pancreatectomy safeguarding the short gastric and gastroepiploic vessels. In case it is necessary to take the splenic artery and vein, the spleen will be kept vascularized. Furthermore, the Warshaw technique is less technically demanding than dissection and conservation of the splenic artery and vein. To the question of conserving the splenic vessels or not, we believe, in accordance with Warshaw, "If the goal is to save the spleen, having options allows the surgeons to match the tactics to the terrain."[28]

Proper Performance

The aims of minimally invasive surgery are not only to minimize parietal damage, but also to diminish the incidence of postoperative complications. In this report the overall complication rate was 31.6%, which included pancreatic leaks as well as splenic complications.

In patients undergoing open surgery, significant morbidity follows distal pancreatic resection. In the literature, pancreas-related complications ranged from 5%–26%.[22,29–31] In the published reports there is a lack of consensus regarding the optimal method of pancreatic stump closure and the contribution of spleen salvage on the development of pancreatic leak. Also, the role for routine use of somatostatin analogues after elective left pancreatectomy remains unclear. In our current series, after laparoscopic pancreatic resection (mechanical stapling), 3 of 19 patients (15.7%) developed a low-volume pancreatic fistula without clinical symptomatology and classified as biochemical leaks. This complication was managed as an outpatient until the drainage decreased

and the drain was discontinued. In a recent report, the incidence of pancreatic leak was reduced significantly when the pancreatic duct was identified, dissected, and ligated during open left pancreatectomy.[30] This technical approach could be incorporated after laparoscopic mechanical stapling of the parenchyma. This technical refinement may result in a reduction of the rate of postoperative pancreatic leaks.

Spleen salvage was possible in the majority of patients. Only in one patient was hand-assisted laparoscopic distal pancreatectomy with en block resection of the spleen thought to be necessary because of the close relation of the tumor (8 cm in diameter) to the splenic hilum. Splenic complications were observed in 3 of 18 patients (16.6%) after laparoscopic spleen-preserving distal pancreatectomy and, interestingly, this complication was only observed in patients undergoing the Warshaw technique. One explanation would be that after division of the splenic vessels in cases of inadvertent injury of the gastroepiploic vessels during dissection of the inferior margin of the tail of the pancreas, the organ receives blood directly from the short gastric vessels and the absence of vascular communications between superior and inferior splenic lobes results in splenic infarct. This complication may be suspected clinically with the presence of fever and left upper abdominal pain. Color Doppler ultrasonography will show the area of infarct. Abscess formation can be prevented with antibiotic administration. A more serious complication is massive necrosis of the organ with local infection that requires splenectomy. Shein et al.[32] reported that splenectomy had to be performed 24 hours after the Warshaw technique because of necrosis of the spleen. However, the reduction of blood supply leading to splenic necrosis may take days, as had happened in our patient, who was discharged 5 days after the operation, but rehospitalized 2 days later with clinical sepsis and splenectomy was performed through a left subcostal incision. It might be that the splenic complications occurring after the Warshaw technique are not the result of failure of the technique, but a failure in the proper performance of the method as it was originally described preserving all the vascular collaterals to nourish the spleen.

Our study suggests that the patients with spleen-preserving distal pancreatectomy after the Warshaw technique should be followed carefully from the immediate postoperative period with color Doppler ultrasonography to detect morphological changes in the spleen for prompt treatment with antibiotics in cases of focal splenic infarct to prevent splenic abscess. It was noteworthy in patients after LapSPDP without splenic vessels preservation that the resistive index at the splenic hilum was in the range between 0.48–0.52, lower than those reported in healthy controls (0.53–0.56). This finding could be attributed to the small caliber of the collateral vessels nourishing the spleen. Similar low resistance arterial waveforms (<0.50) are observed in liver transplant patients with hepatic artery thrombosis in whom collateral arterial vessels are newly formed or in patients with hepatic artery stenosis.[33,34]

In this study the mean hospital stay of the whole group was 5.7 days. This is a notable reduction of the postoperative length of stay in comparison with the largest single institution experience with distal pancreatectomy reporting a mean of stay of 15 days.[22] In a recent report from Massachusetts General Hospital, a decrease in the length of stay from 9 to 7 days in recent periods was demonstrated in patients after undergoing distal pancreatectomy.[31]

CONCLUSIONS

Laparoscopic distal pancreatectomy is feasible with an acceptable complications rate in patients with CyNP. Laparoscopic ultrasound should be routinely used to achieve an adequate margin. Spleen salvage is possible in 94.7% of cases during pancreatic resection with or without splenic vessels preservation. The Warshaw technique is faster and less technically demanding than splenic vessels preservation but associates splenic complications usually managed conservatively. Duplex-Doppler ultrasonography is mandatory in the immediate postoperative period in cases of division of the splenic vessels to detect splenic abnormalities. The advantages of the laparoscopic approach are a reasonably short hospital stay and an early return to previous activities. A cosmetic advantage is also clear because of the absence of long abdominal incisions. Surgical cure can be achieved in most patients with CyNP with complete relief of symptoms. No tumor recurrences were observed but the follow-up is relatively short.

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A Reappraisal of Preoperative Chemoradiation for Localized Pancreatic Head Ductal Adenocarcinoma in a 5-Year Single-Institution Experience

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Resection of localized pancreatic head ductal adenocarcinoma (LPHDA) has a limited impact on survival. Mechanisms of improvement provided by preoperative chemoradiation therapy (CRT) remain under debate. This study analyzes the outcome of patients treated for LPHDA to delineate the benefits of CRT. Among 87 patients with LPHDA, 17 had a pancreaticoduodenectomy alone (group I). Thirty-nine with initially resectable cancers received CRT with 5-fluorouracil–based chemotherapy (group II). Thirty-one with initially unresectable cancers were similarly treated by CRT (group III). Patients in groups II and III were restaged after completion of CRT. In patients with resectable disease, resection was planned. Patients in groups I and II were statistically comparable in terms of age, sex, and pretherapeutic stage. Median survival and 2-year overall survival in group I were 13.7 months and 31%, respectively. In group II, 23 patients (59%) had a pancreaticoduodenectomy (group IIa) and 16 patients (41%) did not have resection (group IIb). Median survival and 2-year overall survival were as follows: group IIa, 26.6 months and 51%; and group IIb, 6.1 months and 0%, respectively. In group IIa, pathologic examination revealed eight major responses (35%) including two sterilized specimens, and none of the patients had locoregional recurrence. In group III, none of the patients had resection, and median survival was 8 months with one 2-year survivor. Patient selection appears to play a major role with regard to results achieved with preoperative CRT followed by pancreaticoduodenectomy. However, a high histologic response rate and excellent local control can also be achieved. (J GASTROINTEST SURG 2004;8:502–510)

KEY WORDS: Pancreatic ductal adenocarcinoma, neoadjuvant chemoradiation, pancreaticoduodenectomy, pathologic response

Pancreatic head adenocarcinoma remains one of the leading causes of cancer deaths worldwide. The incidence of this disease is relatively low but is increasing.[1] The worldwide incidence is stable for now,[2] but the overall 5-year survival rate is only 0.4%.[1] Less than 10% of patients seen at referral centers have resectable lesions[2] and less than 3% in a large epidemiologic study.[3] Despite improvements in surgical techniques and supportive care, the median survival after surgery remains poor—10 to 18 months, with long-term survival rates of 10% to 24%.[1] Tumor resection is traditionally considered the only curative treatment for pancreatic cancer, but surgery alone has not been proved to significantly improve survival.[2] In addition, when survival is analyzed, only chemotherapy and radiation therapy are associated with a significant increase in patient survival.[4] Although postoperative radiotherapy in combination with chemotherapy has been shown to significantly improve survival in a randomized trial,[5] the rationale for considering preoperative chemoradiation therapy (CRT) for localized pancreatic head ductal adenocarcinoma (LPHDA) also seems logical.[6,7] Despite interesting results from recent large series,[8,9] the effectiveness of preoperative CRT remains debatable.[10] This report describes our experience in 87 patients with LPHDA. This was an attempt to delineate the true benefits of CRT in terms of tumor control and patient survival.

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PATIENTS AND METHODS

Eligibility Criteria

Between March 1997 and April 2002, a total of 87 patients were treated at our institution for histologically proved LPHDA. All patients were staged by means of endoscopic ultrasonography (EUS) and thin-section contrast-enhanced helical dual-phase CT. Concerning the EUS and CT signs of portal vein involvement, the lack of interface between the vessel and the tumor was not considered a high-risk sign precluding resection. Only patients with portal thrombosis and/or portal cavernoma and/or direct invasion of the superior mesenteric artery or celiac axis were considered nonresectable. EUS was performed by means of a linear echoendoscope (Pentax-Hitachi, Hamburg, Germany) allowing EUS fine-needle aspiration using propofol. EUS examinations were carried out with the patients under total anesthesia. No systematic antibiotic prophylaxis was administered. EUS and fine-needle aspiration were performed using Wilson-Cook needles (22-gauge, 8 cm in length). Patients with obstructive jaundice underwent endoscopic biliary stenting before treatment.

Patient Characteristics

A complete history was obtained from all patients; additional testing included physical examination, chest radiography, abdominal-pelvic CT, and hematologic, serum chemistry, liver enzyme, and coagulation profiles. There were 42 females and 45 males. Median age was 65 years (range 39 to 89 years). Therapeutic strategies were outlined depending on the surgical resectability of the tumor. Patients with tumors considered to be initially resectable benefited from either surgical resection without any preoperative treatment (group I, n = 17) or preoperative CRT followed by restaging and surgical resection (group II, n = 39). Patients with tumors considered to be initially nonresectable received CRT and were restaged after completion of treatment (group III, n = 31). The treatment algorithm is shown in Fig. 1.

Group I included eight women and nine men. Median age was 65 years (range 50 to 80 years). One patient was referred immediately after a laparotomy, without biopsy, performed at another center and underwent a pancreaticoduodenectomy at our institution. Two patients were operated on after unsuccessful endoscopic biliary drainage. Seven patients refused the complete procedure and opted for surgery alone. In the remaining seven patients, the diagnosis of pancreatic adenocarcinoma could not be proved after two pretherapy endoscopic biopsies.

Surgery included dissection of the porta hepatis, peripancreatic and paraduodenal nodes, dissection of the uncinate process, and complete removal of the aortocaval nodes behind the pancreas. The lymph node dissection included the celiac axis nodes, those along the hepatic artery with dissection of the take off of the right gastric artery and superior mesenteric artery lymphadenectomy. At the time of resection, specimens of the biliary and pancreatic margins were sent for frozen-section analysis and the margins were re-resected if positive. The retroperitoneal margin was inked by the surgeon and evaluated by permanent section analysis.

Group II included 15 women and 24 men. Median age was 65 years (range 39 to 76 years). Written informed consent was obtained from all patients. CRT consisted of a combination of chemotherapy that included continuous infusion of 5-fluorouracil (5-FU; 650 mg/m^2) on days 1 to 5 and days 21 to 25, along with a bolus of cisplatin (80 mg/m^2) on days 2 and 22, and simultaneous radiation therapy. The specifications for the radiotherapy protocol were as follows: The radiotherapy target volumes were established by CT scan. The clinical target volume was defined by the gross tumoral volume, and the regional lymph nodes (peripancreatic and celiac nodes and hepatic pedicle nodes). The planning target

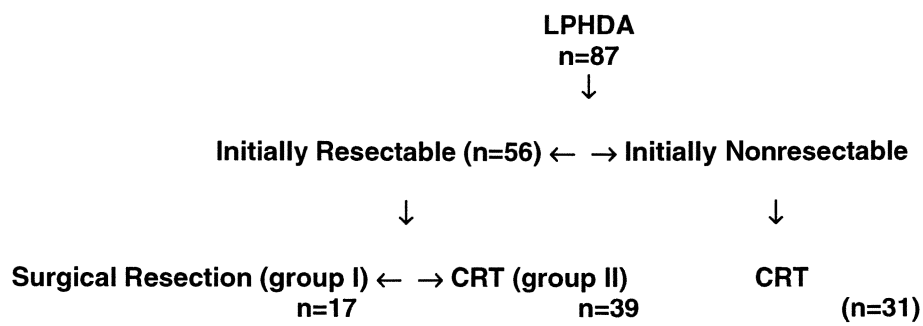

Fig. 1. Patient treatment algorithm. LPHDA = localized pancreatic head ductular adenocarcinoma; CRT = chemoradiation therapy.

volume was defined by the clinical target volume plus a 1 cm margin. Patients were irradiated using the following two methods: (1) split-course radiation therapy, which consisted of two courses of 30 Gy in 10 fractions, each followed by a 2-week rest interval; and (2) standard-fractionation preoperative radiation therapy in a total dosage of 45 Gy divided into 1.8 Gy doses 5 days a week. Radiation treatments delivered 15 MV photons. Field arrangements were delivered using a three-field or four-field plan (one anterior and two laterals or anterior, posterior, and two laterals). There was no prospective limit on the dosage to the fraction of kidney or liver in the radiation field. Chemotherapy included a continuous infusion of fluorouracil (5-FU; 650 mg/m^2) on days 1 to 5 and days 21 to 25 and a bolus of cisplatin (80 mg/m^2) on days 2 and 22. Surgical resection was to be performed 4 to 6 weeks after completion of CRT if there was no disease progression to an unresectable status as determined by repeat abdominal CT scan and EUS, a prohibitive decline in performance status, or other evidence of metastatic disease. For resected patients, surgery was performed as described previously.

Group III included 12 women and 19 men. Median age was 67 years (range 39 to 88 years). Twenty-six patients with portal cavernoma and/or portal thrombosis and/or direct invasion of the superior mesenteric artery or celiac axis were considered initially unresectable. Five patients with associated comorbidity or age over 80 years were considered inoperable. Patients were irradiated using 45 Gy standard-fractionation preoperative radiation therapy. The protocol for radiation and chemotherapy was identical to the one previously described. Surgical resection was to be performed 4 to 6 weeks after completion of CRT if there was progression to a resectable status as determined by a repeat abdominal CT scan and EUS. Patient characteristics are shown in Table 1.

Table 1. Patients' characteristics

	Group I (n = 17)	Group II (n = 39)	Group III (n = 31)
Median age (yr)	65 (range 50–80)	65 (range 39–76)	67 (range 39–88)
Male/female	9/8	24/15	19/12
Method of diagnosis			
FNA by EUS	0	39	31
Surgery	17	0	0
Biliary palliation			
Endoscopic	0	26	22
Surgical	17	6	0
None		7	9

FNA = fine-needle aspiration; EUS = endoscopic ultrasonography.

Pathologic Examination

Pathologic evaluation of pancreatectomy specimens from all patients in groups I and IIa was carried out. The retroperitoneal margin was defined as the soft tissue margin directly adjacent to the proximal 3 to 4 cm of the superior mesenteric artery. This margin was identified immediately on specimen removal by the surgeon. Tumor size was calculated after surgical resection by measuring the greatest transverse diameter of the tumor. All pancreatic specimens were examined macroscopically and microscopically. All margins, including retroperitoneal margins, were evaluated by microscopic examination of a 0.5 mm full-face section of the margin. When no residual tumor was found on the first microscopic examination, serial sectioning of the pancreatic specimen was performed. The presence of nodes in the specimen was noted. An immunohistologic study was systematically performed using monoclonal anti-MUC 1 antibody (H23). All examinations were performed simultaneously by two investigators using a double-headed light microscope.

Follow-Up

Perioperative (in-hospital) deaths and any complications resulting in reoperation and/or transfer to the intensive care unit were recorded. To determine the length of hospital stay, the day of surgery was considered day 1. After the completion of treatment, patients were evaluated every 3 months by means of follow-up physical examination, chest radiography, and abdominal CT. Local recurrence was defined as lesions occurring in the pancreatic bed, whereas disease of the peritoneum, retroperitoneum, liver, lung, and other organs was defined as distant metastases.

Statistical Analysis

Patient records were maintained in a prospective database and supplemented by information obtained from retrospective review of hospital and physician records. Descriptive statistics are reported as frequencies or medians with range. Cause-specific survival was calculated from the date of diagnosis, disease-related death being scored as an event with censoring of other patients at the date of last follow-up or nondisease-related death. Disease-free interval was also calculated from the date of diagnosis, the first recurrence being scored as an event, with censoring of other patients at the time of last follow-up or death. We used Kaplan-Meier estimates to evaluate patient survival.[11] Survival rates were compared by log-rank test.[12]

RESULTS

Pretreatment

Forty-eight patients (69%) in groups II and III with obstructive jaundice underwent endoscopic biliary stenting before treatment. Among patients in groups II and III, the LPHDA diagnoses were obtained on the first attempt using EUS-guided biopsy in 61 patients; another nine patients required a second tissue acquisition (EUS biopsy of the tumor mass in all cases). Immunohistologic studies were systematically performed using monoclonal anti-MUC 1 antibody (H23).[13] The median time in all patients from definitive biopsy to initiation of CRT was 8 days (range 5 to 15 days). The median pretherapeutic tumor diameter, measured on EUS and CT staging, was 32 mm (range 15 to 60 mm). Patients in groups I and II were statistically comparable in terms of age, sex, and pretherapeutic EUS/ CT stage. Pretherapeutic tumor stages are shown in Table 2.

Treatment

Among the 70 patients who received CRT, 12 received 30 Gy split-course radiation and 58 were given a dose of 45 Gy standard-fractionation radiation. CRT was well tolerated, with 100% of patients in group II completing treatment but only 61% (19 patients) in group III because of cancer progression. One patient in group II died of cholangitis-related septic shock after completion of CRT. Eleven patients (23%) had a biliary stent obstruction and required an endoscopically placed new stent. Almost all of the toxic effects encountered involved the gastrointestinal tract with no grade 3 or 4 toxicity (Table 3). None of the patients in group II experienced a delay in surgery because of chemoradiation toxicity. The median range from the last day of CRT to surgical resection was 43 days (range 10 to 90 days). In two patients, medical complications (femoral thrombosis in one and arthritis of the knee in the other) required specific treatment and surgery had to be delayed. None of the patients required unplanned hospitalization prior to restaging and/or interruption or a reduction in the dosage of chemotherapeutic agents because of treatment toxicity. Table 3 shows the grading of chemoradiation toxicities.

Table 3. Grading of toxicities of chemoradiation

Toxicities of chemoradiation	Patients
Stomatitis	
Grade 1 = Painless ulcers, erythema or mild soreness	13 patients
Grade 2 = Painful erythema, edema or ulcers, can eat	None
Grade 3 = Painful erythema, edema or ulcers, cannot eat	None
Grade 4 = Requires parenteral support	None
Nausea	
Grade 1 = Able to eat reasonable intake	4 patients
Grade 2 = Intake significantly decreased but can eat	2 patients
Grade 3 = No significant intake	None
Vomiting	
Grade 1 = 1 episode per day	6 patients
Grade 2 = 2 to 5 episodes per day	None
Grade 3 = 6 to 10 episodes per day	None
Grade 4 = >10 episodes per day or parenteral support required	None
Diarrhea	
Grade 1 = increase of 2–3 stools per day over normal	5 patients
Grade 2 = increase of 4–6 stools	6 patients
Grade 3 = increase of 7–9 stools, incontinence, or severe cramping	None
Grade 4 = increase of >10 stools, bloody diarrhea, or parenteral support required	None

Restaging After Chemoradiation Therapy in Groups II and III

All patients underwent CT and EUS 3 to 4 weeks after completion of CRT. In group II, we defined the following two subgroups after restaging: (1) group IIa: 23 patients (59%) were considered resectable

Table 2. EUS tumor stages

Group	PT T1N0	PT T2N0	PT T3N0	PT T4N0	PT T1N1	PT T2N1	PT T3N1	PTT4N0	Total
Group I	1	6	4	0	1	4	1	0	17
Group II	2	15	9	0	0	9	3	1	39
Group III	0	10	6	0	0	6	9	0	31
Total	3	31	19	0	1	19	13	1	87

T1 = tumor limited to the pancreas, ⩽2 cm at its maximum diameter; T2 = tumor limited to the pancreas, >2 cm at its maximum diameter; T3 = tumor extending directly into the duodenum, bile duct, or peripancreatic tissue; T4 = tumor extending directly into the stomach, spleen, colon, or adjacent large blood vessels; N0 = no regional lymph node metastasis; N1 = regional lymph node metastasis; PT = pretherapeutic EUS and CT scan staging.

after restaging (among these patients, nine [39%] showed a partial response and 14 [61%] showed stable disease); and (2) group IIb: 15 patients (38%) developed distant metastasis (10 patients), local evolution precluding resection (2 patients), both (2 patients), or peritoneal carcinomatosis (1 patient). One patient died of septic shock after completion of CRT. In group III, all patients appeared to have persistent unresectable LPHDA, objectively shown by CT scan and EUS; surgery was not performed in these patients (Fig. 2).

Nonresected Patients

Two patients in group IIb were found to have unresectable disease by local tumor extension to peripancreatic vascular structures at restaging. One patient did not undergo resection because of a histologically proved peritoneal carcinomatosis. In group III no patients were downstaged by radiation and chemotherapy and no patients underwent surgery.

Surgical Results

Patients in groups I and IIa were comparable in terms of age, sex, and pretherapeutic EUS/CT tumor staging. Pathologic tumor sizes were not significantly greater in group IIa (Table 4). In group I all patients had standard Whipple procedures. Two procedures included portal resection. There were two postoperative deaths. One patient had a fatal myocardial infarction, and one had a postoperative left hepatic lobe abscess, was reoperated and subsequently died. The mean length of hospital stay was 20 days (range 12 to 41 days). Three patients developed a postoperative intra-abdominal infection and required percutaneous drainage. Two patients had gastric outlet obstruction and were treated with medication. All patients in group IIa had a standard Whipple procedure. No portal resections were performed. One patient died in the postoperative period. This patient had massive ascites and lethal septic shock on postoperative day 40. The mean length of hospital stay was 21 days (range 11 to 46 days). Five patients had a postoperative intra-abdominal lymphatic infection and required percutaneous drainage. Two patients had gastric outlet obstruction and were treated with medication.

Staging of the Resected Specimen

The pathologist attempted to determine the extent of the cancer and categorized the clinicopathologic response. The 40 resected cancers were macroscopically and microscopically examined, and all resection margins were examined. In group I, the 17 resected tumors ranged in size from 15 to 55 mm (median 31 mm). None of the patients had a grossly positive margin of resection. Retroperitoneal margins were microscopically involved in six cases (35%). No vascular invasion was demonstrated in patients with vascular resection. The mean number of lymph nodes examined was 10.5 (range 7 to 18 nodes). Eleven

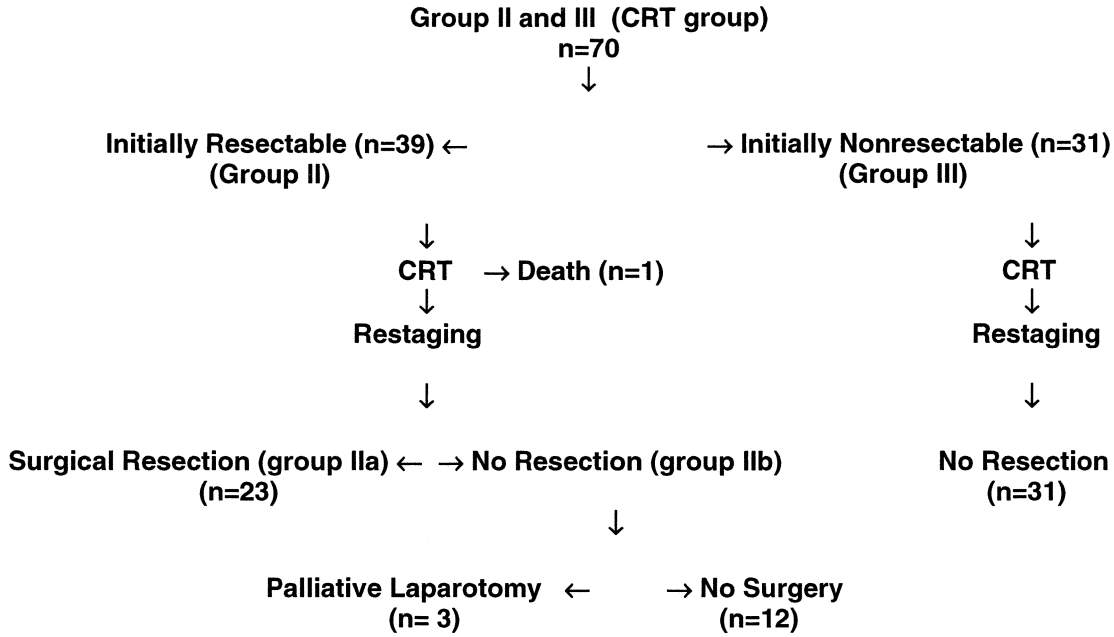

Fig. 2. Restaging in groups II and III.

Table 4. Pretherapeutic characteristics in resected patients

	Group I (n = 17)	Group IIa (n = 23)	
Median age (yr)	65 (range 50–80)	60 (range 39–76)	
Male/female	9/8	13/10	$P = 1$
Tumor size <20 mm	4	2	
Tumor size from 20 to 30 mm	5	5	
Tumor size from 30 to 40 mm	5	10	$P = 0.5$
Tumor size >40 mm	3	6	

patients (65%) had involved lymph nodes. In group IIa, two complete pathologic responses were observed. The 21 remaining resected tumors ranged in size from 12 to 44 mm (median 32 mm). No patients had a grossly positive margin of resection. Retroperitoneal margins were microscopically involved in two cases (9%). The mean number of lymph nodes examined was 10 (range 6 to 18 nodes). Three patients (13%) had lymph node involvement.

Table 5. Pathologic examination

	Group I (n = 17)	Group IIa (n = 23)	
Median tumor size (mm)	31 (15–55)	32 (12–44)	$P = 0.19$
Involved lymph nodes	11 (65%)	3 (13%)	$P = 0.0053$
Involved resection margins	6 (35%)	2 (9%)	

Results of pathologic examination of resected patients are presented in Table 5.

The pathologic findings were helpful in assessing the antitumor effect of CRT. There were six patients with extensive viable pancreatic cancer, nine with moderate to median residual cancer, six with minimal microscopic foci, and two with a complete pathologic response. All residual tumors were positive for monoclonal anti-MUC 1 antibody (H23). The pathologist determined tumoral differentiation, necrosis, inflammation, fibrous stroma, radiation pancreatitis, and vascular or perineural invasion (Table 6).

Table 6. Pathologic findings in group IIa (resected patients after preoperative CRT)

Patients	Residual tumor	Quantification +/++/+++	Differentiation	Necrosis	Inflammation	Fibrous stroma	RP	pTN	Lymph node −/+	Vascular or perineural invasion
1	Yes	+++	Well	0	++	+	++	T2N0	6N−	−/+
2	Yes	++	Well	0	−	+	++	T2N0	17N−	+/+
3	Yes	++	Well	0	−	+	+	T1N0	9N−	−/−
4	Yes	++	Mod	0	−	+	+	T2N1	1N+/12	−/+
5	Yes	+	Mod	0	−	+	+	T2N0	3N−	−/−
6	No						++	T0N0	9N−	
7	Yes	+	Well	0	−	+	++	T2N1	1N+/12	−/−
8	Yes	++	Well	+	−	+	++	T2N0	13N−	−/−
9	Yes	+++	Undiff	++	−	+	+	T2N1	6N−	−/+
10	No						+	T0N0	17N−	
11	Yes	++	Poor	+	−	+	+	T2N1	8N−	+/+
12	Yes	++	Poor	0	−	++	+	T2N0	6N−	+/−
13	Yes	++	Poor	0	−	+++	+	T1N0	13N−	+/+
14	Yes	++	Mod	0	+	+	+	T2N0	10N−	−/+
15	Yes	+	Well	0	+	++	++	T1N0	11N−	−/−
16	Yes	+++	Well	0	++	+	+	T2N0	9N−	+/−
17	Yes	+	Mod	+	−	++	++	T2N0	13N−	+/+
18	Yes	+++	Mod	0	−	+	+	T2N0	6N−	−/+
19	Yes	+	Well	+	−	+++	+	T2N1	6N+/18	+/+
20	Yes	++	Poor	0	+	+	++	T2N0	4N−	+/−
21	Yes	+++	Well	++	−	+	+	T2N0	11N−	+/+
22	Yes	+	Mod	0	−	+	++	T2N0	1N−	+/−
23	Yes	+++	Poor	0	+	++	+	T2N0	10N−	+/+

RP = radiation pancreatitis; Mod = moderate; Undiff = undifferentiated.

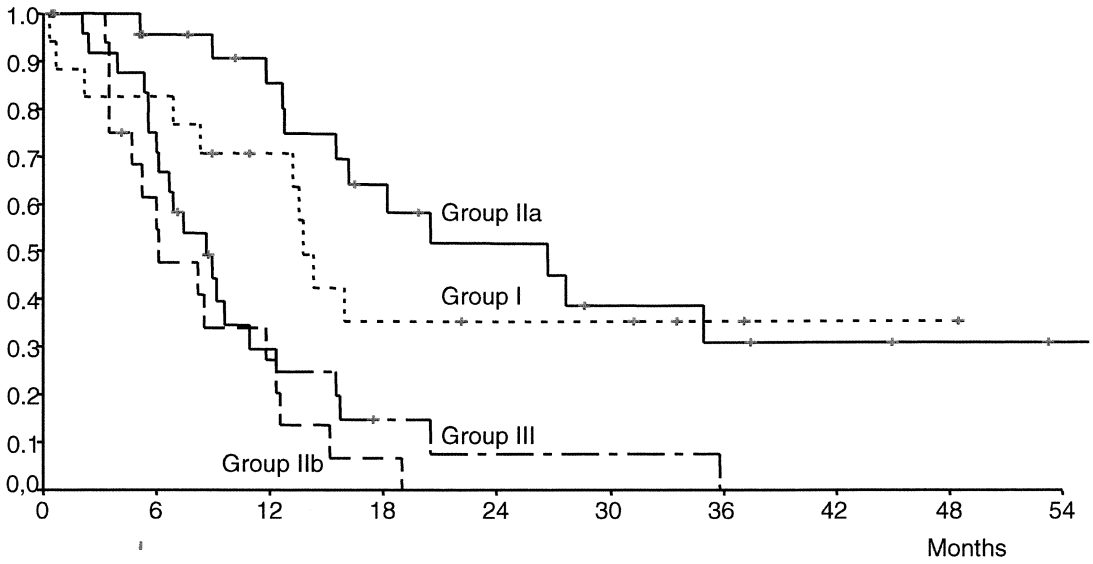

Fig. 3. Survival curves. Survival in patients resected without CRT (group I) was compared to survival in patients resected after CRT (group IIa) and nonresected patients (groups IIb and III).

Late Toxicity in Group IIa

One patient died of acute superior mesenteric artery thrombosis, with complete small bowel infarction, 36 months after the cancer was diagnosed. One patient was operated on for an acute localized small bowel infarction and underwent a 20 cm small bowel resection with immediate anastomosis. Postoperative outcome was uneventful. No clinical evidence of disease relapse was found in either of these patients.

Long-Term Outcome

In group I, six patients experienced metastatic recurrences, including four cases associated with locoregional recurrences, and three patients had locoregional recurrences alone. In group IIa, 10 patients had metastatic recurrences or carcinomatosis but no locoregional recurrence. The overall median survival and the 2-year overall survival rate for the 87 patients were 12.3 months and 23%, respectively. Median survival and 2-year overall survival in group I were 13.7 months and 31%, respectively, and three patients were alive 36, 37, and 40 months after diagnosis. Median survival and 2-year overall survival for the entire group II were 12.7 months and 28%, respectively. In group IIa, median survival and 2-year overall survival were 26.6 months and 51%, respectively. Three patients were alive 40, 49, and 59 months after diagnosis. Six (46%) of 13 patients with a minimal 3-year follow-up were alive 3 years after diagnosis. Median survival in group IIa was significantly higher than in group I ($P < 0.005$). In group IIb, median survival was 6.1 months without any 2-year survivors. The overall median survival for patients in group III was 8.6 months with one 2-year-survivor (Table 7). Overall survival curves for the four groups are shown in Fig. 3.

DISCUSSION

This series reports a single-institution experience with LPHDA treatment. Because of the very poor

Table 7. Long-term outcome

	Entire group (n = 87)	Group I (n = 17)	Group IIa (n = 23)	Group IIb (n = 16)	Group III (n = 31)
		Resected patients		Nonresected patients	
Median survival (mo)	12.3	13.7	26.6	6.1	8.6
2-year survival rate (%)	23	31	51	0	7
Local recurrence alone	3	3	0		
Local recurrence and metastases	5	5	0		
Metastases and/or carcinomatosis	59	2	10	16	31

results of surgical treatment alone in all series,[14,15] and promising results from high-volume centers specializing in preoperative CRT in locally advanced tumors,[16–18] we initiated, in 1997, a neoadjuvant CRT strategy for patients with biopsy-proved LPHDA. Preoperative CRT for most of us is viewed as a method by which a locally advanced primary pancreatic tumor might be rendered surgically resectable,[2,7,19–21] but recent reports show interesting results with preoperative CRT in resectable LPHDA.[8,9] Several points are still under debate.

Feasibility and acceptable overall toxicity are now well demonstrated, but high rates of CRT toxicity-related rehospitalization are frequently reported[8,10] in contrast to our experience. On the other hand, we report a significantly high rate of biliary stent–related problems (23%) requiring an endoscopically placed new stent and one case of fatal angiocholitis. This morbidity appears to be higher than in data from a recent large series.[22] In our study the postoperative in-hospital mortality rate in group IIa was 4%, which is similar to that in recent studies.[8,15] Anastomotic complications of pancreatojejunostomies were uncommon, and this could be related to the radiation-induced pancreatic fibrosis.[23] Meanwhile preoperative CRT could lead to uncommon complications. In our experience, two of the patients who were free of disease experienced late arterial complications including a lethal superior mesenteric artery thrombosis.

The major point to be clarified remains assessment of the real efficacy of CRT. Analysis of the pathologic response has to be separated into pancreatic tumor response (tumor size and resection margins) and downstaging of involved lymph nodes. Pathologic evidence of the response remains scarce in other clinical studies of preoperative CRT.[9,24] Interpretation of pancreatitis and fibrosis observed in the surgical specimen requires caution[10] because these tumors can be associated with a significant fibrotic component without prior CRT. Analysis of all 23 resected specimens demonstrates varying degrees of fibrosis and necrosis, and a clinicopathologic response was clearly present. Eight of the 23 resected patients had a major histologic response (35%) including two complete responses (9%). To our knowledge, pancreatic head ductular adenocarcinoma (PHDA) sterilization was reported in only four centers.[2,7,8,25] The importance of achieving clear margins is supported by several studies,[1,26–28] and residual local tumor after resection is common with extension to surgical margins in up to 51%.[27] In the current series, resection margins were involved in two patients (9%) in group IIa in contrast to group I where margins were involved in six patients (35%). We observed an apparent downstaging of lymph nodes among patients in group IIa. Although most series of resections after CRT report a distribution of up to 50% of node-positive patients,[8,9,29] only 3 (13%) of 23 resected specimens contained positive nodes in group IIa in contrast to 11 (65 %) of 17 resected specimens in group I. This could be a result of both CRT efficacy and patient selection, because 12 patients in group II were found to have metastatic disease at restaging and consequently were included in group IIb. We could hypothesize that most of these patients had initially involved lymph nodes. Thus the "real" rate of involved lymph nodes was probably similar to that in other series ranging from 40% to 70%. The most noteworthy aspects of the study remain the local control provided by CRT. Long-term follow-up showed that none of the patients in group IIa experienced locoregional recurrence in contrast to group I and previous series of patients undergoing surgical resection alone.[15,27] The median survival for patients in group IIa was 26.6 months, which is significantly higher than that in group I, accordingly to previous reports of preoperative CRT and resection.[2,9] Significant improvement in survival duration appears to have been achieved in group IIa inasmuch as, despite a significant response rate, median histologic tumor size remained 32 mm (2 complete responses were excluded) with 16 patients (69.5%) with tumors larger than 3 cm. It is well known that tumor diameter is an important predictor of survival (patients with tumors smaller than 3 cm in diameter had a significantly longer median survival than patients with tumors larger than 3 cm).[15] It is too early to distinguish long-term survivors in group IIa, but three patients are alive 40, 49, and 59 months after diagnosis, and among 13 patients with a minimum 3-year-follow-up, six were alive 3 years after histologic diagnosis. Survival in patients who were initially resectable but who had rapidly progressing disease (group IIb) was extremely low (6.1 months), a finding that is in agreement with a previous report.[6] Median survival in groups I and II was identical. Optimization of patient selection for pancreaticoduodenectomy undoubtedly contributes to the relatively longer median survival duration of patients in group IIa. This factor has not always been analyzed in recent reports[9] but remains the major point to clarify. Because more than one third of initially resectable patients were not resected in our experience, improvement in survival duration could only be attributed to patient selection. Selection advantage is an integral part of the rationale for neoadjuvant treatment sequencing, but proponents of surgical resection alone argue that nonresected patients (group IIb) may miss an opportunity for curative resection. In

our experience, only two patients in group II could not be resected because of locoregional disease progression alone (5%). The individual impact of patient selection and CRT efficiency remains impossible to assess. However, in group IIa we observed a high rate of pathologic response including sterilized specimens with, in addition, no patients experiencing locoregional recurrence. These data permit us to hypothesize the true efficacy of preoperative CRT. Deaths always occurred in group IIa because of metastatic evolution. Further improvements in the duration of survival await the development of more effective systemic therapy in an effort to treat micrometastatic disease.

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COX-2 Inhibition Results in Alterations in Nuclear Factor (NF)-κB Activation But Not Cytokine Production in Acute Pancreatitis

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Acute pancreatitis is characterized by local inflammation and cytokine production, and release is thought to contribute to this process. Nuclear factor (NF)-κB activation and cytokine production are linked and inhibition of NF-κB has been shown to decrease the severity of pancreatitis. We have shown that inhibition of COX-2 ameliorates pancreatitis; however, the mechanism by which this effect occurs is unclear. Swiss Webster mice were injected intraperitoneally with either saline (control) or caerulein (CAE; 50 mg/kg) hourly for 8 hours; mice receiving CAE were further subdivided to receive saline or the cyclooxygenase-2 (COX-2) selective inhibitor (SC-58125; 10 mg, intraperitoneally) at the time of the first injection of CAE. Pancreata were harvested, histologic sections were scored, and protein was extracted to determine cytokine (interleukin [IL]-6, IL-1β) levels and NF-κB subunits by ELISA and NF-κB activation by gel shift. In addition, serum was collected for measurement of cytokines. COX-2 inhibition resulted in decreased inflammation and a decrease in NF-κB activation. IL-6 and IL-1β levels after COX-2 inhibition, however, remained elevated to levels equivalent to those of mice with histologic inflammation after CAE alone. COX-2 inhibition decreases inflammation as well as late-phase NF-κB activation but does not diminish levels of inflammatory cytokines, thus suggesting a two-phase activator of NF-κB. The attenuation of inflammation, despite unaltered cytokine levels, suggests that cytokines may not be critical for the inflammatory phase of pancreatitis. (J GASTROINTEST SURG 2004;8:511–519)

KEY WORDS: Pancreatitis, NF-κB, COX-2, cytokines

INTRODUCTION

Acute pancreatitis is characterized by local pancreatic inflammation as well as a systemic inflammatory response.[1–3] Histologically, acute pancreatitis is characterized by interstitial edema, vacuolization, inflammation, and acinar cell necrosis;[4–6] common etiologies include excessive alcohol consumption, biliary tract disease, certain medications, and invasive procedures of the biliary and pancreatic ducts (e.g., endoscopic retrograde cholangiopancreatography [ERCP]).[4–6] Various cytokines, released locally and systemically, have been implicated in the inflammatory response associated with pancreatitis. Certain cytokines, including interleukin-6 (IL-6) and IL-8, have been shown to correlate with disease severity although their exact function during the course of acute pancreatitis is unclear.[7–11] Other cytokines (e.g., tumor necrosis factor [TNF]-α and IL-1β) are thought to mediate the systemic effects of pancreatitis such as fever, hypotension, and shock.[11] Inhibition of cytokine production has been proposed to decrease the severity of acute pancreatitis;[12–14] however, the cellular mechanisms underlying cytokine production and acute inflammation in acute pancreatitis are not entirely known.

Nuclear factor-κB (NF-κB) is a transcription factor that is important for the activation of many inflammatory mediators, cytokines[15–17] (e.g., IL-6 and IL-β), and the cyclooxygenase-2 (COX-2) enzyme.[18,19] In its inactivated state, NF-κB is sequestered in the cytoplasm bound to its inhibitory protein,

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IκB, which, with stimulation, is degraded thus allowing NF-κB to translocate into the nucleus and activate proinflammatory genes.[18,20] NF-κB activity is increased with pancreatitis;[15,21–23] we and others have shown that the inhibition of NF-κB ameliorates the inflammatory effects of pancreatitis.[15,21–23]

Expression of COX-2, the inducible form of the COX enzyme, is normally undetectable in pancreatic acinar cells.[24] However, COX-2 is markedly induced with acute pancreatitis.[24,25] COX-2 expression is regulated, in part, by NF-κB, certain mitogens, and the proinflammatory cytokines IL-1, IL-6, and TNF-α.[26–28] Recently, we have shown that COX-2 is a crucial and central mediator in the development and severity of acute pancreatitis.[24] Importantly, inhibition of COX-2 by either pharmacologic inhibition or selective genetic deletion markedly attenuated the severity of acute pancreatitis. Unexpectedly, the marked decrease in pancreatic and lung inflammation by COX-2 inhibition was not accompanied with a diminution of serum amylase levels, suggesting a "disconnect" between the injury to the pancreas associated with enzyme activation/release and the inflammation that characterizes acute pancreatitis. Because COX-2, NF-κB, cytokine production, and pancreatitis are linked, we hypothesized that COX-2 inhibition, which attenuates pancreatic inflammation, would result in decreased NF-κB activation and ultimately affect cytokine levels (both local production and systemic release). Therefore, the purpose of the study was to determine the effects of COX-2 inhibition on both NF-κB activation and levels of the cytokines IL-1β and IL-6 in a well-characterized secretagogue-induced model of acute edematous pancreatitis.

MATERIALS AND METHODS

Materials

Caerulein was purchased from Bachem, Inc. (Bachem, Inc., Torrance, CA). The COX-2 selective inhibitor SC-58125 was purchased from Cayman Chemical (Cayman Chemical, Ann Arbor, MI). Cytokine ELISA kits were purchased from Pierce Endogen (Pierce Endogen, Rockford, IL). ELISAs for p65 and p50 were purchased from B & D Biosciences Clontech (B & D Biosciences Clontech, Palo Alto, CA). Bio-Rad protein assay and polyacrylamide were purchased from Bio-Rad Laboratories (Bio-Rad Laboratories, Hercules, CA). The NF-κB oligonucleotide was purchased from Promega (Promega, Madison, WI). Radioactive agents were purchased from Perkin-Elmer (Perkin-Elmer, Boston, MA). All other reagents were of molecular biology grade and purchased from Sigma (Sigma, St. Louis, MO).

Animals and Experimental Design

All mice were maintained in an environment of controlled temperature (23C), humidity, and lighting (12 hours dark/12 hours light) with full access to water and regular chow diet. Young (≅5 weeks old) female Swiss Webster mice (Charles River Breeding Laboratories, Inc., Wilmington, MA) weighing ≅23 g were used. Acute pancreatitis was induced using supramaximal-stimulating concentrations of caerulein (CAE; 50 μg/kg), a stable cholecystokinin (CCK) analogue, given at hourly intervals intraperitoneally for 8 hours for a total of nine injections as previously described.[24,29–33] For COX-2 inhibition, the compound SC-58125 was used; mice were treated with SC-58125 (10 mg/kg) or vehicle immediately before the first injection of CAE. Mice were sacrificed over a time course (i.e., 2, 4, 6, and 8 hours after initiation of injections). Blood was collected, allowed to clot, and centrifuged for measurement of serum cytokine levels. Pancreata and lungs were removed and either placed in formalin for histology or snap frozen in liquid nitrogen.

Histology and Scoring

Pancreata were harvested and placed in 10% buffered formalin at 4C overnight. Tissues were embedded in paraffin, sectioned at a thickness of 4 μm, and stained with hematoxylin and eosin. The entire pancreas of at least 4 mice from each treatment group was examined and semiquantitative assessment was performed based upon inflammation and edema by a pathologist (S.R.) who was blinded as to the treatment. Using a previously described method by Schmidt et al.,[34] the entire sections (a minimum of 100 fields) were examined and scored on a scale of 0–3 with 0 being normal and 3 being severe. These characteristics include the presence of acinar cell ghosts, vacuolization, swelling of the acinar cells, and/or the destruction of the histoarchitecture of whole or parts of the acini.

Electrophoretic Mobility Shift Assay (EMSA)

Tissue extracts were prepared and EMSAs were performed as previously described.[21] Briefly, synthetic oligonucleotide, which corresponds to the NF-κB DNA binding domain, was used. A single strand was end-labeled with γ-^{32}P adenosine triphosphate (ATP), T4 polynucleotide, and 50 μg of protein extract in a final volume of 20 μl. The reaction was incubated for 30 minutes at room temperature. Competitive binding experiments were performed by first incubating unlabeled nucleotide (100-fold molar excess) with tissue extract and binding buffer for 10

minutes at room temperature. The reaction mixtures were resolved on a 4% nondenaturing polyacrylamide gel.

ELISA

For cytokine assessment, serum or protein extract (200 μg) was prepared as described previously[21]; levels of either IL-1β or IL-6 were measured by ELISA according to the manufacturer's protocol (Pierce Endogen). Briefly, the serum or protein was placed in wells that were precoated with antisera for either mouse IL-1β or IL-6. Biotinylated reagent was added and a secondary antibody conjugated with streptavidin-HRP (horseradish peroxidase) was used to detect the cytokine. Wells were then developed and measured at 450 nm.

To assess the importance of various NF-κB subunits, protein levels of p65 or p50 were measured using ELISA analysis according to the manufacturer's protocol (B & D Biosciences Clontech). Briefly, 96 well plates with consensus binding sequences for either p65 or p50 were used. Tissue extracts were incubated in the wells for 1 hour at room temperature. Bound transcription factors were then detected by a primary/HRP secondary conjugated antibody system. Wells were then developed and read at 655 nm.

Statistical Analysis

Experiments at 8 hours were performed on at least three separate occasions. The time course experiments were performed once. Histologic scores were analyzed using the Fisher exact test with PROC FREQ in SAS (SAS Institute, Inc., Cary, NC), Release 8.02. Total NF-κB p50 and p65 were analyzed using analysis of variance for a two-factor experiment. The two factors were trial (a random factor) and treatment (control, CAE, and CAE + SC). Computations were performed using PROC MIXED in SAS (SAS Institute, Inc., Cary, NC), Release 8.02. Because of heterogeneous variability among treatment groups and among trials, IL-6 and IL-1β were analyzed using the Kruskal–Wallis test for each trial. All effects and interactions were assessed at the 0.05 level of significance. The Fisher least significant difference procedure was used for multiple comparisons with Bonferroni adjustment for a number of comparisons.

RESULTS

The severity of acute pancreatitis is attenuated with SC-58125, a selective COX-2 inhibitor. We have previously shown that acute pancreatitis is attenuated by genetic disruption of the COX-2 gene and by chemical inhibition with the COX-2 inhibitor NS-398.[24] Others have confirmed these findings and demonstrated that the COX-2 inhibitor SC-58125 at high doses has a similar effect.[25] To determine whether the compound SC-58125 at a low dose could also attenuate the severity of acute pancreatitis, female Swiss Webster mice were treated with the selective COX-2 inhibitor SC-58125 at a dose of 10 mg/kg immediately before the initiation of supramaximally stimulating doses of the cholecystokinin (CCK) analogue, CAE. This dose of SC-58125 has previously been shown to be safe and reduce COX-2 levels in mice.[35] Histologic sections from representative pancreata are shown in Fig. 1, *A*. Control (CON) animals demonstrated healthy nonedematous acinar cells whereas treatment with CAE resulted in marked edema, necrosis, vacuolization, and inflammatory cell sequestration. Treatment with SC-58125 (10 mg/kg) attenuated the severity of pancreatitis as noted by decreased interstitial edema and reduced neutrophil infiltration.

To assess these changes in a semiquantitative manner, sections of pancreata stained with hematoxylin and eosin were scored as described in the Materials and Methods section. Treatment with SC-58125 (10 mg/kg) significantly reduced the severity of pancreatitis as noted by decreases in pancreatic edema and inflammation to levels that are not statistically different than the controls (Fig. 1, *B*). These results confirm our previous findings that COX-2 inhibition ameliorates the severity of acute pancreatitis and, furthermore, show that lower dosages of the COX-2 inhibitor can be used to decrease the inflammation associated with pancreatitis.

Inhibition of COX-2 with the selective inhibitor SC-58125 results in diminished NF-κB binding. We[21] and others[15,23,36] have shown that NF-κB plays a key role in the development of pancreatitis; NF-κB is activated after the induction of pancreatitis and NF-κB inhibition with the compound NEMO (NF-κB essential modifier) binding domain (NBD),[21] n-acetylcysteine (NAC),[15] or pyrrolidine dithiocarbamate (PDTC)[22] results in the amelioration of acute pancreatitis. To determine whether COX-2 inhibition altered NF-κB activation after induction of acute pancreatitis, one group of mice was injected with a supramaximal stimulating dose of CAE and another group was treated with CAE and the COX-2 inhibitor SC-58125. Pancreata were harvested at the conclusion of the CAE injections, extracted for protein, and analyzed by EMSA for NF-κB activation. NF-κB binding activity was increased in animals treated with CAE alone. COX-2 inhibition combined with induction of pancreatitis resulted in markedly

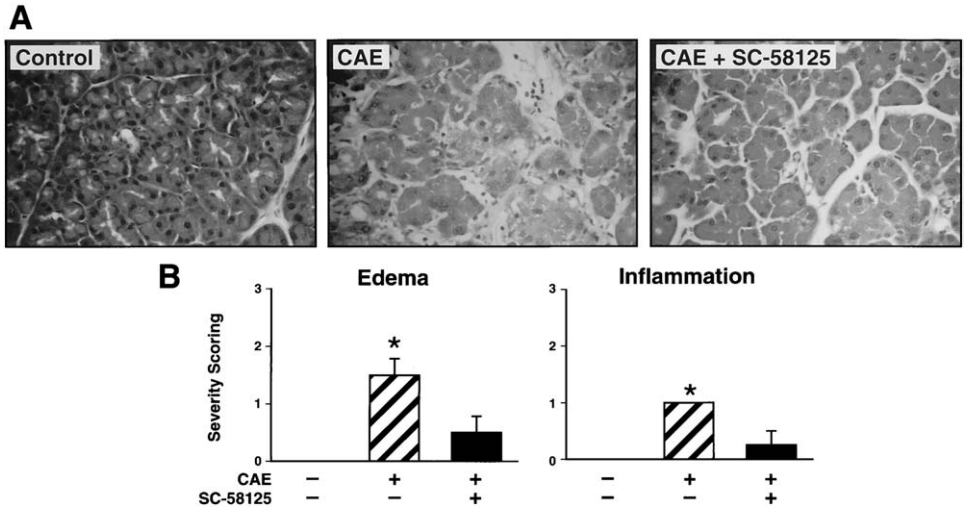

Fig. 1. Effects of the cyclooxygenase-2 (COX-2) inhibitor (SC-58125) on pancreatic inflammatory changes after induction of pancreatitis. (**A**) Representative hematoxylin/eosin-stained sections of pancreata were examined by light microscopy in control (CON) mice not given caerulein, in mice given caerulein (CAE), and in mice given SC-58125 (10 mg/kg) at the same time as the first injection of caerulein (CAE + SC-58125). (**B**) Histologic sections of pancreata harvested at 8 hours after the initiation of injections of saline (CON), CAE alone, or SC-58125 with CAE were scored from 0 (normal) to 3 (severe) for edema and inflammation as described in the Materials and Methods section (mean ± SEM; * = $p < 0.05$ vs. control).

reduced NF-κB activation compared to those animals treated with CAE alone (Fig. 2).

To assess the role of different NF-κB subunits in acute pancreatitis, ELISAs were performed to determine levels of either p50 or p65 in tissue extracts from the pancreas samples. No change was detected in p50 levels after induction of pancreatitis compared to the control group. However, p65 levels were elevated after induction of pancreatitis and returned to baseline levels with COX-2 inhibition (Fig. 3). Together, these data indicate that COX-2 inhibition results in diminished late phase NF-κB activation particularly affecting the p65 subunit.

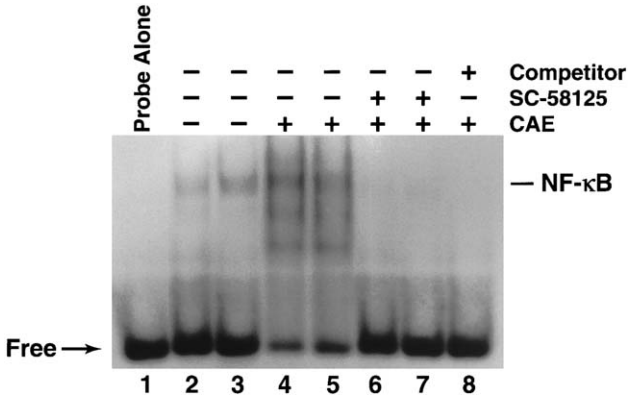

Fig. 2. Effects of cyclooxygenase-2 (COX-2) inhibition on nuclear factor (NF)-κB activation. Protein extracts were prepared from pancreata harvested at 8 hours after initiation of injections in animals treated with saline, caerulein (CAE), or SC-58125 with CAE. Extracts were assayed for NF-κB binding activity by EMSA as described in the Materials and Methods section.

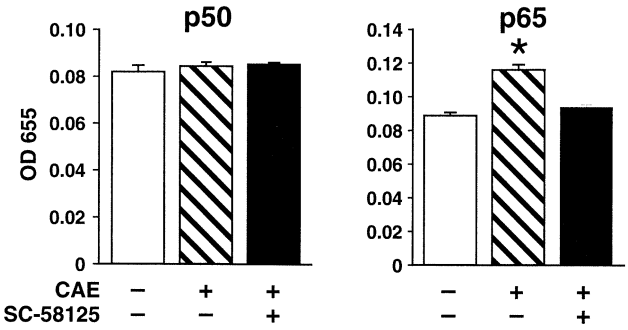

Fig. 3. Levels of nuclear factor (NF)-κB subunits, p50 and p65, after cyclooxygenase-2 (COX-2) inhibition in pancreatitis. Protein extracts were prepared from pancreata harvested at 8 hours after initiation of injections in animals treated with saline (control [CON]), caerulein (CAE) alone, or SC-58125 with CAE. Extracts were assayed for relative p50 and p65 concentrations by ELISA (mean ± SEM; * = $p < 0.05$ vs. control).

COX-2 inhibition does not alter serum or pancreatic IL-6 levels after induction of acute pancreatitis. IL-6 levels are elevated during episodes of acute pancreatitis;[37–39] although the exact function of IL-6 is unknown, levels of this cytokine have been shown to correlate with disease severity.[10] To determine whether serum IL-6 was altered after COX-2 inhibition during acute pancreatitis, mice were treated with the COX-2 inhibitor SC-58125 (10 mg/kg) immediately before supramaximal stimulation with CAE. Mice were sacrificed and blood was collected at 2, 4, 6, and 8 hours after the initiation of injections and serum obtained. IL-6 levels were measured by ELISA. Induction of pancreatitis resulted in significant elevations of serum IL-6. Combination treatment with both CAE and SC-58125 resulted in increased serum IL-6 levels that were elevated at 6 hours and unchanged at 8 hours compared to that of mice treated with CAE alone (Fig. 4 *A*, *B*).

As an additional assessment of IL-6 production, protein was extracted from the pancreatic tissue harvested 8 hours after initiation of CAE injections in the presence and absence of COX-2 inhibition; IL-6 levels were measured by ELISA. Induction of pancreatitis resulted in a significant increase in pancreatic levels of IL-6. Levels of pancreatic IL-6 in mice treated with the COX-2 inhibitor SC-58125, in addition to CAE, were comparable to those of mice treated with CAE alone (Fig. 4, *C*). These data indicate that COX-2 inhibition does not decrease IL-6 levels despite the decrease in histologic severity of acute pancreatitis.

Levels of IL-1β in the pancreas are elevated after COX-2 inhibition in acute pancreatitis. Because IL-1β is thought to be a critical component of the systemic inflammatory response associated with acute pancreatitis,[40–42] we assessed levels of IL-1β in serum and pancreatic tissue over a time course after induction of pancreatitis and treatment with SC-58125. Protein was extracted from the pancreata and ELISA was used to measure IL-1β levels. Over the time course of 2–8 hours, pancreatic IL-1β levels trended upward after pancreatitis induction with CAE; treatment with SC-58125 did not diminish the levels of IL-1β (Fig. 5, *A*). Combined data from two additional experiments performed at 8 hours demonstrate that the induction of pancreatitis with CAE results in a significant increase in IL-1β in the pancreas. COX-2 inhibition, in conjunction with CAE induction of pancreatitis, did not decrease pancreatic IL-1β levels, and, in fact, shows a trend toward an increase in IL-1β over those treated with CAE alone (Fig. 5, *B*). At all the time points assessed, serum IL-1β was undetectable by our assay (data not shown). These results further indicate that COX-2 inhibition does not result in decreased cytokine levels despite the significant changes in histologic severity.

DISCUSSION

The COX-2 isoform, which is induced in response to certain mitogens,[43–45] plays a key role in the pathogenesis of acute pancreatitis.[24,25] Our results further demonstrate that COX-2 inhibition, even at low doses, attenuates the histologic severity of acute pancreatitis. Treatment with the COX-2 inhibitor, SC-58125, decreased NF-κB activation normally seen at 8 hours after induction of acute pancreatitis. Despite this decrease in NF-κB activation, the cytokines IL-1β and IL-6, which are known to correlate with NF-κB activation,[15–17] remain elevated after treatment

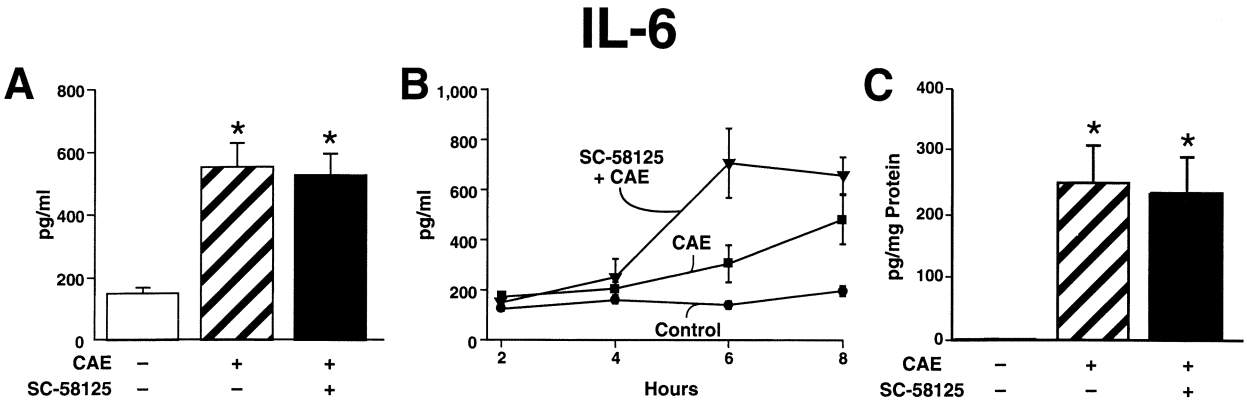

Fig. 4. Interleukin (IL)-6 levels after induction of pancreatitis. (**A**) Serum samples from mice sacrificed 8 hours after initiation of injections of saline (control [CON]), caerulein (CAE) alone, or SC-58125 with CAE were assayed for IL-6 levels by ELISA. (**B**) Serum samples from mice sacrificed over a time course (2, 4, 6, and 8 hours) after initiation of injections were assayed for IL-6 by ELISA. (**C**) Protein extracts from pancreata harvested at 8 hours after initiation of injections were assayed for IL- 6 levels by ELISA (mean ± SEM; * = $p < 0.05$ vs. control).

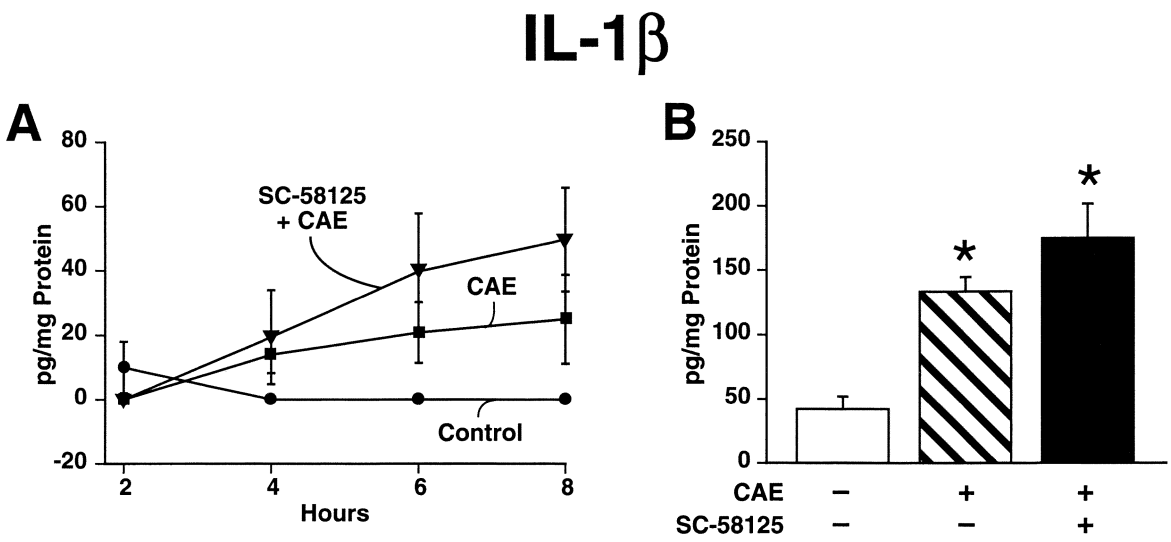

Fig. 5. Interleukin (IL)-1β levels after induction of pancreatitis. (**A**) Protein extracts were prepared from pancreata harvested over a time course (2, 4, 6, and 8 hours) after initiation of injections of saline (control [CON]), caerulein (CAE) alone, or SC-58125 with CAE. Extracts were assayed for IL-1β levels by ELISA. (**B**) Protein extracts were prepared from pancreata harvested at 8 hours after initiation of injections and assayed for IL-1β levels by ELISA (mean ± SEM; * = $p < 0.05$ vs. control).

with CAE despite COX-2 inhibition. Overall, these results indicate that the molecular mechanisms involved in the pathogenesis of acute pancreatitis and the systemic inflammatory response that ensues may involve cytokines but that another mediator is clearly required to produce both the pancreatic inflammation and the systemic inflammatory response often associated with acute pancreatitis.

The results in this study further confirm our previous findings[24] and suggest that COX-2 is a central mediator involved in producing both local inflammation and inciting the systemic inflammatory response. Unexpectedly, we found an apparent "disconnect" between injury to the pancreas and the resulting inflammation. In our previous study, we showed that amylase levels in mice that were either treated with a COX-2 inhibitor or genetically deficient in COX-2 were elevated compared to controls (to the same degree as CAE-treated animals) despite the diminished histologic severity.[24] Furthermore, we have also demonstrated a decrease in the histologic severity of the lung injury associated with pancreatitis in animals genetically deficient in COX-2,[24] indicating that the systemic inflammatory response is blunted by COX-2 inhibition as well. We propose that COX-2 may be the critical link between the "injury phase" and the "inflammation phase" of acute pancreatitis.

Our current study demonstrates that IL-1β levels are not attenuated by COX-2 inhibition after CAE induction; however, a decrease in inflammation is noted. There are several possible explanations for this finding. Investigators have shown that inhibition of IL-1β, both by competitive inhibition with IL-1 receptor antagonist (IL-1RA) or by genetic deletion, can ameliorate pancreatitis and improve survival.[12–14] However, in these studies, a decreased level of amylase was noted with IL-1 antagonism. These findings indicate that the ameliorating effects of cytokine inhibition may be the result of decreased injury to the pancreas rather than direct anti-inflammatory effects. Another explanation involves the IL-1β to IL-1 receptor antagonist (IL-1RA) ratio. IL-1RA can be endogenously produced and is elevated during inflammation.[12] Recent studies suggest that it is not the absolute level of IL-1β that produces systemic effects, but the ratio of IL-1β to IL-1RA.[46,47] Although we have demonstrated similar levels of IL-1β in the CAE treated animals and in those that received CAE plus the COX-2 inhibitor SC-58125, we did not evaluate levels of IL-1RA. It is possible that COX-2 inhibition produces a disproportionate increase in IL-1RA leading to competitive inhibition of IL-1β and decreased IL-1β effects. A third possibility is that IL-1β exerts some of its effects through COX-2 activation, which is markedly decreased during COX-2 inhibition.

The role of IL-6 is similarly complex. Multiple studies have correlated disease severity and levels of IL-6.[10,37–39,48–50] In fact, some studies have suggested that levels of IL-6 in patients with acute pancreatitis may be predictive of disease severity.[49] For example, Pezzilli et al.[49] demonstrated that IL-6 showed a

100% sensitivity, 86% specificity, and a 91% diagnostic accuracy in mild pancreatitis patients.

Despite these previous studies showing links between IL-6 levels and increased severity of acute pancreatitis, recent studies suggest that IL-6 may have an anti-inflammatory role during pancreatitis. Cuzzocrea and colleagues[51] have found that mice genetically deficient in IL-6 exhibited a more severe pancreatitis after CAE injections than wild type mice. Our results indicate that IL-6 levels are elevated in mice treated with or without SC-58125 despite attenuated pancreatic inflammation with COX-2 inhibition. This finding suggests that the stimulus for IL-6 secretion remains intact; however, it is still unclear whether IL-6 is mechanistically linked to the amelioration of pancreatitis during COX-2 inhibition.

As both IL-1β and IL-6 levels are elevated, it is clear that COX-2 inhibition does not interfere with the signaling pathways that precede the induction of these cytokines. Both cytokines are thought to be induced, at least partially, by NF-κB activation.[15–17] Previous studies by Gukovsky et al.[15] demonstrate that the kinetics of NF-κB activation after induction of pancreatitis are biphasic in nature; NF-κB is initially activated as early as 15 minutes after CAE administration, peaks at 30 minutes, decreases over the next hour, and then demonstrates a second peak between 3 and 6 hours. Our data indicate that COX-2 inhibition affects this second phase of NF-κB activation; one possible explanation for this is a feedback inhibition. A second possibility is that the second phase, as suggested by Gukovsky et al.,[15] is mediated by inflammatory cells that have infiltrated the pancreas; COX-2 inhibition significantly decreases the amount of neutrophil sequestration in the pancreas after treatment with caerulein as demonstrated by both histologic assessment and myeloperoxidase assay (MPO).[24,25] Thus, the absent later phase of NF-κB activation during COX-2 inhibition may be the result of insufficient inflammatory infiltrate to produce this secondary response. Song et al.[25] demonstrate that mice genetically deficient in COX-2 exhibit a decreased NF-κB response at 6 hours similar to our findings with the COX-2 inhibitor SC-58125; they also demonstrate that COX-2 knockout mice have an intact NF-κB activation at 30 minutes after CAE injection. Because IL-6 has been previously shown to be mediated by NF-κB activation,[15] we postulate that the initial peak of NF-κB remains intact after COX-2 inhibition, thus resulting in IL-6 release.

Multiple studies have sought to elucidate the role of NF-κB in acute pancreatitis.[15,21,36] To summarize, NF-κB inhibition resulted in decreased amylase release in some reports[15,23] and remained unchanged in others.[22,36] IL-6 production was decreased after NF-κB activation.[15] Some NF-κB inhibitors demonstrate an improvement in histologic severity of acute pancreatitis,[24] but others do not.[22,36] However, Satoh et al.[22] reported improved survival in an experimental model of taurocholate-induced acute pancreatitis in rats despite a lack of attenuation of histologic severity. The differing results may be due to differences in the mechanisms of action of the various NF-κB inhibitors. Of note, none of the studies measured serum or pancreatic IL-1β. Unlike COX-2 inhibition, direct NF-κB inhibition attenuates both the early (15–30 minutes) activation and the later (3–6 hours) activation. We propose that these findings may explain the "disconnect" between the injury and the inflammation phase of acute pancreatitis.

The release of IL-1β has not been shown to be mediated through NF-κB; in fact, the mechanism for IL-1β release may be release from microvesicles after mitogen stimulation.[52] This mechanism may explain the early transient increase in serum IL-1β reported previously.[11] If IL-1β release is not transcriptionally regulated, it is unlikely mediated by NF-κB, at least in the initial phase. Thus, it is predicted that IL-1β is elevated, even in the presence of NF-κB inhibition, and affects pancreatic cell injury leading to amylase release. Some NF-κB inhibitors may inhibit release of IL-1β from microvesicles, which accounts for the conflicting results.

CONCLUSION

We are proposing a mechanism by which acute pancreatitis is initiated and propagated in caerulein-induced pancreatitis. After a stimulus (e.g., supramaximal CCK stimulation), an injury phase is induced during which IL-1β is released and NF-κB is activated and IL-6 produced. COX-2 expression is increased through NF-κB activation[28,53–56] and induces the sequestration of neutrophils within the pancreas, which marks a major component of inflammation. These infiltrating neutrophils produce the second peak in NF-κB activation and elaborate secondary mediators that lead to edema, necrosis, and vacuolization. COX-2 inhibition does not affect amylase release or the levels of IL-1β or IL-6 and yet dramatically decreases the local and systemic inflammatory response seen in pancreatitis. Our data suggest that COX-2 may be a central mediator in converting the injury phase of acute pancreatitis into the inflammatory phase. Our current study extends previous findings suggesting a "disconnect" between pancreatic enzyme and cytokine release and pancreatic inflammation. Importantly, our results challenge current concepts regarding pancreatic cytokine

production and inflammation by showing that pancreatic inflammation can be attenuated with COX-2 inhibition despite induction of pancreatic cytokine levels in this mouse model of acute pancreatitis.

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Celiac Axis Occlusion With Replaced Common Hepatic Artery and Pancreatoduodenectomy

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A rare case of intraductal papillary mucinous tumor of the pancreas associated with a replaced common hepatic artery and celiac axis occlusion, which was treated by pancreatoduodenectomy, is reported. In this patient, the celiac trunk was occluded at its root and the splenic and left gastric artery could be visualized serially via the enlarged collateral artery on superior mesenteric arteriography. At surgery, the collateral artery was carefully preserved and pancreatoduodenectomy was successfully performed without ischemia of the stomach, spleen, and remnant pancreas. Although celiac axis occlusion is an uncommon finding for patients undergoing pancreatoduodenectomy, we recommend performing celio-mesenteric angiography before pancreatoduodenectomy, and, at surgery, clamping of the gastroduodenal artery is required for patients with celiac axis occlusion. (J GASTROINTEST SURG 2004;8:520–522)

KEY WORDS: Celiac axis occlusion, replaced common hepatic artery, pancreatoduodenectomy

INTRODUCTION

It is quite important to evaluate anatomic variations of the hepatic arteries before pancreatoduodenectomy, because patterns of arterial blood supply to the liver are variable and accidental ligation of aberrant hepatic arteries may cause hepatic necrosis. According to the previous literature, the entire common hepatic artery arising from the superior mesenteric artery is a rare variant occurring in 1.5%–4.5% of individuals.[1–8] Occlusion of the celiac axis is also an uncommon finding.[9–15] Pancreatoduodenectomy for a patient with celiac axis occlusion may result in postoperative ischemic necrosis of the liver, stomach, and remnant pancreas, because the procedure requires ligation and division of the gastroduodenal artery which participates in the rich anastomotic network between the celiac and superior mesenteric arteries. However, there are no previous reports of a patient with a replaced common hepatic artery and celiac axis occlusion undergoing pancreatoduodenectomy. We report herein a rare case of intraductal papillary mucinous tumor of the pancreas associated with a replaced common hepatic artery and celiac axis occlusion, which was successfully treated by pancreatoduodenectomy.

CASE REPORT

A 61-year-old male was admitted to our hospital with abdominal pain. Past history and family history was unremarkable. On admission, physical examination demonstrated normal vital signs and there was no tumor or tenderness on palpation of the abdomen. Laboratory evaluation was unremarkable and serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal ranges. Abdominal ultrasonography and computed tomography demonstrated a cystic tumor measuring 4×5 cm with a mural nodule at the head of the pancreas. Endoscopic retrograde pancreatography showed dilatation of the main pancreatic duct and cystic dilatation of the branch pancreatic duct. Superior mesenteric angiography did not demonstrate any irregularity of the pancreaticoduodenal artery, and there was no tumor stain. However, the common hepatic artery arose from the superior mesenteric artery and the celiac

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trunk was occluded at its root. The splenic and left gastric artery could be visualized serially via the enlarged collateral artery on superior mesenteric arteriography (Fig. 1). Coronal image processed by multislice computed tomography showed the replaced common hepatic artery, which ran ventrally to the portal vein and gave rise to the collateral artery (Fig. 2).

Under a diagnosis of intraductal papillary mucinous tumor of the pancreas, pylorus-preserving pancreatoduodenectomy was performed. At surgery, the common hepatic artery originating from the superior mesenteric artery was found. The common hepatic artery ran ventrally to the portal vein and trifurcated into the gastroduodenal artery, proper hepatic artery, and enlarged collateral artery. The enlarged collateral artery ran dorsally along the stomach to the splenic hilum. There was no celiac axis compression by the median arcuate ligament. The common hepatic artery, gastroduodenal artery, enlarged collateral artery, left gastric artery, and splenic artery were isolated and taped. Only the gastroduodenal artery was ligated and divided. By preserving the enlarged collateral artery, pulsations of the splenic and left gastric artery were maintained and there were no ischemic changes detected in the spleen and stomach. After pylorus-preserving pancreatoduodenectomy was completed, reconstruction of the alimentary tract was accomplished by pancreatogastrostomy, duodenojejunostomy, and hepaticojejunostomy. On subsequent pathological examination, the tumor was adenocarcinoma in adenoma with papillary growth.

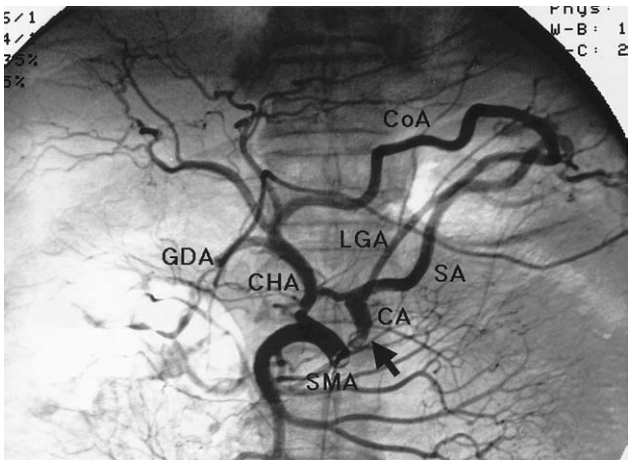

Fig. 1. Superior mesenteric angiography showing the entire common hepatic artery arising from the superior mesenteric artery. Celiac trunk is occluded at its root (*arrow*) and the splenic and left gastric arteries are serially visualized via the enlarged collateral artery. CA = celiac artery; CHA = common hepatic artery; CoA = collateral artery; GDA = gastroduodenal artery; LGA = left gastric artery; SA = splenic artery; SMA = superior mesenteric artery.

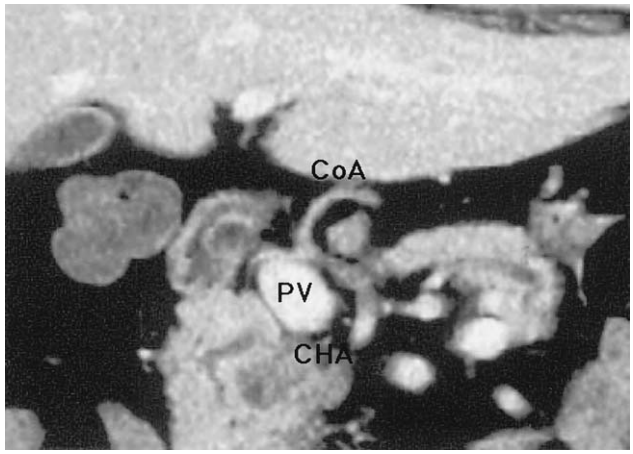

Fig. 2. Coronal image processed by multislice computed tomography showing the common hepatic artery, which runs ventrally to the portal vein and gives rise to the collateral artery. CHA = common hepatic artery; CoA = collateral artery; PV = portal vein.

The postoperative course of the patient was uneventful. There was no necrosis of the spleen or stomach. The patient was discharged 4 weeks after surgery and has survived for 10 months without signs of recurrence on imaging examinations.

DISCUSSION

There are many variations in surgical anatomy of the hepatic arteries. Hiatt et al.[7] analyzed surgical anatomy of the hepatic arteries in 1000 cases undergoing orthotopic liver transplantation and reported that variant patterns of the hepatic arteries were found in 24.3% of patients. According to the other large series of anatomical studies on the hepatic arteries, variant arterial hepatic anatomy has been reported in 24%–49% of cases based on cadaveric and angiographic reports.[1–8] However, of all variant hepatic arteries, the common hepatic artery arising from the superior mesenteric artery is very rare, with a reported incidence of 1.5%–4.5%.[1–8] In our case the entire common hepatic artery arose from the superior mesenteric artery and trifurcated into the proper hepatic artery, the gastroduodenal artery, and the enlarged collateral artery.

Thompson et al.[9] reported that the incidence of celiac axis occlusion was 10% for angiographic study of patients scheduled for pancreatoduodenectomy. However, this report seems to be a gross overestimation, because several authors have recently reported that the incidence of celiac axis occlusion is 2%–3%

of patients undergoing pancreatoduodenectomy.[11,15] In our institution, where 116 pancreatoduodenectomies have been performed in recent years, we have encountered only 1 patient with celiac axis occlusion (this case), which suggests an actual frequency of 1%. The etiology of celiac axis occlusion is divided into two types: atherosclerosis[9,11,13,15] and arcuate ligament compression.[10,12,14,15] For extrinsic compression by the arcuate ligament surgical restoration of the celiac circulation by division of the ligament is recommended, because it is an easy and safe procedure.[15] However, it has not been determined whether routine revascularization, including celiac trunk reimplantation, aorto-hepatic bypass, and mesenterico-splenic bypass must be performed when occlusion is caused by atherosclerotic change. For this reason, performance of pancreatoduodenectomy with vascular anastomosis carries the risk of overwhelming hemorrhage in the case of pancreatoenteric anastomotic leakage. Moreover, the pancreatoduodenal arterial network usually meets blood requirements in the celiac territory after division of the gastroduodenal artery. Berney et al.[15] recommended trial clamping of the gastroduodenal artery before division of the gastroduodenal artery and indicated that if the pulse of the hepatic artery, left gastric artery, and splenic artery stopped or decreased, a revascularization procedure should be performed. In our case, preoperative angiography showed celiac axis occlusion with a replaced common hepatic artery. As the splenic and left gastric artery were serially visualized via the enlarged collateral artery, the collateral artery was carefully preserved and, as a result, ischemia of the spleen, stomach, and remnant pancreas was successfully prevented.

CONCLUSION

The necessity of performing preoperative celiomesenteric angiography for pancreatoduodenectomy remains controversial. Sahani et al.[16] described that multidetector CT provided valuable preoperative information about abdominal vascular architecture and could be used as a noninvasive alternative to catheter angiography before surgery. However, it is not clear that these new modalities, including CT angiography or magnetic resonance angiography, can definitely visualize celiac axis occlusion. Therefore, we recommend performing celio-mesenteric angiography with portal vein phase before pancreatoduodenectomy.

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