An Initial Evaluation of Pelvic Floor Function and Quality of Life of Bladder Exstrophy Patients After Ureterosigmoidostomy

Jennifer Miles-Thomas, M.D., John P. Gearhart, M.D., Susan L. Gearhart, M.D.

Classic bladder exstrophy is characterized by displaced pelvic floor musculature and significant skeletal and genitourinary defects. A paucity of data exist evaluating long-term pelvic floor function in exstrophy patients after ureterosigmoidostomy. This study is an initial attempt to evaluate the prevalence of urofecal incontinence, pelvic organ prolapse, and overall quality of life in patients who have had ureterosigmoidostomies. Fifty-two individuals who underwent ureterosigmoidostomy between 1937 and 1990 were identified through the Ureterosigmoidostomy Association and the Johns Hopkins bladder exstrophy database and mailed questionnaires approved by the Institutional Review Board (Johns Hopkins). Data were analyzed with SigmaStat 3.0 (SPSS, Inc., Chicago, IL). Eighty-three percent of the subjects responded, with a mean age of 44.4 years (range, 14–73 years) and mean of 40.9 years (range, 14–65 years) after ureterosigmoidostomy. Prevalence of daily urinary and fecal incontinence was 48% (n = 20) and 26% (n = 11), respectively, whereas the prevalence of weekly combined urofecal incontinence was 63% (n = 27). The incidence of pelvic organ prolapse in this cohort was 48% (n = 20). In these patients, a significant risk of urofecal incontinence and pelvic organ prolapse exists. Long-term follow-up studies are needed to understand the role of pelvic floor musculature in this complex birth defect.
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KEY WORDS: Bladder exstrophy, incontinence, ureterosigmoidostomy

Bladder exstrophy is a major congenital birth defect involving the abdominal wall from the umbilicus to the tip of the urethra. The pelvic bones are separated, and the bladder lies externally between the two pubic rami. The urinary sphincters are absent. This abnormality is seen in 1 in 40,000 newborns.[1] Ureterosigmoidostomy is a surgical procedure historically used in the treatment of bladder exstrophy, where the ureters are inserted into the taenia of the sigmoid colon in a nonrefluxing manner. The use of the sigmoid colon allows the patient to maintain continence and evacuate urine through the anus, thus eliminating the need for a cutaneous urinary diversion or catheterizable abdominal stoma. This procedure is typically done in patients where the native bladder is not amenable to reconstruction. Ureterosigmoidostomy is associated with a preserved body image and improved quality of life.[2] However, many long-term effects from this procedure, including pyelonephritic renal damage, nephrolithiasis, and neoplasia have been reported. What is unknown regarding ureterosigmoidostomy is long-term pelvic floor function, including urofecal incontinence. The purpose of this study was to evaluate this function in a cohort of patients with a longstanding ureterosigmoidostomy. Currently, to our knowledge, no studies exist evaluating the quality of life and long-term pelvic floor outcomes of adult ureterosigmoidostomy patients in the United States.

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MATERIAL AND METHODS

After approval by the Institutional Review Board (Johns Hopkins), patients who were members of the Ureterosigmoidostomy Association or had a documented ureterosigmoidostomy in the institutionally approved Johns Hopkins exstrophy database were sent a four-page questionnaire. This questionnaire contained a modified version of the commonly used Fecal Incontinence Severity Index. The identical questionnaire was also available on a secure website. Reminder e-mails and letters were sent to patients 3 weeks after the initial mailing. Data were analyzed with SigmaStat 3.0 (SPSS, Inc., Chicago-IL). Continuous variables were calculated as mean $\pm$ standard deviation. Categorical variables were summarized as percent. Multiple logistic regressions were used to investigate relationships between sex, uterine prolapse, and fecal incontinence. *T* tests were used to compare means of categorical variables. All statistical analyses were performed with SigmaStat 3.0 (SPSS, Inc.). All *P* values are two-sided and considered significant at $P \leqslant 0.05$. Results were assessed from returned questionnaires 1 month after the initial mailing.

RESULTS

Fifty-two questionnaires were mailed to participants, and 83% (n = 43) were returned either by mail or online. The respondents had a mean and median age of 44.4 and 43.5 years, respectively (Table 1). The number of male and female respondents was nearly equivalent (n = 22 and n = 21, respectively). Over 90% (n = 39) of respondents underwent ureterosigmoidostomy for bladder exstrophy. The mean and median number of years after ureterosigmoidostomy was 40.9 and 42 years, respectively, with a range of 14–65 years. Eighty-four percent of respondents (n = 36) were married, and this was distributed equally among men and women. Fifty-five percent of female respondents had children, with a mean parity of 1.85 live births. Overall, 53.8% of all respondents reported the frequency of sexual activity was as much as he or she desired; however, 77.2% (n = 17) of women and 71.4% (n = 16) of men had been sexually active within the past month.

Table 1. Patient characteristics

	Male (n = 22)	Female (n =21)
Age	48.5 (range 33–73)	40.1 (range 14–67)
Years with ureterosigmoidostomy Mean	45	36.7
Marital status (%)	18 (82)	17 (81)
Respondents with children (%)	n/a	14 (63.6)
Mean parity	n/a	1.85

In patients who have undergone ureterosigmoidostomy, incontinence frequently results in the loss of stool and urine. We have termed this situation as urofecal incontinence. Urofecal incontinence was present in 56% (n = 24) of respondents. Half of all male respondents experienced urofecal incontinence (11/22), as did 62% (13/21) of female respondents (OR 1.79; 95% CI, 0.52-6.10). When frequency of incontinence was assessed, we found the prevalence of overall daily urinary incontinence was 48% (n =20). The prevalence of daily overall fecal incontinence was 26% (n = 11), whereas the prevalence of overall weekly combined urofecal incontinence was 63% (n = 27).

Age was not independently associated with urofecal incontinence (Fig. 1). However, when adjusted for age greater than 40, men were 70% more likely to be continent than women were. Women greater than 40 years of age were 45% more likely to have urofecal incontinence than their younger counterparts were (OR, 1.45). Women who did not have urofecal incontinence had a higher parity than women with urofecal incontinence did, but this was not statistically significant. The incidence of pelvic organ prolapse in this cohort of patients was 48% (n = 20). There was no significant difference in urofecal incontinence or pelvic organ prolapse with respect to gender. In our study, 50% (10/20) of patients with uterine prolapse also experienced urofecal incontinence. However, 30% without uterine prolapse also experienced incontinence (Fig. 2). In addition, 40% of female survey respondents did not answer the question. Only four respondents reported a history of hysterectomy. Of those, two experienced urofecal incontinence.

Despite the above findings, 86% (n = 37) of respondents were pleased with the results of their surgery and did not wish to have additional diversion surgery (Fig. 3). However, despite the fact that respondents were generally happy with their results after ureterosigmoidostomy, 90% (n = 39) of all respondents needed additional surgery for their genitourinary disorder. When comparing male and female respondents, 77.8% (n = 17) of men and 100% (n = 43) of women had undergone additional surgery ($P = 0.06$). Overall, 1.4% (n = 6) of respondents stated that they would consider another form

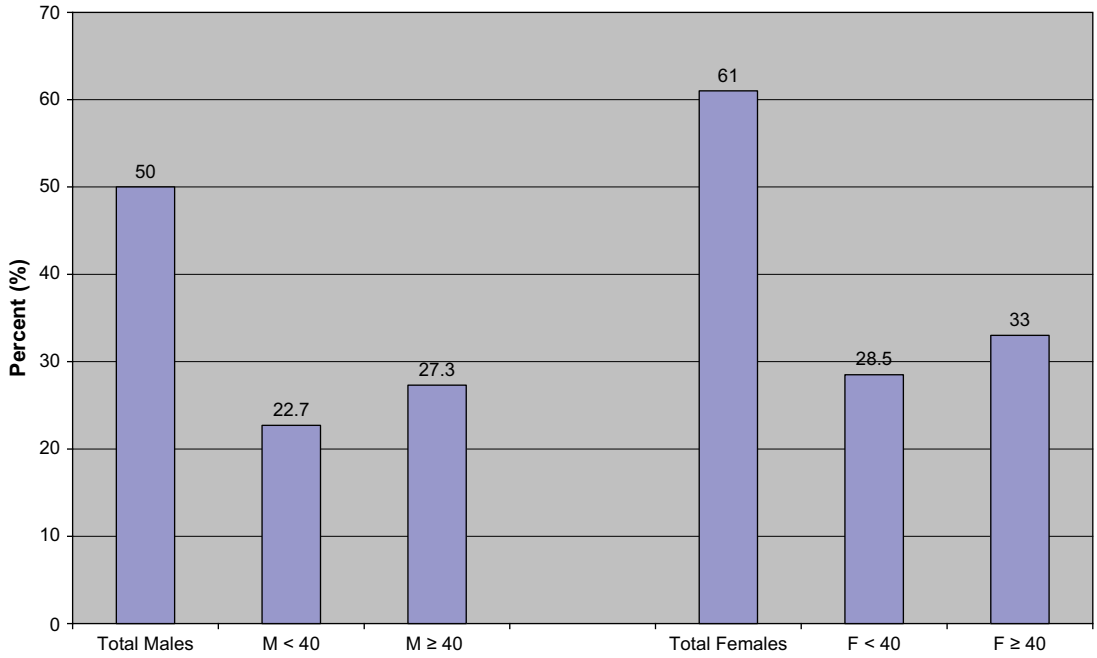

Fig. 1. The prevalence of urofecal incontinence in males and females as a function of age.

of diversion, either continent urinary diversion (n = 4) or cutaneous urinary diversion (n = 2).

Of note, given the increased risk of developing adenocarcinoma at the ureterocolonic junction after ureterosigmoidostomy, questions regarding colon cancer screening and visits to the urologist were also submitted. In this cohort of participants, 7% (n = 3) were diagnosed with colorectal adenocarcinoma at 47, 40, and 33 years after the initial diversion. It is interesting to note that 11% (n = 5) of

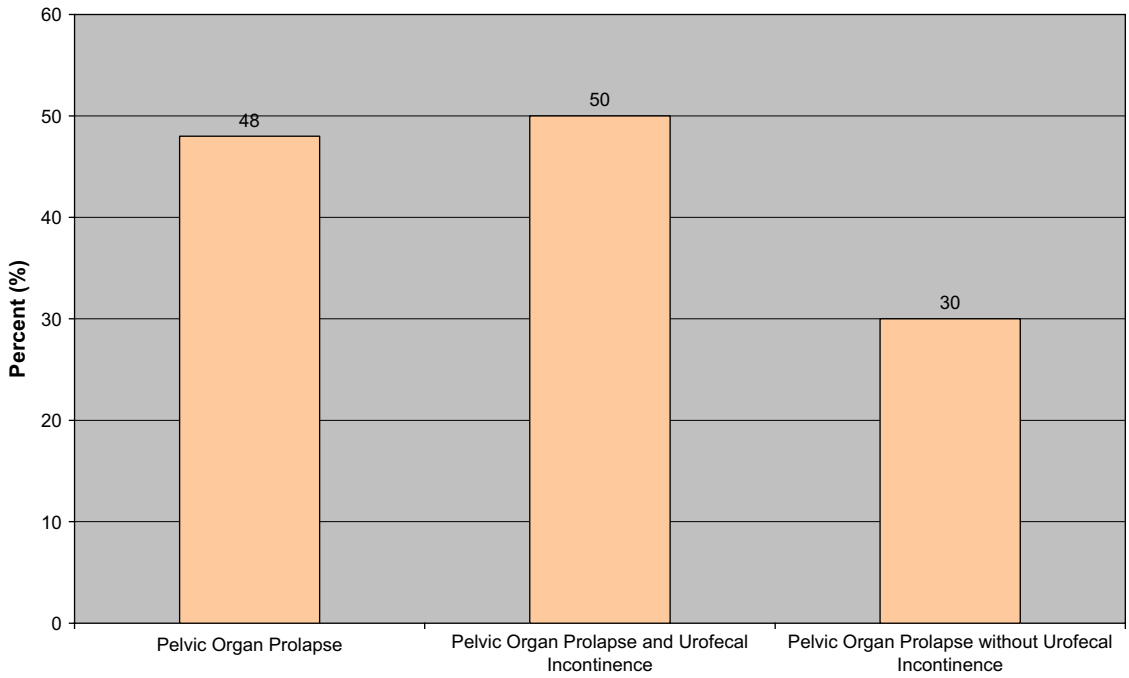

Fig. 2. The prevalence of pelvic organ prolapse and urofecal incontinence.

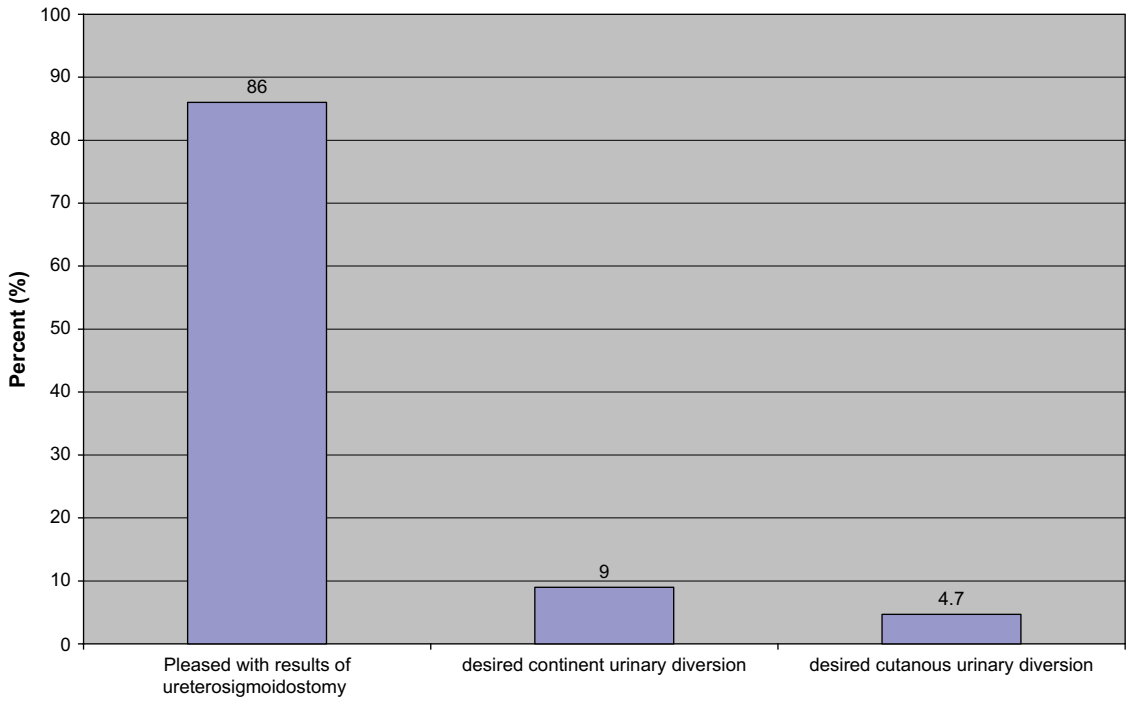

Fig. 3. Respondent satisfaction after ureterosigmoidostomy.

all respondents have never had a sigmoidoscopy, whereas 42% (n = 18) fulfill current recommendations and undergo annual flexible sigmoidoscopy.

DISCUSSION

This study represents the first study to evaluate long-term pelvic floor function in patients who have undergone ureterosigmoidostomy. In this cohort of patients obtained from the Ureterosigmoidostomy Association and the Johns Hopkins bladder exstrophy database, the prevalence of bladder exstrophy was 90% (n = 39). The Johns Hopkins institutionally approved exstrophy database currently contains 848 patients, 11 of whom have undergone ureterosigmoidostomies. Currently, ureterosigmoidostomies are still performed in some European and South American countries; however, this is not done at our institution. Other reasons for performing this procedure include cancer and other major malformations of the urogenital tract. Previously, bladder exstrophy was thought to be more prevalent in males, with a male to female ratio of 2.5:1. However, current studies, including the present study, have demonstrated an equal prevalence in male and females.[3] Currently, primary closure of the bladder, in the neonatal period if the bladder template is suitable, is the standard of care. If primary closure is not possible, diversions including colonic conduits and ureterosigmoidostomy are considered.[4] The objective of urinary diversion is no longer solely to preserve renal function. Current objectives include maintaining an acceptable body image for patients while preserving a good quality of life.[4] Although ureterosigmoidostomy may provide an acceptable external appearance and functional result, additional elements of the long-term outcome must be considered.

A major recognized complication of ureterosigmoidostomy is neoplasia, and it is for this reason the procedure is used very judiciously in a few centers worldwide. The risk of adenocarcinoma of the colon at the ureteral implantation site has been documented between 500 and 7000 times more frequently than the general population.[5] The incidence of carcinoma after ureterosigmoidostomy may reach as high as 24% in long-term follow-up studies.[6] The incidence increases over time, with the mean time of cancer formation at 17.2 years after ureterosigmoidostomy; therefore, annual surveillance with flexible sigmoidoscopy to just beyond the ureteral anastomoses is recommended. Lesions at the anastomosis should be biopsied. Routine biopsies are not recommended.[6]

It is well known that significant musculoskeletal defects exist in patients with bladder exstrophy.[7,8] However, the effect of these defects on pelvic floor

function, including prolapse and fecal continence, is not known. Recently, magnetic resonance imaging and three-dimensional CT imaging of the pelvic floor musculature has been performed in patients with bladder exstrophy.[7,8] These studies have confirmed that the sacroiliac joints and the anterior and posterior pelvis are externally rotated with a 30% shortage of bone in the anterior pelvis.[8] Furthermore, an alteration in the elliptical shape of the levator muscles exists such that 70% of the levator mass is posterior to the rectum and only 30% is anterior. In normal pelvic floor anatomy, the levator mass is evenly split between the anterior and posterior pelvis, providing circumferential support to the rectum and anterior support to the vagina, uterus, and bladder in the female and prostate and bladder in the male. These findings in patients with bladder exstrophy are likely secondary to the major bony abnormalities described above.[9] Given the abnormalities in the levator musculature, we hypothesized that bladder exstrophy patients are intrinsically predisposed to more urofecal incontinence after ureterosigmoidostomy.

This study demonstrated a significant number of respondents with urofecal incontinence. Furthermore, 90% (n = 39) of respondents needed further surgery for their urogenital disorder. This condition worsened with both age and parity among females. Furthermore, although it is known that bladder exstrophy patients are more prone to pelvic organ prolapse, this study demonstrated a significant number of female patients with prolapse. Those patients with prolapse tended to suffer more from urofecal incontinence, although this was not statistically significant. We are unable to determine whether prolapse and urofecal incontinence was a result of persistent loose stools, conscious constant squeezing of the external sphincter to remain dry, or an effect of the aberrant levator musculature. Current repair of bladder exstrophy includes the performance of a pelvic osteotomy that allows for closure of the pubic bone diastasis and correction of the sacroiliac joint rotation, thus bringing the major muscle groups to a more midline position. This closure of the pelvic floor may allow for improved pelvic floor function; however, long-term follow-up on these patients is currently not available.

Throughout the literature, a high degree of patient satisfaction has been reported after ureterosigmoidostomy.[4,10,11] In this study, we found that 86% (n = 37) of respondents were happy overall with an ureterosigmoidostomy. Improved body image, good long-term outcomes, and freedom from external collection devices and intermittent self-catheterization are an important part of the overall happiness of the patient. However, the findings of this study indicate that not only should patients be counseled regarding the risk of neoplasia but also regarding the risk of significant urofecal incontinence. This is particularly prevalent in women over the age of 40 years. Furthermore, the new application of these imaging modalities may allow an improved understanding of pelvic floor function and allow surgeons who perform ureterosigmoidostomy better patient selection and better outcomes.

CONCLUSION

Bladder exstrophy patients have complex bony and musculoskeletal abnormalities. After undergoing ureterosigmoidostomy, a significant risk of urofecal incontinence and pelvic organ prolapse is present. Additional studies are warranted to further evaluate the anomalies of the pelvic floor musculature in this complex birth defect.

REFERENCES

1. Gearhart JP. Exstrophy, epispadias, and other bladder anomalies. In: Walsh PC, ed. Campbell's Urology, 8th ed. Philadelphia: WB Saunders, 2002, p 2136.
2. Donnard G, Dumotier J, Le Dantec P, Suppini A, Quinot JF. Hyperammonemia encephalopathy after ureterosigmoidostomy. Cah Anesthesiol 1996;44:149–151.
3. Nelson CP, Dunn RL, Wei JT. Comtemporary epidemiology of bladder exstropy in the United States. J Urol 2005; 173:1728–1731.
4. Mansi MK. Continent urinary undiversion to modified ureterosigmoidostomy in bladder exstrophy patients. World J Surg 1999;23:207–213.
5. Woodhouse CRJ. Guidelines for monitoring patients with ureterosigmoidostomy. Gut 2002;51(Suppl V):v15–v16.
6. Huang A, McPherson GA. Colonic carcinoma after ureterosigmoidostomy. Postgrad Med J 2000;76:579–581.
7. Stec AA, Pannu HK, Tadros YE, Sponseller PD, Wakim A, Fishman EK, Gearhart JP. Evaluation of the bony pelvis in classic bladder exstrophy by using 3D-CT: Further insights. Urology 2001;58:1030–1035.
8. Stec AA, Pannu HK, Tadros YE, Sponsellor PD, Fishman EK, Hearhart JP. Pelvic floor anatomy in classic bladder exstrophy using 3-dimensional computerized topography: Initial insights. J Urol 2001;166:1444–1449.
9. Williams AM, Solaiyappan M, Pannu HK, Bluemke D, Schechter G, Gearhart JP. 3-dimensional magnetic resonance imaging modeling of the pelvic floor musculature in classic bladder exstrophy before pelvic osteotomy. J Urol 2004;172:1702–1705.
10. Golbano Ablanque JM, Serrano Pascual A, Otero Tejero I, Merino Hernaez C, Chicharro Almarza J, Gonzalez-Permato Gutierrez P. Detubularized ureterosigmoidostomy Mainz II: A diversion with a future? Arch Esp Urol 2001;54:123–128.
11. Stein R, Stockle M, Fisch M, Nakai H, Muller SC, Hohenfellner R. The fate of the adult exstrophy patient. J Urol 1994;152:1413–1416.

Early Perioperative Outcomes and Pancreaticoduodenectomy in a General Surgery Residency Training Program

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Current trends in national health care are triggering a reassessment of training in general surgery. Currently, 75% of general surgery residents seek postgraduate fellowship training, and significant debate has occurred regarding the best manner for surgeons to acquire competency in performing complex operations. Pancreaticoduodenectomy (PD) is a complex procedure performed infrequently by most surgical graduates. From 1990 through 1997, the average number of PD operations performed per general surgery graduate ranged from 1.5 to 2.5. We examine the surgical outcomes following PD performed by surgical resident staff in a university-based general surgery training program. Between January 2001 and October 2004, 164 patients underwent PD for periampullary disease. Data were prospectively entered into a computerized database, including resident participation. We analyzed 30-day mortality and morbidity rates. Perioperative outcomes were 30-day mortality (2.2%), pancreatic fistula (6.1%), reoperation (2.2%), average length of hospital stay (13.5 days), mean operating time (489 minutes), and median estimated blood loss (1274 ml per case). PD can be performed with an acceptable morbidity and mortality within the teaching structure of a general surgery training program. These outcomes are likely related to the performance of PD at a high-volume, tertiary center by a single surgeon and compare favorably to best-practice benchmark outcomes. (J GASTROINTEST SURG 2006;10:478–482) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: General surgery training, outcomes, pancreaticoduodenectomy, vascular resection

Current trends in national health care are triggering a reassessment of training in general surgery. Early specialization (including advanced gastrointestinal surgery) has been suggested by a blue ribbon panel of the American Surgical Association, the American Board of Surgery, and The American College of Surgeons.[1,2] According to resident operative experience reported to the Accreditation Committee for Graduate Medical Education for the academic years 1990–1997, the average number of pancreaticoduodenectomy (PD) operations performed per graduate ranged from 1.5 to 2.5.[3] The average urban teaching hospital performs approximately 2.7 PD operations per year,[4] while the top high-volume pancreatic surgery centers perform over 100 procedures per year.[5–7] Many of these high-volume hospitals are centers for postgraduate fellowship training.[7] Recent data support that volume and experience of the surgical provider correlate with improved clinical and economic outcomes in complex gastrointestinal surgery.[8–10,13] Given recent debate surrounding surgical training and complex procedures, we sought to analyze early surgical outcomes after PD within a university-based general surgery training program and to compare our results with national benchmark outcomes.

PATIENTS AND METHODS

Patients

Data for all patients who underwent PD at a single tertiary urban teaching institution between January

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2001 and October 2004 were prospectively entered into a computerized database, including resident participation. A single fellowship-trained attending surgeon supervised all PD operations performed by general surgical residents. The surgical resident was designated as the primary surgeon when the trainee performed the entire resection and reconstruction phases of the operation. When these criteria are not met, the attending surgeon was designated as the primary surgeon. The chief resident was designated as the primary surgeon at the beginning of all procedures.

Preoperative Evaluation

Patients with a preoperative diagnosis of periampullary neoplasm fulfilled the following criteria of resectibility: (1) no evidence of extrapancreatic metastatic disease, (2) no invasion of the abdominal aorta or its branches, and (3) patency of the portal and superior mesenteric vein and presence of a 2.0 cm segment of superior mesenteric vein, uninvolved by tumor.[11] Patients with a preoperative diagnosis of chronic pancreatitis fulfilled the following criteria for surgical resection: (1) presence of narcotic-requiring abdominal pain and (2) evidence of an inflammatory mass within the head of pancreas.

Surgical Technique

PD was performed as described by Warshaw and Thayer.[12] The final step involved complete dissection of the head of pancreas and uncinate, from the lateral surface of the portal vein and the anterolateral surface of the superior mesenteric artery. In cases of local-regionally advanced neoplasms, vascular resection was performed as described by Tseng et al.,[11] when such a surgical maneuver would yield an R_0 resection status.

Perioperative Complications

Major perioperative complications were defined as follows: perioperative mortality (death within the first 30 days after surgery); need for reoperation; pancreatic fistula (defined as $\geqslant$50 ml of amylase-rich fluid >4 times the upper limit of normal serum amylase from a surgical drain on postoperative day 7 or via a catheter placed with use of interventional radiology); postoperative intra-abdominal hemorrhage requiring any blood transfusion; intra-abdominal fluid collection (sterile or abscess); myocardial infarction or sudden cardiac death; pulmonary complications including pneumonia; gastrointestinal bleeding; and length of intensive care unit stay of longer than 7 days. Hospital stay was calculated by considering the day of surgery as day 1.

RESULTS

Between January 2001 and October 2004, a total of 164 patients underwent PD for periampullary disease. Of 164 patients, 38 had tumor extension to a major vessel that necessitated vascular resection and reconstruction with the goal of an R0 resection (Table 1), Supervised surgical residents performed 138 of 164 PD operations, of which 12 required major vascular resection. Twenty-six operations were performed by the attending, as the resident surgeon did not complete the entire resection and reconstruction. The nomenclature developed by Tseng and Evans for vascular resection was used[11] (Table 1). Among the 138 patients, 88 (64%) underwent PD for adenocarcinoma of the pancreas. The median operative time was 489 minutes, the mean hospital stay was 13.5 days, and the estimated blood loss was 1274 ml per case. Table 2 shows the operative characteristics and perioperative complications. The hospital and 30-day mortality among the 138 patients was 2.2%. The perioperative complications included reoperation (2.2%), pancreatic fistula (6.5%), intra-abdominal hemorrhage (0.73%), delayed gastric emptying (33%), myocardial infarction

Table 1. Patient demographics, disease histology, and type of vascular resection

Variable	(n = 138)
Gender	
Male	73
Female	65
Age (years)	
Median	61.5
Range	24–93
Neoplasm	
Pancreas	88 (64%)
Bile duct	8 (6%)
Duodenum	1 (0.7%)
Ampullary	3 (2.7%)
Neuroendocrine	1 (0.7%)
Inflammation	
Chronic pancreatitis	37 (27%)
Vascular resection (Type)	
V1	9 (75%)
V2	0
V3	0
V4	0
V5	0
Hepatic artery	3 (25%)
Inferior vena cava	0

Table 2. Operative characteristics and perioperative complications

Variable	Number (n = 138)
Estimated blood loss (cc)	
Mean	1274
Range	173–2900
Median operative time in minutes	489
(range)	(297–1449)
Median hospital stay (days)	13.5
(range)	(6–34)
Perioperative death	3 (2.2%)
Major perioperative complications	
Reoperation	3 (2.2%)
(range)	(8–29)
Pancreatic fistula	9 (6.5%)
Neoplasm	6 (4.3%)
Chronic pancreatitis	3 (2.2%)
Intraabdominal hemorrhage	1 (0.73%)
Delayed gastric emptying	38 (33%)
Intraabdominal fluid collection	
Sterile	13 (9.4%)
Abscess	9 (6.5%)
Myocardial infarction	3 (2.2%)
Pulmonary complication	12 (8.7%)
Gastrointestinal bleeding	2 (1.4%)
ICU stay > 7 days	8 (5.8%)

Table 3. Perioperative outcomes and recent surgical literature

Variable	(n = 139)	Literature[16] (n = 2730) 1997–2003
Gender (men %)	52.8%	56%
Age in years	61.5%	63.3
Mortality (%)	2.2%	1.9%
OR time in minutes	489	431
(range)	(297–1449)	(412–531)
Estimated blood loss in cc	1274	1183
(range)	(173–2900)	(982–1600)
Length of stay in days	13.5	17.7
(range)	(6–34)	
Pancreatic anastomosis leak (range)	6.5%	9.9% (0–18)
Delayed gastric emptying at post-operative day 14	33%	13.9% (2.5–22)
Reoperation (range)	2.2%	3.8% (0.8–9)

(2.2%), pulmonary complications (8.7%), gastrointestinal bleeding (1.4%), and intensive care unit stay of longer than 7 days (5.8%). We compared the outcomes of patients who underwent PD in our series with those of 2730 cases from 16 published reports from 1997 to 2003[16] (Table 3). Similar perioperative outcomes in this series and these benchmark outcomes are noted.

DISCUSSION

U.S. surgical training will likely undergo dramatic changes in the near future, and reorganization of general surgery training is a subject of debate. Recent data have emphasized the relationship between surgeon and hospital experience, and operative mortality as well as cancer-free survival[7,8] for PD. Given the low numbers of PD procedures performed by most general surgical trainees,[3] one must question if the average general surgery graduate is prepared to perform elective PD. Currently, the American Board of Surgery certifies graduates in general surgery to perform PD. It is unknown whether graduates from low-volume surgical training programs have different outcomes for PD than do graduates from high-volume training programs or graduates of fellowship training programs. The case has been made that training in complex gastrointestinal surgery might be best performed in postgraduate fellowships.[15] Given the debate regarding training and complex surgical operations, we analyzed perioperative outcomes for PD performed within the teaching structure of a general surgery residency. Perioperative outcomes for PD performed by general surgery residents, under supervision of a single fellowship-trained surgeon, appear to compare favorably with best-practice national outcomes for PD. These outcomes are likely related to the performance of PD at a high-volume tertiary center by a single surgeon and compare favorably to outcomes published from large pancreatic surgery centers, in which fellows performed PD.[7] Based upon these data, perioperative outcomes for PD appear to be more closely linked to hospital and surgeon experience than to the status of the trainee performing the operation. Indeed, excellent perioperative outcomes have been published from departments of general surgery, where PD is performed with general surgery resident staff; without postgraduate fellows.[5,6]

When comparing data from this series with best-practice national outcomes published in the surgical literature, mortality was slightly higher (2.2% versus 1.9%), operative time longer (489 minutes versus 431 minutes), and estimated blood loss slightly higher (mean, 1274 ml versus 1193 ml). However, the rate of pancreatic fistula was lower in our series than in published benchmark data (6.5% versus 9.9%), and the average length of stay was less (13.5

days versus 17.7 days). Pancreatic fistula was less common in patients undergoing PD for chronic pancreatitis versus neoplasm (2.2% versus 4.3%). The increased blood loss observed may be related to increased operative time observed in this study as well as the relatively high percentage of patients undergoing vascular resection and reconstruction.

The stated position of the American Board of Surgery is to broadly train general surgeons who are capable of the diagnosis and surgical management of a wide range of hepatobiliary diseases, including periampullary neoplasms and the performance of PD. Multiple arguments have been made to preserve the breadth and depth of general surgical practice,[17,18] stating that a well-trained surgical generalist is needed by the majority of patients seeking surgical care in the United States. However, surgery has changed dramatically in the past 25 years, with increasing use of complex technology, a rapidly increasing body of scientific knowledge, and declining morbidity and mortality for complex surgical procedures performed by specialists.[14,15] A reassessment of how to train competent surgical specialists has also been stimulated by (1) limitations of trainee work hours, (2) increased public scrutiny of the health care system (and of the quality of care provided by surgeons), and (3) medical-legal concerns. The American Surgical Association Blue Ribbon Committee has recognized these factors and has recommended early specialization for complex gastrointestinal surgery, including hepatobiliary and pancreatic surgery. It is unclear under this model if general surgeons without subspecialty training would continue to be certified to perform PD. PD performed in training programs might be reserved for subspecialist trainees, in the areas of surgical oncology, hepatobiliary and pancreatic surgery, and transplant surgery.

The proposed changes in surgical training aim to streamline surgical training, recognizing that 75% of surgical graduates seek postgraduate fellowship training.[2] Our data seem to indicate that outcomes for PD, performed in a training program, are more closely linked to the experience and volume of attending surgical providers who supervise trainees. Such a training program would be appropriate for training in complex gastrointestinal surgery for either general surgery residents or postgraduate fellows. If the scope of general surgery practice is to be limited in the future by the American Board of Surgery, perhaps PD should be reserved for postgraduate trainees in the field of complex gastrointestinal surgery. This study demonstrates that PD performed in a general surgery residency can be performed with perioperative results comparable with best-practice national data. This study, however, is unable to provide comment upon the competency of trainees (who perform PD under supervision), when trainees become attending providers. Data regarding trainee performance of complex surgical procedures, and follow-up of results when graduates become attending providers, should help surgical educators in planning the surgical training program of the future that best serves the interests of trainees and patients alike.

CONCLUSION

PD can be performed with an acceptable morbidity and mortality within the teaching structure of a general surgery training program.

REFERENCES

1. Debas HT, Bass BL, Brennan MF, et al. American Surgical Association Blue Ribbon Committee Report on Surgical Education: 2004. Ann Surg 2005;241:1–8.
2. Pellegrini CA, Warshaw AL, Debas HT. Residency training in surgery in the 21st century: a new paradigm. Surgery 2004; 136:953–965.
3. Parsa CJ, Organ CH Jr, Barkan H. Changing patterns of resident operative experience from 1990 to 1997. Arch Surg 2000;135:570–573; discussion 573–575.
4. Kotwall CA, Maxwell JG, Brinker CC, et al. National estimates of mortality rates for radical pancreaticoduodenectomy in 25,000 patients. Ann Surg Oncol 2002;9:847–854.
5. Balcom JHt, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–398.
6. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248–257; discussion 257–260.
7. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638–645.
8. Birkmeyer JD, Warshaw AL, Finlayson SR, et al. Relationship between hospital volume and late survival after pancreaticoduodenectomy. Surgery 1999;126:178–183.
9. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003;237:509–514.
10. Urbach DR, Bell CM, Austin PC. Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization. CMAJ 2003;168:1409–1414.
11. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004;8:935–949; discussion 949–950.
12. Warshaw AL, Thayer SP. Pancreaticoduodenectomy. J Gastrointest Surg 2004;8:733–741.

13. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786–795.
14. Gordon TA, Bowman HM, Bass EB, et al. Complex gastrointestinal surgery: impact of provider experience on clinical and economic outcomes. J Am Coll Surg 1999;189: 46–56.
15. Hunter JG. The case for fellowships in gastrointestinal and laparoendoscopic surgery. Surgery 2002;132:523–525.
16. Traverso LW, Shinchi H, Low DE. Useful benchmarks to evaluate outcomes after esophagectomy and pancreaticoduodenectomy. Am J Surg 2004;187:604–608.
17. Ferguson CM. The arguments against fellowship training and early specialization in general surgery. Arch Surg 2003; 138:915–916.
18. Cheadle WG, Franklin GA, Richardson JD, Polk HC Jr. Broad-based general surgery training is a model of continued utility for the future. Ann Surg 2004;239:627–632; discussion 632–636.

Postchemotherapy Characteristics of Hepatic Colorectal Metastases: Remnants of Uncertain Malignant Potential

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Accepted management for colorectal cancer (CRC) involves resection of the primary neoplasm and chemotherapy; the debate continues over the most beneficial order of these components. Preoperative chemotherapy aimed at liver metastases may result in complete pathologic response and replacement of the malignancy with scar. The McGill University liver diseases database was retrospectively reviewed. Forty-one patients receiving treatment between December 2003 and August 2004 were identified, their medical records examined, and liver histology reviewed. The histology of the remnants was linked to the appearance of the lesions on preresection imaging and to the primary colorectal neoplasms. Twenty-seven of the 41 patients (66%) received preoperative chemotherapy (oxaliplatin or irinotecan). Features of the primary neoplasm that predicted resolution of the metastases were absence of tumor budding ($P = 0.04$), absence of a diffusely infiltrative tumor margin ($P = 0.02$), and loss of expression of the DNA repair gene O6-methylguanine-DNA methyltransferase ($P = 0.08$). Oxaliplatin and irinotecan demonstrate beneficial effects in treating hepatic colorectal metastases and should be considered in such patients before resection. We propose the acronym RUMP to denote the remnants of uncertain malignant potential remaining. Further investigation is required to determine any correlation between the drug received and the resulting lesion. (J GASTROINTEST SURG 2006;10:483–489) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Chemotherapy, colorectal cancer, metastasis, liver, surgical pathology

The accepted management of patients with hepatic colorectal cancer (CRC) metastases is to proceed directly to liver resection when feasible, with chemotherapy delivered during the postoperative course. Debate continues over whether or not patients with resectable hepatic metastases benefit from chemotherapy before liver surgery.

Current management for the primary CRC involves resection of the site followed by postoperative chemotherapy where appropriate. The chemotherapeutic agents oxaliplatin and irinotecan (CPT-11) are given for metastatic disease, hepatic or otherwise, with the goals of extending life, palliation, or downstaging for possible resection. However, literature reports of chemotherapy used to specifically target hepatic metastases generally pertain to patients with unresectable disease confined to the liver and it is used in an attempt to achieve a resectable state. In up to 12.5% of these patients, resectability is successfully attained after chemotherapy.[1]

Neoadjuvant chemotherapy is based on the belief that targeting the neoplasm before resection will reduce overall neoplasm burden and improve the effective result of local therapy. There are multiple reports of a beneficial response of CRC liver metastases to neoadjuvant chemotherapy with 5-fluorouracil/leukovorin and oxaliplatin or irinotecan. Several Japanese reports document a significant response of liver lesions to this treatment as seen from imaging studies.[2,3] With advances in chemotherapeutic

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agents, some patients demonstrate a complete pathologic response denoted by neoplasm disappearance on imaging studies. Nevertheless, the histological changes that occur in human colorectal metastases after chemotherapy and their clinical significance have not been documented in the available body of literature. One could expect that changes similar to the complete necrosis and fibrosis that have been identified in residual neoplasia from treated testicular cancer might be present.[4]

Therefore, we present our analysis of patients given neoadjuvant chemotherapy for hepatic metastases from CRC, regardless of resectability status. We suggest that complete pathologic response can sometimes be achieved and that particular pathological features of the primary neoplasm may predict chemoresponsiveness. Remnants that remain visible on imaging studies may differ from typical metastatic deposits by showing histological changes consistent with tumor regression. This theory will be explored further to determine how easily a fully necrotic lesion can be identified, and if so, whether these lesions require surgical resection.

METHODS

Patient Identification

The database for liver diseases at McGill University Health Centre and Royal Victoria Hospital was reviewed for patients treated between December 24, 2003 and August 12, 2004. Forty-one patients were identified and their charts retrospectively reviewed. Liver metastases were classified as synchronous (occurring within 12 months or less of diagnosis of the primary neoplasm) or metachronous (occurring after 12 months of diagnosis of the primary neoplasm).

Upon first consultation with the surgeon, the patients were offered chemotherapy unless it was felt that they were too frail or elderly to benefit from the treatment. The decision to begin irinotecan or oxaliplatin at this point was therefore largely patient-specific. Those patients referred from oncologists and already undergoing chemotherapy continued on their regimen, and operation was scheduled after completion of the chemotherapy.

Neoadjuvant chemotherapy was defined as receiving oxaliplatin or irinotecan in addition to 5-FU/leucovorin within 4 to 6 weeks before operation for the liver metastases. The inability to detect viable neoplasm histopathologically in a lesion seen on imaging studies before chemotherapy was considered as a complete pathologic response. The study (A12-M114) was approved by the McGill Institutional Review Board.

Pathology Review

Pathology reports from the patients' metastatic and primary colorectal neoplasms were obtained and reviewed, and representative pathologic specimens were acquired from source hospitals. All primary and secondary neoplasm specimens for patients who underwent resection after preoperative irinotecan or oxaliplatin were reexamined by a core group of pathologists to assess the histological components.

Formalin-fixed, paraffin-embedded cancer tissues of the primary and secondary neoplasms were obtained from the Pathology Department at the McGill University Health Centre or the source hospital, and sections were prepared and stained with hematoxylin and eosin, a standard microscopy stain. Immunostaining for the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) was carried out using mouse anti-MGMT monoclonal antibody (clone MT3.1, NeoMarkers, Fremont, CA), as described previously.[5]

MGMT was used as a marker, because it is methylated in 40% of CRCs, and DNA methylation has been shown to be an adverse prognostic marker in CRC.[6] DNA methylation also seems to be a good predictive marker for chemoresponsiveness that is independent of p53 status and DNA microsatellite instability status.[7] An excellent outcome was recently shown in a small group of patients with CRC that had MGMT methylation and was treated with adjuvant therapy.[8] In this study, we were evaluating patients with manifestly adverse factors (given liver metastases) who nevertheless showed a substantial response with adjuvant chemotherapy. We therefore inferred that loss of MGMT expression (secondary to MGMT methylation) within the primary tumor might explain the combination of aggressive behavior and good chemoresponsiveness in a subset of CRCs.

Scoring of pathology features in hepatic metastases was based on the deposit with the largest amount of the particular feature. Metastases were given a score from 0 to 3 for foreign body giant cell reaction and a percentage score for fibrosis, mucus, and necrosis. Primary cancers were evaluated for lymphocytic infiltration and deemed + or − for peritumoral infiltration, tumor infiltration leukocytes, and Crohn-like reaction. They were also scored (+ or −) for "dirty" necrosis, fibrosis, mucus, tumor infiltrating lymphocytes, Crohn-like reaction, peritumoral lymphocytes, "tumor budding," and a diffuse pattern of infiltration. Dirty necrosis describes the presence of eosinophilic intraluminal material admixed with basophilic cell debris (Fig. 1).[9] Tumor budding (Fig. 2) was deemed to be present when clusters of up to

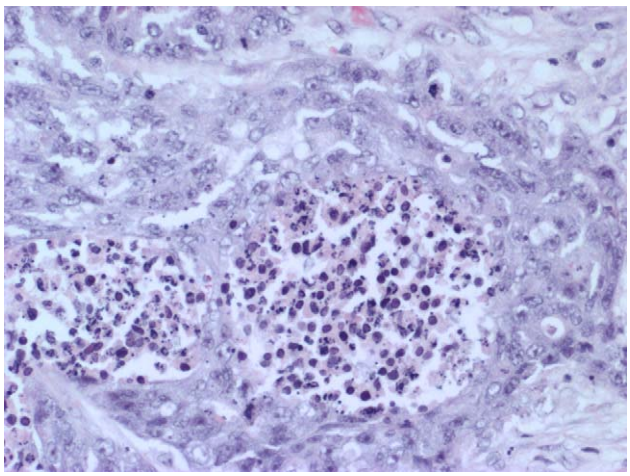

Fig. 1. The lumen of the malignant gland is filled with necrotic and apoptotic cells containing shrunken basophilic nuclei and nuclear debris. This feature has been described as "dirty necrosis." Hematoxylin-eosin staining.

four cells were observed at the invasive margin in hematoxylin and eosin stained sections as previously defined.[10]

Radiology Interpretation

The initial number of hepatic lesions was determined from the most recent CT scan or magnetic resonance imaging scan before beginning chemotherapy. Where the radiology report read "multiple lesions," the number of lesions was based on the pathology assessment. Where the radiologist reported a choice between two numbers, the lower possible number of lesions was chosen. Where imaging information was not available, radiologic correlation for that patient was omitted. The number of lesions from the imaging study was compared with the number of lesions found at pathological assessment of the resected liver specimen. Postchemotherapy restaging imaging was not consistently available for comparison, and because we chose to concentrate on pathology, we did not consider this a goal of this project. However, we do believe that correlation of the prechemotherapy and postchemotherapy restaging imaging would be both interesting and important, and this will be pursued for an update publication.

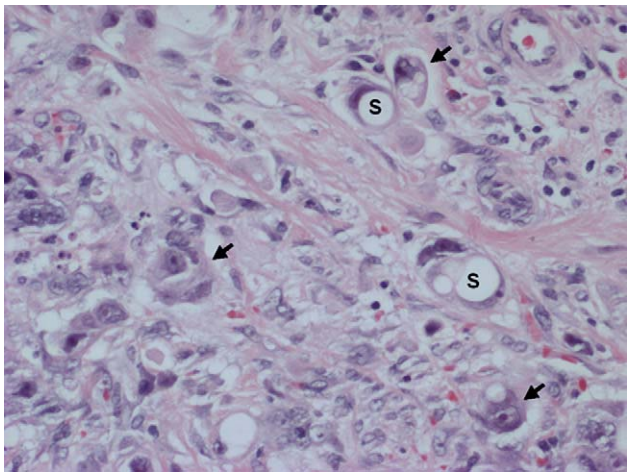

Fig. 2. Tumor budding (*black arrows*), known also as dedifferentiation, at the invasive margin of a cancer. A tumor bud comprises single cells or isolated cell clusters of up to four cells that sometimes appear to bud from differentiated glandular structures (not shown). S = signet ring cell. Hematoxylin-eosin staining.

Statistical Analysis

Microsoft Excel 4.0 and StatView software (Version 5.0, SAS Institute Inc., Cary, NC) was used for data processing and analysis. Continuous variables were compared with the Mann-Whitney *U* test for nonparametric data as indicated. Significance was defined as $P < 0.05$.

RESULTS

Patient Demographics

Forty-one patients were identified with a mean age of 59 ± 13 years (range, 24 to 86 years; Table 1). Of the group identified, 13 did not receive metastatic chemotherapy (oxaliplatin or irinotecan) before operation. Of the 27 who were treated with neoadjuvant chemotherapy, five were unresectable at operation (one because of peritoneal studding, one gross ascites, two overwhelming neoplasm volume, and one excessive neoplasm volume on the background of fatty liver).

Among 22 patients undergoing resections, there were four right hepatectomies, six left hepatectomies, three left lateral segmentectomies, one right

Table 1. Patient demographics

	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	All
N	27	14	41
Age (years)	57 ± 13	63 ± 13	59 ± 13
No. of hepatic lesions	3.8 ± 3.2	2.0 ± 1.4	3.2 ± 2.8
No. of patients with unresectable disease at surgery	4	1	5
Hospital mortality	0	0	0
Follow-up (weeks)	31 ± 18	42 ± 22	35 ± 20

trisegmentectomy, and 25 nonanatomic resections in 14 patients. Thirteen of the patients had synchronous metastases and three had metachronous lesions. Irinotecan (CPT-11) was received preoperatively by 12 patients, oxaliplatin by three patients, and both by one patient.

Among the patients with unresectable metastases, three had synchronous metastases. Three of these patients received irinotecan preoperatively, and one received oxaliplatin.

Pathology

Histological components of metastases. The median nodule size in the neoadjuvant chemotherapy group was 1.6 cm (range, 0.1 to 8.6 cm), with a median of three neoplasms per patient (range, 1 to 5).

The following results are reported as median (%), followed by interquartile range (in parentheses). A median of 20% (0% to 60%) viable neoplasm was seen per recovered lesion. Tumor composition from dirty necrosis, mucus, and fibrosis per lesion were 10% (5% to 50%), 0% (0% to 21%), and 40% (8% to 80%), respectively. The median score for foreign body giant cell reaction (score, 0 to 3) was 0 (range, 0 to 3). Out of our sample size, there were three patients who had no detectable viable tumor cells in any lesions.

Upon review of the pathology reports of the resected specimens for the nonchemotherapy group, all lesions in all patients who had not received preoperative neoadjuvant chemotherapy demonstrated metastatic adenocarcinoma consistent with CRC origin.

Histological components of primary neoplasms. It was possible to obtain matching primary and metastatic neoplasms from 14 subjects. The presence or absence of pathology features (Figs. 1 to 4) in the primary neoplasms is recorded in Table 2. Table 2 also shows the percentage (median results) of viable neoplasm in resected hepatic metastases stratified according to whether or not particular pathology features were present in the primary neoplasms.

Correlation of primary and secondary pathology. There was significantly more viable malignant epithelium in hepatic metastases when the matching primary neoplasms showed either tumor budding ($P = 0.03$) or a diffusely infiltrative tumor margin ($P = 0.02$; Table 2). By contrast, there was less viable neoplasia in hepatic metastases in which primary neoplasms showed loss of expression of the DNA repair gene MGMT (Figs. 3 and 4). Although the MGMT findings did not reach statistical significance (Table 2), it is notable that two thirds of the MGMT negative cases showed complete regression in all hepatic metastases. Despite our small numbers, this provides an interesting preliminary observation that warrants further research.

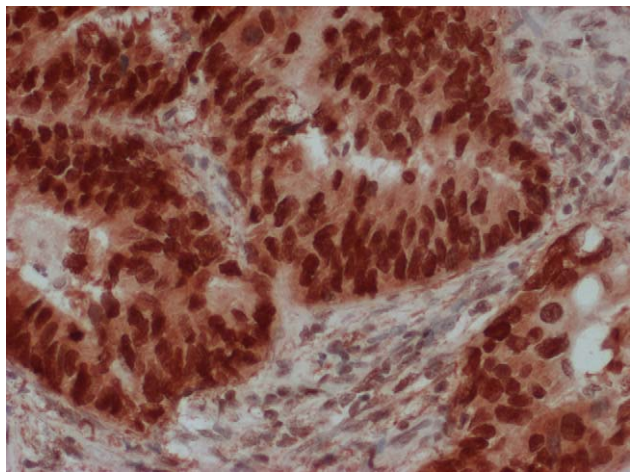

Fig. 3. Normal expression of MGMT (O6-methylguanine-DNA methyltransferase) in the nuclei of both malignant cells and stromal cells. Avidin-biotin complex technique.

There was no correlation between nonmalignant elements in primary neoplasms versus hepatic metastases. However, dirty necrosis in primary lesions showed a trend toward a positive correlation with necrosis in metastases (Mann-Whitney U test, $P = 0.06$).

Radiology

When the number of lesions reported on the index imaging study was compared with the number of lesions at pathology, a decrease in the number

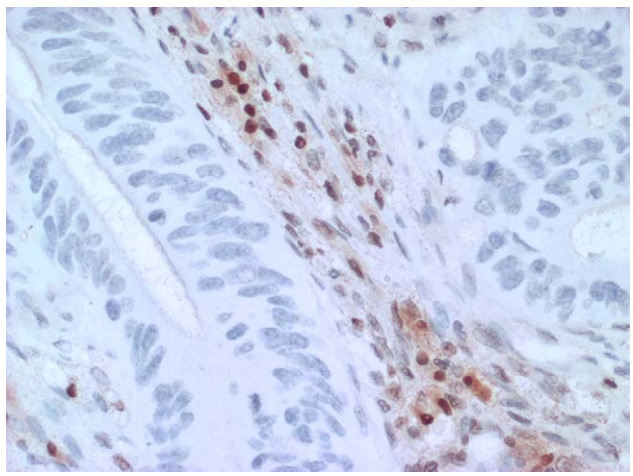

Fig. 4. Complete loss of nuclear expression of MGMT (O6-methylguanine-DNA methyltransferase) in colorectal cancer nuclei (compare with darkly stained nuclei in Fig. 3). Stromal cells remain positive (darkly stained nuclei) as an internal control of the reaction. Avidin-biotin complex technique.

Table 2. Pathology features in primary neoplasms versus percentage of residual neoplasm in liver

Feature	Residual neoplasm in liver (%)*		*P* value†
	−	+	
Budding	9	5	0.03
	5 (0–22)	60 (31–80)	
Diffuse	9	5	0.02
	5 (0–20)	60 (34–80)	
MGMT loss	11	3	0.07
	30 (9–75)	0 (0–8)	
TIL	11	3	0.8
	20 (1–54)	20 (5–72)	
CLR	9	5	0.74
	20 (4–65)	20 (0–46)	
PTL	10	4	0.22
	25 (10–60)	0 (0–45)	
LN	3	11	0.56
	0 (0–68)	20 (6–54)	
Necrosis	5	9	0.16
	35 (22–82)	10 (0–30)	
Mucin	10	4	0.6
	25 (5–60)	10 (10–55)	
Fibrosis	2	12	0.16
	2.5 (0–5)	25 (5–70)	

MGMT = O^6-methylguanine-DNA methyltransferase; TIL = tumor infiltration leukocytes; CLR = Crohn-like reaction; PTL = peritumoral lymphocytes; LN = lymph nodes. Median % within hepatic deposit containing largest amount of viable neoplasm.
*First line: number of cases with pathology feature; second line, median (interquartile range).
†Mann-Whitney *U* test.

of lesions was noted in eight patients. In one patient, four lesions were seen on the imaging study before chemotherapy, but of these, only one nodule had viable neoplasia at pathology. In another patient, only two lesions were seen at pathology, with one of these having no viable neoplasia, where six lesions were seen on the index-imaging scan. In a third patient, 11 lesions before chemotherapy became three lesions on pathology, with two lesions containing no viable neoplasia. In three patients, there was at least one additional lesion found at pathology that was not seen on the index-imaging scan.

Outcome

There was no perioperative hospital mortality and no significant morbidity. Mean follow-up time was 35 ± 20 weeks (range, 2 to 91 weeks). At the end of follow-up, there was one mortality from the resected group. Because of our short follow-up period, we cannot comment on outcome at this time. We plan to revisit the mortality and the rate of recurrence in this group of patients in the near future.

DISCUSSION

Although surgical resection is accepted as a necessary part of curative treatment for hepatic metastases from CRC, the evolution of chemotherapeutic agents now calls into question the order in which this should be performed. Many surgeons prefer to proceed directly to operation for resectable lesions, and some recommend that preoperative chemotherapy not be used in these cases.[11] However, there is evidence that preoperative chemotherapy can be of significant benefit, and this can prove useful when planning a resection.

One study retrospectively looked at 104 patients who had resections for CRC after chemotherapy for initially unresectable lesions.[12] In this group, 15 patients had a response to chemotherapy, enabling resection. Eleven patients showed a response so dramatic that it resulted in the inability to locate the liver metastases on preoperative imaging or at laparotomy. This evidence underlines the power of chemotherapy today and suggests that it should be used whenever possible as an adjunct to treatment for CRC. Unfortunately, this group did not provide details of the pathologic results and with a follow-up of 31 months in only 11 patients, it is difficult to comment on the natural history of these lesions.

The ability of chemotherapy to convert unresectable CRC liver lesions to resectable ones has been documented previously.[13–15] Overall, a resectability rate of 10% to 40% has been described after preoperative chemotherapy for initially unresectable metastases. The chemotherapeutic regimen has generally involved 5-fluorouracil and leucovorin with oxaliplatin or irinotecan given for five to 10 months. Patients who have achieved a status conducive to resection have demonstrated long-term survival comparable to those who were initially resectable.[16] One large, prospective, nonrandomized trial compared 5-year survival rates in patients with initially resectable lesions from CRC and those which became resectable after neoadjuvant chemotherapy. Out of 701 patients initially deemed unresectable, 95 became resectable and of the 87 patients completing the follow-up period, 5-year survival from the time of resection was 35%.

These results demonstrating the profound effect of chemotherapy could encourage their use preoperatively, even in resectable cases. Reasons why surgeons might proceed directly to operative intervention in resectable cases include patient apprehension toward the perceived time delay with chemotherapy and beliefs of increased perioperative complications. However, the evaluation of 61 patients who had received chemotherapy within 6 months of major liver

resection found no difference in mean blood loss, hospital duration of stay, or mortality compared with 47 patients who received no chemotherapy.[17] In fact, the use of CPT-11 was associated with a higher rate of resection, although this did not reach significance. Likewise, two other groups using neoadjuvant 5-fluorouracil, folinic acid, and oxaliplatin found no increase in perioperative morbidity.[18,19]

In this report, we have presented our results of response in CRC liver metastases to neoadjuvant chemotherapy despite initial neoplasm resectability. We have identified the resulting histology after chemotherapy as lesions containing dirty necrosis, fibrosis, mucus, and foreign body giant cell reaction. In some metastatic lesions, only these non-neoplastic elements were identified. Markers of adverse prognosis in CRC, including tumor budding[20] and diffuse tumor infiltration, were obtained through study of the primary lesion.

In this study, both tumor budding and diffusely infiltrative tumor growth in the primary lesions were associated with viable neoplasia in hepatic metastases. Although both features have been associated with poor prognosis in CRC,[10] there is evidence that budding may also be relevant to chemoresponsiveness. Specifically, tumor buds have been shown to express P-glycoprotein, a membrane integral protein that mediates multidrug resistance by functioning as an energy-driven transporter.[21] By contrast, primary neoplasms showing loss of expression of the DNA repair gene MGMT were more likely to have complete regression of neoplasm in hepatic metastases. This finding fits with a report correlating increased chemoresponsiveness of CRC with hypermethylation and therefore loss of expression of MGMT.[8] Larger studies are needed to confirm this observation.

Despite the positive features that we have identified, there are definite limitations to chemotherapeutic benefit. Of our patients who received preoperative chemotherapy, five were unresectable. These patients presented with borderline resectability, but open the concern of tumor progression during medical therapy. It is widely accepted that medical and surgical treatments must work in partnership to treat CRC and that neither is capable in isolation of curing advanced forms of this disease.

Our results answer some important questions and lead to possible future changes in management of CRC. We have shown that complete responses to irinotecan or oxaliplatin do occur, given the high proportion of hepatic metastases comprising only fibrous tissue and inert mucin, as well as the reduction in the number of lesions found at pathology compared with the pretreatment imaging study. Although certain features in primary neoplasms may predict chemoresponsiveness (see above), there was little correlation between primary and metastatic lesions in terms of the presence of non-neoplastic elements, with the possible exception of dirty necrosis within malignant lumina. It is conceivable that fibrosis in the hepatic lesions could arise through organization of necrosis induced specifically by chemotherapy, and that there could therefore be no equivalent tissue reaction in the primary lesion. Neoplastic mucin production may increase when there is cancer regression, analogous to the finding in rectal cancer treated preoperatively by radiotherapy.[22] Foreign body giant cell reactions are rarely observed in primary CRC, and their presence in hepatic metastases may be peculiar to the use of adjuvant therapy. On the other hand, the production of intraluminal dirty necrosis may be a marker of differentiation[9] that is present in both the primary neoplasm and in metastatic lesions.

Given our relatively small sample size and short follow-up time, we are unable to comment on improvement in outcome achieved by the protocol of neoadjuvant chemotherapy followed by resection. Despite the complete disappearance of some of the metastatic foci, we continue to recommend resection of these remnants of uncertain malignant potential (RUMP). One group quoted above showed a 27% recurrence rate in 31 months after cessation of chemotherapy that had produced a complete clinical response.[12] This implies that viable neoplastic cells remain behind in some lesions, despite evading detection by histological assessment. In addition, increased survival with hepatic resection after chemotherapy compared with chemotherapy alone has been shown despite pathologic response to medical therapy (32 vs. 24 months).[23]

We have now identified a spectrum of pathologic lesions that can result from treatment with chemotherapy, but several questions remain to be answered. The major constituent of a remaining RUMP lesion (i.e., mucin pool vs. dirty necrosis) has a yet undefined impact on outcome, and the development of these lesions might be multifactorial. It may be that some of these lesions have a higher risk of malignant recurrence, and further work will be needed to determine whether it could be possible that some do not warrant resection. Importantly, the type of resulting RUMP lesion might directly correlate to the chemotherapeutic agent received. There is a suggestion that a regimen containing oxaliplatin might increase the rate of resectability to 18% compared with 7% for irinotecan,[13] although these results are preliminary. Further work with markers in the parent neoplasm might answer these questions and permit treatment to be tailored to a given patient.

CONCLUSION

Current neoadjuvant chemotherapy is useful preoperatively in CRC metastases to the liver. The postchemotherapy RUMP lesions that result require further investigation with respect to their significance and impact on long-term survival or cancer recurrence. Until these aspects are delineated, we recommend resection of the affected liver where possible and further research into the benefits of preoperative chemotherapy.

REFERENCES

1. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long-term survival. Ann Surg 2004;240:644–657.
2. Matsukura S, Samejima R, Tanaka M, Hidaka K. Retrospective study of irinotecan plus fluorouracil and l-leucovorin chemotherapy for advanced and metastatic colorectal cancer [in Japanese]. Gan To Kagaku Ryoho 2004;31:893–896.
3. Morishita Y, Kasakura Y, Fujii M, et al. A case report of colon cancer with liver and lung metastases responding to combination chemotherapy with l-LV, 5-fluorouracil and CPT-11 [in Japanese]. Gan To Kagaku Ryoho 2004;31:427–430.
4. Fossa SD, Aass N, Ous S, et al. Histology of neoplasm residuals after chemotherapy in patients with advanced nonseminomatous testicular cancer. J Urol 1989;142:1239–1242.
5. Whitehall VLJ, Walsh MD, Young J, Leggett BA, Jass JR. Methylation of O6-methylguanine DNA methyltransferase characterizes a subset of colorectal cancer with low-level DNA microsatellite instability. Cancer Res 2001;61:827–830.
6. Ward RL, Cheong K, Ku SL, Meagher A, O'Connor T, Hawkins NJ. Adverse prognostic effect of methylation in colorectal cancer is reversed by microsatellite instability. J Clin Oncol 2003;21:3729–3736.
7. Van Rijnsoever M, Elsaleh H, Joseph D, McCaul K, Iacopetta B. CpG island methylator phenotype is an independent predictor of survival benefit from 5-fluorouracil in stage III colorectal cancer. Clin Cancer Res 2003;9:2898–2903.
8. Nagasaka T, Sharp GB, Notohara K, et al. Hypermethylation of O6-methylguanine-DNA methyltransferase promoter may predict nonrecurrence after chemotherapy in colorectal cancer cases. Clin Cancer Res 2003;9:5306–5312.
9. Greenson JK, Bonner JD, Ben-Yzhak O, et al. Phenotype of microsatellite unstable colorectal carcinomas: Well-differentiated and focally mucinous neoplasms and the absence of dirty necrosis correlate with microsatellite instability. Am J Surg Pathol 2003;27:563–570.
10. Ueno H, Murphy J, Jass JR, Mochizuki H, Talbot IC. Neoplasm "budding" as an index to estimate the potential of aggressiveness in rectal cancer. Histopathology 2002;40: 127–132.
11. Rougier P, Guimbaud R, Mitry E, Vaillant JN. Chemotherapy with curative intent before (neoadjuvant) or after (adjuvant) surgery for colorectal cancer liver metastases. Bull Acad Natl Med 2003;187:881–892.
12. Elias D, Youssef O, Sideris L, et al. Evolution of missing colorectal liver metastases after inductive chemotherapy and hepatectomy. J Surg Oncol 2004;86:4–9.
13. Ong SY. Neoadjuvant chemotherapy in the management of colorectal metastases: A review of the literature. Ann Acad Med Singapore 2003;32:205–211.
14. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509–520.
15. Frena A, Martin F, La Guardia G, et al. Liver resection after downstaging with neoadjuvant chemotherapy for "unresectable" colorectal metastases [in Italian]. Chir Ital 2004;56: 351–357.
16. Adam R, Avisar E, Ariche A, et al. Five-year survival after hepatic resection after neoadjuvant therapy for nonresectable colorectal [liver] metastases. Ann Surg Oncol 2001;8: 347–353.
17. Parikh AA, Gentner B, Wu TT, Curley SA, Ellis LM, Vauthey JN. Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy. J GASTROINTEST SURG 2003;7:1082–1088.
18. Lorenz M, Staib-Sebler E, Gog C, et al. Prospective pilot study of neoadjuvant chemotherapy with 5-fluorouracil, folinic acid and oxaliplatin in resectable liver metastases of colorectal cancer. Analysis of 42 neoadjuvant chemotherapies. Zentralbl Chir 2003;128:87–94.
19. Wein A, Riedel C, Bruckl W, et al. Neoadjuvant treatment with weekly high-dose 5-fluorouracil as 24-hour infusion, folinic acid and oxaliplatin in patients with primary respectable liver metastases of colorectal cancer. Oncology 2003;64: 131–138.
20. Jass JR, Barker M, Fraser L, et al. APC mutation and neoplasm budding in colorectal cancer. J Clin Pathol 2003;56: 69–73.
21. Weinstein RS, Jakate SM, Dominguez JM, et al. Relationship of the expression of the multidrug resistance gene product (P-glycoprotein) in human colon carcinoma to local aggressiveness and lymph node metastasis. Cancer Res 1991; 51:2720–2726.
22. Nagtegaal I, Gaspar C, Marijnen C, Van De Velde C, Fodde R, Van Krieken H. Morphological changes in neoplasm type after radiotherapy are accompanied by changes in gene expression profile but not in clinical behaviour. J Pathol 2004;204:183–192.
23. Amaya K, Nishimura G, Sasaki S, et al. Four cases of multiple liver metastasis of colorectal cancer treated with hepatic resection after chemotherapy [in Japanese]. Gan To Kagaku Ryoho 2001;28:1768–1771.

The Usefulness of Drain Data to Identify a Clinically Relevant Pancreatic Anastomotic Leak After Pancreaticoduodenectomy?

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Pancreatic anastomotic leak (leak) remains a persistent problem after pancreaticoduodenectomy (PD). Recent reports indicate a mean occurrence of 10% with a range of 2%–28% of patients. However, valid comparisons for these studies cannot be made because the definition of leak is variable, and many patients deemed to have a leak are not sick. The aim of this study was to determine the meaning of the volume and amylase content of the effluent from surgical drains by comparing these values to actual clinical outcomes. From January 1996 to July 2002, 207 consecutive patients underwent PD. We considered a leak to be present if greater than 30 ml/day of drainage was observed from drains and if that drainage contained an amylase-rich fluid (greater than 5X serum) on or after postoperative day (POD) 5. Cases were then divided into three groups—no leak, chemical leak only (leak but asymptomatic), and a clinical leak group (leak that required therapeutic intervention, reoperation, readmission, or prolonged length of stay). Then the drainage volume and its amylase concentration for every postoperative day were compared between the three groups. There were no operative or hospital deaths, and the mean length of stay (LOS) was 11.2 ± 6.1 days. Prolonged LOS was set at greater than 17 days (one standard deviation beyond the mean LOS for all cases). Leak was observed in 14% of cases (n = 29) and the patients were subsequently divided into these groups: no leak (n = 178), chemical leak only (n = 12), and clinical leak (n = 17). Surprisingly, the daily drain amylase values did not differ between the chemical leak group and the clinical leak group. The daily volume of drainage on POD 5–8 for the clinical leak group was significantly greater than the volumes of the other two groups, so that a combination of greater than 200 ml/day of drainage on POD 5 with an amylase greater than 5X serum had a positive predictive value (PPV) of 84% and a negative predictive value (NPV) of 99% for a clinically relevant leak. We used broad criteria from drainage effluent to include as many potential leaks as possible. This broad definition of leak selected 14% of the PD patients as having a leak; within this group, all of the clinical complications of leak occurred. By increasing the volume criteria from greater than 30 ml per day to greater than 200 ml per day, the PPV was increased from 59% to 84% while keeping NPV at 99%. Drain data based on the volume and amylase criteria of this study may be useful for early detection of a leak that will have clinical impact. This study's criteria for leak may be a good definition to design a clinical trial. (J GASTROINTEST SURG 2006;10:490–498) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Pancreaticoduodenectomy, pancreaticojejunostomy, pancreatic leak, drain fluid amylase, drain fluid volume, surgical complication

Recent advances in surgical techniques and perioperative management have reduced mortality rates after pancreaticoduodenectomy (PD). Pancreatic anastomotic leak (leak) remains the most common major complication.[1–7] If not recognized and treated, this unfortunate complication can increase the morbidity

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and mortality associated with PD. Recent series use a variety of definitions for leak and report a large range of leak rates (from 2%–28%).[8–12]

Currently, the most popular method for detecting leak is based on perianastomotic drain effluent, both its daily fluid volume output and its amylase concentration.[13–17] Guidelines for interpretation of drain volumes and amylase concentration would be useful to detect a potential leak. We believe an analysis of drain data and subsequent clinical outcomes would be useful to develop an acceptable definition. The drain data might identify the patient that needs close monitoring, rather than waiting for clinical signs before considering intervention. Perhaps drain information might miss a developing leak, that is, the patient still develops a complication of leak even with negative drain data. Little is known how the dynamic postoperative changes of drain volume and/or its amylase concentration might correlate with clinical outcomes.[18,19]

The aim of this study was to use actual case drain data and the clinical outcomes to determine if drain volume and/or amylase levels are helpful to detect a leak, and then how many of these leaks based on drain data might be clinically relevant. Also which is more important—the drain volume or its amylase concentration, or both, and on which postoperative days (PODs)?

PATIENTS AND METHODS

A retrospective chart review was performed to include all patients who had undergone PD by one of us (L.W.T.) at a tertiary referral multispecialty resident training center between January 1996 and July 2002. Data included patient demographics (age, gender, diagnosis), type of procedure performed (standard or pylorus-preserving PD), length of operation, estimated blood loss, need for blood transfusion, hospital mortality, complications, postoperative length of stay (LOS), need for postoperative percutaneous drainage, reoperation, and readmission.

All patients had one or two closed bulb suction drains placed at the time of surgery in close proximity to the pancreatic anastomosis. The volume and amylase concentration in the drainage fluid were measured daily from POD 1 until drain removal. We used the broad definition of leak developed in a recent multicenter randomized trial that we had found useful during that trial.[17] A group of experienced pancreatic surgeons had devised this definition as likely to include almost all leak cases. The criteria for leak was met if the volume from all of the drains was $\geqslant$30 ml/day and if its drain amylase was greater than five times the upper limit of normal of the serum amylase value on or after POD 5. The upper limit of normal of the serum amylase value in our hospital was 100 U/L.

The cases that met the definition of leak were then divided into two groups. The "chemical leak only" group was defined as meeting the broad definition of leak, using drain data. These patients were clinically asymptomatic. They did not require interventions and did not have a prolonged LOS. A "clinical leak" group was defined as any patient meeting the broad definition of leak plus any of the following: required a therapeutic intervention (either by interventional radiology or by surgical exploration), experienced delayed gastric emptying (DGE), had prolonged LOS, or required readmission. DGE was defined as not tolerating unlimited oral intake of any diet after POD 10. Prolonged LOS was defined as one standard deviation beyond the mean LOS of all patients.

Surgical Technique

The pancreaticojejunostomy was performed as follows. A retrocolic jejunal limb was brought through a window in the left transverse mesocolon and an end-to-side pancreaticojejunal anastomosis was made in two layers. The inner layer was a duct-to-mucosa connection made with interrupted 5-0 absorbable sutures over a 4 cm long, 3 Fr radiodense internal stent.[20] The outer layer was a seromuscular envelope with interrupted 3-0 silk Lembert sutures. Just downstream from the pancreatic anastomosis, an end-to-side choledochojejunostomy was fashioned. Finally an end-to-side antecolic duodenojejunostomy, or in the case of concomitant antrectomy, a gastrojejunostomy, was completed. Closed suction drainage used a round 15F silicone rubber tube that was placed from the right upper quadrant dorsal to the choledochojejunal and pancreaticojejunal anastomoses. Earlier in the study, an additional drain was placed from the left upper quadrant into the area anterior to the pancreatic anastomosis, but this method was discontinued after the anterior drain was observed to rarely contain an amylase-rich fluid.

Statistical Analyses

Data are presented as the mean $\pm$ standard deviation (SD), unless otherwise specified. Statistical analyses used Student's t test, repeated-measures analysis of variance (ANOVA), chi-square test, or the Fisher exact test, when appropriate. Values of $P < 0.05$ were considered statistically significant, a priori.

RESULTS

A total of 207 consecutive patients underwent PD with pancreaticojejunostomy (standard PD = 12 and

pylorus preserving PD = 195). There were 108 men and 99 women, with a mean age of 59.7 years (median 61 years; range, 18–91 years). The mean operating time was 425 minutes (median 425 minutes; range, 236–951 minutes) and the mean blood loss was 300 ml (median 300 ml; range, 0–2400 ml). Two patients (0.9%) received an intraoperative blood transfusion. Indications for surgery were periampullary neoplasm (76%), chronic pancreatitis (23%), and miscellaneous disease (1%).

There were no operative or hospital deaths. Complications occurred in 61 patients (29%). The two most common complications were a chemical pancreatic leak in 29 (14%) and DGE in 18 (9%). Mean postoperative LOS for all patients was 11.2 ± 6.1 days, therefore prolonged LOS for this study was set at greater than 17 days (more than one standard deviation beyond the mean). Prolonged LOS was noted in 15 patients (7%). Reoperation was needed in one patient (0.5%) for afferent limb syndrome due to an acute adhesion. Readmission to hospital was noted in 10 patients (5%).

Of the 29 patients with a pancreatic anastomotic leak, 12 were asymptomatic (or 6% of all patients) and were placed into the chemical leak only group, whereas 17 met the criteria for both chemical leak and clinical leak (8% of all patients) and were placed into the clinical leak group. Therefore, 178 patients remained in a no leak group. None of the no leak group developed a subsequent complication attributable to a leak, that is, drain data had a 100% negative predictive value (NPV).

Comparisons of postoperative outcome among the no leak, chemical leak only, and clinical leak groups are shown in Table 1. Because of our study definition for clinical leak, the LOS of the clinical leak group was significantly higher at 16.8 days. As per our definition, the clinical leak group had significantly more other complications—DGE, percutaneous drainage, and readmission as compared with the chemical leak group. All of the clinical leak group's data was significantly different from the no leak group. The period of drainage was longer in both the chemical leak (13.5 days) and the clinical leak group (50.5 days) versus the no leak group (9.5 days).

The clinical course of the 17 patients in the clinical leak group is shown in Table 2. All patients in this group were managed nonoperatively using either continuation of closed suction drains (n = 4) or CT-guided percutaneous drainage of a peripancreatic fluid collection or abscess (n = 13). Time to percutaneous drainage was 18.9 ± 25.1 (median 10; range, 2–101 days). Six patients needed readmission for leak, and two of them required multiple readmissions. None of these patients died.

Amylase concentrations in the drain fluid for the three groups were compared (Fig. 1). The raw data is listed in Table 3. The amylase of the drainage fluid was significantly higher in the clinical leak group versus the no leak group on all days except POD 2. The amylase in the chemical leak group was significantly higher than the no leak group on POD 4–10.

Daily drain volumes per day between the three groups were compared as shown in Fig. 2 and Table 4. The drainage fluid volume was significantly greater on POD 5–13 (except day 9) in the clinical leak group compared with the other two groups—chemical leak only versus no leak. As shown in Fig. 2, the daily volume of the drainage fluid in the chemical and no leak groups decreased gradually after POD 5, whereas it did not decrease in the clinical leak group. After POD 5, the daily volume in the drainage fluid remained greater than 200 ml/day in 16 of 17 patients (94%) of the clinical leak group, whereas 3 of 12 patients (25%) of the

Table 1. Comparison of postoperative outcome

		Leak (n = 29)	
	No leak (n = 178)	**Chemical leak (n = 12)**	**Clinical leak (n = 17)**
LOS (days)	10.6 ± 6.1	11.4 ± 2.1	16.8 ± 6.1*,†
Mean ± SD (median, range)	(9, 6–79)	(11, 9–16)	(18, 7–27)
Days of drainage (days)	9.5 ± 5.2	13.5 ± 5.7	50.5 ± 55.2*,†
Mean ± SD (median, range)	(8, 3–34)	(12, 8–25)	(30, 14–219)
LOS > 17 days	6 (3%)	0 (0%)	9 (53%)*,†
Readmission	4 (2%)	0 (0%)	6 (35%)*,†
Any other complication	32 (18%)	3 (25%)	16 (94%)*,†
Requiring postoperative percutaneous drainage	0 (0%)	0 (0%)	13 (76%)*,†
Delayed gastric emptying	13 (7%)	0 (0%)	5 (29%)*

LOS = postoperative length of stay.
*$P < 0.05$, clinical leak vs. no leak.
†$P < 0.05$, clinical leak vs. chemical leak.

Table 2. Management, disposition, and outcome of 17 patients with clinical leak

Patient								
Age (years)	Gender	Management	Initial LOS (days)	No. of readmissions	Total LOS (days)	Time to PC drainage (days)	Days of drainage (days)	Disposition
59	M	PC drain	27	0	27	2	41	Home
49	M	PC drain	27	0	27	9	26	Home
75	M	PC drain	22	0	22	10	41	Home
46	F	PC drain	22	0	22	9	21	Home
69	F	PC drain	21	0	21	3, 15	20	Home
40	M	PC drain	18	5	43	9	219	Home
72	F	PC drain	16	1	25	20	30	Home
68	F	PC drain	15	1	21	7	71	Home
57	M	PC drain	14	0	14	7	14	Home
83	F	PC drain	9	1	16	10	25	Home
60	M	PC drain	9	0	9	43	53	Home
68	M	PC drain	8	1	23	29	44	Home
52	M	PC drain	7	3	22	10, 101	157	Home
62	M	Maintain OP drain	20	0	20	—	14	Home
52	M	Maintain OP drain	18	0	18	—	18	Home
32	M	Maintain OP drain	18	0	18	—	16	Home
74	M	Maintain OP drain	15	0	15	—	50	Home

LOS = postoperative length of stay; PC = percutaneous; OP = operation.

chemical leak only group had a volume of greater than 200 ml/day ($P < 0.001$). Although it seems in Fig. 2 and Table 4 that the no leak group had a mean volume of greater than 30 ml/day (and should meet leak criteria) on days 5 through 11, none of these patients also had an elevated amylase.

Table 5 compares the predictive value of just drain fluid amylase concentration at greater than

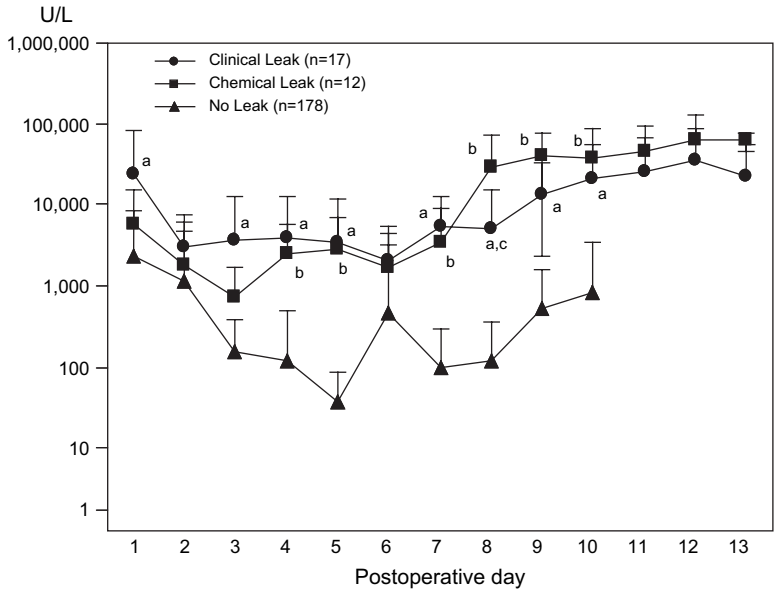

Fig. 1. Postoperative change in amylase concentration (mean ± SD) in the drainage fluid comparing no leak (n = 178) to chemical leak only (n = 12) and clinical leak (n = 17). The drainage fluid amylase was significantly higher in the clinical leak group versus the no leak group in all days except POD 2, and the chemical group was significantly higher than the no leak group on POD 4–10. Except POD 8, there was no difference between the amylase levels of the two leak groups, for example, chemical versus clinical leak groups. a = $P < 0.05$, clinical leak versus no leak; b = $P < 0.05$, chemical leak only versus no leak; c = $P < 0.05$, clinical leak versus chemical leak only; n = number of patients.

Table 3. Comparison of postoperative amylase concentration in the drainage fluid in U/L

				Leak (n = 29)					
	No leak (n = 178)			Chemical leak (n = 12)			Clinical leak (n = 17)		
POD	Mean ± SD	Median (range)	N	Mean ± SD	Median (range)	N	Mean ± SD	Median (range)	N
1	2380 ± 6140	253 (5–49,472)	145	5579 ± 9612	923 (60–24,192)	10	23,738 ± 58,102*	6553 (301–238,568)	16
2	1161 ± 4985	129 (4–43,742)	81	1766 ± 3001	910 (22–10,059)	10	3091 ± 4237	1241 (157–14,132)	11
3	156 ± 233	58 (2–1168)	75	713 ± 998	157 (19–2492)	8	3752 ± 8817*	538 (114–32,504)	13
4	120 ± 368	18 (3–2970)	76	2547 ± 3150†	943 (11–8828)	9	3881 ± 8910*	372 (16–30,096)	13
5	37 ± 51	14 (2–251)	67	2756 ± 3964†	846 (19–12,441)	10	3359 ± 8552*	112 (5–29,546)	12
6	451 ± 2780	18 (1–22,550)	69	1658 ± 2661	510 (41–7741)	8	2041 ± 3289	101 (58–8524)	11
7	94 ± 198	17 (2–1101)	48	3332 ± 5580†	928 (11–16,655)	8	5533 ± 6996*	2005 (5–18,980)	11
8	121 ± 245	26 (4–1283)	37	28,630 ± 44,165†	2,541 (288–136,160)	9	5110 ± 9935‡	1426 (8–33,549)	11
9	510 ± 1108	77 (9–3988)	15	39,308 ± 36,957†	88,744 (2747–88,779)	5	13,354 ± 18,643*	3709 (80–57,130)	10
10	817 ± 2512	17 (4–9812)	15	37,193 ± 48,447†	27,437 (2562–20,976)	5	21,365 ± 34,287*	9120 (97–28,918)	13
11	4315 ± 4027	439 (5–6380)	4	45,624 ± 47,327	22,224 (7181–111,078)	5	25,084 ± 40,819	10,282 (32–133,608)	10
12	20		1	60,650 ± 63,078	50,000 (3574–28,375)	3	35,464 ± 48,737	10,500 (1294–43,286)	9
13	117 ± 157	117 (6–228)	2	61,066 ± 15,650	61,066 (50,000–72,132)	2	21,780 ± 34,033	8,815 (435–102,599)	8

POD = postoperative day.
*0.05, clinical leak vs. no leak.
†0.05, clinical leak vs. no leak.
‡0.05, clinical leak vs. chemical leak.

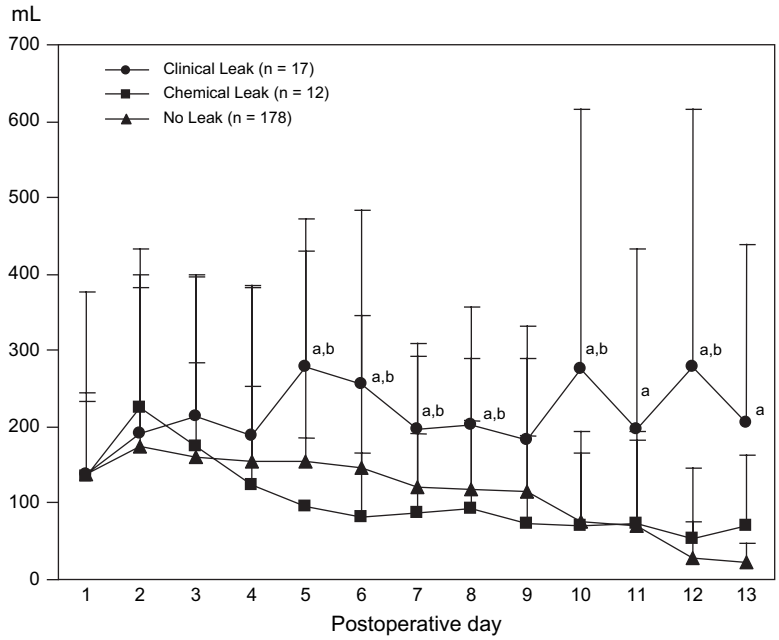

Fig. 2. Postoperative change in volume (mean ± SD) in the drainage fluid comparing no leak (n = 178) to chemical leak only (n = 12) and clinical leak (n = 17). The daily volume in the drainage fluid decreased gradually after POD 5 in both the no leak and chemical leak only groups, whereas no decrease was observed in the clinical leak group. a = $P < 0.05$, clinical leak versus no leak; b = $P < 0.05$, clinical leak versus chemical leak only; n = number of patients.

5X, just drain volume of greater than 30 ml/day or greater than 200 ml/day, or a combination of amylase and volume. According to our study's broad definition of leak (greater than 5X amylase + 30 ml/day on or after POD 5), the positive predictive value (PPV) and NPV for a clinical leak were 59% and 100%, respectively. Using the greater than 5X amylase + 200 ml/day criteria increased PPV to 84% without decrease in NPV.

Table 4. Comparison of postoperative amount in the drainage fluid in ml/24 hours

				Leak (n = 29)					
	No leak (n = 178)			Chemical leak (n = 12)			Clinical leak (n = 17)		
POD	Mean ± SD	Mean (range)	N	Mean ± SD	Mean (range)	N	Mean ± SD	Mean (range)	N
1	138 ± 240	70 (5–2485)	173	134 ± 98	129 (10–305)	12	137 ± 107	120 (25–405)	17
2	175 ± 258	83 (2–2350)	170	224 ± 174	233 (10–560)	12	192 ± 189	115 (30–680)	17
3	159 ± 241	70 (0–2275)	172	175 ± 109	164 (14–370)	12	214 ± 183	195 (10–605)	17
4	154 ± 227	74 (0–1825)	168	124 ± 128	92 (5–420)	12	189 ± 196	115 (5–790)	17
5	155 ± 276	70 (0–2600)	164	97 ± 87	80 (0–275)	12	278 ± 192*,†	259 (38–675)	16
6	146 ± 199	60 (0–1185)	149	83 ± 84	54 (0–250)	12	255 ± 227*,†	179 (20–875)	16
7	120 ± 173	36 (0–995)	134	87 ± 104	53 (5–372)	12	196 ± 112*,†	187 (28–420)	16
8	118 ± 172	50 (0–1085)	101	92 ± 116	44 (4–320)	12	204 ± 153*,†	147 (45–565)	14
9	115 ± 176	35 (0–1030)	65	74 ± 116	35 (2–370)	9	183 ± 148	160 (40–545)	14
10	76 ± 118	25 (0–645)	41	71 ± 95	40 (6–290)	8	275 ± 342*,†	230 (30–1390)	14
11	70 ± 113	18 (1–355)	21	74 ± 120	28 (5–315)	6	196 ± 238*	63 (5–810)	14
12	28 ± 47	8 (0–170)	14	54 ± 92	25 (0–217)	5	278 ± 339*,†	125 (12–925)	14
13	22 ± 25	7 (1–160)	8	70 ± 92	70 (5–135)	2	205 ± 234*	128 (1–765)	14

POD = postoperative day.
*$P < 0.05$, clinical leak vs. no leak.
†$P < 0.05$, clinical leak vs. chemical leak.

Table 5. Predictive values for a clinically relevant leak calculated from drain information obtained on postoperative day 5

On POD 5	PPV	NPV
>5X Amylase only	45%	100%
>30 ml/day only	11%	100%
>200 ml/day only	21%	99%
>5X + 30 ml/day	59%	100%
>5X + 200 ml/day	84%	99%

POD = postoperative day; PPV = positive predictive value; NPV = negative predictive value.

DISCUSSION

We analyzed these drain data to determine how useful they were to identify patients that were at high risk for a clinical complication due to leak. We also wished to define a reasonable definition for leak that could be used for clinical trials. We began by using the drain criteria for leak that had proven useful in a previous multicenter trial.[17] According to this definition, 29 or 14% of our 207 patients undergoing PD had a pancreatic anastomotic leak. The definition was sufficiently accurate that every clinical event associated with leak occurred in this smaller group.

After analysis of this enormous quantity of drain data, what take-home message can be given to the clinician? The factors from drain data are amylase content, drain volume, and the time postoperative. No factor alone could provide a sufficient PPV to focus attention on the patient as likely to be developing a leak complication. All three factors had to be combined. Drain volume after POD 5 appeared to be more important than drain amylase to detect leak. Before POD 5, drain volume did not predict a clinically relevant leak. The daily amount of drainage on POD 5–8 was significantly greater in the clinical leak group versus the chemical leak only group. In other words, the daily volume in the drainage fluid decreased gradually after POD 5 in the groups without a clinically relevant leak but stayed above 200 ml/day in 16 of 17 patients (94%) with clinical sequelae. In the chemical leak only group, 3 of 12 patients (25%) had a volume of greater than 200 ml/day after POD 5 ($P < 0.001$). Perhaps the drain volume increased in this group due to exocrine stimulation as the patient began eating, usually on POD 5. More pancreatic juice would be expected to pass through the leaking anastomosis. However, detection of a leak using volume alone was helpful but not enough.

Surprisingly, there was no significant difference in the amylase concentration of the drainage fluid for either leak group; however, both groups had a significant higher amylase concentration than those without leak on or after POD 3. We surmise that some patients have a minimal leakage of pancreatic juice in the postanastomosis period that seals off and may be possibly related to leakage around needle holes or between tissue surfaces that have not yet sealed. Yet, in other patients, the persistence of volume and amylase become clinically relevant. The latter leak might signal a technical error in the anastomosis allowing more leakage, presence of a significant downstream obstruction, or a failure to heal an anastomosis secondary to infection or malnutrition.

What guidelines for the clinician can be gleaned from these results? Measuring drain amylase or volume before POD 5 cannot be supported because volume and amylase were not elevated in the clinical leak group until that time. Drain data after POD 5 detects a clinically relevant leak. Table 5 of predictive values illustrates that if a patient meets the 5X amylase + 30 ml/day or the 5X amylase + 200 ml/day they should have close clinical monitoring. Perhaps these patients might be the ones that could benefit from a somatostatinlike agent or a CT scan when mildly symptomatic. However, a caveat is that the power of clinical observation must always be used because the drain data using the higher volume had an 84% PPV; a few patients had falsely positive tests.

Can the drain data of volume/amylase on POD $\geqslant$ 5 be used to design clinical studies? Until drain data is standardized in clinical reports, it will have limited usefulness as reflected in the many published definitions of pancreatic leakage.[7,11,13,15,16,21–31] Table 6 contains a partial summary of the various definitions of a pancreatic leak. The variability in the definition is reflected by the marked variation of reported leak rates of 2%–28%. We believe that the best definition of leak for a clinical trial is to combine drain data and clinical outcomes, for instance, first using the leak definition such as in our study, patients likely to have a leak are selected, and then within that selected group, a clinical severity score is applied to further refine the patient group. Unfortunately, this severity score has also not been standardized.

A classification of leak based on clinical outcomes would benefit by a severity score of a pancreatic anastomotic leak because of the potential difference in outcomes between a patient who has an asymptomatic leak and one who needs intervention. What data points connote severity of a leak? Strasberg et al.[13] reported that the term "clinically relevant fistula" has been used to indicate cases requiring prolonged parenteral nutrition, interventional procedures, or operation. These authors also felt that some fistulas (leaks) were much more

Table 6. Partial summary of biochemical definitions of pancreatic leak after pancreaticoduodenectomy

Authors	No. of all patients	No. of pancreatic leak	POD at which the definition applies	Drainage amylase concentration	Drainage volume per day
Strasberg et al., 2002[13]	123	4 (3%)	⩾ 10	>3X serum amylase	>50 ml
Grobmyer et al., 2000[16]	59	10 (17%)	⩾ 10	>3X serum amylase	>50 ml
Yeo et al., 1997[6]	650	92 (14%)	⩾ 10	>3X serum amylase	>50 ml
Buchler et al., 2000[23]	331	7 (2.1%)	> 10	>5000 units	⩾30 ml
Brooks et al., 2000[22]	111	15 (14%)	> 10	Amylase-rich fluid	>50 ml
Balcom et al., 2001[11]	137	12 (9.2%)	> 7	Amylase-rich fluid	>30 ml
Rios et al., 1999[25]	98	13 (13%)	> 7	High amylase	Not defined
Sarr et al., 2003[17]	275	78 (28%)	⩾ 5	>5X serum amylase	>30 ml
Okamoto and Tsuruta, 2000[30]	162	5 (3%)	> 5	>3X serum amylase	>30 ml
Lowy et al., 1997[15]	110	17 (15%)	⩾ 3	>2.5X serum amylase	Not defined
Roder et al., 1999[27]	85	15 (18%)	Not defined	>3X serum amylase	>50 ml
Ohwada et al., 2001[21]	100	4 (4%)	Not defined	>3X serum amylase	Not defined
O'Neil et al., 2001[31]	102	9 (8.8%)	Not defined	>2X serum amylase	>50 ml
Bottger et al., 1999[17]	221	30 (14%)	Not defined	>2000 U/L	Not defined
Sato et al., 1998[29]	62	9 (15%)	Not defined	>1000 U/L	Not defined
Povoski et al., 1999[26]	240	25 (10%)	Not defined	Elevated	Not defined
Present series	207	29 (14%)	⩾ 5	>5X serum amylase	>30 ml

POD = postoperative day.

morbid than others were. The chemical leak patients in the current study seemed equivalent to the no leak patients because they all recovered uneventfully and were discharged after a median LOS of 12 days. The drain data helps to define the presence of a leak, but the leak severity is best graded by clinical outcomes.

Fahy et al.[32] proposed a grading system of pancreatic leaks. Their grading system defined pancreatic leaks as "mild," "moderate," and "severe." The first grade of mild is a leak that is clinically asymptomatic, requiring no therapeutic intervention. The intermediate grade of moderate implies mild clinical symptomatology (e.g., nausea, persistent fever) associated with prolonged drainage time but resolves without further intervention. Finally the grade of severe implies significant symptomatology (e.g., intra-abdominal sepsis) and additional therapeutic intervention (either by interventional radiology or by surgical exploration). Recently, an international group of surgeons[33] interested in the pancreas, headed by Christos Dervenis of Athens and Claudio Bassi of Verona, met in Athens to discuss the grading of the pancreatic anastomotic fistula. The consensus that followed established three categories similar to those suggested by Fahy et al.,[32] but termed grade A through C. Also agreed upon was that a large number of actual leak cases had to be analyzed before a clinical grading system could be fine-tuned, especially the intermediate grade B.

In conclusion, a clinically relevant pancreatic leak will have at least one of the following: DGE, prolonged LOS, will require percutaneous drainage, will require reoperation, or will need readmission. Over half of the patients with a leak, according to the drain volume/amylase criteria of the current study, will be clinically relevant. Monitoring drain volume and its amylase concentration after POD 5 should provide an early detection of a clinically relevant pancreatic leak in most patients, enabling the timely use of conservative measures. The drain data helps to define the presence of a leak, but the severity is best graded by clinical outcomes. For clinical trials designed to study and improve leak rates, a clinical grading score would be more useful than drain data alone. The best compromise would be a pancreatic leak grading system based on both drain information (to define the asymptomatic leak group) and clinical outcomes (to define the severest grades). Our study cannot help establish a clinical severity score. Only 8% (n = 17) of our cases had a clinically relevant leak. The need for a multicenter sharing of drain and clinical data is required to obtain sufficient cases to develop a pancreatic leak severity grading system.

REFERENCES

1. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993;217: 430–435.
2. Trede M, Schwall G, Saeger HD. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447–458.

3. Fernandez-del Castillo C, Rattner DW, Warshaw AL. Standards for pancreatic resection in the 1990s. Arch Surg 1995; 130:295–299.
4. Neoptolemos JP, Russell RC, Bramhall S, Theis B. Low mortality after resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units. UK Pancreatic Cancer Group. Br J Surg 1997;84:1370–1376.
5. Traverso LW, Kozarek RA. Pancreaticoduodenectomy for chronic pancreatitis: Anatomic selection criteria and subsequent long-term outcome analysis. Ann Surg 1997;226: 429–438.
6. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: Pathology, complications, and outcomes. Ann Surg 1997;226:248–260.
7. Bottger TC, Junginger T. Factors influencing morbidity and mortality after pancreaticoduodenectomy: Critical analysis of 221 resections. World J Surg 1999;23:164–172.
8. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: Incidence, significance, and management. Am J Surg 1994;168:295–298.
9. Strasberg SM, Drebin JA, Soper NJ. Evolution and current status of the Whipple procedure: An update for gastroenterologists. Gastroenterology 1997;113:983–994.
10. Yeo CJ. Management of complications after pancreaticoduodenectomy. Surg Clin North Am 1995;75:913–924.
11. Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: Changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2000;136: 391–398.
12. Poon RT, Lo SH, Fong D, Fan ST, Wong J. Prevention of pancreatic anastomotic leakage after pancreaticoduodenectomy. Am J Surg 2002;183:42–52.
13. Strasberg SM, Drebin JA, Mokadam NA, et al. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: Effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002;194:746–760.
14. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232:419–429.
15. Lowy AM, Lee JE, Pisters PW, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg 1997;226:632–641.
16. Grobmyer SR, Rivadeneira DE, Goodman CA, Mackrell P, Lieberman MD, Daly JM. Pancreatic anastomotic failure after pancreaticoduodenectomy. Am J Surg 2000;180:117–120.
17. Sarr MG and the Pancreatic Surgery Group. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: A prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg 2003;196:556–565.
18. Shyr YM, Su CH, Wu CW, Lui WY. Does drainage fluid amylase reflect pancreatic leakage after pancreaticoduodenectomy? World J Surg 2003;27:606–610.
19. Hashimoto N, Ohyanagi H. Pancreatic juice output and amylase level in the drainage fluid after pancreatoduodenectomy in relation to leakage. Hepatogastroenterology 2002; 49:553–555.
20. Biehl T, Traverso LW. Is stenting necessary for a successful pancreatic anastomosis? Am J Surg 1992;163:530–532.
21. Ohwada S, Ogawa T, Kawate S, et al. Results of duct-to-mucosa pancreaticojejunostomy for pancreaticoduodenectomy Billroth I type reconstruction in 100 consecutive patients. J Am Coll Surg 2001;193:29–35.
22. Brooks AD, Marcus SG, Gradek C, et al. Decreasing length of stay after pancreatoduodenectomy. Arch Surg 2000;135: 823–830.
23. Buchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'Graggen K. Pancreatic fistula after pancreatic head resection. Br J Surg 2000;87:883–889.
24. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: Risk factors and the impact of hospital volume. Ann Surg 2000;232:786–795.
25. Rios G, Conrad A, Cole D, et al. Trends in indications and outcomes in the Whipple procedure over a 40-year period. Am Surg 1999;65:889–893.
26. Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome after pancreaticoduodenectomy. Ann Surg 1999;230:131–142.
27. Roder JD, Stein HJ, Bottcher KA, Busch R, Heidecke CD, Siewert JR. Stented versus nonstented pancreaticojejunostomy after pancreatoduodenectomy: A prospective study. Ann Surg 1999;229:41–48.
28. Papadimitriou JD, Fotopoulos AC, Smyrniotis B, Prahalias AA, Kostopanagiotou G, Papadimitriou LJ. Subtotal pancreatoduodenectomy: Use of a defunctionalized loop for pancreatic stump drainage. Arch Surg 1999;134: 135–139.
29. Sato N, Yamaguchi K, Chijiiwa K, Tanaka M. Risk analysis of pancreatic fistula after pancreatic head resection. Arch Surg 1998;133:1094–1098.
30. Okamoto A, Tsuruta K. Fistulation method: Simple and safe pancreaticojejunostomy after pancreatoduodenectomy. Surgery 2000;127:433–438.
31. O'Neil S, Pickleman J, Aranha GV. Pancreaticogastrostomy after pancreaticoduodenectomy: Review of 102 consecutive cases. World J Surg 2001;25:567–571.
32. Fahy BN, Frey CF, Ho HS, Beckett L, Bold RJ. Morbidity, mortality, and technical factors of distal pancreatectomy. Am J Surg 2002;183:237–241.
33. Bassi C, Butturini G, Dervenis C, et al. Postoperative pancreatic fistula: A consensus definition. Surgery 2005; 138:8–13.

Combined Antioxidant Therapy Reduces Pain and Improves Quality of Life in Chronic Pancreatitis

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Patients with chronic pancreatitis (CP) typically suffer intractable abdominal pain that is resistant to most analgesic strategies. Recent research indicates that the pain of CP may be in part due to oxygen free radical induced pancreatic damage. Using a randomized, double-blind, placebo-controlled crossover trial, we evaluated the efficacy of a combined antioxidant preparation in the management of CP. Patients with confirmed chronic pancreatitis (N = 36) were randomized to receive treatment with either Antox, which contains the antioxidants selenium, betacarotene, L-methionine, and vitamins C and E, or placebo for 10 weeks. Each group of patients then switched to receive the alternative treatment for a further 10 weeks. Markers of antioxidant status were measured by blood sampling, whereas quality of life and pain were assessed using the SF-36 questionnaire. Nineteen patients completed the full 20 weeks of treatment. Treatment with Antox was associated with significant improvements in quality of life in terms of pain (+17 antioxidant vs. −7 placebo), physical (+9 vs. −3) and social functioning (+8 vs. −7), and general health perception (+10 vs. −3). We conclude that treatment with antioxidants may improve quality of life and reduce pain in patients suffering from chronic pancreatitis. (J GASTROINTEST SURG 2006;10:499–503) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Antioxidants, chronic pancreatitis, pain, quality of life

Chronic pancreatitis (CP) is a progressive inflammatory disorder that is characterized by recurrent episodes of severe abdominal pain. Affected patients typically suffer years of disabling pain, and conventional therapeutic interventions are often unable to offer satisfactory analgesia. The majority of cases in Europe and the United Kingdom are associated with alcohol abuse; these patients often become dependent on opiate analgesics and are usually unable to remain in employment. Relationships may also become difficult to maintain, and patients often become physically and socially isolated.

Recent literature suggests that heightened free radical activity and oxidative stress may be important in the pathogenesis of chronic pancreatitis.[1–3] In normal metabolism, exogenous nonbiologic chemicals (xenobiotics) are metabolized via the mitochondrial enzyme cytochrome P450 (cP450) pathway. During this process, reactive oxygen free radicals are produced that are capable of causing cell damage by peroxidation of lipids and lipoproteins in the cell membrane. Endogenous antioxidants, in particular, products of methionine metabolism such as glutathione are important in preventing cellular damage caused by these free radical species.

Induction of the cP450 pathway by chronic ingestion of alcohol or anticonvulsants can increase the yield of reactive oxygen species released by metabolism of xenobiotic materials. Combined with a deficiency in antioxidant defense mechanisms, increased levels of oxygen free radicals may be capable of impairing normal pancreatic structure and function.

In the last decade, evidence has emerged which suggests that levels of oxidants and antioxidants are altered in patients with chronic pancreatitis. In

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1990, Guyan et al.[2] demonstrated increased levels of oxygen free radicals in the serum and pancreatic secretions of patients with the condition. Subsequent research has identified three main factors that are thought to increase oxidative stress in patients with chronic pancreatitis:[4–8] (a) chronic induction of the cP450 enzyme system, with increased levels of the products of lipid peroxidation;[9] (b) increased exposure to exogenous chemicals metabolized by the cP450 system;[10] and (c) a relative deficiency of antioxidant substances such as carotenoids, vitamins C and E, methionine, and selenium, which are essential to maintain adequate levels of glutathione.[11,12]

These findings suggest that antioxidant therapy in patients with chronic pancreatitis might reduce levels of reactive oxygen species, thereby reducing cellular damage and alleviating symptoms of pain. Initial reports of trials of antioxidant therapy were limited to the use of single antioxidants in small numbers of patients,[13,14] but more recent studies have examined the administration of combinations of antioxidants in patients with chronic pancreatitis.[15,16] These studies suggested that vitamin C and methionine were effective in reducing background pain and preventing further attacks of chronic pancreatitis, but the authors noted problems with delivery and obtaining satisfactory bioavailability of the administered antioxidants.[17] There were also problems with compliance, as treatment involved taking as many as 14 tablets per day. A combined antioxidant preparation (Antox) has since been developed that contains selenium, vitamins C, E, betacarotene, and methionine. This preparation is based on those used in previous studies[17,18] and has been shown to possess improved bioavailability compared to individually administered preparations. This study examined its efficacy and used quality of life as an outcome measure of relief of symptoms in patients with chronic pancreatitis.

METHODS

Patients appearing at the Department of Surgery, Royal Victoria Hospital between 1996 and 1999 with abdominal pain suspected to be due to chronic pancreatitis were considered for inclusion in this study. Three criteria were used to confirm the presence of chronic pancreatitis in these patients: (1) radiological abnormality of the pancreas consistent with CP (e.g., calcification), (2) pancreatic duct abnormality at endoscopic retrograde cholangiopancreatography, and (3) evidence of exocrinepancreatic insufficiency on para-aminobenzoic acid testing.

Patients with chronic abdominal pain and at least one of these criteria were invited to enter the study. Patients with gallstones and those requiring surgical intervention were excluded. Those under 16 and over 75 years of age were also excluded. In total, 36 patients (23 men and 13 women) were recruited. Ethical approval was obtained from the local Ethics Committee.

The study was designed as a double blind, placebo-controlled, crossover trial. The trial period was 20 weeks; treatment was allocated using a randomized block design and started with either Antox or placebo. After an initial 10 weeks of treatment, patients changed to the alternative treatment for a further 10 weeks. By the inherent nature of the recruitment policy, many of the patients had alcohol and/or drug dependence problems, and their level of compliance to the protocol was expected to be poor. In an effort to improve compliance and reduce drop-out rates, no "washout period" was incorporated into the study.

The constituents of each Antox tablet were as follows: 75 μg of selenium, 3 mg betacarotene, 47 mg d-alpha-tocopherol acetate (vitamin E), 150 mg ascorbic acid (vitamin C), and 400 mg methionone.

This formulation was based on the combination of antioxidants employed in previous studies[16,17] but utilizing tablets with a higher concentration of active ingredients. Placebo tablets were identical in appearance to Antox tablets but lacked any antioxidant components. Patients were instructed to take one tablet four times daily with food and to complete a daily pain diary. They were also asked to record adverse reactions and any additional analgesic requirements. Patients were interviewed and assessed at the start of the study and at 5, 10, 15, and 20 weeks thereafter. Venous blood sampling was performed at each attendance to measure plasma levels of the administered antioxidants selenium, betacarotene, tocopherol, and ascorbic acid. As an estimate of endogenous antioxidant status, retinol, α-carotene, and lycopene were measured. Four other indicators of antioxidant capacity were also estimated: malondialdehyde, glutathione peroxidase, serum total antioxidant capacity, and ferrous oxidation in xylenol orange.

The pain diaries used three visual analogue scales to assess pain intensity, pain relief, and mood. Patients were asked to fill in each of these scales on a daily basis. The impact of treatment on general health and quality of life was also assessed using the short form 36 (SF-36) questionnaire.[19] This is a generic quality of life instrument, which has been fully validated[20,21] and shown to be reliable in a wide range of diseases.[21,22] It comprises 36 questions which address physical, emotional, and social functioning, mental health, energy, pain, and health

perception. Subjects receive a score of between −100 to +100 in each of nine dimensions. Each questionnaire was administered at personal interview by the investigator at the start of the study and again 10 and 20 weeks thereafter. The change in dimensional scores was calculated over the treatment period, with each subject acting as his/her own control. The mean change in SF-36 score was determined for each treatment period. Data were analyzed using a one-tailed Student's *t* test with the alternative hypothesis (antioxidant greater than placebo). Statistical significance was accepted at the 5% level.

RESULTS

Nineteen subjects (13 men and 6 women) completed both periods of treatment. Eight of these were from the group given placebo treatment first and 11 were from those given Antox first. The other 17 patients either decided to withdraw from the study or failed to attend for follow-up. Two patients complained of nausea and one of an unpleasant taste during treatment with Antox. This was probably due to the presence of methionine, which is a sulfur-containing amino acid. No side effects were reported during treatment with the placebo.

Analysis of data from visual analogue scales in the pain diaries showed that their completion was inconsistent and erratic. There was also evidence that data had been entered retrospectively rather than on a daily basis. Because of these factors, further analysis on data from the pain diaries was not performed.

Analysis of data from the SF-36 questionnaire showed that treatment with Antox was associated with a significant improvement in quality of life in six of the nine dimensions when compared with the placebo (Fig. 1). There was a reduction in pain, and an improvement in physical and social functioning, and in health perception. No differences were detected in emotional functioning, energy, or mental health. There was no significant difference in quality of life between those patients who had received Antox in the first or second 10-week period.

Treatment with Antox was also associated with a significant increase in plasma levels of selenium, vitamin C, vitamin E, and betacarotene compared with placebo (Table 1). No difference was detected in serum levels of lycopene, retinol, α-carotene, nor in total serum antioxidant capacity. Analysis of data from patients treated with Antox in the first treatment period suggested that the serum levels of water-soluble antioxidants such as vitamins C and selenium tended to return to pretreatment levels within 5 weeks, whereas those of fat-soluble vitamins such as vitamin E tended to remain slightly elevated until the end of the study.

DISCUSSION

Long-term pain control in chronic pancreatitis can be difficult to achieve.[23–25] Affected patients

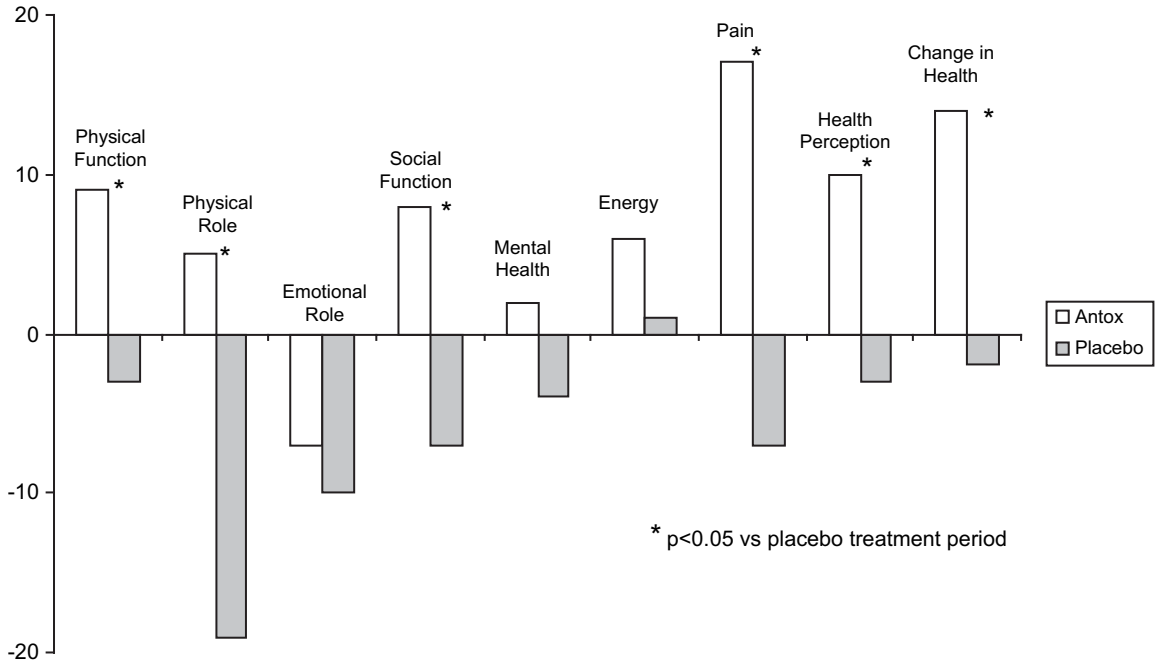

Fig. 1. Change in SF-36 quality of life dimensional scores after treatment period (Antox vs. placebo).

Table 1. Mean serum concentration of various antioxidants after 10 weeks of treatment

	Antox	Placebo
Vitamin C (mmol/L)	25.7 ± 7.1*	17.94 ± 5.4
Selenium (mmol/L)	1.43 ± 0.11*	1.03 ± 0.07
Retinol	2.03 ± 0.19	1.90 ± 0.22
Tocopherol	40.7 ± 5.3*	30.0 ± 2.2
Lycopene	0.070 ± 0.012	0.084 ± 0.021
α carotene	0.013 ± 0.003	0.018 ± 0.003
Betacarotene	0.53 ± 0.14*	0.23 ± 0.05
MDA (μM)	2.60 ± 0.45	1.87 ± 0.25
TAC (mmol/L)	1.4 ± 0.02	1.39 ± 0.02
FOX 1 (μM)	3.24 ± 0.48	2.55 ± 0.335
GPX (Iu)	300 ± 19	293 ± 15

FOX 1 = ferrous oxidation in xylenol orange; GPX = glutathione peroxidase; MDA = malondialdehyde; TAC = serum total antioxidant capacity.
*$P < 0.05$ vs. placebo.

typically require repeated hospital admissions for pain relief and often become dependent on opiate analgesia. A multidisciplinary approach to their management is required, with appropriate dietary and lifestyle modification. Diagnostic differential nerve blockade can help identify the visceral pain of CP and recognize those who may benefit from celiac nerve blockade. Thoracoscopic splanchnicectomy is usually reserved for those with intractable symptoms.

Surgery for chronic pancreatitis is still widely practiced, and a decision to proceed is largely based on pancreatic duct morphology. Typical procedures involve resection of all or part of the pancreas, or decompression of the pancreatic duct. Although these procedures have been associated with pain relief in the immediate postoperative period, many patients report a recurrence of pain in the longer term.[26] Pancreatic surgery is also not without risk, and carries a significant perioperative morbidity and mortality.[27] Total pancreatectomy results in endocrine and exocrine insufficiency. Although many of the symptoms of exocrine dysfunction can be controlled, patients often develop brittle diabetes mellitus, which in itself has significant long-term morbidity and mortality. For these reasons, surgery for chronic pancreatitis has fallen from favor in many centers.

Recent research has implicated oxidative stress as a factor in the causation of chronic pancreatitis and suggested that antioxidant therapy may reduce pancreatic damage and improve symptoms in this condition. The utilization of this therapeutic strategy would avoid the risks and complications associated with pancreatic surgery and would also have the advantage of preserving remaining pancreatic function.

The study presented here examined the effects of antioxidant treatment under controlled conditions for the relief of symptoms in chronic pancreatitis. It is the first such study to show a significant improvement in quality of life and reduction in pain levels associated with the combined antioxidant preparation Antox in patients with chronic pancreatitis.

Only 19 of the 36 patients recruited (53%) completed the entire study period. The remainder either withdrew or failed to attend for follow-up. Such a high dropout rate had been anticipated in this group of patients due to the length of the study period, poor patient motivation, and in some cases, ongoing problems with alcohol dependence. The study was designed as a crossover trial without a washout period in an attempt to reduce the length of the study and to limit the dropout rate further. In those patients who did complete the trial, compliance was good and was confirmed by serum estimation of the various antioxidants (Table 1). The incidence of side effects was also low, with only two patients reporting nausea while undergoing the antioxidant treatment. There is some evidence that selenium may accumulate in the presence of renal failure, but no toxicity was observed in the population studied. There was some evidence that serum levels of the fat-soluble vitamins remained elevated for a short time after switching from antioxidant treatment to placebo, but levels were noted to return to baseline by the end of the treatment period.

Data in the pain diaries were poorly recorded and were often incomplete. We quickly learned that this information was of limited value, so the pain diaries were abandoned and pain was assessed using the SF-36 questionnaire only. This questionnaire was also used to compare subjective changes in the quality of life during the two treatment periods of the study. Eight of the nine dimensions of the SF-36 analyzed were found to have improved in the antioxidant treatment period, and changes in six of these dimensions were confirmed as statistically significant (Fig. 1). The two most striking improvements were observed in pain (+17 antioxidant vs. −7 placebo) and physical functioning (+9 antioxidant vs. −3 placebo). There were also significant benefits observed in physical role (+5 vs. −19), social functioning (+8 vs. −7), health perception (+10 vs. −3), and overall change in health (+14 vs. −2). Despite improvement, remaining changes in mental health (+2 vs. −4) and energy level (+6 vs. +1) did not reach statistical significance.

With no washout period, one potential source of error in our study may have been prolonged elevation of fat-soluble antioxidants after stopping treatment. Because the quality of life score reached at the end

of the first period acted as the baseline for the second, bias could have been introduced and could have affected whether a patient's score changed. Taking this into account, and with baseline adjustments, statistical analyses were, as expected, more conservative but still statistically significant in the same six modalities where a positive result had been observed.

These findings confirm those of previous studies that investigated the effects of individual antioxidants and demonstrated a reduction in pain levels and a decrease in the requirement for surgical intervention.[15–18,24] The improved pain scores demonstrated by this study suggest that antioxidant therapy should be considered as a means of pain relief in patients with chronic pancreatitis and may be of use as an adjunct, particularly where other pain-relieving strategies have failed.

The data from this short study strongly show that the effects of antioxidant therapy are not only limited to pain relief, but are also capable of improving several aspects in the quality of life of patients with chronic pancreatitis. These findings indicate that a longer period of treatment with a combined antioxidant preparation may prove effective in improving the day-to-day function of patients with chronic pancreatitis, as well reducing their pain. A larger and longer term intervention trial of antioxidant therapy in chronic pancreatitis is now required to confirm these findings and to establish the role of this treatment in the management of this disabling condition.

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REFERENCES

1. Basso D, Panozzo MP, Fabris C, et al. Oxygen derived free radicals in patients with chronic pancreatic and other digestive diseases. J Clin Pathol 1990;43:403–405.
2. Guyan PM, Uden S, Braganza JM. Heightened free radical activity in pancreatitis. Free Radic Biol Med 1990;8:347–354.
3. Schoenberg MH, Birk D, Beger HG. Oxidative stress in acute and chronic pancreatitis. Am J Clin Nutr 1995;62 (6 Suppl):1306S–1314S.
4. Tsai K, Wang SS, Chen TS, et al. Oxidative stress: An important phenomenon with pathogenetic significance in the progression of acute pancreatitis. Gut 1998;42: 850–855.
5. Szuster-Ciesielska A, Daniluk J, Kandefer-Szerszen M. Oxidative stress in blood of patients with alcohol-related pancreatitis. Pancreas 2001;22:261–266.
6. Sweiry JH, Mann GE. Role of oxidative stress in the pathogenesis of acute pancreatitis. Scand J Gastroenterol Suppl 1996;219:10–15.
7. Salim AS. Role of oxygen-derived free radical scavengers in the treatment of recurrent pain produced by chronic pancreatitis. A new approach. Arch Surg 1991;126:1109–1114.
8. Braganza JM. Pancreatic disease: A casualty of hepatic "detoxification"? Lancet 1983 29;2:1000–1003.
9. Acheson DW, Hunt LP, Rose P, Houston JB, Braganza JM. Factors contributing to the accelerated clearance of theophylline and antipyrine in adults with exocrine pancreatic disease. Clin Sci (Lond) 1989;76:377–385.
10. McNamee R, Braganza JM, Hogg J, Leck I, Rose P, Cherry NM. Occupational exposure to hydrocarbons and chronic pancreatitis: A case-referent study. Occup Environ Med 1994;51:631–637.
11. Rose P, Fraine E, Hunt LP, Acheson DW, Braganza JM. Dietary antioxidants and chronic pancreatitis. Hum Nutr Clin Nutr 1986;40:151–164.
12. Uden S, Acheson DW, Reeves J, et al. Antioxidants, enzyme induction, and chronic pancreatitis: A reappraisal following studies in patients on anticonvulsants. Eur J Clin Nutr 1988;42:561–569.
13. Braganza JM, Jeffrey IJ, Foster J, McCloy RF. Recalcitrant pancreatitis: Eventual control by antioxidants. Pancreas 1987;2:489–494.
14. Braganza JM, Thomas A, Robinson A. Antioxidants to treat chronic pancreatitis in childhood? Case report and possible implications for pathogenesis. Int J Pancreatol 1988;(3): 209–216.
15. Uden S, Bilton D, Nathan L, Hunt LP, Main C, Braganza JM. Antioxidant therapy for recurrent pancreatitis: Placebo-controlled trial. Aliment Pharmacol Ther 1990;4: 357–371.
16. Uden S, Schofield D, Miller PF, Day JP, Bottiglier T, Braganza JM. Antioxidant therapy for recurrent pancreatitis: Biochemical profiles in a placebo-controlled trial. Aliment Pharmacol Ther 1992;6:229–240.
17. McCloy R. Chronic pancreatitis at Manchester, UK. Focus on antioxidant therapy. Digestion 1998;59(Suppl 4):36–48.
18. Braganza JM. The pathogenesis of chronic pancreatitis. QJM 1996;89:243–250.
19. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992;30:473–483.
20. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–263.
21. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care 1988;26:724–735.
22. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40–66.
23. Andren-Sandberg A. Pain relief in pancreatic disease. Br J Surg 1997;84:1041–1042.
24. Moossa AR. Surgical treatment of chronic pancreatitis: An overview. Br J Surg 1987;74:661–667.
25. Trapnell JE. Chronic relapsing pancreatitis: A review of 64 cases. Br J Surg 1979;66:471–475.
26. Huang JJ, Yeo CJ, Sohn TA, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 2000; 231:890–898.
27. Sohn TA, Campbell KA, Pitt HA, et al. Quality of life and long-term survival after surgery for chronic pancreatitis. J GASTROINTEST SURG 2000;4:355–364.

Long-term Results of Frey's Procedure for Chronic Pancreatitis: A Longitudinal Prospective Study on 40 Patients

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Only limited prospective data are available regarding the long-term outcome of local resection of the pancreatic head in combination with longitudinal pancreaticojejunostomy in patients with chronic pancreatitis. From 1997 to 2001, 40 patients affected by chronic pancreatitis were subjected to the Frey's procedure. Preoperative selection criteria included confirmed diagnosis of chronic pancreatitis, dilation of Wirsung's duct to a diameter greater than 6 mm, and the absence of obstructive chronic pancreatitis secondary to fibrotic stenosis at the pancreatic body or tail. Preoperative pain was present in 38 cases (95%), and follow-up was performed in all patients at least once yearly up to 2003 (median 60 months, inter percentile range 20.1–79.6). Postoperative morbidity occurred in three cases (7.5%). The percentage of pain-free patients was 94.7%, 93.7%, 87.5%, and 90% at 1, 2, 3, and 4/5 years after surgical operation, respectively. After surgery, three patients developed diabetes. Both the body mass index and quality of life showed statistically significant improvements at all follow-up intervals. Whenever surgery is indicated, the short-term and long-term outcomes confirm that Frey's procedure is an appropriate means of management for patients with chronic pancreatitis in the absence of doubts of neoplasia and/or distal ductal obstruction.
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KEY WORDS: Chronic pancreatitis, pancreaticojejunostomy, Frey's procedure

Chronic pancreatitis is often accompanied by severe and disabling pain[1,2] that requires surgery,[1,3,4] although the most appropriate means of intervention, varying from highly aggressive procedures to more conservative management,[5–10] remains to be established. All of the currently used procedures provide an acceptable frequency of morbidity and mortality, and in general, satisfactory results are usually obtained, especially regarding the control of pain.[11–15] In fact, more than 70% of cases remain pain-free for at least 5 years after surgery.[11,13,15] Although radical procedures are unavoidable in patients when malignancy is suspected,[16,17] more conservative approaches have considerable advantages. The preservation of the greatest amount of parenchyma possible is highly favored when considering that the disease usually progresses, leading to exocrine and endocrine insufficiency.[2,18] Moreover, less complicated surgical procedures also allow a reduction in morbidity and mortality.[19,20] Partington-Rochelle pancreaticojejunostomy is the most commonly used type of operation.[3,21] However, some of the failures of this procedure can be attributed to the lack of drainage of Wirsung's duct in the pancreatic head.[21] In fact, the extent of drainage seems to be directly proportional to the degree of pain-relief.[22] Thus, the excision of a small portion of the pancreatic head as described by Frey and Smith[9] allows for the decompression of the entire duct from the papilla to the tail. Various authors have described similar results in terms of morbidity that, for the most part, show good outcome considering short-term and long-term pain relief.[18–20,23–25] The aim of the present study was to prospectively analyze the outcome in a series of patients with chronic pancreatitis operated upon via pancreaticojejunostomy as described by Frey.

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PATIENTS AND METHODS

From 1997 to 2001, 40 patients suffering from chronic pancreatitis underwent pancreaticojejunostomy according to Frey's procedure (Fig. 1). Diagnosis of chronic pancreatitis was based on clinical and imaging findings, which are the gold standard for diagnosis and evaluation of exocrine and/or endocrine insufficiency.[26] Preoperative selection criteria included unequivocal diagnosis of chronic pancreatitis, dilation of Wirsung's duct to a diameter greater than 6 mm, and the absence of obstructive chronic pancreatitis secondary to fibrotic stenosis at the level of the pancreatic body or tail. Before surgical procedure and at yearly intervals thereafter, patients were asked to rate their subjective quality of life on a nonvalidated scale from 0–10, with a score of 10 being the best (i.e., normal life). All surgical procedures were performed as previously described.[9,21] After surgery, patients were followed-up at yearly intervals, with clinical and imaging studies. The last date of follow-up was December 2003.

Statistical Analysis

For continuous variables, the median and interpercentile range (IPR), interpercentile range (the 2.5th and 97.5th percentiles), were considered. Preoperative and postoperative variables were compared using Friedman's test for nonparametric variables and McNemar tests for marginal homogeneity. A P value < 0.05 was considered statistically significant.

RESULTS

Study Population

The median age of the patient cohort (N = 40) was 50.1 years (IPR, 19.9–67.6); there were 29 males (72.5%) and 11 females (27.5%). At the time of surgical procedure, the median body weight was 64.5 kg (IPR, 42.2–93.5). Thirty-two (80%) patients smoked a median of 20 cigarettes per day (IPR, 5–60), whereas 30 patients (75%) drank a median of 100 g alcohol per day (IPR, 10–400 g/day). Diabetes mellitus was present in 10 patients (25%), which was controlled with diet alone in one case (2.5%), with antidiabetic agents in two cases (5%), and with insulin in the remaining seven cases (17.5%). Pain was present in 38 of 40 cases (95%), with an average of six episodes (IPR, 2–365) per year before surgery. A previous episode of severe acute pancreatitis was reported in eight cases (20%). Twelve patients (30%) had previous surgeries, including two gastric resections for peptic ulcers, five open cholecystectomies, and five procedures involving the pancreatic gland. Pancreatico-jejunal anastomosis, according to Partington-Rochelle, was performed in four cases (with two concomitant biliary bypasses and with cyst-jejunal anastomosis in the remaining cases). Before

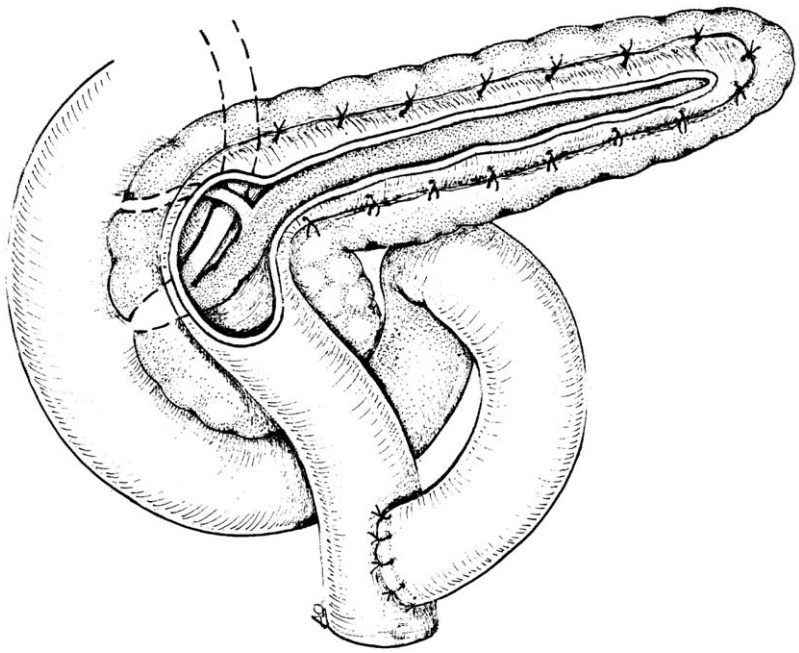

Fig. 1. Frey's procedure. The cored anterior part of the pancreatic head is drained in continuity with a dilated Wirsung's duct with a Roux-en-Y loop. Both the Santorini and the main pancreatic ducts are wide open.

surgery, six cases (15%) presented with jaundice, whereas no patients complained of symptoms due to upper digestive tract obstruction. Ascites of pancreatic origin was present in one patient (2.5%). With the exception of the six patients hospitalized for jaundice, preoperative or intraoperative examination revealed a dilated bile duct (diameter greater than 7 mm) in three cases (7.5%) and cholelithiasis in eight cases (20%). Moreover, pancreatic calcifications were present in 22 patients (55%), whereas nine cases (22.5%) presented with one or more pseudocysts localized primarily at the pancreatic head. The chronic pancreatitis was alcohol related in 27 patients (67.5%), obstructive in eight cases (20%), and hereditary in one patient (2.5%). The cause was unknown in the remaining four cases (10%). The most frequent indication for surgery was the presence of disabling intractable pain (32 cases, 80%), for which 28 patients regularly assumed an association of paracetamol and codeine and four opiate analgesics. Surgery was indicated in six cases (15%) for pseudocysts causing biliary obstruction, and in one case for pancreatic ascites (15%).

Surgical Results

All pseudocysts suspected by preoperative examinations were confirmed intraoperatively. The surgical strategy was not modified by the presence of pseudocysts in any case, because it was possible to access the pancreatic head for drainage together with the pancreatic duct. Selected intraoperative and postoperative data are shown in Table 1. During the surgical procedure, alcohol celiac nerve block was never performed. Recovery was unremarkable in 37 patients (92.5%). Two patients (5%) developed external pancreatic fistulae, and one patient developed focal bronchopneumonia with concomitant pleural effusion that was treated conservatively. There were no postoperative deaths.

Table 1. Principal perioperative and postoperative data in 40 patients undergoing pancreaticojejunostomy according to Frey's procedure

	Median	IPR
Duration of surgical intervention (min)	230	140.3–393.1
Units of blood transfused	0	0–2
Postoperative hospitalization time (days)	9	6–27
	No. of patients	**%**
Concomitant surgical procedures	16	40
Hepaticojejunostomy	10	25
Cholecystectomy*	14	35
Morbidity	3	7.5
Mortality	0	0

*Eight associated with biliary bypasses.

Long-term Results

The median follow-up time was 60 months (IPR, 20.1–79.6). No patients were lost to follow-up, and there were no deaths during the follow-up period. Three patients underwent a second intervention. In one case, a hepaticojejunostomy for jaundice was done 38 months later, whereas two patients were operated upon for neoplasms involving the pharynx and kidney at 2 and 3 years, respectively, after Frey's procedure. Although 38 patients presented with pain before surgery, at 1 year after pancreatic surgery 36 of these 38 cases (94.7%) were pain-free. At 2, 3, and 4 years after surgery, 93.7% (30/32), 87.5% (28/32), and 89.3% (25/28) of cases, respectively, remained pain-free. The percentage of patients pain-free at 5 years was 90.5% (19/21). This data is shown graphically in Fig. 2. The percentage of patients absolutely free of narcotic use was in agreement with this figure. The median number of pain episodes was dramatically reduced from six per year (IPR, 0.4–223.3) before intervention to one per year during the first postoperative year (IPR, 0–1). This was also demonstrated by a reduction of the median number of hospitalization days (preoperative: 20/year, IPR, 2–40; postoperative: 0). During the follow-up, none of the patients required regular analgesics. For those patients who assumed opiate analgesics, a specific detoxication program was applied by a dedicated service. The differences in the preoperative and postoperative parameters were statistically significant (pain, 30.3, $P = 0.0001$, Friedman's test; number of hospitalization days, 17.4, $P = 0.004$, respectively) and remained at later follow-up times. Three patients did not benefit from surgery. Of these, two were nondrinkers and the remaining individual continued to consume alcohol, albeit in reduced quantities. Of the 30 patients that consumed alcohol before surgery, 11 continued to consume alcohol after surgery ($P = 0.0001$), although the intake was significantly reduced (median preoperative: 100 g/day and IPR, 10–400; median postoperative: 30 g/day and IPR, 20–60). After surgery, only four patients (12.5%) of the 32 smokers has quit smoking, even though the median number of cigarettes smoked daily was significantly decreased (median preoperative: 20 cigarettes/day and IPR, 5–60; median postoperative: 15 cigarettes/day and IPR, 5–60; $P = 0.001$). During follow-up, the number of patients with diabetes rose to 12 (30%). One patient that showed preoperative

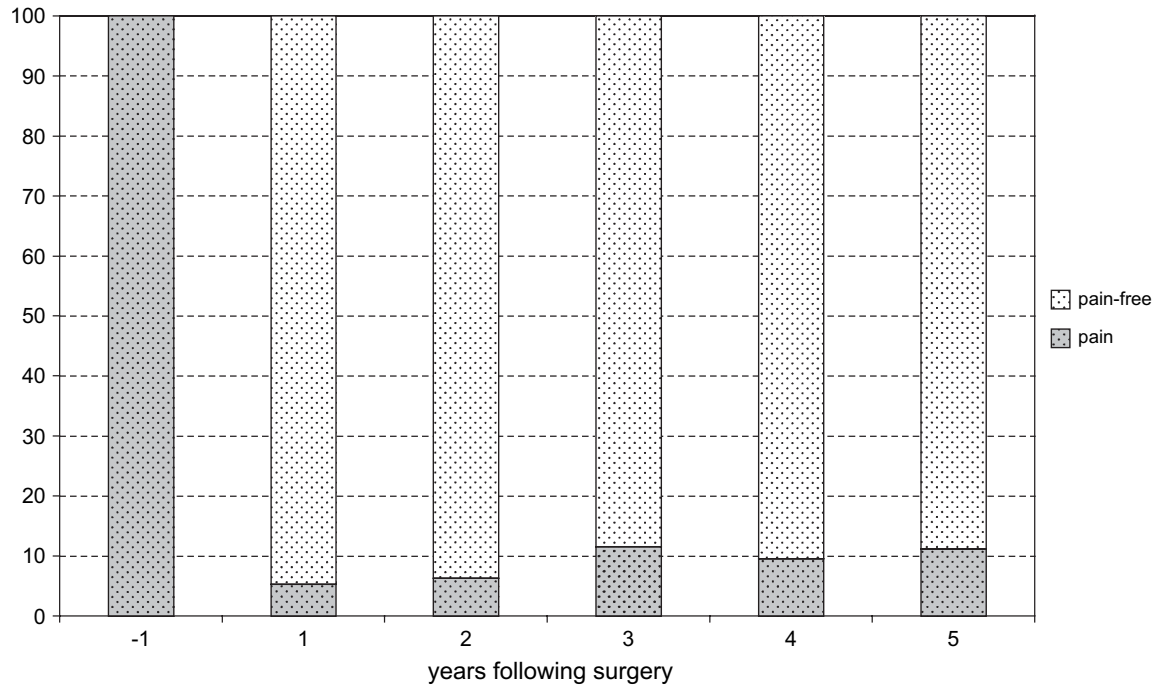

Fig. 2. Percentage of patients pain-free after surgery (data on the 38 patients presenting with pain before intervention; $P = 0.0001$).

glucose intolerance had a normal oral glucose tolerance test after surgery. In the two cases that were in therapy with antidiabetic agents, one was stable, whereas the other needed insulin therapy at 15 months. Of the seven patients suffering from insulin-dependent diabetes before surgery, three remained stable and four showed improvement and no longer required insulin therapy, but only antidiabetic oral therapy. Thus, after surgery, either new or worsening diabetes was observed in three patients; one case developed noninsulin-dependent diabetes at 16 months, whereas the other two cases required insulin therapy after 15 and 38 months, respectively. The median body mass index significantly improved during the postoperative period (median preoperative: 21.5 and IPR, 15.7–29.5; median postoperative: 22.9 and IPR, 17.9–30.3; $P = 0.0001$; Fig. 3). A total of 31 patients (77.5%) took pancreatic enzymes for exocrine insufficiency, although the frequency was not significantly different from that observed before surgery. The median score of subjective assessment of the quality of life during the year after surgery was significantly higher compared with that before surgery (median preoperative: 4.2 and IPR, 1.7–8.2; median postoperative at 1 year: 7.0 and IPR, 4.1–10). In the period following surgery, the median was 8.0 (IPR, 6.2–10) at year 2, 8.3 (IPR, 6.7–10) at year 3, 8.2 (IPR, 6.9–10) at year 4, and 8.2 (IPR, 6.9–10) at year 5, respectively. After surgery, 28 patients resumed normal work-related activities, whereas 12 patients ceased to work, three due to retirement.

DISCUSSION

Given the variety of clinical presentations of chronic pancreatitis, it is widely believed that there is no surgical option that is clearly superior to others.[18–20,23,24] There is little doubt that resection should be performed in the case of suspicious neoplasia,[3,20,27] when pseudocysts that involve the spleen are detected,[3] or when cystic dystrophy of the duodenal wall is present.[15,28,29] In the case of certain diagnosis of chronic pancreatitis, there is general agreement about the necessity of conserving the integrity of the duodenum and the pancreatic parenchyma as much as possible, in light of the tendency toward endocrine and/or exocrine insufficiency.[22] When pain relief is considered, which is usually the principal indication for surgery, outcomes are good even at long-term follow-up periods. Among conservative procedures, lateral pancreaticojejunostomy using the Partington-Rochelle modification has been most widely used due to the low morbidity, mortality, and percentage of pain-free patients in the long term.[19] When long time periods are considered, the percentage of failure—representing up to 30% of cases—has been attributed in part to the fact that

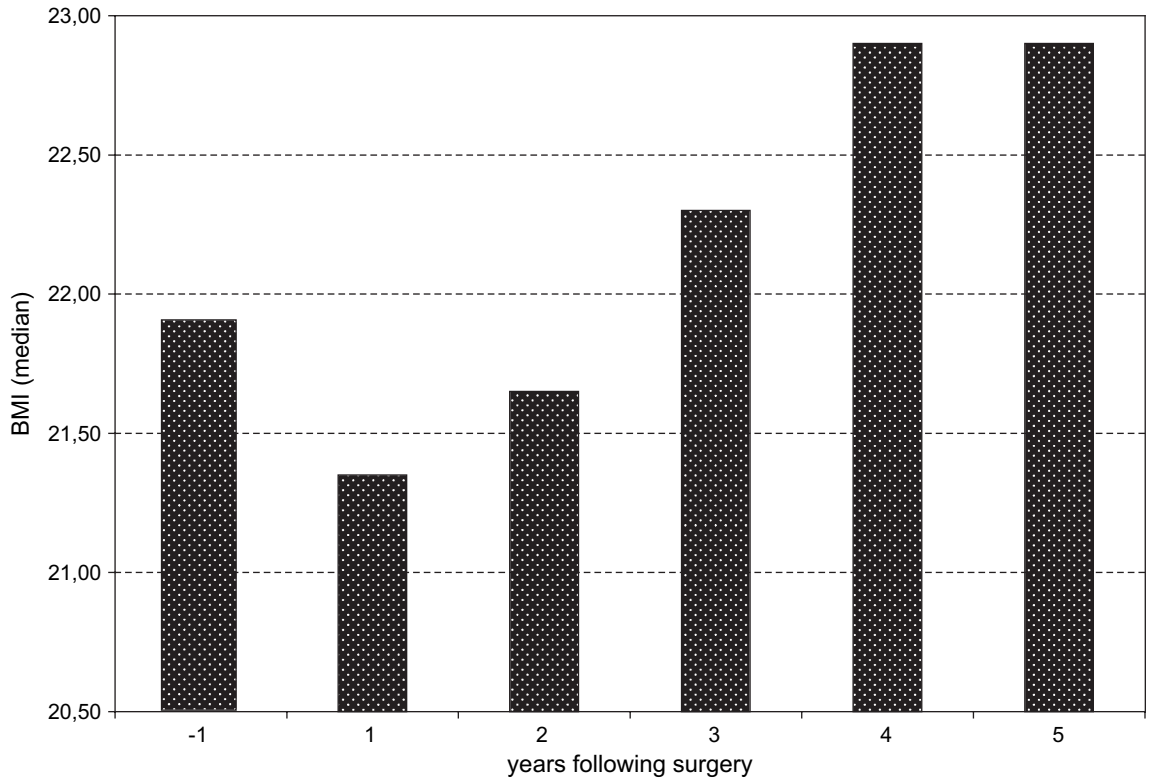

Fig. 3. Variations in the body mass index (BMI) after surgery in 40 patients undergoing pancreaticojejunostomy according to Frey's procedure ($P = 0.0001$).

many patients continue to drink alcohol, but is mostly due to the lack of complete decompression of the ducts of Wirsung and Santorini as well as the collateral ducts located on the pancreatic head.[19] To overcome this, two newer procedures have been proposed: duodenum-preserving pancreatic head resection (DPPHR) as described by Beger et al.[8] and local resection in combination with longitudinal pancreaticojejunostomy (LR-LPJ) as described by Frey and Smith.[9] Whereas the rationale behind these two procedures is different, the results of a prospective randomized study have shown that they are highly similar in terms of short-term and long-term pain relief.[23] However, LR-LPJ has a postoperative morbidity that is significantly lower compared with DPPHR (9% vs. 20%, respectively; $P < 0.05$), because a lesser quantity of parenchyma is resected and the section of the gland at the level of the superior mesenteric vein root is no longer necessary.[23] From this viewpoint, the results of the present study are particularly favorable and are among the best reported to date (Table 2).[18–20,23–25] In particular, the postoperative morbidity in the present series was 7.5% compared to 39% recently reported by Chaudhary and colleagues.[30] Moreover, they report that a second intervention was necessary in 44% of cases, mostly due to septic complications.[30] However, it should be stressed that a preoperative pancreatic endoscopic stent was not employed in any of the patients in the present series, which seems to be a predisposing factor for complications.[30] Even considering a more extended follow-up period, the long-term results are in accordance with previously published reports, with 90.4% of patients pain-free at 5 years after surgery. The postoperative results regarding diabetes are worthy of comment. The various series of previously reported cases have documented percentages of de novo diabetes during the follow-up period, varying from 12.9% to 25%. In our study, only three cases developed diabetes (10%), whereas for four patients, insulin therapy was no longer necessary after surgery. In another case, a normal oral glucose tolerance test was achieved. Nonetheless, at least one other case of improvement in diabetes has been reported.[19] One interesting interpretation would be that surgical intervention may improve exocrine/endocrine function.[22] However, it is more probable that these improvements are related to a more correct food habit and the fact that the patients had stopped drinking alcohol. At any rate, the low percentage of new cases of diabetes and

Table 2. Relevant clinical data and outcome of previously reported patient cohorts undergoing pancreaticojejunostomy according to Frey's procedure

	Frey and Amikura, 1994[19]	Izbiki et al,* 1995[23]	Ho and Frey, 2001[21]	Amikura et al, 1997[18]	Izbiki et al,* 1998[20]	Kelemen and Horvath,* 2002[25]	Present series†
No. of patients	50	22	75	11	31	13	40
M/F	28/22	16/6	—	10/1	25/6	13/0	29/11
Average age (SD)	43	44.1 (5.9)	—	NR	43.1 (6.5)	45.9 (36–58)	48.8 (11.9)
Preoperative pain, No. of patients (%)	50 (100)	22 (100)	—	NR	31 (100)	12 (100)	38 (95)
Average time from diagnosis to intervention, yr (SD)	NA	6.4 (2.8)	—	NR	5.5 (2.3)	NA	3 (4.3)
No. of patients with weight loss (%)	18 (36)	20 (90.9)	—	NR	17 (54.8)	5 (38)	25 (62.5)
Cholestasis No. of patients (%)	12 (24)	13 (59)	—	NR	18 (58)	8 (61)	9 (22.5)
Average duration of surgery, min (SD)	NA	289 (89)	—	NR	245 (62)	288 range (192–342)	231.7 (61)
Average units blood transfused (SD)	NA	25 (2.3)	—	NR	1.2 (0.8)	2.2 (0–3)	0.05 (0.3)
Days postoperative hospitalization time (range)	13.5 (7–40)	NA	—	NR	NA	7.5 (7–11)	10.3 (6–28)
Morbidity %	22	9	—	18.2	19	0	7.5
Mortality %	0	0	0	NR	3.2	0	0
Median follow-up mo (range)	37 mean	17 (6–24)	38.4 mean	25 (6–44)	24 (12–36)	20.6 (3–46)	60 (20–79)
Pain-free at the end of follow-up %	86.7	94	88	90	90	57.1	88.8
Increased body mass No. of patients (%)	25/39 (64)	17/22 (77)	—	NR	25/31 (81)	8/12 (62)	26/40 (65)
De novo diabetes No. of patient (%)	4/31 (12.9)	1/4 (25)	—	NR	2/10 (20)	3/12 (25)	3/30 (10)

*Only patients undergoing pancreaticojejunostomy according to Frey's procedure were considered; NR, not reported.
†Data may differ from the written test since they are reported as average (± SD) to compare with other studies.

the increase in the body mass index observed after surgery demonstrate that intervention does not aggravate the progression of the disease. Lastly, all cases reported subjective increases in the quality of life after surgical intervention, even if it is difficult to assess.[31–33]

CONCLUSIONS

The results of this study confirm that the Frey's procedure for longitudinal pancreaticojejunostomy is one of the best options for management of patients with chronic pancreatitis requiring surgery, in the absence of a suspicion of neoplasm. In our opinion, the Partington-Rochelle procedure should be restricted to cases of obstructive chronic pancreatitis limited at pancreatic body/tail secondary to fibrotic stenosis of the main duct, which is often related to a previous necrotizing pancreatitis.

REFERENCES

1. Sakorafas GH, Tsiotou AG. Proximal pancreatectomy in the surgical management of chronic pancreatitis. J Clin Gastroenterol 2002;34:72–76.
2. Falconi M, Casetti L, Salvia R, et al. Pancreatic head mass, how can we treat it? Chronic pancreatitis: Surgical treatment. JOP 2000;1:154–161.
3. Prinz RA. Surgical options in chronic pancreatitis. Int J Pancreatol 1993;14:97–105.
4. Eddes EH, Masclee AM, Gooszen HG, Frolich M, Lamers CB. Effect of duodenum-preserving resection of the head of the pancreas on endocrine and exocrine pancreatic function in patients with chronic pancreatitis. Am J Surg 1997;174:387–392.
5. Puestow CB, Gillesby WJ. Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. Arch Surg 1958;76:898–907.

6. Partington PF, Rochelle RE. Modified Puestow procedure for retrograde drainage of the pancreatic duct. Ann Surg 1960;152:1037–1043.
7. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978; 146:959–962.
8. Beger HG, Krautzberger W, Bittner R, Buchler M, Limmer J. Duodenum-preserving resection of the head of the pancreas in patients with severe chronic pancreatitis. Surgery 1985;97:467–473.
9. Frey CF, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. Pancreas 1987;2:701–707.
10. Gloor B, Friess H, Uhl W, Buchler MW. A modified technique of the Beger and Frey procedure in patients with chronic pancreatitis. Dig Surg 2001;18:21–25.
11. Prinz RA. Pancreatic duct drainage for chronic pancreatitis. In: Beger HC, Buchler MW, eds. Standards in Pancreatic Surgery. Berlin, Heidelberg: Springer Verlag, 1993, pp 554–564.
12. Pederzoli P, Falconi M, Bassi C. Derivative surgical treatment. In: Pederzoli P, Cavallini G, Bassi C, Falconi M, eds. Facing Pancreatic Dilemma. Berlin, Heidelberg: Springer Verlag, 1994, pp 199–213.
13. Beger HG, Buechler M. Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis with inflammatory mass in the head. World J Surg 1990;14:83–87.
14. Sawyer R, Frey CF. Is there still a role for distal pancreatectomy in surgery for chronic pancreatitis? Am J Surg 1994; 168:6–9.
15. Falconi M, Valerio A, Caldiron E, et al. Changes in pancreatic resection for chronic pancreatitis over 28 years in a single institution. Br J Surg 2000;87:428–433.
16. Izbicki JR, Yekebas EF, Strate T, et al. Extrahepatic portal hypertension in chronic pancreatitis: An old problem revisited. Ann Surg 2002;236(1):82–89.
17. Sakorafas GH, Farnell MB, Nagorney DM, Sarr MG, Rowland CM. Pancreatoduodenectomy for chronic pancreatitis: Long term results in 105 patients. Arch Surg 2000;135: 517–524.
18. Amikura K, Arai K, Kobari M, Matsuno S. Surgery for chronic pancreatitis-extended pancreaticojejunostomy. Hepatogastroenterology 1997;44:1547–1553.
19. Frey CF, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. Ann Surg 1994;220:492–504.
20. Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T, Broelsch CE. Extended drainage versus resection in surgery for chronic pancreatitis: A prospective randomized trial comparing the longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus-preserving pancreatoduodenectomy. Ann Surg 1998;228:771–779.
21. Ho HS, Frey CF. The Frey procedure: Local resection of pancreatic head combined with lateral pancreaticojejunostomy. Arch Surg 2001;136:1353–1358.
22. Nealon WH, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression. A longitudinal prospective analysis of the modified Puestow procedure. Ann Surg 1993;217:458–466.
23. Izbicki JR, Bloechle C, Knoefel WT, Kuechler T, Binmoeller KF, Broelsch CE. Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis. A prospective, randomized trial. Ann Surg 1995;221:350–358.
24. Ho HS, Frey CF. Current approach to the surgical management of chronic pancreatitis. Gastroenterologist 1997;5: 128–136.
25. Kelemen D, Horvath OP. Clinical experience with different techniques of pancreatic head resection for chronic pancreatitis. Dig Surg 2002;19:28–34.
26. Lankisch PA, Andren-Sandberg A. Standard for the diagnosis of chronic pancreatitis and for the evaluation of treatment. Int J Pancreatol 1993;14:205–212.
27. Sakorafas GH, Zobolas B. Lateral pancreatojejunostomy in the surgical management of chronic pancreatitis. Current concepts and future perspectives. Dig Liver Dis 2001;33: 187–191.
28. Wind P, Pardies P, Roullet MH, Rouzier R, Zinzindohoue F, Cugnenc PH. [Cystic dystrophy of the duodenal wall in aberrant pancreas (French)]. Ann Surg 1999;53:164–167.
29. Bittar I, Cohen Solal JL, Cabanis P, Hagege H. Cystic dystrophy of an aberrant pancreas. Surgery after failure of medical therapy. Presse Med 2000;29:1118–1120.
30. Chaudhary A, Negi SS, Masood S, Thombare M. Complictions after Frey's procedure for chronic pancreatitis. Am J Surg 2004;188:277–281.
31. Glasbrenner B, Adler G. Evaluating pain and the quality of life in chronic pancreatitis. Int J Pancreatol 1997;22:163–170.
32. Johnson CD, Fitzsimmons D. Quality of life assessment in chronic pancreatitis. Int J Pancreatol 1998;24:63–64.
33. Talamini G, Bassi C, Butturini G, et al. Outcome and quality of life in chronic pancreatitis. JOP 2001;2:117–123.

Patterns of Recurrence After Curative Resection of Pancreatic Cancer, Based on Autopsy Findings

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The autopsy findings of patients who died of recurrence after curative resection of pancreatic cancer may afford a reliable guide to increase long-term survival after surgery. Recurrence patterns were analyzed for 27 autopsied patients who had undergone potentially curative resection of pancreatic cancer. The pattern of recurrence was classified as follows: (1) local recurrence, (2) hepatic metastasis, (3) peritoneal dissemination, (4) para-aortic lymph node metastasis, and (5) distant metastasis not including hepatic metastasis, peritoneal dissemination, and para-aortic lymph node metastasis. Of the 27 autopsied patients, recurrence was confirmed for 22 of 24 patients, except for three who died of early postoperative complications. Eighteen (75%) of the 24 patients had local recurrence, 12 (50%) had hepatic metastasis, and 11 (46%) had both. For four patients, local recurrence confirmed by autopsy was undetectable by computed tomography, because the recurrent lesions had infiltrated without forming a tumor mass. Peritoneal dissemination, para-aortic lymph node metastasis, and distant metastasis were found for eight (33%), five (21%), and 18 (75%) of the cases, respectively. Twenty patients died of cancer, but local recurrence was judged to be the direct cause of death of only four. Local recurrence frequently occurs, but is rarely a direct cause of death, and most patients died of metastatic disease. Therefore, treatment that focuses on local control cannot improve the survival of patients with resectable pancreatic cancer, and thus, treatment regimens that are effective against systemic metastasis are needed. (J GASTROINTEST SURG 2006;10:511–518) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Autopsy, curative resection, pancreatic cancer, recurrence

Significant advances have been made with regard to the surgical management of pancreatic cancer over the past several decades. As a result, institutes that specialize in surgery to treat pancreatic cancer often report mortality rates of less than 5%. Despite advances in surgical techniques and perioperative care, limited progress has been made in improving the survival rate of patients with resectable pancreatic cancer, and thus, the chances for long-term survival are still poor.[1,2] The 5-year survival rates range from 13% to 25% for patients with pancreatic cancer who undergo potentially curative resection.[2–5] When extended lymph node dissection is performed, particularly in Japan, favorable 5-year survival rates are achievable.[6–9] However, two recent randomized trials could not determine the overall survival advantages for extended lymphadenectomy for patients with pancreatic cancer.[10,11] The value of extended lymph node dissection thus remains to be determined.

The central obstacle to the postsurgical cure of pancreatic cancer is the persistent burden of subclinical locoregional disease that remains even after curative resection is performed. Adjuvant therapy is used to improve survival following curative resection by treating any residual microscopic disease.

Randomized controlled trials involving adjuvant therapy for resectable pancreatic cancer have been limited, but they have guided the current approach to the adjuvant treatment of pancreatic cancer.[12–14] In 1985, the Gastrointestinal Tumor Study Group (GITSG) found a significant survival advantage for adjuvant chemoradiotherapy over surgery alone,[12] and subsequent registered-to-treatment analysis by the same group confirmed the survival benefits of adjuvant chemoradiotherapy.[15] A phase III trial conducted by the European Organization for Research and Treatment of Cancer, however, failed to confirm this benefit.[13] The European Study Group for Pancreatic Cancer recently completed a large scale

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randomized controlled trial involving adjuvant chemoradiotherapy or chemotherapy for patients who underwent potentially curative resection of pancreatic cancer (ESPAC-1 trial).[14] The ESPAC-1 showed a survival advantage for adjuvant chemotherapy, but not one for chemoradiotherapy. The value of adjuvant therapy for resectable pancreatic cancer is inconclusive, but the results of ESPAC-l could have a major impact on future systems that deliver adjuvant therapy.

With few opportunities for early diagnosis, aggressive therapeutic strategies should be established to improve patient outcome based on the assessment of recurrence patterns after curative resection of pancreatic cancer. To increase long-term survival, it is necessary to elucidate the biological properties of the cancer. Autopsy findings of patients who died of recurrence may afford a reliable guide for this purpose. The present study determined the sites of recurrence after curative resection of pancreatic cancer by histopathological examination of autopsied specimens and found that treatment of resectable pancreatic cancer can be refined by increased knowledge of the mode of cancer recurrence.

MATERIAL AND METHODS

Patient Characteristics and Operative Procedures

Between September 1986 and August 2004, 85 patients with invasive ductal cancer of the pancreas underwent potentially curative resection at the Tochigi Cancer Center Hospital. Sixty-seven of these patients had already died, and 27 patients underwent autopsy 2 to 101 months after surgery. Written informed consent to perform an autopsy was obtained from each patient's family. All autopsied patients had undergone pancreatectomy with extended lymph node dissection and en bloc removal of retroperitoneal soft tissues and extrapancreatic nerve plexi, especially around the superior mesenteric, common hepatic, and celiac arteries. Lymph nodes were extensively dissected for group 1 and group 2 lymph nodes as determined by the Classification of Pancreatic Cancer of the Japan Pancreas Society.[16] Dissection of para-aortic lymph nodes from the level of the celiac artery to the inferior mesenteric artery was also carried out on 21 of the 27 patients. Combined resection of the portal vein in 17 patients was carried out when the tumor was inseparable from the wall of the vein, or a diagnosis of vascular invasion had been made based on preoperative imaging studies. Details of the operative procedures are presented in Table 1.

Adjuvant Therapy

Between September 1986 and August 1994, adjuvant radiotherapy administered at our institute consisted of intraoperative radiotherapy (IORT) and/or postoperative external beam radiotherapy applied to the retroperitoneum (EBRT) for patients 1 to 10 and 25 to 27 as shown in Table 1. IORT was administered just after tumor resection, for which electron beam energies ranging from 6 to 12 MeV were used to deliver 16 to 30 Gy to the treatment field. The treatment field included the tumor bed, roots of the celiac and superior mesenteric arteries, and the 2 cm-long remnant pancreas stump. EBRT was usually started 2 to 3 weeks after surgery, using the same radiation field marked out with surgical clips for IORT at the time of surgery. Patients were treated with 10 MV X-rays using opposing anterior-posterior portals at a dose of 45.0 to 57.6 Gy. Only patient 2, who received EBRT, was concomitantly given 5-fluorouracil (5-FU).

In 1988 and 1992, Komaki et al.[17,18] observed a decreased incidence of liver metastasis in patients with locally advanced and non metastatic cancer of the pancreas when treated with prophylactic hepatic irradiation (PHI). The decrease as a result of PHI prompted us to use this modality in adjuvant settings combined with pancreatectomy.[19] Since September 1994, PHI has been used as an adjuvant therapy, and 13 patients (patients 11 to 23) in this series received PHI. In addition, these patients also received IORT (Table 1). PHI was initiated 2 to 4 weeks after surgery using 10 MV X-rays with opposing anteroposterior pair fields. The whole liver was almost equally irradiated with an error of less than 10% of the planned target dose, and the doses varied from 19.8 to 22.0 Gy19. For all patients, 5-FU was concurrently administered by continuous infusion throughout the PHI period.

Stage Classification and Definition of Recurrence Patterns

The sixth edition of the UICC pTNM classification was used to determine the stage grouping.[20] Patterns of recurrence were classified into five types: (l) local recurrence, (2) hepatic metastasis, (3) peritoneal dissemination, (4) para-aortic lymph node metastasis, and (5) distant metastasis not including hepatic metastasis, peritoneal dissemination, and para-aortic lymph node metastasis. Local recurrence was defined as any failure in the retroperitoneum around the superior mesenteric and celiac arteries, including the tumor bed, remnant pancreas, hepatic hilum, or its regional nodes.

Table 1. Treatment details of 26 autopsied patients

Patient no.	Age	Gender	Operative procedure	Portal vein resection	Artery resection	Dissection of para aortic lymph nodes	IORT Gy (MeV)	EBRT Gy	PHI Gy
1	75	M	PPPD	+	—	+	16 (12)	38.4	—
2	57	F	TP	+	—	+	—	57.6	—
3	73	M	DP	–	CA, CHA	–	30 (7)	—	—
4	58	M	PD	+	—	+	16 (12)	50.0	—
5	59	F	PPPD	+	—	+	—	55.8	—
6	74	M	PPPD	–	—	+	16 (9)	50.4	—
7	72	F	PD	+	—	+	30 (9)	—	—
8	37	M	PPPD	+	SMA	+	16 (9)	49.6	—
9	62	M	DP	–	CA, CHA	–	20 (9)	45.0	—
10	53	F	PPPD	–	—	+	16 (9)	50.4	—
11	74	F	PPPD	+	—	–	20 (6)	—	19.8
12	65	F	DP	+	CHA	–	30 (9)	—	22.0
13	72	M	PPPD	–	—	+	30 (9)	—	22.0
14	62	M	PPPD	+	—	+	30 (9)	—	20.0
15	61	M	PD	+	—	+	30 (9)	—	21.8
16	44	M	PPPD	+	—	+	30 (9)	—	22.0
17	56	M	PPPD	+	—	+	30 (9)	—	22.0
18	58	M	PPPD	-	—	+	25 (9)	—	19.8
19	70	F	PPPD	+	—	+	20 (9)	—	19.8
20	79	M	DP	-	CA, CHA	+	30 (9)	—	20.0
21	60	M	PPPD	-	—	+	30 (9)	—	22.0
22	79	M	TP	+	—	+	16 (9)	—	20.0
23	71	F	PD	+	—	-	30 (9)	—	20.0
24	77	F	DP	–	—	–	—	—	—
25	70	M	PPPD	–	—	+	16 (9)	49.2	—
26	74	M	PD	+	—	+	20 (9)	—	—
27	56	F	TP	+	—	+	16 (12)	—	—

CA = celiac artery; CHA = common hepatic artery; DP = distal pancreatectomy; EBRT = postoperative external beam radiotherapy to the retroperitoneum; IORT = intraoperative radiotherapy; PD = pancreatoduodenectomy; PHI = prophylactic hepatic irradiation; PPPD = pylorus preserving pancreatoduodenectomy; SMA = superior mesenteric artery; TP = total pancreatectomy.

RESULTS

Pathological Findings of Surgically Resected Specimens

Two patients (patients 3 and 9) had microscopically positive surgical margins with a positive cut margin of the pancreas and positive retroperitoneal margin adjacent to the superior mesenteric artery, respectively. The remaining 25 patients were confirmed to have had negative surgical margins (Table 2).

Nine patients had Stage IIA cancers (pT3 pN0 M0), 13 Stage IIB (pT3 pNl M0), 2 Stage III (1: pT4 pN0 M0, 1: pT4 pNl M0), and 3 Stage IV (pT3 pNl pMl).

For three patients who had Stage IV cancer, microscopic metastasis was found in the dissected para-aortic lymph nodes, and for two with pT4 cancer, resected arteries (one patient superior mesenteric artery; one patient celiac artery) had been invaded by the cancer. Nineteen patients showed cancer invasion of the retropancreatic tissues, 13 invasion of extrapancreatic nerve plexi, and 12 had both. Fourteen (82%) of 17 patients who underwent combined resection of the portal vein were confirmed to have cancer invasion of the portal vein wall. For the remaining three patients, the cancer remained outside of the adventitia (Table 2).

Sites and Incidences of Recurrence Based on Autopsy Findings

Three patients (25 to 27) who died of early postoperative complications had no recurrence or residual cancer (Table 2), and the sites of recurrence and their incidences were evaluated for the remaining 24 patients (patients 1 to 24). Two (patients 21 and 22) who died of noncancerous disease after 12 and 15 months, respectively, after surgery had no recurrence, and recurrence was confirmed for the remaining 22 patients (Table 2). Eighteen (75%) of the 24 patients had local recurrence, 12 (50%) hepatic metastasis, and 11 (92%) of 12 who had hepatic

Table 2. Demographics and patterns of recurrence for 26 autopsied patients

		UICC Stage				Pathology of resected specimens						Pattern of recurrence					
Patient no.	Surgical margin	pT	pN	pM	pTNM	Histological type	RP	PL	PV	Survival time (mo)	Cause of death	L	H	P	LN	M	Sites of distant metastasis not including H, P, or LN
1	−	3	0	0	IIA	tub2	−	−	−	5	Liver abscess	•	•	−	−	•	Lung
2	−	3	0	0	IIA	tub2	+	+	+	15	DOC	•	•	•	•	•	Mesenteric lymph nodes
3	+	3	0	0	IIA	tub2	+	+		19	DOC	•	•	•	•	•	Lung, heart, adrenal
4	−	3	1	0	IIB	tub2	+	−	+	12	DOC	•	•	−	•	•	Lung, heart, kidney, skin, thyroid, testis
5	−	3	1	0	IIB	tub2	+	−	−	18	DOC	•	−	−	•	•	Bone, bronchus, adrenal, perigastric lymph nodes
6	−	3	1	0	IIB	tub2	−	−		13	DOC	•	−	•	−	•	Pleura, perigastric lymph nodes
7	−	3	1	0	IIB	tub1	+	+	+	24	DOC	•	−	−	−	•	Lung
8	−	4	1	0	III	tub2	+	+	+	6	DOC	•	−	•	−	•	Lung, pleura
9	+	4	0	0	III	tub2	+	+		42	DOC	−	−	•	−	•	Pleura
10	−	3	1	1	IV	por	+	+		21	DOC	−	•	−	−	•	Abdominal wall, bone
11	−	3	0	0	IIA	tub2	+	+	+	101	DOC (local)	•	−	−	−	−	
12	−	3	0	0	IIA	tub2	+	−	+	11	DOC	•	•	−	−	•	Perigastric lymph nodes
13	−	3	0	0	IIA	tub2	−	−		14	DOC (local)	•	•	−	−	−	
14	−	3	1	0	IIB	por	+	−	+	8	DOC	•	•	•	−	•	Lung, stomach, adrenal, perigastric lymph nodes
15	−	3	1	0	IIB	tub2	+	−	+	17	DOC	•	•	−	−	−	
16	−	3	1	0	IIB	tub2	+	−	+	41	DOC	•	•	•	−	•	Lung, pleura, mesenteric lymph nodes
17	−	3	1	0	IIB	tub2	+	+	−	19	DOC	•	•	−	•	•	Adrenal, bone marrow
18	−	3	1	1	IV	tub2	+	+		33	DOC (local)	•	•	−	−	•	Lung
19	−	3	0	0	IIA	tub2	+	−	+	16	Myocardial infarction	−	−	−	−	•	Lung
20	−	3	1	0	IIB	tub2	+	+		17	DOC	−	−	•	−	−	
21	−	3	0	0	IIA	tub2	−	−		12	Liver insufficiency	−	−	−	−	−	
22	−	3	1	0	IIB	tub2	+	+	+	15	Miliary tuberculosis	−	−	−	−	−	
23	−	3	1	0	IIB	tub2	+	+	+	12	DOC (local)	•	−	−	−	•	Lung
24	−	3	1	1	IV	por	−	−		24	DOC	•	−	−	−	•	Lung
25	−	3	0	0	IIA	pap	−	−		2	DOP	−	−	−	−	−	
26	−	3	1	0	IIB	tub2	−	+	+	2	DOP	−	−	−	−	−	
27	−	3	1	0	IIB	tub2	−	−	+	2	DOP	−	−	−	−	−	

tub1 = well-differentiated tubular adenocarcinoma; tub2 = moderately differentiated tubular adenocarcinoma; nor = poorly differentiated tubular adenocarcinoma; pap = papillary adenocarcinoma; RP = retroperitoneal invasion; PL = extrapancreatic nerve plexus invasion; PV = portal vein invasion; DOC = died of cancer; DOP = died of postoperative complications; L = local recurrence; H = hepatic metastasis; P = peritoneal dissemination; LN = para-aortic lymph node dissection; M = distant metastasis other than H,P, and LN.

metastasis had local recurrence. For one patient (patient 11), "local" was the sole site of recurrence. There were no patients for whom the liver was the only site of recurrence. Seven (54%) of 13 patients (11 to 23) who received PHI developed hepatic metastasis, and all had local recurrence. Eight (33%) developed peritoneal dissemination, para-aortic lymph node metastasis was found in five (21%), and distant metastasis was recognized in 18 (75%), 11 of whom had pulmonary metastasis (Table 2).

Details of Local Recurrence

Local recurrence was usually associated with cancer infiltration of the nerves, lymphatic vessels, and connective soft tissues to various extents (Fig. 1). For four patients (patients 1, 4, 8, and 14), local recurrence confirmed by histological examination at autopsy could not be detected by computed tomography (CT) before death, because the recurrent lesions had infiltrated the retroperitoneum without forming a tumor mass. For this type of recurrence, cancer cells were scattered in the dense fibrous stroma (Fig. 2). The remaining 14 patients with local recurrence were diagnosed with local recurrence by CT before death. Patient 9, who had undergone microscopically noncurative resection with a positive surgical margin adjacent to the superior mesenteric artery, had no local recurrence (Table 2).

For 11 (61%) of the 18 cases of local recurrence, cancer infiltration extended from the retroperitoneum to the remnant pancreas, and for seven, metastasis to the lymph nodes in the retroperitoneum and/or in the hepatic hilum was recognized as a part of the local recurrence. Six (67%) of nine pN0 patients and 12 (80%) of 15 pNl patients had local recurrence (Table 3). Also, 14 (74%) of 19 patients who had cancer invasion of extrapancreatic nerve plexi and/or retropancreatic tissues in the surgically resected specimens developed local recurrence. Four (80%) of five patients who had neither cancer invasion of extrapancreatic nerve plexi nor cancer invasion of retropancreatic tissues had local recurrence. Among 23 patients who received IORT and/or EBRT to the retroperitoneum, 17 (74%) developed local recurrence (Table 3). The irradiated field was microscopically confirmed to be involved by local recurrence for 16 (except patient 23) of the 17 patients (Table 3).

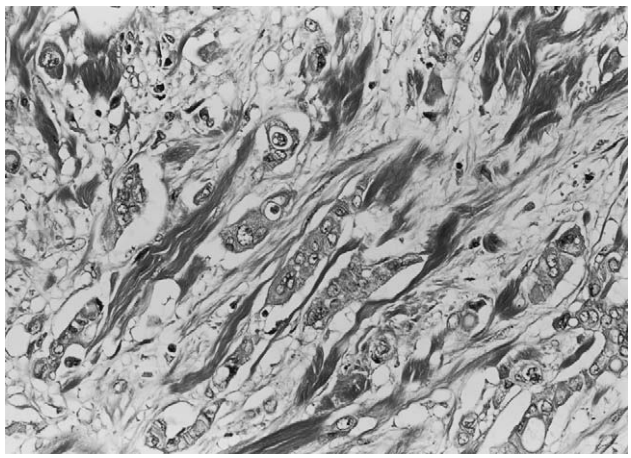

Fig. 2. Histological findings for an autopsy specimen (patient 4) having local recurrence that could not be detected by CT. Cancer cells are scattered in the dense fibrous stroma. (H & E staining; original magnification, ×280)

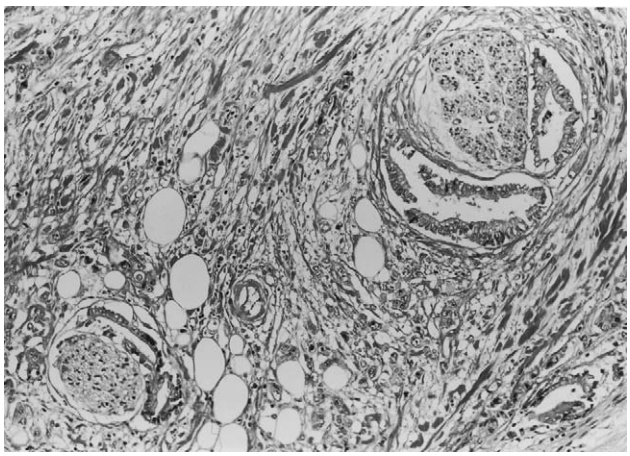

Fig. 1. An autopsy specimen (patient 17) showing local recurrence of pancreatic cancer consisting mainly of perineural and connective tissue invasion in the retroperitoneum. (H & E staining; original magnification, ×200)

Table 3. The incidence of local recurrence

			Local recurrence (+) n = 18	Local recurrence (−) n = 6
Hepatic metastasis	(+)	n = 12	11	1
	(−)	n = 12	7	5
pN0		n = 9	6	3
pN1		n = 15	12	3
PL (+) and/or RP (+)		n = 19	14	5
PL (−) and RP (−)		n = 5	4	1
Radiotherapy applied to the retroperitoneum	(+)	n = 23	17	6
	(−)	n = 1	1	0

PL = extrapancreatic nerve plexus invasion; RP = retropancreatic tissue invasion.

Cause of Deaths

For two of 22 patients who had cancer recurrence, the causes of death were liver abscess (patient 1) and heart failure due to myocardial infarction (patient 19; Table 2), and the remaining 20 died of cancer. A majority of the patients died of metastatic disease. Local recurrence was confirmed to be the direct cause of death for only four patients (patients 11, 13, 18, and 23), among which patient 11 died of massive intestinal bleeding from the local recurrence lesion without recurrence at the other sites. This local recurrence, arising from the remnant pancreas adjacent to the anastomosis to the jejunum, was found by CT 95 months after surgery, and chemoradiotherapy was then carried out. The tumor may have been the second primary cancer of the remnant pancreas rather than due to local recurrence. Two patients (patients 13 and 18) with a small volume of hepatic metastasis had tumor thrombi extending from their local recurrence lesions to the lumen of the portal vein. The tumor thrombi had further invaded into the intrahepatic branches of the portal vein and then induced liver failure by insufficiency of portal blood flow. Patient 23 without hepatic metastasis developed local recurrence at the hepatic hilum that occluded the portal vein and also widely spread along the intrahepatic Glisson's sheaths, resulting in liver insufficiency. In addition, this patient had no recurrence in the IORT field.

DISCUSSION

Less than 20% of patients with pancreatic cancer are suitable for resection owing to the presence of locally advanced or metastatic disease, but surgical resection is still the treatment of choice. A recent multicentric randomized controlled trial held in Japan that compared the outcome of surgical resection with that of chemoradiotherapy concluded that locally advanced pancreatic cancer without involvement of the common hepatic artery or superior mesenteric artery can be successfully and surgically treated by experienced surgeons at specialized centers.[21] In addition, the surgery group had a significantly better survival rate than did the chemoradiotherapy group.[21] To further enhance survival after surgical treatment, recurrence patterns following surgery should be evaluated. Most studies have assessed the recurrence patterns of resectable pancreatic cancer based on imaging diagnostics, but this is not considered sufficient grounds, without autopsy findings. Thus, we analyzed the recurrence data of autopsied patients with resectable pancreatic cancer by examining the largest series of autopsied patients to have undergone curative resection of pancreatic cancer.

Two major patterns of recurrence following the curative resection of pancreatic cancer are local recurrence and liver metastasis.[22–25] The high incidence of local recurrence has led a number of investigators to administer adjuvant chemoradiotherapy to the pancreatic bed. However, the incidence of local recurrence remains high even after adjuvant chemoradiotherapy. Eighteen (51%) of the 35 patients in the two groups in the GITSG study that received adjuvant chemoradiotherapy developed local recurrence.[15] Johnstone and Sindelar[24] reported on 12 autopsied patients who underwent complete resection of pancreatic cancer and documented that five (56%) of nine patients who received adjuvant radiotherapy had locoregional recurrence. The present series also showed a higher incidence of local recurrence even though IORT and/or EBRT were delivered. It is noteworthy that the autopsies disclosed local recurrence that was undetectable by CT for four patients who had received radiotherapy to the retroperitoneum. Thus, the accurate diagnosis of local recurrence requires an autopsy as well as imaging studies, especially for irradiated patients. The incidence of local recurrence may be higher than that of reports that only used imaging studies. Local recurrences missed by CT were found to have infiltrated the retroperitoneum in the radiation field without forming a tumor mass, suggesting a favorable radiation effect on cancer growth. Hiraoka and Kanemitsu[8] reported on 10 autopsied patients who underwent extended resection combined with 30 Gy IORT and found that four had only local microscopic recurrence enclosed by thick connective tissue within the radiation field. They also noted that two patients with incomplete tumor clearance had no local recurrences.[8] In our series, one patient who had a positive surgical margin exhibited no local recurrence. These observations also suggest a substantial effect due to radiotherapy. However, most patients with negative surgical margins who received radiotherapy developed local recurrence, showing that it cannot be completely controlled even if curative resection combined with adjuvant radiotherapy is performed. Thus, the rationale for the routine use of adjuvant radiotherapy remains questionable.

Another way to control local recurrence after the resection of pancreatic cancer may be by extended resection, particularly so in Japan.[6,7] The present study, however, found a high local recurrence rate even after this procedure was carried out. Kayahara et al.[23] also reported a local recurrence rate of more than 80% after radical resection with extended

dissection of lymph nodes and extrapancreatic nerve plexi. They also documented that 15 autopsied patients had recurrence and 12 of the 15 had local recurrence. Our data showed that 74% of the patients who had had cancer invasion of extrapancreatic nerve plexi and/or retropancreatic soft tissues in the surgically resected specimens developed local recurrence. In the series reported by Kayahara et al.,[23] the majority of patients with these factors also developed local recurrence. It is likely that patients with these factors are at high risk for local recurrence. However, clearance of retroperitoneal tissue or a nerve plexus that may be left in place by "standard" resection does not necessarily improve local control. Although the number of patients examined was small, four of five who had neither retropancreatic soft tissue invasion nor extrapancreatic nerve plexus invasion developed local recurrence, showing that local control is also difficult for less advanced pancreatic cancer, using usual extended resection. The distances of surgical margins that can be obtained for pancreatic cancer are limited even with extended resection, unless combined resection of major arteries such as the superior mesenteric artery is performed. This may explain why patients who undergo extended resection with negative surgical margins frequently develop local recurrence. However, combined resection of major arteries, which is often accompanied by complications, is unlikely to improve long-term survival even though local control can be achieved.[26]

As many investigators have documented, surgeons must pursue curative resection to improve survival when faced with resectable pancreatic cancer.[9,27] However, some forms of effective prophylactic treatment for metastatic disease are necessary to further enhance survival. It cannot be determined whether hepatic metastasis originates from local recurrence or not, because local recurrence can not always be diagnosed prior to detecting this type of metastasis. However, patients who survive for a certain length of time between surgery and recurrence are likely to develop hepatic metastasis originating from local recurrence. In our series, two patients with local recurrence and hepatic metastasis had tumor thrombi present in the portal vein. Their tumor thrombi were growing outward from the local recurrence, suggesting that cancer cells in local recurrence lesions have the potential to migrate into the portal vein and metastasize to the liver. In view of the high incidence of hepatic metastasis after surgery, we have adopted PHI as an adjuvant therapy to treat micrometastasis or cancer implantation into the liver as a result of surgical manipulation.[19] However, our autopsy findings suggest that PHI cannot prevent hepatic metastasis that originates from local recurrence, because PHI patients who developed hepatic metastasis were always found to have local recurrence on autopsy. Although a close relationship between local recurrence and hepatic metastasis was suggested, most patients in the present series developed not only hepatic metastasis but also metastases to other sites, and died of cachexia due to metastatic disease regardless of the presence of local recurrence. Therefore, we advocate a combined modality of systemic therapy as well as treatment directed at the major site of recurrence to improve long-term survival following surgery.

CONCLUSION

An autopsy as well as imaging studies is necessary for the accurate diagnosis of local recurrence. In this study, autopsies disclosed that local recurrence after curative resection of pancreatic cancer frequently occurs. However, only a few recurrences were the direct cause of death, and instead most patients died of metastatic disease. It is likely that treatment focused on local control cannot improve the survival of patients with resectable pancreatic cancer. Local recurrence may be only one component of systemic metastasis, and thus, more successful treatment regimens that impact on systemic metastasis are needed.

REFERENCES

1. Niederhuber JE, Brennan MF, Menck HR. The national cancer data base report on pancreatic cancer. Cancer 1995; 76:1671–1677.
2. Matsuno S, Egawa S, Fukuyama S, et al. Pancreatic cancer registry in Japan: 20 years of experience. Pancreas 2004;28: 219–230.
3. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas- 616 patients: Results, outcomes, and prognostic indicators. J GASTROINTEST SURG 2000;4:567–579.
4. Cleary SP, Gryfe R, Guindi M, et al. Prognostic factors in resected pancreatic adenocarcinoma: Analysis of actual 5-year survivors. J Am Coll Surg 2004;198:722–731.
5. Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003;27:324–329.
6. Ishikawa O, Ohhigashi H, Sasaki Y, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. Ann Surg 1988;208:215–220.
7. Nagakawa T, Nagamori M, Futakami F, et al. Results of extensive surgery for pancreatic carcinoma. Cancer 1996; 77:640–645.
8. Hiraoka T, Kanemitsu K. Value of extended resection and intraoperative radiotherapy for resectable pancreatic cancer. World J Surg 1999;23:930–936.

9. Takahashi S, Ogata Y, Miyazaki H, et al. Aggressive surgery for pancreatic duct cell cancer: Feasibility, validity, limitation. World J Surg 1995;19:653–660.
10. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2. Randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002;236:355–368.
11. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: A multicenter, prospective, randomized study. Ann Surg 1998;228:508–517.
12. Kalser MH, Ellenberg SS. Pancreatic cancer: Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899–903.
13. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: Phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776–784.
14. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–1210.
15. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer 1987;59:2006–2010.
16. Japan Pancreas Society. Classification of Pancreatic Carcinoma, 2nd English ed. Tokyo: Kanehara & Co., Ltd., 2003.
17. Komaki R, Hansen R, Cox JD, Wilson JF. Phase I-II study of prophylactic hepatic irradiation with local irradiation and systemic chemotherapy for adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys 1998;15:1447–1452.
18. Komaki R, Wadler S, Peters T, et al. High-dose local irradiation plus prophylactic hepatic irradiation and chemotherapy for inoperable adenocarcinoma of the pancreas: A preliminary report of a multi-institutional trial (Radiation Therapy Oncology Group Protocol 8801). Cancer 1992;69:2807–2812.
19. Hishinuma S, Ogata Y, Tomikawa M, et al. J Hepatobiliary Pancreat Surg 2005;12:235–242.
20. Sobin LH, Wittekind C. Prophylactic hepatic irradiation following curative resection of pancreatic cancer. UICC TNM Classification of Malignant Tumours, 6th ed. New York: John Wiley & Sons, Inc., 2002.
21. Imamura M, Doi R, Imaizumi T, et al. A randomized multicenter trial comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer. Surgery 2004; 136:1003–1011.
22. Griffin JF, Smalley SR, Jewell W, et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer 1990;66:56–6l.
23. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer 1993;72:2118–2123.
24. Johnstone PA, Sindelar WF. Patterns of disease recurrence following definitive therapy of adenocarcinoma of the pancreas using surgery and adjuvant radiotherapy: Correlations of a clinical trial. Int J Radiat Oncol Biol Phys 1993;27: 831–834.
25. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997;21:195–200.
26. Fortner JG. Regional pancreatectomy for carcinoma of the pancreas, ampulla, and other related sites: Tumor staging and results. Ann Surg 1984;199:418–425.
27. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004;91:586–594.

Aortic Occlusion Balloon Catheter Technique Is Useful for Uncontrollable Massive Intraabdominal Bleeding After Hepato-Pancreato-Biliary Surgery

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Massive intraabdominal hemorrhage sometimes requires urgent hemostatic surgical intervention. In such cases, its rapid stabilization is crucial to reestablish a general hemodynamic status. We used an aortic occlusion balloon catheter in patients with massive intraabdominal hemorrhage occurring after hepato-pancreato-biliary surgery. An 8-French balloon catheter was percutaneously inserted into the aorta from the femoral artery, and the balloon was placed just above the celiac artery. Fifteen minutes inflation and 5 minutes deflation were alternated during surgery until the bleeding was surgically controlled. An aortic occlusion balloon catheter was inserted on 13 occasions in 10 patients undergoing laparotomy for hemostasis of massive hemorrhage. The aorta was successfully occluded on 12 occasions in nine patients. Both systolic pressure and heart rate were normalized during aortic occlusion, and the operative field became clearly visible after adequate suction of leaked blood. Bleeding sites were then easily found and controlled. Hemorrhage was successfully controlled in 7 of 10 patients (70%), and they were discharged in good condition. The aortic occlusion balloon catheter technique was effective for easily controlling massive intraabdominal bleeding by hemostatic procedure after hepato-pancreato-biliary surgery.
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KEY WORDS: Complications, hepato-pancreato-biliary surgery, postoperative bleeding

Although the safety of surgical procedures has generally improved by virtue of major advances in surgical techniques and perioperative management,[1–3] postoperative hemorrhage remains one of the most mortal complications, especially in hepato-pancreato-biliary surgery.[4,5] Massive intraabdominal hemorrhage requires rapid surgical intervention for patient survival; however, the copious bleeding obliterates the surgical field, preventing a successful surgery. In addition, hypotension at laparotomy can also prove perilous. An aortic occlusion balloon catheter has been used in patients with abdominal trauma and ruptured abdominal aortic aneurysm.[6,7] Thus, in 1992 we introduced the aortic occlusion method by balloon catheter for the management of intraabdominal hemorrhage occurring after hepato-pancreato-biliary surgery, and have since treated 10 such patients. In the present study, we retrospectively analyzed our experiences with the aortic occlusion balloon catheter for this emergency and tried to elucidate the clinical efficacy of this procedure.

PATIENTS AND METHODS

Patients

Between January 1992 and December 2003, 10 patients (eight men and two women, 50–74 years old [mean, 62.7 years]) developed intraabdominal massive bleeding after hepato-pancreato-biliary surgery and underwent surgical hemostasis with aortic occlusion balloon catheters at the Second Department of Surgery, Chiba University Hospital. Massive bleeding was defined as hemorrhage requiring transfusion of at least 2 units of packed red blood cells within the first 2 hours after onset. Patients with bleeding within the first 24 hours after initial surgery

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were excluded, as the bleeding complication was closely related to the initial surgical procedure.

Primary neoplasms of initial surgery were intraductal papillary mucinous neoplasm of the pancreas (three patients), distal bile duct carcinoma (three patients), intrahepatic cholangiocarcinoma (two patients), serous cyst adenoma of the pancreas (one patient), and ampullary adenocarcinoma (one patient). The procedures of the initial surgery were Whipple's pancreatoduodenectomy (four patients), pylorus-preserving pancreatoduodenectomy (two patients), left hepatic and caudate lobectomy with extrahepatic bile duct resection (two patients), duodenum-preserving pancreas head resection (one patient), and middle segment pancreatectomy (one patient).

Aortic Occlusion

An aortic occlusion balloon catheter was inserted in patients who were to undergo relaparotomy for postoperative massive hemorrhage. An 8-French aortic occlusion balloon catheter (Occlusion Balloon Catheter, Medi-tech, Boston Scientific, Natick, MA; Fig. 1.) was inserted through a 14-French introducer percutaneously via the right femoral artery. The catheter carried a 34.5 ml capacity occlusion balloon, which was positioned immediately above the celiac artery. The position of the catheter was determined by squaring the length of insertion with that from the site of puncture to the xiphoid process. After positioning the catheter, the occlusion balloon was inflated with a total of 20–30 ml of saline. Fifteen-minute inflation was alternated with 5-minute deflation intervals during surgery to pinpoint and control the bleeding sites.

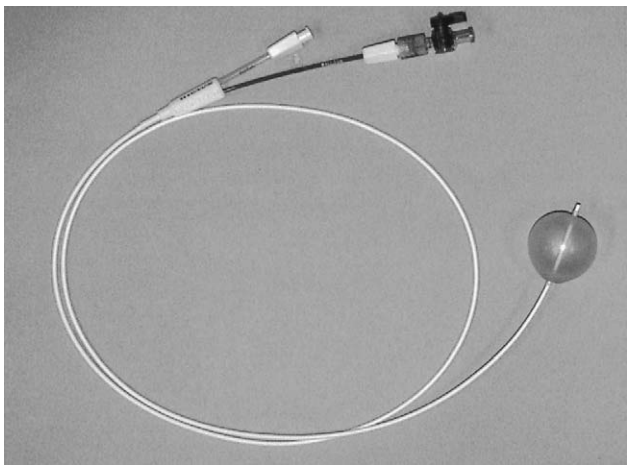

Fig. 1. An 8-French aortic occlusion balloon catheter (Medi-tech, Boston Scientific) carrying a 34.5 cc capacity occlusion balloon at the tip.

RESULTS

An aortic occlusion balloon catheter was tried on 13 occasions in 10 patients with intraabdominal arterial hemorrhage. All the patients underwent relaparotomy to control the bleeding. The interval between initial surgery and first surgical intervention was 5–39 days (mean, 18.4 days) in the 10 patients. Three patients required secondary relaparotomy. The bleeding sites of the 13 occasions were the gastroduodenal artery stump in five; common hepatic artery and splenic artery in two each; and suture line, jejunal limb, right hepatic artery, and posterior superior pancreatico duodenal artery in one each. Aortic occlusion balloon catheter insertion was attempted in the operating room on seven occasions, and before transport to the operating room on six occasions. On two occasions, the balloon catheter was advanced under fluoroscopic guidance. The results showed that 12 of the 13 attempts (92%) were successful. On those 12 occasions, insertion of the balloon catheter was accomplished within 20 minutes. In one patient, the aorta was so convoluted that the balloon catheter could not be advanced above the celiac trunk. Thus, the aorta was occluded on 12 occasions in nine patients.

At relaparotomy, because the operative field in the abdominal cavity was full of blood, the aorta was occluded by balloon catheter to stop the hemorrhaging and to obtain a clear view of the operative field. Soon after the first occlusion, systolic blood pressure of the upper limb elevated and heart rate decreased. One patient went into cardiac arrest soon after the start of the relaparotomy, recovering by cardiopulmonary resuscitation under occlusion of the aorta. Cycles of 15 minutes of aortic occlusion and 5 minutes of rest were repeated until bleeding was controlled. The bleeding sites could be detected easily and bleeding was stopped by suturing, with the aorta being occluded in all 12 events of the nine patients. At relaparotomy, leakage of pancreaticojejunostomy was found in five patients. In one patient undergoing DPPHR, perforation of the lower bile duct and the third duodenal portion was found. In three of the other four patients without anastomotic leakage or perforation, inflammation around the pancreas caused by lymph node dissection performed at the initial surgery was observed. In one patient with suture line bleeding, there was no sign of inflammation at relaparotomy. In all eight patients with pancreatico-enteric anastomosis, the anastomosis was disassembled irrespective of whether leakage

was major or minor, and tube-pancreatostomy was performed in seven of them.

Seven of the 10 patients (70%) were discharged in good condition. Three patients died of hepatic failure at 11, 14, and 40 postoperative day of their initial operation, respectively. The interval between the onset of bleeding and the first aortic occlusion was from 0.5–23 hours. In two patients, transcatheter arterial embolization (TAE) was performed before relaparotomy, but the bleeding could not be controlled. Consequently, the intervals between the onset of bleeding and first occlusion in these patients were long — 23 hours in one patient and 8 hours in the other — with both patients dying of hepatic failure. The other 10 intervals of the seven patients were 0.5–6 hours (mean, 2.2 hours), and these patients survived in good condition.

In one patient, aortic dissection from the right femoral artery to the descending aorta at the level of the celiac trunk was revealed after discharge. There were no complications related to the catheter insertion in the other patients.

DISCUSSION

Despite a declining mortality rate after major hepato-pancreato-biliary surgery,[2,3,8] recent studies report that the procedures are still associated with a high postoperative complication rate.[8,9] In particular, intraabdominal hemorrhage is a very serious complication.[5,10] Massive bleeding has a disastrous clinical outcome, with a reported mortality rate of 20%–50%.[5,11,12] With the recent advances in interventional radiology, TAE has been used widely and has gained acceptance for the treatment of visceral aneurysms or pseudoaneurysms. In various reports of TAE for postoperative ruptured pseudoaneurysm, the success rates were 0% (zero of two cases),[12] 50% (one of two cases),[5] 63% (five of eight cases),[13] 88% (seven of eight cases),[14] and 100% (four of four cases).[15] Although TAE can achieve temporary control of hemorrhage and hemodynamic stabilization, further surgery should be reserved for patients with uncontrolled intraabdominal septic conditions to prevent possible recurrent bleeding.[13,14] As peripancreatic inflammation due to anastomotic leakage can cause rebleeding after pancreatic surgery, we think that relaparotomy is the first choice of treatment for this postoperative hemorrhage. At relaparotomy, the pancreatico-enteric anastomosis is removed, and tube-pancreatostomy is performed to detect the source of bleeding by improving the operative field as well as to prevent rebleeding. Liver infarction or ischemia has been reported as a mortal complication of TAE for pseudoaneurysms arising from hepatic arteries.[13,15] In our series, liver infarction or liver ischemia did not occur. Another advantage of surgical intervention over TAE is the ability to stop bleeding of the hepatic artery without blocking blood flow.

Decompression of the abdominal wall tamponade by laparotomy could cause sudden cardiovascular collapse.[16,17] Indeed, in our study, one patient went into cardiac arrest soon after relaparotomy. Intraluminal aortic occlusion was developed to prevent sudden cardiac arrest after laparotomy in patients with intraabdominal bleeding due to abdominal trauma and ruptured abdominal aortic aneurysm.[6,7] This procedure was first described in experiments on dogs by Edwards et al.[18] in 1953, and reports on clinical applications followed.[19–22] It was reported that five patients with abdominal aneurysms were successfully controlled by occluding the aorta proximal to the site of the ruptured aneurysm.[6] We therefore introduced the aortic occlusion balloon catheter method to stabilize the hemodynamics of patients and to provide operative fields clear enough to detect the bleeding site. In this study, elevation of systolic blood pressure of the upper limb and a decrease in heart rate were immediately shown after the aortic occlusion by balloon catheter in patients with massive intraabdominal bleeding. We speculate that the hemodynamics of the upper half of the body of the patient stabilized, because the bleeding was almost stopped and the amount of circulating blood of the upper half of the body increased immediately by venous return from the lower half of the body by the aortic occlusion.

There is another problem related to reoperation for intraabdominal hemorrhage. Identification of the bleeding site is often difficult because of postoperative adhesions and hyperemic operative field.[13,23] Yoon et al.[23] performed reoperation for postoperative hemorrhage after pancreatoduodenectomy in seven cases, achieving complete hemostasis in only two. In our series, the bleeding sites could be detected easily, and bleeding was stopped by suturing while the aorta was being occluded in all 12 events of nine patients. We would like to emphasize that the aortic occlusion balloon catheter technique can provide not only hemodynamic stability but also a good view of the operative field.

The interval between the onset of bleeding and the first aortic occlusion seemed to be important; in the discharged patients it was 0.5–6 hours (mean, 2.2 hours), whereas in the two patients who died the intervals were longer (8 and 23 hours). This highlights the importance of performing aortic occlusion as soon as possible after bleeding has begun.

Ischemic damage to the organs of the lower body might be an important side effect of aortic occlusion. The risk of spinal cord damage is inherent in thoracic aortic occlusion. The incidence of hind limb paralysis secondary to aortic occlusion in hypovolemic and hypotensive dogs has been reported to be considerable.[24] Ischemic damage to the kidney or spinal cord is thought to occur after 30 minutes of complete uninterrupted occlusion.[25] Intermittent aortic occlusion is reported to be much better tolerated than continuous complete occlusion.[26,27] On the basis of these previous reports, we limited the single occlusion time to 15 minutes, and we encountered no complications from ischemic damage. Another possible adverse effect is aortic dissection. To prevent vascular complications, insertion of the catheter under fluoroscopic guidance is advisable if at all possible.

CONCLUSION

The aortic occlusion balloon catheter method is feasible for use in postoperative massive bleeding, after major hepato-pancreato-biliary surgery, to control oligemic shock and to obtain a good view of the operative field. For best results, occlusion of the aorta should be started as soon as possible.

REFERENCES

1. Shimada H, Ochiai T, Okazumi S, et al. Clinical benefits of steroid therapy on surgical stress in patients with esophageal cancer. Surgery 2000;128:791–798.
2. Cameron JL, Pitt HA, Yeo CJ, et al. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993;217:430–435; discussion 435–438.
3. Pellegrini CA, Heck CF, Raper S, et al. An analysis of the reduced morbidity and mortality rates after pancreaticoduodenectomy. Arch Surg 1989;124:778–781.
4. Grobmyer SR, Rivadeneira DE, Goodman CA, et al. Pancreatic anastomotic failure after pancreaticoduodenectomy. Am J Surg 2000;180:117–120.
5. Brodsky JT, Turnbull AD. Arterial hemorrhage after pancreatoduodenectomy. The 'sentinel bleed'. Arch Surg 1991; 126:1037–1040.
6. Ng AC, Ochsner EC. Use of Fogarty catheter tamponade for ruptured abdominal aortic aneurysms. AJR Am J Roentgenol 1977;128:31–33.
7. Wolf RK, Berry RE. Transaxillary intra-aortic balloon tamponade in trauma. J Vasc Surg 1986;4:95–97.
8. Grace PA, Pitt HA, Tompkins RK, et al. Decreased morbidity and mortality after pancreatoduodenectomy. Am J Surg 1986;151:141–149.
9. Yamaguchi K, Tanaka M, Chijiiwa K, et al. Early and late complications of pylorus-preserving pancreatoduodenectomy in Japan 1998. J Hepatobiliary Pancreat Surg 1999;6: 303–311.
10. Miedema BW, Sarr MG, van Heerden JA, et al. Complications following pancreaticoduodenectomy. Current management. Arch Surg 1992;127:945–949; discussion 949–950.
11. Lerut JP, Gianello PR, Otte JB, et al. Pancreaticoduodenal resection. Surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984;199:432–437.
12. van Berge Henegouwen MI, Allema JH, van Gulik TM, et al. Delayed massive haemorrhage after pancreatic and biliary surgery. Br J Surg 1995;82:1527–1531.
13. Sato N, Yamaguchi K, Shimizu S, et al. Coil embolization of bleeding visceral pseudoaneurysms following pancreatectomy: The importance of early angiography. Arch Surg 1998;133:1099–1102.
14. Shibata T, Sagoh T, Ametani F, et al. Transcatheter microcoil embolotherapy for ruptured pseudoaneurysm following pancreatic and biliary surgery. Cardiovasc Intervent Radiol 2002;25:1.
15. Reber PU, Baer HU, Patel AG, et al. Superselective microcoil embolization: Treatment of choice in high-risk patients with extrahepatic pseudoaneurysms of the hepatic arteries. J Am Coll Surg 1998;186:325–330.
16. Sankaran S, Lucas C, Walt AJ. Thoracic aortic clamping for prophylaxis against sudden cardiac arrest during laparotomy for acute massive hemoperitoneum. J Trauma 1975;15: 290–296.
17. Ledgerwood AM, Kazmers M, Lucas CE. The role of thoracic aortic occlusion for massive hemoperitoneum. J Trauma 1976;16:610–615.
18. Edwards W, Salter P, Carnaggio V. Intraluminal aortic occlusion as a possible mechanism for controlling massive intra-abdominal hemorrhage. Surg Forum 1953;4:496–499.
19. Hughes C. Use of an intra-aortic balloon catheter tamponade for controlling intra-abdominal hemorrhage in man. Surgery 1954;36:65.
20. Hesse F, Kletschka H. Rupture of abdominal aortic aneurysm: Control of hemorrhage by intraluminal balloon tamponade. Ann Surg 1962;155.
21. Heimbecker R. An aortic tampon for emergency control of ruptured abdominal aneurysm. Can Med Assoc J 1964;91: 1024–1025.
22. Robicsek F, Daugherty HK, Mullen DC. The elective use of balloon obstruction in aortic surgery. Surgery 1970;68: 774–777.
23. Yoon YS, Kim SW, Her KH, et al. Management of postoperative hemorrhage after pancreatoduodenectomy. Hepatogastroenterology 2003;50:2208–2212.
24. Berkoff HA, Carpenter EW, Frey CF. Evaluation of balloon tamponade of the abdominal aorta. An adjunct to the treatment of hemorrhagic shock. J Surg Res 1971;11:496–500.
25. Low RB, Longmore W, Rubinstein R, et al. Preliminary report on the use of the Percluder occluding aortic balloon in human beings. Ann Emerg Med 1986;15:1466–1469.
26. Laschinger JC, Cunningham JN Jr, Nathan IM, et al. Experimental and clinical assessment of the adequacy of partial bypass in maintenance of spinal cord blood flow during operations on the thoracic aorta. Ann Thorac Surg 1983; 36:417–426.
27. Neglen P, Eklof B, Thomson D. Temporary incomplete ischemia of the legs induced by aortic clamping in man. Metabolic and hemodynamic effects of temporary extracorporeal by-pass. Scand J Thorac Cardiovasc Surg 1983;17: 289–298.

Influence of Bactibilia After Preoperative Biliary Stenting on Postoperative Infectious Complications

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The aim of this study was to correlate the bactibilia found after preoperative biliary stenting with that of the bacteriology of postoperative infectious complications in patients with obstructive jaundice. One hundred thirty-eight patients (83% malignant and 17% benign etiologies) with obstructive jaundice had both their bile and all postoperative infectious complications cultured. Eighty-six (62%) had preoperative biliary stents (stent group) and 52 (38%) did not (no-stent group). There were no differences for age, sex, incidence of malignancy, type of operation, estimated blood loss, transfusion requirements, hospital length of stay, morbidity, or mortality rates between the two groups. Of 31 infectious complications, 23 were in the stent group and eight were in the no-stent group ($P > 0.05$), but only 13 (42%) infectious complications had bacteria that were also cultured from the bile. Only wound infection ($P = 0.03$) and bacteremia ($P = 0.04$) were more likely to occur in stented patients. Taken together, these data show that preoperative biliary stenting increases the incidence of bactibilia, bacteremia, and wound infection rates but does not increase morbidity, mortality, or hospital length of stay. Jaundiced patients can undergo preoperative biliary stenting while maintaining an acceptable postoperative morbidity rate.
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KEY WORDS: Bacteremia, bactibilia, biliary stenting, pancreaticoduodenectomy, wound infection

Extrahepatic (nonhilar) biliary tract obstruction can be caused by benign, inflammatory, or malignant conditions located in either the distal common bile duct, duodenum, or head of the pancreas. Comprehensive evaluation and staging of these diseases frequently requires endoscopic retrograde cholangiopancreatography (ERCP) where cholangiography, brushings, and biopsy can often distinguish benign (gallstones, strictures) from malignant (pancreatic cancer) conditions.[1,2] During this investigation, if a biliary obstruction is found, most experts recommend establishing effective biliary drainage by placement of an endoscopic biliary endoprosthesis to prevent postprocedure cholangitis.[3] After their diagnosis and staging, many patients with obstructive jaundice (both benign and malignant etiologies) are referred on for surgical management.

From a surgical perspective, it has been well established that operations on jaundiced patients carry an elevated morbidity and mortality rate.[4,5] Theoretical advantages of preoperative biliary stenting include improvement in the nutritional, metabolic, and immunologic functions of a jaundiced patient by redirecting bile into their gastrointestinal tract. Implicit in this logic is that preoperative stenting, by accomplishing these goals, will reduce a patient's perioperative morbidity and mortality rate.[6–8] Stenting also provides time for additional preoperative investigation and appropriate referral to high-volume centers.[9] Opponents of preoperative biliary stenting cite an increased incidence of bactibilia and inflammation in a biliary system in which a stent has been placed, which can lead to an increase in postoperative infectious complications, morbidity, and mortality.[10–12] Despite a large body of data on preoperative biliary stenting and its relationship to postoperative morbidity and mortality rates, there remains little data on the precise bacteriology of bile in patients who have had preoperative biliary stenting and the relationship of this bactibilia to their postoperative infectious complications.

The aims of this study are (1) to define the bacteriology of bile in patients with obstructive jaundice and to identify differences between those who have,

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and those who have not, undergone preoperative biliary stenting; (2) to quantitate the influence of preoperative biliary stenting on postoperative morbidity, both infectious and noninfectious, and mortality; and (3) correlate the bacteria found in bile with the bacteria cultured from postoperative infectious complications.

MATERIAL AND METHODS

One hundred eighty-seven patients with obstructive jaundice from both malignant and benign diseases were operated on by two surgeons (J.A.M., T.J.H.) at Indiana University Medical Center over a 10-year period (January 1994 to January 2004) to relieve the patient's biliary obstruction. Of these, 138 patients (85 men and 53 women, with mean age of 60 years) are included for analysis because they had both their bile cultured prospectively for aerobic, anaerobic, and fungal organisms at the time of bile duct transaction and had all postoperative infectious complications cultured. This study was approved by the Institutional Review Board at Indiana University Purdue University at Indianapolis. All operations were elective, and all patients were free from skin, soft tissue, urinary, or pulmonary tract infection at the time of surgery. Patients received prophylactic antibiotics consisting of either a second- or third-generation cephalosporin or ampicillin\sulbactam intravenously before their abdominal incision, and this regimen was continued for 24 hours postoperatively. At operation, 85 patients had pylorus-preserving pancreaticoduodenectomy, 28 patients had standard pancreaticoduodenectomy, six patients had total pancreatectomy, nine patients had choledochojejunostomy Roux-en-Y, five patients had hepaticojejunostomy Roux-en-Y, and three patients had choledochoduodenostomy. All received standard postoperative care by the surgical house staff under the direction of the attending surgeon, and 92 patients (67%) spent at least 1 postoperative day in the intensive care unit. Medical records were reviewed and clinical variables were collected into an Access database housed in the Department of Surgery. Collected variables included age, gender, preoperative stenting, operative procedure, pathology, blood loss, transfusion requirements, operative time, culture result, postoperative complication, hospital length of stay, and postoperative death. Eighty-six patients had either endoscopic or percutaneous preoperative biliary stenting before operation and were included in the stent group, whereas 52 patients were operated on without preoperative stenting and were included in the no-stent group.

Preoperative Biliary Stenting

Preoperative biliary stenting was defined as either an endoscopic biliary endoprosthesis or a percutaneous transhepatic stent that was placed across the area of obstruction in the distal common bile duct and into the duodenum to serve as a conduit for decompression. Patients who underwent transhepatic biliary stenting all had initial percutaneous transhepatic cholangiography and then received a transhepatic biliary stent under fluoroscopic guidance. Endoscopic stenting was done after patients underwent endoscopic retrograde cholangiopancreatography (ERCP). All transhepatic stents were done at our institution and all patients received a dose of systemic antibiotics (ceftriaxone and ampicillin) before the procedure. Seventy-five of the 83 patients who had ERCP and placement of a biliary endoprosthesis were done at our institution and all had preprocedure prophylactic antibiotics consisting of either a fluoroquinolone or piperacillin tazobactam. We have no data on the use of preprocedure prophylactic antibiotics in the eight patients included in the study who had their ERCP and biliary stent placed at an outside institution.

Culture Techniques

Intraoperative biliary samples were collected at the time of operation for bacteriologic examination and were routinely cultured for 5 days (120 hours) afterwards. Four aerobic media (chocolate agar, colistin nalidixic acid agar, MacConkey agar, and thio broth) and two anaerobic media (anaerobic blood agar and phenylethanol agar) were used to detect the aerobic, anaerobic, and fungal organisms. When postoperative infectious complication were diagnosed or suspected, the sample was taken from the presumed site of infection (urine, sputum, blood, or pus) and also cultured for aerobic and anaerobic microorganisms. Cultures were kept for 120 hours and carefully evaluated for *Candida* species and other yeast.

Postoperative Complications

Infectious complications were defined as any complication occurring with a fever and\or leukocytosis, which was localized by physical exam, laboratory test, or an imaging study and confirmed by the culture of microorganisms from the suspected fluid. Wound infections were identified by an area of erythema or purulent drainage from the wound, which

yielded pus on drainage and grew bacteria on culture. Bacteremia was defined as a positive blood culture for bacteria obtained from two separate sites from the same patient during the same febrile (temperature, >38.5° C) episode. Intra-abdominal abscess was defined as a postoperative intra-abdominal fluid collection identified on imaging study and associated with a fever or leukocytosis that grew bacteria on culture. Pneumonia required radiographic evidence of an infiltrate associated with either a fever and\or leukocytosis, or a positive sputum culture. A pancreatic fistula was defined as the secretion of greater than 50 ml of amylase-rich fluid (three times the concentration of serum amylase) beyond the 10th postoperative day. Bile leak was defined clinically by an elevated bilirubin level in fluid obtained from intraperitoneal drains placed in proximity to the biliary-enteric anastomosis at the time of pancreaticoduodenectomy or biliary bypass, or in fluid obtained from CT-guided drainage of subhepatic fluid collections. Delayed gastric emptying was defined as the need for persistent nasogastric decompression or inability to tolerate a regular diet after postoperative day 10. Postoperative death was defined as death during the index hospitalization or within 30 days after surgery.

Statistical Methods

The demographic characteristics, operative procedure, pathology results, intraoperative parameters, postoperative morbidity, and mortality of patients stented (stent group) were compared with those of unstented patients (no-stent group). SAS version 9.0 (SAS Institute, Cary, NC) was used to perform all the statistical analysis. Pearson chi-square test or the Fisher exact test was used as appropriate to compare the categorical variables; the Wilcoxon rank sum test was used to compare the median values of continuous data. A two-sided P value less than 0.05 would be considered as significant.

RESULTS

The comparison of demographics and clinical features in 138 patients with obstructive jaundice who were cultured at the time of biliary-enteric anastomosis is summarized in Table 1. When segregated into preoperative biliary stent versus no-stent groupings, we found no differences for age, gender, or the pathology of the biliary tract obstruction. The majority of patients (83 of 86, 96%) underwent endoscopic retrograde cholangiopancreatography in the stent group compared with only 22 (32%) patients in the no-stent group ($P < 0.0001$). Three (4%) of the patients stented who did not undergo ERCP had percutaneous transhepatic cholangiography and transhepatic stent placement.

Table 1. Demographic and clinical features of 138 patients with obstructive jaundice segregated into those who had a preoperative biliary stent (stent group) versus those who did not (no stent group)

	Stent group (n = 86)	No-stent group (n = 52)	*P* value
Age (mean ± SD)	61 ± 13	59 ± 14	0.36
Gender			0.72
Male	52 (60)	33 (63)	
Female	34 (40)	19 (37)	
Pathologic diagnosis			0.20
Malignant	74 (86)	38 (73)	
Pancreatic adenocarcinoma	51 (70)	23 (61)	
Biliary adenocarcinoma	15 (20)	8 (21)	
Ampullary adenocarcinoma	4 (6)	3 (8)	
Duodenal adenocarcinoma	2 (2)	1 (3)	
Other (islet cell tumor, large cell tumor)	2 (2)	3 (7)	
Benign	12 (14)	14 (27)	
Chronic pancreatitis	10 (83)	12 (86)	
Intraductal papillary mucinous neoplasm	2 (17)	2 (14)	
ERCP			<0.0001
Yes	83	22	
No	3	30	

Values are number (percentage) unless otherwise indicated.

The operative and postoperative variables are summarized in Table 2. These data show that the two groups were similar for all variables analyzed. Specifically, there were no differences found in type of operation, estimated blood loss, transfusion requirements, or length of operation. The overall incidence of postoperative complication was 43% in the stent group and 37% in the no-stent group ($P = 0.45$), and there were no differences in length of hospital stay between the two groups. There were three postoperative deaths in this series (overall mortality rate, 2%), two in the stent group and one in the no-stent group. One patient in the stent group died of multisystem organ failure after suffering from postoperative pneumonia, renal failure, and adult respiratory distress syndrome; the other patient died of an acute myocardial infarction after surgery. One patient in the no-stent group died of acute renal failure. The specific postoperative complications are detailed in Table 3. When subdivided into infectious and noninfectious complications, the incidences of infectious complication were also not significantly different between the two groups (27% in stent group

Table 2. Operative and postoperative variables in 138 patients with obstructive jaundice treated by biliary-enteric anastomosis

	Stent group (n = 86)	No-stent group (n = 52)	*P* value
Operation type			0.16
Pylorus-preserving Whipple	55 (64)	30 (58)	
Standard Whipple	16 (19)	12 (23)	
Total pancreatectomy	3 (3)	3 (6)	
Hepaticojejunostomy Roux-en-Y	11 (13)	5 (10)	
Choledochoduodenostomy	1 (1)	2 (3)	
Estimated blood loss (ml)			0.52
Mean ± SD	1166 ± 1008	1223 ± 1504	
Median	850	800	
Transfusion requirements (units)			0.85
Mean ± SD	1.4 ± 2.1	1.5 ± 2.6	
Median	0	0	
Length of procedure (hour)			0.51
Mean ± SD	5.3 ± 2.2	5.5 ± 2.1	
Median	5	6	
Overall complication rate	37 (43)	19 (37)	0.45
Postoperative death	2 (2.3)	1 (1.9)	0.99
Hospital length of stay (day)			0.77
Mean ± SD	13.1 ± 9.5	12.4 ± 7.7	
Median	10	9	

Values are number (percentage) unless otherwise indicated.

vs. 15% in no-stent group; $P = 0.12$). There were differences, however, in two subsets of infectious complications, wound infection rates (14% in stent group vs. 2% in no-stent group; $P = 0.03$), and bacteremia (8% in stent group vs. 0% in no-stent group; $P = 0.04$), which were both significantly more likely to occur in the stent group when compared with the no-stent group. All other infectious complications including intra-abdominal abscess, pneumonia, urinary tract infection, and *clostridium difficile colitis* were similar between the two groups. In noninfectious complications, myocardial infarction, pancreatic leak, and renal failure were the most common but again, no significant differences were found between groups.

Table 4 shows the results of intraoperative bile cultures. Ninety-one (66%) patients of 138 of the entire series were found to have bacteria in their bile. Stent patients were significantly more likely to have bacteria cultured from their bile than no-stent patients (80% vs. 42%, respectively; $P < 0.0001$). Positive intraoperative bile cultures were polymicrobial in 47 (55%) of 86 stent patients versus only 7 (14%) of 52 no-stent patients ($P = 0.003$). Both Gram-positive and Gram-negative microorganisms were more likely to grow in the bile of the stent patients rather than that of the no-stent patients ($P < 0.01$). Fungus and anaerobes had a low incidence in both groups, without a significant difference found between the two groups ($P > 0.05$). The specific microorganisms isolated from the bile of patients in this study are summarized in Table 5. The dominant microorganisms isolated from the bile in all patients was *Enterococcus* species (57%), followed by *Klebsiella* species (30%), yeast (21%), *Escherichia coli* (18%), *Staphylococcus aureus* (14%), *Enterobacter* species (14%), and *Lactobacillus* species (14%). Microorganisms cultured in the stent group followed this precise order; however, the dominant microorganisms found in the no-stent group were slightly different, with *Klebsiella* species (41%) being the most frequent organism cultured, followed by yeast (32%), *Enterobacter* species (23%), and *Enterococcus* species (23%).

When correlating the microorganisms cultured from bile with those cultured from postoperative infectious complications, 13 (42%) of 31 infectious complications cultured bacteria that was also present in the patient's bile. Wound infection was the most common postoperative infectious complication and occurred in 9% (13 of 138) of the series. Eleven (85%) of 13 patients with a wound infection had a positive intraoperative bile culture. Seven (64%) of 11 wound infections were polymicrobial. The dominant microorganisms isolated from wound infections were *Enterococcus* species (55%), *S aureus* (45%), alpha streptococci (36%), *Klebsiella* species (27%), and *Enterobacter* species (18%). Fifty-five percent (6 of 11) of the culture-proven wound infections

Table 3. Postoperative complications in 138 patients after biliary-enteric anastomosis

	Stent group (n = 86)	No-stent group (n = 52)	*P* value
Noninfectious complication*			
Myocardial infarction	4 (5)	1 (2)	0.65
Biliary leak	2 (2)	1 (2)	1.00
Pancreatic leak	2 (2)	2 (4)	0.63
Renal failure	2 (2)	2 (4)	0.63
Atrial fibrillation	2 (2)	1 (2)	1.00
Hemorrhage	2 (2)	0 (0)	0.53
Delayed gastric emptying	2 (2)	1 (2)	1.00
Small bowel obstruction	2 (2)	0 (0)	0.53
Prolonged ileus	1 (1)	1 (2)	1.00
Gastric outlet obstruction	0 (0)	3 (6)	0.05
Infectious complication*			
Wound infection	12 (14)	1 (2)	0.03*
Intra-abdominal abscess	2 (2)	4 (8)	0.20
Bacteremia	7 (8)	0 (0)	0.04*
Pneumonia	4 (5)	1 (2)	0.65
Urinary tract infection	2 (2)	2 (4)	0.63
Clostridium difficile colitis	0 (0)	1 (2)	0.38

Values are number (percentage) unless otherwise indicated.
*More than one complication can be recorded per patient.

had a positive intraoperative bile culture; five (83%) of these six patients had one or more of the same microorganisms in both the intraoperative bile culture and the wound infection culture. Among the seven stented patients who developed postoperative bacteremia, six (86%) had positive bile cultures and five of these six had correlation between the organism cultured in the bile and that causing the bacteremia. The microorganisms found in bacteremias were yeast, *S aureus*, *Enterobacter* species, *Klebsiella* species, and *E coli*.

To assess the contribution of simple instrumentation of the biliary system without endoscopic stent placement, we broke down the 52 patients without stents into those who had ERCP and those who did not. When comparing the 22 patients who had ERCP with the 30 patients who did not, we found no significant differences for age, gender, pathology, type of operation, length of operation, intraoperative blood transfusion, or estimated blood loss (Table 6). Overall morbidity, infectious complications, and hospital length of stay were also similar between groups ($P > 0.05$).

Table 4. Bile culture characteristics in stent and no-stent patients

	Stent group (n = 86)	No-stent group (n = 52)	*P* value
Positive isolate	69 (80)	22 (42)	<0.0001
Multiple isolate	47 (55)	7 (14)	0.003
Gram-positive	54 (63)	9 (17)	<0.0001
Gram-negative	39 (45)	12 (23)	0.009
Fungus	17 (20)	7 (14)	0.34
Anaerobes	15 (17)	4 (8)	0.11

Values are number (percentage) unless otherwise indicated.

Table 5. Bile bacteriology in 91 patients

Microorganisms	All patients with positive results (n = 91)	Stent group (n = 69)	No-stent group (n = 22)
Enterococcus species	52 (57)	47 (68)	5 (23)
Klebsiella species	27 (30)	18 (26)	9 (41)
Yeast	21 (23)	14 (20)	7 (32)
Escherichia coli	16 (18)	16 (23)	0
Staphylococcus aureus	13 (14)	10 (14)	3 (14)
Enterobacter species	13 (14)	8 (12)	5 (23)
Lactobacillus species	8 (9)	8 (12)	0
Veillonella species	7 (8)	6 (9)	1 (5)
Clostridium perfringens	6 (7)	6 (9)	0
Fusobacterium nucleatum	6 (7)	6 (9)	0
Alpha streptococci	6 (7)	4 (6)	2 (9)
Bacteroides species	4 (4)	2 (3)	2 (9)
Prevotella species	4 (4)	4 (6)	0
Torulopsis glambrata	2 (2)	2 (3)	0
Citrobacter species	2 (2)	1 (1)	1 (5)
Others	10 (11)	8 (12)	2 (9)

Values are number (percentage) unless otherwise indicated.

DISCUSSION

The results of this study support the concept that preoperative biliary stenting does not increase the postoperative morbidity or mortality rates in patients with obstructive jaundice who are undergoing an operation directed at relieving their biliary tract obstruction. These results are consistent with other reports whose main focus was on complications after pancreaticoduodenectomy in patients who had undergone preoperative biliary stenting.[13–19] Although the overall morbidity (41%) and mortality (2%) rates in our study are similar to those of other mixed (both resection and bypass) surgical populations reported in the literature,[4,5,14] we found that preoperative biliary stenting increased the incidence of positive intraoperative bile cultures, wound infection rates, and risk of bacteremia, observations that have been made by other investigators.[15,18–20] Despite the wealth of information on the influence of preoperative biliary stenting on the postoperative complication rates,

Table 6. Effect of biliary instrumentation (ERCP) in 52 no-stent patients who underwent biliary-enteric anastomosis

	ERCP (n = 22)	No ERCP (n = 30)	*P* value
Age	57 ± 14	60 ± 15	0.42
Gender			0.25
Male	12	21	
Female	10	9	
Pathology findings			0.33
Malignant	18	17	
Benign	4	13	
Surgery procedure			0.16
Resection	20	22	
Bypass	2	8	
Length of procedure (hour)			0.26
Mean	5.2 ± 2.0	5.7 ± 2.1	
Median	5	6	
Estimated blood loss (ml)			0.27
Mean	1225 ± 1276	1222 ± 1677	
Median	1200	700	
Red blood cell transfusion (unit)			0.83
Mean	1.2 ± 2.0	1.8 ± 3.1	
Median	0	0	
Morbidity	7 (32%)	12 (40%)	0.55
Infectious complication	1 (5%)	7 (23%)	0.12
Length of hospital stay (day)			0.24
Mean	12.0 ± 6.8	12.6 ± 8.4	
Median	9	9	

relatively few studies[12,14,20] have focused specifically on the relationship between the bacteria cultured in bile after stent placement and the corresponding pathogen cultured from the infectious complication encountered.

In 1996, Karsten and colleagues[14] retrospectively reviewed the charts of a consecutive series of 241 patients with tumors in the pancreatic head, obstructing the extra hepatic biliary tract, who had undergone operation. In this study, 184 (76%) patients had preoperative biliary drainage, of which 149 (62%) were endoscopic biliary endoprostheses, 25 (10%) were simple papillotomy, and 10 (4%) were external biliary drainage. They assess the effects of preoperative biliary drainage on postoperative complication rates and death. Similar to our study, they had a mixed group of patients consisting of both resection and drainage operations, including 163 Whipple resections, 33 total pancreatectomies, and 45 biliary-enteric bypasses. All patients in their series received preoperative prophylactic antibiotics (amoxicillin + gentamicin), starting during anesthetic induction and continuing for 48 hours. Their findings were similar to ours in many respects; they reported that preoperative biliary drainage had no effect on postoperative complication rates or operative mortality, even though the intraoperative bile cultures were more frequently positive for bacteria in patients who had preoperative biliary drainage. Patients with preoperative biliary drainage had an overall morbidity rate of 56% compared with 61% in patients who did not undergo preoperative biliary drainage. In all patients in this series, intra-abdominal abscess (28%) was their most frequent complication, followed by wound infection (19%) and hemorrhage (17%). They also found a 5% incidence of catheter-related sepsis in their patient cohort. Our data show an overall morbidity rate of 43% in the stent group and a 37% rate in the no-stent group, with wound infection (9%), bacteremia (5%), and intra-abdominal abscess (4%) being the most common complications identified. These minor discrepancies between the two studies can be explained by differing patient populations (Karsten and colleagues,[14] 100% malignancy vs. our study, 81% malignancy), types of operations (Karsten and colleagues[14]: Whipple 68%, total pancreatectomy 14%, biliary-enteric bypass 18%; our study, Whipple 82%, total pancreatectomy 4%, biliary-enteric bypass 14%), and perioperative antibiotic regimens (Karsten and colleagues,[14] gentamicin and amoxicillin; our study, second- or third-generation cephalosporin or ampicillin/sulbactam). In a subgroup analysis, Karsten and colleagues[14] found that postoperative infectious complications were similar in patients whose bile grew bacteria when compared with patients whose bile was sterile (42% vs. 45%). These findings are also consistent with our results (data not shown). The overall incidence of bactibilia in their stent patients was 92%, and in their no-stent patients 43%, with their top three isolates being *Klebsiella* (52%), *Enterobacter* species (45%), and *E coli* (40%). We report an overall incidence of bactibilia of 80% in our stent group, of 42% in our no-stent group, and our top three bacterial isolates are *Enterococcus* (57%), *Klebsiella* (30%), and *E coli* (18%). Where we found a 23% incidence of yeast colonization in the bile of our patients (20% stent group vs. 32% no-stent group), Karsten and colleagues[14] found only 10% of isolates identified as yeast. Whereas Karsten and colleagues reported that 65% of the bacteria cultured from postoperative infections matched the bacteria that they cultured from the patients bile, this value was calculated using only patients who had a positive bile culture. If one looks at all 84 of their postoperative infectious complications, only

40 (48%) of 84 cultured the same bacteria as that found in bile. This is almost identical to the rate of infectious complications (13 of 31, 42%) we found that cultured the same bacteria as was cultured from bile. Unfortunately, their postoperative complications were not specified or discussed in great detail, so direct comparisons between subsets of postoperative complications in stent and no-stent groups in each study could not be made.

A second study by Povoski et al.[12] assessed the impact of preoperative biliary drainage on intraoperative bile cultures, postoperative infectious complications, and mortality in 161 consecutive patients undergoing pancreaticoduodenectomy at Memorial Sloan-Kettering Cancer Center in New York. In this study, the authors found a 58% incidence of bactibilia, with 70% of cultures being polymicrobial. Postoperative infectious complications occurred in 29% of patients, most commonly wound infection (14%) or intra-abdominal abscess (12%). Eighty-nine percent of patients with intra-abdominal abscess ($P = 0.003$) and 87% of patients with wound infection ($P = 0.003$) had positive intraoperative bile cultures. Microorganisms cultured from the bile in 14 (74%) of 19 patients were predictive of the microorganisms cultured from the subsequent intra-abdominal abscess, and bile cultures were 69% predictive of organisms cultured from a wound infection. In our study, of the seven patients with postoperative bacteremia, only one (14%) had the same organism as that cultured from the bile (*Klebsiella pneumoniae*). In 11 postoperative wound infections, only six (55%) patients had a positive intraoperative bile culture, and of these, 5 (45%) cultured the same organisms from both the bile and their subsequent wound infection. Similar to our results, their data showed that preoperative biliary drainage increased the incidence of positive intraoperative bile cultures ($P < 0.001$) and postoperative wound infection rates ($P = 0.045$). In contrast to our findings, they also reported that preoperative biliary drainage increased postoperative infectious complications ($P = 0.022$), intra-abdominal abscess ($P = 0.061$), and death ($P = 0.021$). These marked differences in the influence of preoperative biliary stenting on postoperative morbidity and mortality rates are likely due to the complex, selective referral pattern to Memorial Sloan-Kettering Cancer Center as evidenced by the fact that 22 (23%) of 94 patients had more than one biliary drainage procedure and 8 (9%) of 94 patients had a surgical drainage procedure before operation. In addition, 22 (23%) of 94 patients in this series reported fever and chills within 1 week of their operation, implying a poorly functioning stent and possibly low-grade cholangitis. Subsequent studies looking at a similar number of patients with periampullary malignancies, treated by preoperative biliary stents and undergoing subsequent pancreaticoduodenectomy, have shown only an increased risk of postoperative wound infections but have been unable to substantiate an increase in perioperative morbidity or mortality rates.[15–19]

In the most recent observational study reported by Jagannath et al.,[20] 74 stent patients and 70 no-stent patients were analyzed after undergoing pancreaticoduodenectomy between 1992 and 2001. This study specifically emphasizes the importance of the duration of preoperative biliary stenting and its relationship to postoperative morbidity and mortality rates. Using logistic regression analysis, a positive intraoperative bile culture was the only factor significantly associated with operative morbidity ($P < 0.001$) and mortality ($P = 0.019$). Although biliary stenting per se was not significantly associated with a positive culture ($P = 0.073$), stenting that resulted in complications ($P = 0.006$) or biliary drainage for less than 6 weeks ($P = 0.011$) was significantly associated with a higher rate of positive cultures. It should be emphasized that uncomplicated stenting in this study was found to not increase the perioperative morbidity or mortality rate. Although stent placement in their series had an acceptable 92% success rate, all six stent placement failures (8% of total group) were included in the preoperative biliary drainage group on an intention-to-treat basis. Furthermore, post-stenting complications occurred in a rather large percentage of patients (18 of 74, 24%) when compared with most contemporary ERCP trials, even when carried out in a district general hospital setting.[21] Forty-seven percent of patients who had preoperative biliary drainage grew bacteria on culture (31% positive cultures in the group without stents), of which the two most common bacteria were *E coli* (56%) and *Klebsiella* (32%). These data are consistent with both our study and others.[12,14] In contrast to other culture data from preoperative endoscopic stenting, however, the authors report[20] a 25% incidence of *Pseudomonas aeruginosa* cultured from the bile. This virulent pathogen, likely a contaminant introduced during ERCP and biliary instrumentation, can certainly contribute to an increase in postoperative morbidity and mortality rates.[3]

Although human bile is considered sterile under normal conditions, infection can occur as a consequence of biliary tract obstruction, inflammation, or stone formation. Obstructive jaundice is considered to be a risk factor for bile infection.[17] In both our study and the two most recent studies[14,21] where routine intraoperative biliary cultures were taken, bactibilia was identified in 42% (our study), 34%[14],

and 20%[21] of patients with obstructive jaundice whose biliary tracts had not been previously instrumented. Although preoperative biliary stenting is assumed to improve biliary drainage, relieve jaundice, and prevent cholangitis, stenting of the bile duct, particularly when associated with significant trauma and inflammation (i.e., complicated stenting), it may provide a better microenvironment for bacterial survival.[6] It is therefore not surprising that in the majority of studies referenced, the incidence of positive bile cultures was higher in the preoperative stent group.[15–19] In our study, bacteria were cultured from the bile in 80% of the stent group, but in only 42% of the no-stent group ($P < 0.0001$). This high incidence of bactibilia, however, does not necessarily produce a higher incidence of postoperative infectious complication as many other factors contribute to their development in these long, technically demanding operations.[22] In this study, all patients received a regimented course of perioperative antibiotics targeted at the dominant pathogenic organisms cultured from the bile, and the influence of this practice on our overall postoperative infectious complication rates is unknown. Only 42% of postoperative infectious complications in our series were caused by bacteria cultured from the bile, the other 58% representing common skin flora or gastrointestinal tract contaminates encountered during biliary-enteric anastomosis. Appropriately timed and delivered perioperative antibiotics targeting the most common organisms cultured from the bile, as well as common skin contaminants, should help to reduce the rate of postoperative infectious complication.[23]

In summary, our data support the observation that preoperative biliary stenting in jaundiced patients does not increase the incidence of postoperative infectious complication or mortality from operations directed at relieving the patient's bile duct obstruction. Jaundiced patients who require an additional period of preoperative assessment, or more time to allow referral to an appropriate high-volume center for surgery, should undergo preoperative biliary drainage by endoscopists with a low procedure-related complication rate.[9] Routine perioperative prophylactic antibiotics should be targeted at the most commonly found organisms, started before the initial skin incision to ensure adequate tissue levels at the time of contamination, redosed during the operation every two serum half-lives (i.e., every 3–4 hours), and continued for 24 hours postoperatively.[23] Careful attention to maintaining perioperative normothermia and the use of supplemental perioperative oxygen may also improve the postoperative wound infection rate.[24,25]

CONCLUSION

Preoperative biliary stenting does not increase morbidity, mortality, hospital length of stay, or overall infectious complications in patients with obstructive jaundice undergoing surgery directed at relieving their obstruction. Stenting does increase the incidence of bactibilia, bacteremia, and wound infection rates. Less than half of all postoperative infectious complications are caused by bacteria cultured from the bile; the rest are caused by common skin flora or contaminates from the opened gastrointestinal tract. Jaundiced patients who require a further period of preoperative assessment or additional time before referral to an appropriate high volume surgery center should undergo preoperative biliary drainage by endoscopists with a low procedure-related complication rate.

REFERENCES

1. American Society for Gastrointestinal Endoscopy. The role of ERCP in disease of the biliary tract and pancreas. Gastrointest Endosc 1999;50:915–920.
2. Obertop H, Gouma DJ. Essentials of biliopancreatic staging: A decision analysis. Ann Oncol 1999;10(Suppl 4): 150–152.
3. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management. An attempt at consensus. Gastrointest Endosc 1991;37:383–393.
4. Dixon JM, Armstrong CP, Duffy SW, Elton RA, Davies GC. Factors affecting morbidity and mortality after surgery for obstructive jaundice: A review of 373 patients. Gut 1983; 24:845–852.
5. Lacaine F, Fourtanier G, Fingerhut A, Hay JM. Surgical mortality and morbidity in malignant obstructive jaundice: A prospective multivariate analysis. Eur J Surg 1995;161: 729–734.
6. Kimmings AN, van Deventer SJ, Obertop H, Rauwas EA, Huibregtse K, Gouma DJ. Endotoxin, cytokines, and endotoxin binding proteins in obstructive jaundice and after preoperative biliary drainage. Gut 2000;46:725–731.
7. Gouma DJ, Roughneen PT, Kumar S, Moody FG, Rowlands BJ. Changes in nutritional status associated with obstructive jaundice and biliary drainage in rats. Am J Clin Nutr 1986;44:362–369.
8. Lygidakis NJ, van de Heyde MN, Lubbers MJ. Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. Acta Chir Scand 1987;153: 665–668.
9. Pisters PWT, Lee JE, Vauthey JN, Evans DB. Letter to the editor. Ann Surg 2003;237:594–596.
10. Hatfield AR, Tobias R, Terblanche J, et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet 1982;2:896–899.
11. McPherson GA, Benjamin IS, Hodgson HJ, Bowley NB, Allison DJ, Blumgart LH. Pre-operative percutaneous transhepatic biliary drainage: The results of a controlled trial. Br J Surg 1984;71:371–375.
12. Povoski SP, Karpeh MS, Conlon KC, Blumgart LH, Brennan MF. Preoperative biliary drainage: Impact on

intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J GASTROINTEST SURG 1999;3:496–505.
13. Saleh MM, Norregaard P, Jorgensen HL, Andersen PK, Matzen P. Preoperative endoscopic stent placement before pancreaticoduodenectomy: A meta-analysis of the effect on morbidity and mortality. Gastrointest Endosc 2002;56: 529–534.
14. Karsten TM, Allema JH, Reinders M, et al. Preoperative biliary drainage, colonization of bile and postoperative complications in patients with tumours of the pancreatic head: A retrospective analysis of 241 consecutive patients. Eur J Surg 1996;162:881–888.
15. Sohn TA, Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? J GASTROINTEST SURG 2000;4: 258–268.
16. Martignoni ME, Wagner M, Krahenbuhl L, Redaelli CA, Friess H, Buchler MW. Effect of preoperative biliary drainage on surgical outcome after pancreatoduodenectomy. Am J Surg 2001;181:52–59.
17. Sewnath ME, Birjmohun RS, Rauws EA, Huibregtse K, Obertop H, Gouma DJ. The effect of preoperative biliary drainage on postoperative complications after pancreaticoduodenectomy. J Am Coll Surg 2001;192:726–734.
18. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001;234:47–55.
19. Hodul P, Creech S, Pickleman J, Aranha GV. The effect of preoperative biliary stenting on postoperative complications after pancreaticoduodenectomy. Am J Surg 2003;186: 420–425.
20. Jagannath P, Dhir V, Shrikhande S, Shah RC, Mullerpatan P, Mohandas KM. Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. Br J Surg 2005;92:356–361.
21. Rao KJ, Varghese NM, Blake H, Theodossi A. Endoscopic biliary stenting in a district general hospital. Gut 1995;37: 279–283.
22. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT. Risk factors for complications after pancreatic head resection. Am J Surg 2004;187:201–208.
23. Page CP, Bohnen JMA, Fletcher JR, McManus AT, Solomkin JS, Wittmann DH. Antimicrobial prophylaxis for surgical wounds: Guidelines for Clinical Care. Arch Surg 1993;128:79–88.
24. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996;334: 1209–1215.
25. Greif R, Akça O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342:161–167.

Oncolytic Herpes Viral Therapy is Effective in the Treatment of Hepatocellular Carcinoma Cell Lines

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The rising incidence of hepatocellular carcinoma (HCC) in western countries, along with the poor prognosis offered by present-day treatment modalities, makes novel therapies for this disease necessary. Oncolytic herpes simplex viruses (HSV) are replication-competent viruses that are highly effective in the treatment of a wide variety of experimental models of human malignancies. This study seeks to investigate the effectiveness of oncolytic herpes viruses in the treatment of primary HCC cell lines. Sixteen commercially available human HCC cell lines were studied. G207 is an attenuated, replication-competent, oncolytic HSV engineered to selectively replicate within cancer cells. Cell lines were tested for viral sensitivity to G207 and their ability to support viral replication using standard cytotoxicity and viral replication assays. Eleven of 16 cell lines were moderately to highly sensitive to G207 viral oncolysis. HCC cell lines additionally demonstrated the ability to support viral replication in vitro with as high as 800-fold amplification of the administered viral dose observed. G207 is cytotoxic to, and efficiently replicates within, HCC cell lines in vitro. From these data, we suggest that oncolytic HSV therapy may have a role in the treatment of HCC, and in vivo studies are warranted. (J GASTROINTEST SURG 2006;10:532–542) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: G207, gene therapy, hepatocellular carcinoma, herpes simplex virus

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with a global annual incidence of nearly 1 million cases.[1–3] Although the incidence throughout Asia and Africa remains relatively stable, western countries are experiencing a rise in the incidence of this disease. The American Cancer Society surveillance data estimated 18,920 new cases in 2004, representing a significant rise from previous years.[4] It was also estimated that 14,270 deaths occurred as a result of the disease in 2004. Whereas surgical resection presently remains the only curative option for this disease, the majority of patients who undergo resection eventually succumb to the disease. It is clear that novel therapies are needed for the treatment of this aggressive cancer.

Oncolytic herpes simplex viruses (HSV) have recently been shown to be effective in the treatment of a wide variety of human malignancies in animal models including brain, colorectal, lung, gastric, prostate, breast, bladder, and head and neck cancers.[5-17] These attenuated, replication-competent viruses present an exciting new treatment modality in cancer therapy through their ability to selectively replicate within cancer cells while sparing normal cells.[10]

This study examines the effectiveness of oncolytic herpes viruses in the treatment of primary hepatocellular carcinoma cell lines in vitro. As such, it provides a framework for in vivo studies investigating the use of an oncolytic herpes virus in the treatment of primary hepatocellular carcinoma. In doing so, we have also established a comprehensive compilation characterizing all known human HCC cell lines.

MATERIAL AND METHODS

Cell Lines

All known commercially available human HCC cell lines were studied. Hep 3B2.1-7 (Hep3B, Hep 3B, Hep-3B, HB-8064), Hep G2 (HepG2, HB-8065), PLC/PRF/5 (PLC5, CRL-8024), and SK-HEP-1 (HTB-52) cell lines were obtained from the

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American Type Culture Collection (ATCC, Manassas, VA). They were grown in vitro in ATCC medium with phenol red control (Eagle's minimum essential medium with 2 mmol/L L-glutamine and Earle's BSS adjusted to contain 1.5 g/L sodium bicarbonate with 0.1 mmol/L nonessential amino acids, and 1.0 mmol/L sodium pyruvate, 100 U/ml penicillin, and 100 mg/ml streptomycin with 10% fetal calf serum [FCS, Atlanta Biologicals, Norcross, GA]). An additional 12 human HCC cell lines (SNU-182, SNU-354, SNU-368, SNU-387, SNU-398, SNU-423, SNU-449, SNU-475, SNU-739, SNU-761, SNU-878, and SNU-886) were obtained from the Korean Cell Line Bank (KCLB, Seoul, South Korea) and were grown in phenol red controlled RPMI 1640 with 20 mmol/L HEPES, 2.0 g/L sodium bicarbonate, 100 U/ml penicillin and 100mg/ml streptomycin, and 10% FCS. African green monkey kidney cells (Vero cells, ATCC) for viral plaque assays were grown in minimum essential medium containing 10% FCS, 100 U/ml penicillin, and 100mg/ml streptomycin. All cells were maintained in a 5% CO_2 humidified incubator at 37° C.

Virus

G207 is an attenuated, replication-competent, oncolytic herpes simplex virus type-1 (HSV-1) whose construction has been previously described in detail.[14,18] G207, a second-generation virus derived from R3616, a construct by Dr. Roizman (University of Chicago, IL), is attenuated by the deletion of a single copy of the diploid ICP6 gene and deletion of both copies of the $\gamma_1$34.5 neurovirulence gene.[14,18–20] The virus also contains an insertion of the *Escherichia coli* β-galactosidase (lacZ) gene into the U_L39 gene that serves as a marker of an infection.[14,18] Disruption of the U_L39 gene eliminates ribonucleotide reductase activity and increases specificity of the virus for proliferating cells such as tumor cells.[18,21–23] G207 was measured by standard plaque assay as previously described.[14,17,18]

Cytotoxicity Assay

All HCC cell lines were plated at a density of 1×10^4 cells per well in 12-well flat-bottom plates (Costar, Corning Inc., Corning, NY) in 1 ml of media. After incubation for 6 hours, G207 (diluted in 50 μl phosphate buffered saline [PBS]) was added to each well at a multiplicity of infection (MOI, the ratio of viral plaque forming units [pfu] per tumor cell) of three dilutions ranging from 0.01 to 3.0. On days 1, 3, 5, 7, and 9 after infection, supernatant samples were collected and frozen, and wells were washed with PBS. Cells were then lysed with Triton-X (Dow, Midland, MI) (1.35%) to release intracellular lactate dehydrogenase (LDH). LDH was quantified using a Cytotox 96 nonradioactive cytotoxicity assay (Promega, Madison, WI), which is a colorimetric analysis measuring the conversion of a tetrazolium salt into a red formazan product in the presence of LDH.[24–26] The amount of color formed is directly proportional to the number of lysed cells. Absorbance was measured at 450 nm using a microplate spectrophotometer (EL312e, Bio-Tek Instruments, Winooski, VT). Results are expressed as the surviving fraction of cells as determined by the measured absorbance of each sample relative to control, untreated, cell lysates. All samples were analyzed in triplicate, and each experiment was repeated in triplicate to ensure reproducibility.

Viral Replication Assay

Supernatant samples were collected and frozen from all wells of the cytotoxicity (MOI 0.01, 0.1, and 1.0) experiments (days 1–8) after infection with G207. Vero cells were grown to confluence on 6-well flat-bottom plates (Costar, Corning, Inc.). Supernatant samples were thawed, and serial 10-fold dilutions of the samples were incubated on Vero cells for 4 hours. Wells were then gently washed with media and covered with 1% agarose with media. After 48 hours of incubation, 2 ml of neutral red solution was added, and after an additional 24 hours of incubation, viral plaques were counted. All samples were analyzed in triplicate.

Tumorigenic Assay

Six-week old athymic nude mice (National Cancer Institute, Bethesda, MD) were used to assess tumorigenicity of all HCC cell lines. All animal procedures were performed with the approval of the Memorial Sloan-Kettering Institutional Animal Care and Use Committee. Animals were anesthetized with inhalational isoflurane for all experimental procedures. Flank tumors were established by injection of 1×10^7 tumor cells in 50 μl of PBS into the subcutaneous flanks of athymic nude mice. Tumor development and growth was assessed by measuring tumor dimensions 3 times a week. Animals were weighed and monitored closely for signs of distress, including poor grooming, cachexia, respiratory distress, cutaneous ulcerations, or tumor progression. Animals without any evidence of tumor progression or toxicity were monitored for up to 3 months.

Table 1. General characteristics of HCC cell line **(27-41)**

Cell bank					
		Cell shape in culture	HBV gene integration	Biosafety level	
Generic name	Origin	Growth morphology	HBx DNA detect	Tumorigenicity	Cellular products and protein expression
ATCC					
Hep 3B	Human, HCC, black male	Polygonal, epithelial Monolayer, adherent	Yes Yes	II Yes	HBsAg, HBx protein, alpha-FP, albumin, alpha-2 macroglobulin, alpha-1 antitrypsin, transferrin, haptoglobulin, alpha-1 antichymotrypsin, celuloplasmin, plasminogen, C3, C4, C3 activator, fibrinogen, alpha-1 acid glycoprotein, alpha-2 HS glycoprotein, beta lipoprotein, retinol binding protein, Gc globulin
Hep G2	Human, HCC, white male	Polygonal-round, epithelial Multilayer hump, adherent	No No	I No	Alpha-FP, albumin, alpha-2 macroglobulin, alpha-1 antitrypsin, transferrin, alpha-1 antichymotrypsin, haptoglobulin, celuloplasmin, plasminogen, C4, C3 activator, fibrinogen, alpha-1 acid glycoprotein, alpha-2 HS glycoprotein, beta lipoprotein, retinol binding protein, IGF-II, 3-hydroxy-3methylglutary1 CoA reductase, hepatic triglyceride lipase
SK-Hep-1	Human, HCC, white male	Spindle-round, epithelial	No	I	Alpha-1 antitrypsin, IGF-binding protein 3
		Monolayer, adherent	No	Yes	
PLC/PRF/5	Human, HCC, black male	Polygonal Monolayer, adherent	Yes No	II Yes	HBsAg, alpha-FP
KCLB					
SNU-182	Human, HCC, Asian male	Polygonal Monolayer, adherent	Yes Yes	II Yes	HBsAg
SNU-354	Human, HCC, Asian male	Polygonal Monolayer, adherent	Yes Yes	II No	HBsAg, HBx protein, MDR1 gene, albumin
SNU-368	Human, HCC, Asian male	Polygonal Monolayer, adherent	Yes Yes	II Yes	HBsAg, HBx protein, MDR1 gene,transferrin, IGF-II
SNU-387	Human, HCC, Asian female	Polygonal-spindle Monolayer, adherent	Yes Yes	II Yes	HBsAg
SNU-398	Human, HCC, Asian male	Round-spindle Monolayer, adherent, floating	Yes Yes	II Yes	HBsAg

(*continued*)

Table 1. (*continued*)

Cell bank		Cell shape in culture	HBV gene integration	Biosafety level	
Generic name	Origin	Growth morphology	HBx DNA detect	Tumorigenicity	Cellular products and protein expression
SNU-423	Human, HCC, Asian male	Polygonal-spindle Monolayer, adherent	Yes No	II Yes	HBsAg
SNU-449	Human, HCC, Asian male	Polygonal Monolayer, adherent	Yes Yes	II Yes	HBsAg
SNU-475	Human, HCC, Asian male	Polygonal-round Monolayer, adherent	Yes Yes	II No	HBsAg
SNU-739	Human, HCC, Asian male	Spindle Monolayer, adherent	Yes Yes	II No	HBsAg, HBcAg, HBx protein
SNU-761	Human, HCC, Asian male	Polygonal Monolayer, adherent	Yes Yes	II No	HBsAg, HBcAg, HBx protein, albumin
SNU-878	Human, HCC, Asian female	Polygonal Monolayer, adherent	Yes Yes	II Yes	HBsAg, HBcAg, HBx protein, albumin, transferrin
SNU-886	Human, HCC, Asian male	Polygonal-spindle Monolayer, adherent	Yes Yes	II Yes	HBsAg, HBcAg, HBx protein, albumin, transferrin

HBV = hepatitis B virus; HBx = the X gene product of the human hepatitis B virus; HCC = hepatocellular carcinoma.

RESULTS

Cell Lines

The hepatocellular carcinoma cell lines Hep3B, HepG2, PLC5, and SK-HEP-1 (ATCC) and SNU-182, SNU-354, SNU-368, SNU-387, SNU-398, SNU-423, SNU-449, SNU-475, SNU-739, SNU-761, SNU-878, and SNU-886 (KCLB) grew readily in culture. Previously determined characteristics of these cell lines, including origin, morphology, hepatitis B virus (HBV) gene integration, the X gene product of the human hepatitis B virus (HBx) DNA status, cellular products, and protein expression, are listed in the Table 1.[27–41]

Viral Cytotoxicity

The ability of G207 to kill HCC cell lines was assessed. Three of the four cell lines obtained from the ATCC were sensitive to G207 cytotoxicity. HepG2 and PLC5 demonstrated nearly 100% cell kill by day 7 after infection at an MOI of 1.0 (Fig. 1, *A*, *B*). At an MOI of 0.5, Hep3B similarly showed near-complete cell kill (Fig. 1, *C*). Even at an MOI of 0.1, these three cell lines demonstrated 93.0%, 83.7%, and 83.8% cytotoxicity by day 7, respectively (HepG2, PLC5, Hep3B). In contrast, only SK-HEP-1 was resistant to viral infection with no significant cytotoxicity demonstrated at an MOI as high as 3.0 (Fig. 1, *D*).

Four of the 12 HCC cell lines obtained from the KCLB were highly sensitive to G207 cytotoxicity. SNU-182, SNU-387, SNU-886, and SNU-878 demonstrated 71.5%, 59.8%, 65.5%, and 70.4% cell kill, respectively, by day 9 after infection at an MOI of 1.0 (Fig. 2, *A–D*). Even at an MOI of 0.01, only 60.6%, 53.4%, 50.4%, and 50.6% of cells, respectively, remained viable by day 9 after infection. Four cell lines demonstrated moderate sensitivity to viral infection. At an MOI of 1.0, SNU-368, SNU-449, SNU-739, and SNU-761 showed 22.4%, 22.4%, 43.2%, and 29.9% cell kill, respectively (Fig. 2, *E–H*). In contrast, the remaining four cell lines of KCLB origin (SNU-398, SNU-475, SNU-354, and SNU-423) were resistant to viral infection with no significant cytotoxicity demonstrated 9 days after infection (Fig. 2, *I–L*).

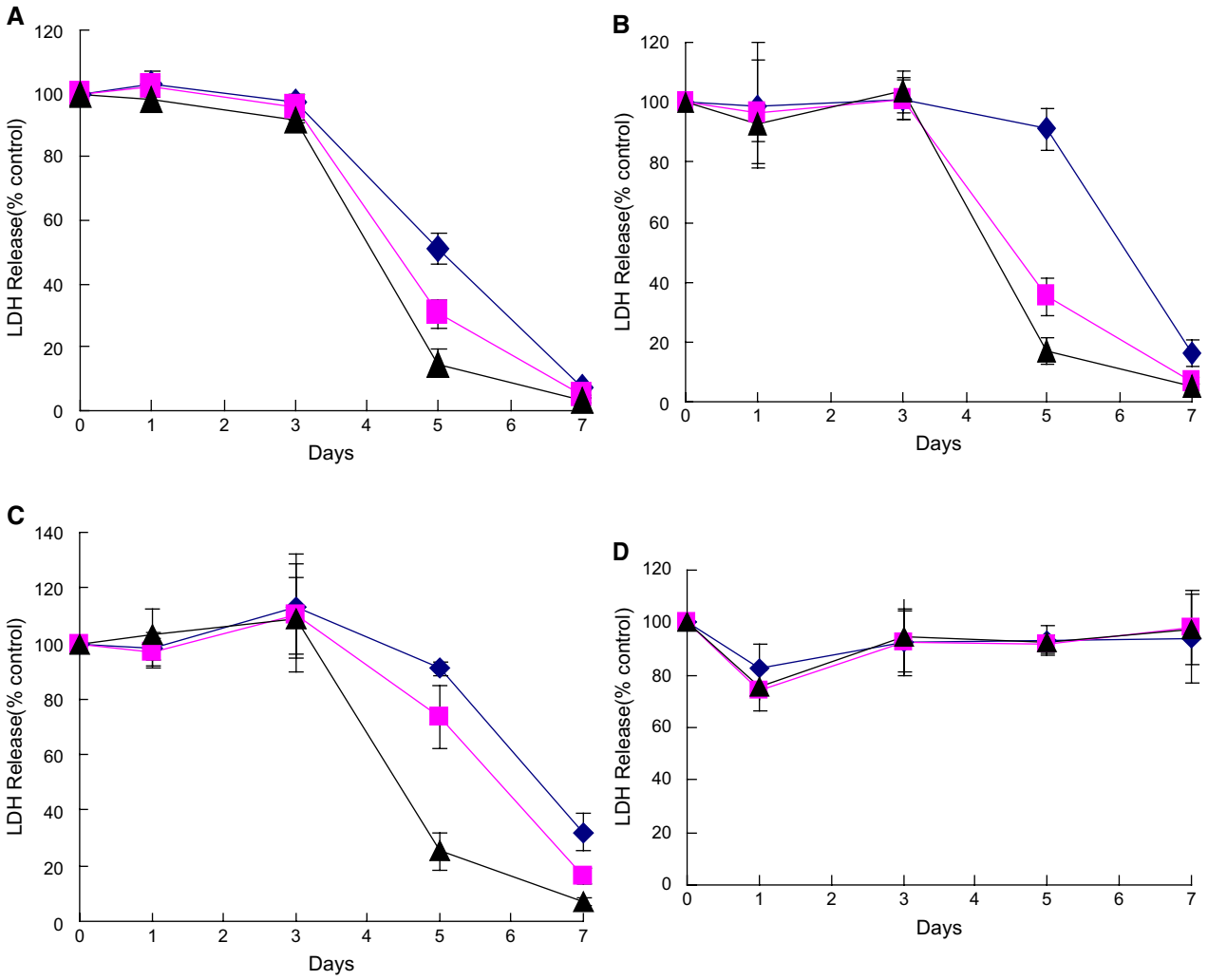

Fig. 1. Cytotoxicity of G207 against hepatocellular carcinoma (HCC) cell lines of ATCC origin in vitro. HCC cell lines HepG2 (**A**), PLC/PRF/5 (**B**), and Hep3B (**C**) were sensitive to G207 viral oncolysis, whereas SK-HEP-1 (**D**) was not sensitive. Doses of virus used were MOI = 0.1 (diamond), MOI = 0.5 (square), and MOI = 1 (triangle). MOI represents the ratio of the number of viral particles to the number of tumor cells.

Viral Replication

The ability of G207 to replicate in human HCC cell lines was also demonstrated. Representative data are shown in Fig. 2. Hep3B strongly supported logarithmic viral proliferation with peak viral titers measuring 2.5×10^5 pfu 5 days after infection, with G207 at an MOI of 0.01 (3×10^2 pfu; Fig. 3, *A*). This represents a greater than 800-fold amplification of the initial viral dose after 5 days. HepG2 and PLC5 also supported G207 viral replication 7 days after infection at an MOI of 0.1 (3×10^3 pfu), demonstrating peak infectious virion recovery of 5×10^4 pfu and 2.5×10^4 pfu, respectively (Fig. 3, *B–C*).

Tumorigenicity

Tumorigenicity of all 16 HCC cell lines was examined and is listed in the Table 1.[27–41] The ability of Hep3B, PLC5, and SK-Hep1 to form tumors in nude athymic mice was already known from previous reports.[27–41] Of the ATCC-obtained cell lines, only HepG2 does not form tumors in nude mice. Eight of 12 cell lines of KCLB origin (SNU-182, SNU-368, SNU-387, SNU-398, SNU-423, SNU-449, SNU-878, and SNU-886) produced flank tumors within two weeks of tumor cell implantation into nude mice, with tumor diameters ranging from 3 mm to 18 mm. The remaining four cell lines (SNU-354, SNU-475 SNU-739, and SNU-761)

failed to develop tumors as long as three months after implantation.

DISCUSSION

Primary HCC is one of the most common malignancies worldwide.[1–3] There are clear geographic epidemiologic differences, with the highest incidences seen in Asia and Africa.[3,42,43] Western countries, however, are experiencing a surge in the incidence of this disease. In the United States, the incidence of HCC increased from 1.4 per 100,000 population in 1980 to 2.4 per 100,000 population in 1995. It further increased to 6.7 per 100,000 population for men and 3.1 for women in the year 2000.[44,45] In 2004, American Cancer Society surveillance data estimated 18,920 new cases and 14,270 deaths due to HCC.[4] Major risk factors for the development of HCC include chronic hepatitis B and C infection and alcohol consumption, and it is an increase in incidence of these factors that are thought to be responsible for this rise.

In a recent review, median survival of patients who underwent curative resection for HCC was only 39 months, with 1- and 3-year survival rates of 81% and 54%, respectively.[46] In this series, patients who underwent tumor ablation demonstrated a median survival of 15 months with 1- and 3-year survival rates of 56% and 21%, respectively.[46] Patients treated with systemic chemotherapy or supportive care demonstrated a median survival of only 9 months, with a 44% 1-year survival rate and no 3-year survivors.[46]

Although hepatic resection remains the best curative option, there are many instances where curative resection cannot be performed, including advanced patient age, underlying severe comorbidities or poor liver function, and locally advanced disease. Whereas numerous alternative treatment modalities have been employed in this setting, including percutaneous microwave coagulation

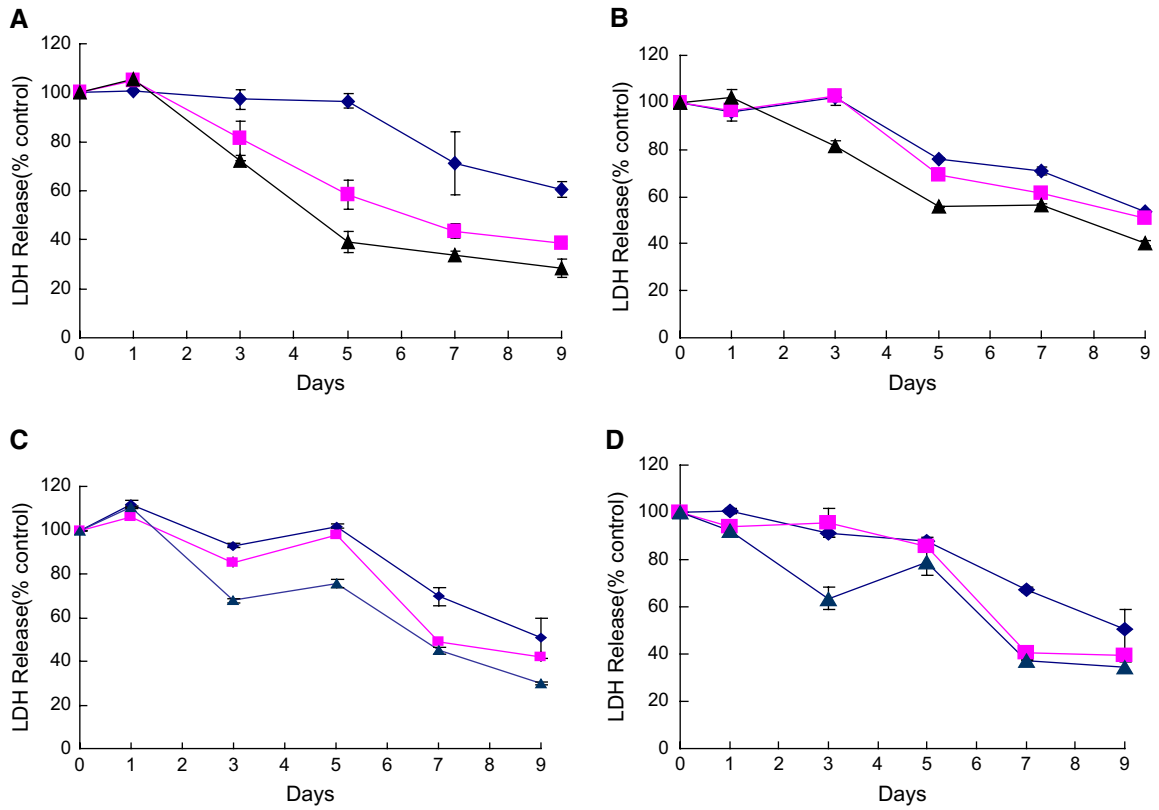

Fig. 2. Cytotoxicity of G207 against hepatocellular carcinoma cell lines of KCLB origin in vitro. Four cell lines, SNU-182 (**A**), SNU-387 (**B**), SNU-878 (**C**), and SNU-886 (**D**) were highly sensitive to viral oncolysis, and four cell lines, SNU-368 (**E**), SNU-449 (**F**), SNU-739 (**G**), and SNU-761 (**H**), demonstrated moderate sensitivity. SNU-354 (**I**), SNU-398 (**J**), SNU-423 (**K**), and SNU-475 (**L**) showed minimal sensitivity to on the viral oncolysis. Doses of virus used were MOI = 0.01 (diamond), MOI = 0.1 (square), and MOI = 1 (triangle). MOI represents the ratio of the number of viral particles to the number of tumor cells.

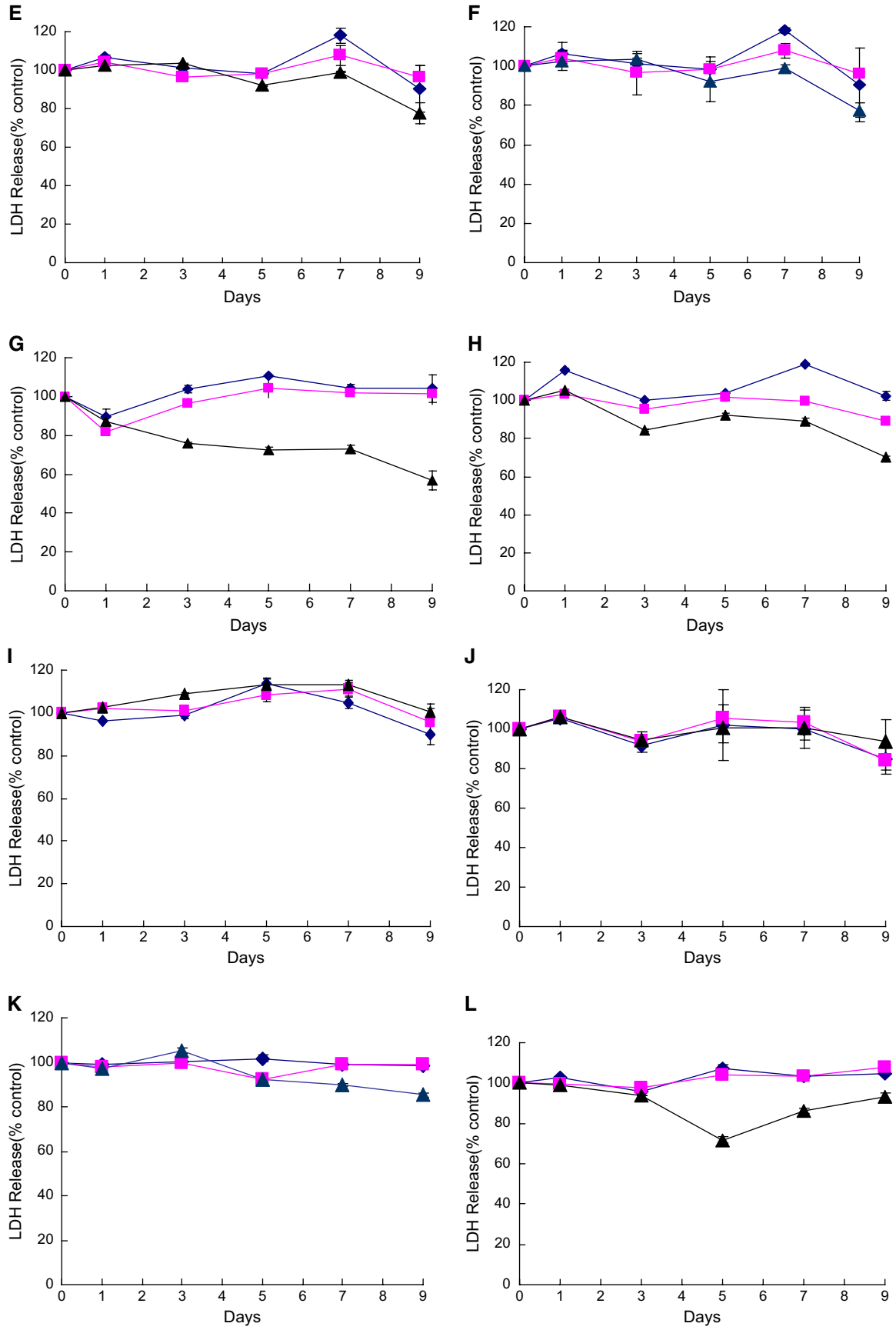

Fig. 2. (*Continued*)

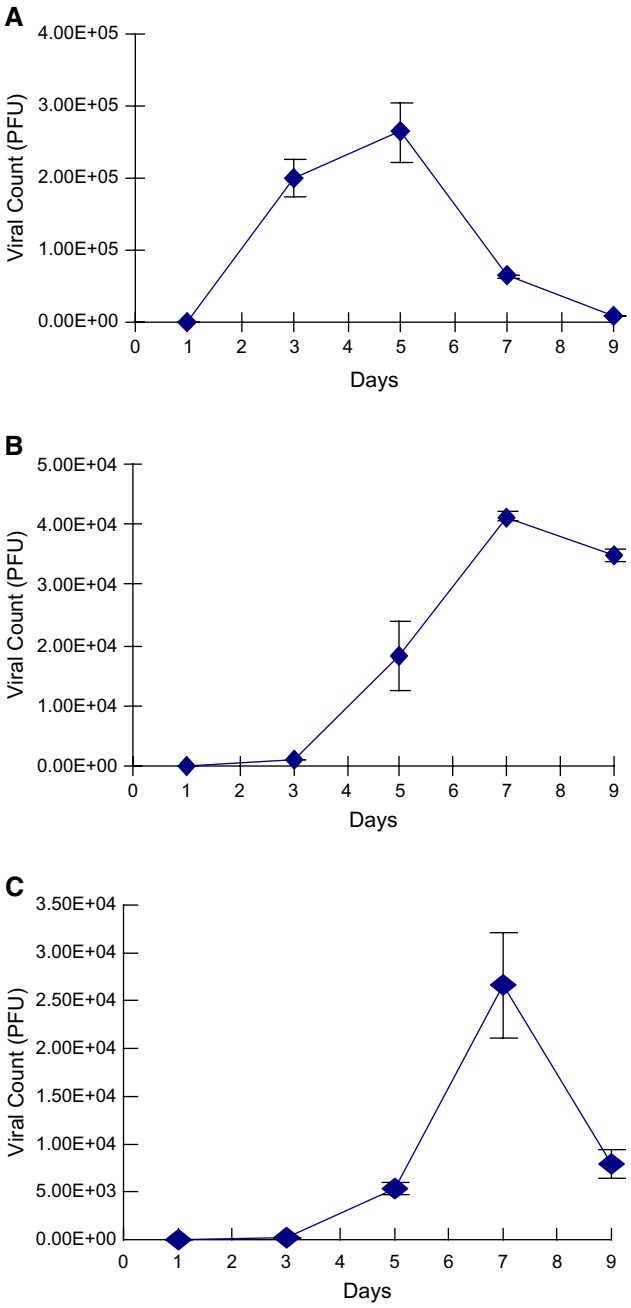

Fig. 3. Viral replication is supported by hepatocellular carcinoma (HCC) cell lines. Viral plaque assay demonstrates high viral yield in Hep3B (**A**), HepG2 (**B**), and PLC/PRF/5 (**C**) after infection with G207. Hep3B most strongly supported viral proliferation with peak viral titers measuring 2.5×10^5 pfu 5 days after infection with G207 (3×10^2 pfu), representing a greater than 800-fold amplification of the initial viral dose. Doses of virus used were MOI = 0.01 for Hep3B, MOI = 0.1 for HepG2 and PLC5. MOI represents the ratio of the number of viral particles to the number of tumor cells.

therapy, percutaneous ethanol infusion, regional hyperthermia therapy, and interstitial radiotherapy and radiofrequency interstitial tissue ablation, none have yet been demonstrated to improve patient survival.[47–53] It is clear that novel therapies are needed.

Attenuated, replication-competent oncolytic HSV offer an exciting new modality in the armamentarium of anticancer agents. A wealth of recent experiments has demonstrated the effectiveness of these oncolytic herpes viruses in the treatment of a wide variety of human cancer cell lines. We now show that the majority of all known human HCC cell lines are also sensitive to treatment with an oncolytic herpes virus, G207. Eleven of 16 cell lines tested were moderately to highly sensitive to viral infection. In addition, these cell lines also demonstrated the ability to support viral replication, resulting in the exponential amplification of infectious virions. Conversely, five cell lines were resistant to viral infection. Although the mechanism of resistance of cancer cells to viral infection remains largely unknown, our laboratory is actively exploring the genetic and molecular biologic factors thought to be involved.

These viruses have the potential to infect and selectively replicate within cancer cells—sparing normal cells.[11] The specificity of oncolytic viruses in cancer therapy depends upon an interplay of the intrinsic properties of these viruses and cellular alterations of transformed cells. For example, the second-generation HSV mutant G207, containing mutations in genes required for viral replication including ribonucleotide reductase, is dependent on a high level of homologous host-cell enzymes—characteristic of cancer cells—to complete its lifecycle.[17,54] The specificity of oncolytic HSV for malignant cells—sparing normal hepatocytes—in the context of HCC and hepatic metastases has already been explored by our laboratory using an in vivo model of liver regeneration. Delman et al.[55] investigated the ability of normal murine hepatocytes to permit viral replication of G207 after portal administration. Using histochemical staining for the viral marker gene lacZ and immunohistochemical and quantitative polymerase chain reaction-based detection of viral particles, the authors demonstrated no measurable viral presence or replication in normal, resting murine hepatocytes. Interestingly, this work did show that regenerating hepatocytes were capable of supporting viral replication during peak hepatocyte DNA synthesis after partial hepatectomy. The authors further demonstrated that this period of permissive viral replication correlated with up-regulated hepatocyte ribonucleotide reductase activity—the viral homologue of which is deleted from G207 for attenuation. Viral administration immediately after resolution of liver regeneration, as early as 7 days after hepatectomy, resulted in no measurable viral replication in the liver or any other organ.

Although the maximum clinically achievable MOI in humans is not well-defined, it is generally thought that it approaches 1.0. More important, however, is the potential for in vivo amplification of the administered dose of this novel form of therapy—unlike all other standard therapies. As such, delivery of large initial doses is not necessary. Successful completion of the viral life cycle within cancer cells, in addition to causing cell death via lysis or apoptosis, results in the extracellular release of infectious viral progeny, and hence, an exponential amplification of the effective dose. Viral amplification is limited only to the extent that there are viable cancer cells present to support viral replication. Several human clinical trials investigating the use of oncolytic herpes viruses as anticancer agents have begun to answer this question. A phase I trial from our institution was the first to demonstrate that oncolytic herpes viruses can be safely injected into the bloodstream of patients with colorectal hepatic metastases.[56] The maximum therapeutic dose was not reached but was determined to be greater than 1.3×10^7 pfu.[56] In a phase I trial investigating the effectiveness of G207 in the treatment of recurrent gliomas, investigators delivered a maximum dose of 3×10^9 pfu directly into tumors.[57,58]

Current management of HCC is inadequate, and alternative treatment options are needed. Oncolytic herpes viruses have already been demonstrated to be effective in the treatment of colorectal liver metastases via portal and hepatic arterial delivery in animal models, and human clinical trials are presently ongoing. This work provides a framework for future studies exploring the in vivo effectiveness of oncolytic HSV as potential therapy for patients with HCC.

CONCLUSIONS

This study demonstrates that an oncolytic herpes virus effectively infects, replicates within, and lyses the majority of all known HCC cell lines. We suggest from this data that oncolytic HSV therapy may have a role in the treatment of HCC in the future. Additionally, this compilation of all commercially available HCC cell lines can be used to guide further in vitro and in vivo experiments for the treatment of HCC by using oncolytic herpes viruses and other experimental treatment modalities.

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REFERENCES

1. Staib F, Hussain SP, Hofseth LJ, Wang XW, Harris CC. Tp53 and liver carcinogenesis. Hum Mutat 2003;21:201–216.
2. Wang XW, Hussain SP, Huo TI, et al. Molecular pathogenesis of human hepatocellular carcinoma. Toxicology 2002; 181–182:43–47.
3. Okuda K. Hepatocellular carcinoma. J Hepatol 2000;32: 225–237.
4. American Cancer Society. Cancer Statistics Presentation 2004. American Cancer Society, 2004. Website http://www.cancer.org/docroot/pro/content/pro_1_1_cancer_statistics_2004_presentation.asp. Last accessed 14 Feb 2006.
5. Toda M, Rabkin SD, Martuza RL. Treatment of human breast cancer in a brain metastatic model by G207, a replication-competent multimutated herpes simplex virus 1. Hum Gene Ther 1998;9:2177–2185.
6. Todo T, Rabkin SD, Chahlavi A, Martuza RL. Corticosteroid administration does not affect viral oncolytic activity, but inhibits antitumor immunity in replication-competent herpes simplex virus tumor therapy. Hum Gene Ther 1999; 10:2869–2878.
7. Chahlavi A, Todo T, Martuza RL, Rabkin SD. Replication-competent herpes simplex virus vector G207 and cisplatin combination therapy for head and neck squamous cell carcinoma. Neoplasia 1999;1:162–169.
8. Coukos G, Makrigiannakis A, Montas S, et al. Multi-attenuated herpes simplex virus-1 mutant G207 exerts cytotoxicity against epithelial ovarian cancer but not normal mesothelium and is suitable for intraperitoneal oncolytic therapy. Cancer Gene Ther 2000;7:275–283.
9. Oyama M, Ohigashi T, Hoshi M, et al. Intravesical and intravenous therapy of human bladder cancer by the herpes vector G207. Hum Gene Ther 2000;11:1683–1693.
10. Cozzi P, Burke PB, Bhargava A, et al. Oncolytic viral gene therapy for prostate cancer using two attenuated, replication competent, genetically-engineered herpes simplex viruses. Prostate 2002;53:95–100.
11. Stanziale SF, Fong Y. Novel approaches to cancer therapy using oncolytic viruses. Curr Mol Med 2003;3:61–71.
12. Ebright MI, Zager JS, Malhotra S, et al. Replication-competent herpes virus NV1020 as direct treatment of pleural cancer in a rat model. J Thorac Cardiovasc Surg 2002;124:123–129.
13. Bennett JJ, Malhotra S, Wong RJ, et al. Interleukin 12 secretion enhances antitumor efficacy of oncolytic herpes simplex viral therapy for colorectal cancer. Ann Surgery 2001;233: 819–826.
14. Bennett JJ, Kooby DA, Delman K, et al. Antitumor efficacy of regional oncolytic viral therapy for peritoneally disseminated cancer. J Mol Med 2000;78:166–174.
15. Carew JF, Kooby DA, Halterman MW, Federoff HJ, Fong Y. Selective infection and cytolysis of human head and neck squamous cell carcinoma with sparing of normal mucosa by a cytotoxic herpes simplex virus type 1 (G207). Hum Gene Ther 1999;10:1599–1606.
16. Cozzi PJ, Malhotra S, McAuliffe P, et al. Intravesical oncolytic viral therapy using attenuated, replication-competent herpes simplex viruses G207 and NV1020 is effective in the treatment of bladder cancer in an orthotopic syngeneic model. FASEB J 2001;15:1306–1308.
17. Yazaki T, Manz HJ, Rabkin SD, Martuza RL. Treatment of human malignant meningiomas by G207, a replication-

competent multimutated herpes simplex virus 1. Cancer Res 1995;55:4752–4756.
18. Mineta T, Rabkin SD, Yazaki T, Hunter WD, Martuza RL. Attenuated multi-mutated herpes simplex virus-1 for the treatment of malignant gliomas. Nat Med 1995;1:938–943.
19. Chou J, Kern ER, Whitley RJ, Roizman B. Mapping of herpes simplex virus-1 neurovirulence to gamma 134.5, a gene nonessential for growth in culture. Science 1990;250: 1262–1266.
20. Whitley RJ, Kern ER, Chatterjee S, Chou J, Roizman B. Replication, establishment of latency, and induced reactivation of herpes simplex virus gamma 1 34.5 deletion mutants in rodent models. J Clin Invest 1993;91:2837–2843.
21. Carroll NM, Chiocca EA, Takahashi K, Tanabe KK. Enhancement of gene therapy specificity for diffuse colon carcinoma liver metastases with recombinant herpes simplex virus. Ann Surg 1996;224:323–329.
22. Goldstein DJ, Weller SK. Factor(s) present in herpes simplex virus type 1-infected cells can compensate for the loss of the large subunit of the viral ribonucleotide reductase: Characterization of an ICP6 deletion mutant. Virology 1988;166:41–51.
23. Goldstein DJ, Weller SK. Herpes simplex virus type 1-induced ribonucleotide reductase activity is dispensable for virus growth and DNA synthesis: Isolation and characterization of an ICP6 lacZ insertion mutant. J Virol 1988;62:196–205.
24. Decker T, Lohmann-Matthes ML. A quick and simple method for the quantitation of lactate dehydrogenase release in measurements of cellular cytotoxicity and tumor necrosis factor (TNF) activity. J Immunol Methods 1988; 115:61–69.
25. Korzeniewski C, Callewaert DM. An enzyme-release assay for natural cytotoxicity. J Immunol Methods 1983;64:313–320.
26. Weidmann E, Brieger J, Jahn B, Hoelzer D, Bergmann L, Mitrou PS. Lactate dehydrogenase-release assay: A reliable, nonradioactive technique for analysis of cytotoxic lymphocyte-mediated lytic activity against blasts from acute myelocytic leukemia. Ann Hematol 1995;70:153–158.
27. Park JG, Lee SK, Hong IG, et al. MDR1 gene expression: Its effect on drug resistance to doxorubicin in human hepatocellular carcinoma cell lines. J Natl Cancer Inst 1994;86:700–705.
28. Fogh J, Fogh JM, Orfeo T. One hundred and twenty-seven cultured human tumor cell lines producing tumors in nude mice. J Natl Cancer Inst 1977;59:221–226.
29. Kang MS, Lee HJ, Lee JH, et al. Mutation of p53 gene in hepatocellular carcinoma cell lines with HBX DNA. Int J Cancer 1996;67:898–902.
30. Kim SO, Park JG, Lee YI. Increased expression of the insulin-like growth factor I (IGF-I) receptor gene in hepatocellular carcinoma cell lines: Implications of IGF-I receptor gene activation by hepatitis B virus × gene product. Cancer Res 1996;56:3831–3836.
31. Park JG, Lee JH, Kang MS, et al. Characterization of cell lines established from human hepatocellular carcinoma. Int J Cancer 1995;62:276–282.
32. Alexander JJ, Bey EM, Geddes EW, Lecatsas G. Establishment of a continuously growing cell line from primary carcinoma of the liver. S Afr Med J 1976;50:2124–2228.
33. Gilligan A, Bushmeyer S, Knowles BB. Variation in EGF-induced EGF receptor downregulation in human hepatoma-derived cell lines expressing different amounts of EGF receptor. Exp Cell Res 1992;200:235–241.
34. Macnab GM, Urbanowicz JM, Geddes EW, Kew MC. Hepatitis-B surface antigen and antibody in Bantu patients with primary hepatocellular cancer. Br J Cancer 1976;33: 544–548.
35. Kawai HF, Kaneko S, Honda M, Shirota Y, Kobayashi K. Alpha-fetoprotein-producing hepatoma cell lines share common expression profiles of genes in various categories demonstrated by cDNA microarray analysis. Hepatology 2001; 33:676–691.
36. Heffelfinger SC, Hawkins HH, Barrish J, Taylor L, Darlington GJ. SK HEP-1: A human cell line of endothelial origin. In Vitro Cell Dev Biol 1992;28A:136–142.
37. Gucev ZS, Oh Y, Kelley KM, Labarta JI, Vorwerk P, Rosenfeld RG. Evidence for insulin-like growth factor (IGF)-independent transcriptional regulation of IGF binding protein-3 by growth hormone in SKHEP-1 human hepatocarcinoma cells. Endocrinology 1997;138:1464–1470.
38. Turner BM, Turner VS. Secretion of alpha 1-antitrypsin by an established human hepatoma cell line and by human/mouse hybrids. Somatic Cell Genet 1980;6:1–14.
39. ATCC. American Type Culture Collection. ATCC. 2004. 2004. Website www.atcc.org. Last accessed 14 Feb 2006.
40. Sharkey FE, Fogh J. Metastasis of human tumors in athymic nude mice. Int J Cancer 1979;24:733–738.
41. KCLB. Korean Cell Line Bank. KCLB. 2005. 2004. Website http://cellbank.snu.ac.kr/ENG/default.htm. Last accessed 14 Feb 2006.
42. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer 2002;97:72–81.
43. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37(Suppl 8): S4–S66.
44. El Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340: 745–750.
45. Department of Health and Human Services, Centers for Disease Control and Prevention, National Cancer Institutes. US Cancer Statistics Working Group. United States Cancer Statistics: 2000 Incidence. pp 50–77. 2003. Atlanta, GA.
46. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg 1999;229:790–799.
47. Hamazoe R, Hirooka Y, Ohtani S, Katoh T, Kaibara N. Intraoperative microwave tissue coagulation as treatment for patients with nonresectable hepatocellular carcinoma. Cancer 1995;75:794–800.
48. Fong Y. A promising technique for liver cancer? Cancer J Sci Am 1999;5:339–340.
49. Giorgio A, Ferraioli G. Radiofrequency thermal ablation versus percutaneous ethanol injection for small hepatocellular carcinoma. Radiology 2004;230:886–887.
50. Zuber-Jerger I, Geissler M, Spangenberg HC, Mohr L, Weizsacker F, Blum HE. Local ablation of malignant lesions of the liver - potential applications and limitations of the different methods. Z Gastroenterol 2004;42:31–38.
51. Segawa T, Tsuchiya R, Furui J, Izawa K, Tsunoda T, Kanematsu T. Operative results in 143 patients with hepatocellular carcinoma. World J Surg 1993;17:663–667.
52. Lau WY, Arnold M, Guo SK, Li AK. Microwave tissue coagulator in liver resection for cirrhotic patients. Aust N Z J Surg 1992;62:576–581.
53. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228:235–240.

54. Kramm CM, Chase M, Herrlinger U, et al. Therapeutic efficiency and safety of a second-generation replication-conditional HSV1 vector for brain tumor gene therapy. Hum Gene Ther 1997;8:2057–2068.
55. Delman KA, Zager JS, Bhargava A, et al. Effect of murine liver cell proliferation on herpes viral behavior: Implications for oncolytic viral therapy. Hepatology 2004;39:1525–1532.
56. Fong Y, Kemeny N, Jarnagin W, et al. Phase 1 study of a replication-competent herpes simplex oncolytic virus for treatment of hepatic colorectal metastases. Proc Am Soc Clin Oncol 2002;21:8a.
57. Lin E, Nemunaitis J. Oncolytic viral therapies. Cancer Gene Ther 2004;11:643–664.
58. Markert JM, Medlock MD, Rabkin SD, et al. Conditionally replicating herpes simplex virus mutant, G207 for the treatment of malignant glioma: Results of a phase I trial. Gene Ther 2000;7:867–874.

Arterioportal Fistulas: Introduction of a Novel Classification With Therapeutic Implications

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Arterioportal fistulas (APFs) are arteriovenous communications between the splanchnic arteries and the portal vein that represent an infrequent cause of presinusoidal portal hypertension. They can be acquired or congenital. Penetrating hepatic trauma, including liver biopsies, represent the most common etiology. They can be asymptomatic or manifest with portal hypertension. An abdominal bruit is a valuable physical finding. Persistence of an APF can cause hepatoportal sclerosis and possibly portal fibrosis. A detailed radiologic evaluation is mandatory. One must differentiate between small peripheral intrahepatic APFs (type 1) and large central APFs (type 2). The former usually resolve spontaneously, whereas the latter can cause portal hypertension and hepatic parenchymal changes. Type 1 APFs caused by needle injury can be followed by Doppler ultrasound. All other fistulas need treatment. Arterioportal fistulas are first treated by transcatheter embolization. Surgical approaches are reserved for complex cases. Congenital APFs (type 3) are diffuse and intrahepatic and can be difficult to manage. Overall, the prognosis is good. Herein, we propose a novel classification for arterioportal fistulas with therapeutic implications. (J GASTROINTEST SURG 2006;10:543–550) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Arterioportal fistula, hepatoportal fistula, arteriovenous fistula, portal hypertension, embolization

Arterioportal fistulas (APFs) are a complex group of arteriovenous fistulas that have intrigued surgeons for over a century. The term encompasses all fistulas between any of the splanchnic arteries and the portal veins. They can either be acquired or congenital and can present with a myriad of clinical manifestations owing to their specific physical characteristics and flow pressure parameters. Although rare, the incidence of APF is rising secondary to increased interventional procedures to the liver[1–3] and the improved survival of patients with hepatic trauma.[4] The purpose of this report is to provide a comprehensive review of the literature and to introduce a new classification, with emphasis on therapeutic implications.

HISTORY

The first description of APF in the literature was by Weigert in 1886. In 1892, Sachs reported on a patient who died of bleeding esophageal varices and who was found to have a ruptured hepatic artery aneurysm on postmortem examination.[5–7] APF as a complication of liver biopsy was first described by Preger in 1967.[8] In 1971, Van Way et al.[6] comprehensively reviewed the clinical characteristics of these interesting arteriovenous fistulas. In 1997, Vauthey provided a contemporary analysis of the APF syndrome and made important therapeutic recommendations.[9]

CLASSIFICATION

APFs are classified by their etiology, size, involved vessels, and location. They can either be congenital or acquired, large or small, intrahepatic or extrahepatic, central or peripheral, traumatic or spontaneous. Their inflow can be from any of the splanchnic arteries, most commonly, the hepatic artery (hepatoportal fistula) (65%), followed in incidence by the splenic artery (splenoportal fistula) (11%) and the superior mesenteric artery (10%).[9] It is critical to classify the APF properly in order to select appropriate therapy. In this article we

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propose a new classification of APFs into types 1, 2, and 3 (Table 1).

Type 1

These are small, peripheral, intrahepatic fistulas with minimal physiologic consequences. The most common etiology is percutaneous liver biopsies. Patients are usually asymptomatic and their APF generally thromboses within 1 month. The suggested treatment is close follow-up with Doppler ultrasound. If the fistula persists for longer than 1 month or if the patient becomes symptomatic, transcatheter embolization is recommended.

Type 2

Larger, more central fistulas with enough flow to cause elevated portal pressures are type 2. They can be either intrahepatic or extrahepatic. Examples are those caused after penetrating abdominal trauma or by erosion of a splenic artery aneurysm into the portal system. They cause portal hypertension and hepatoportal sclerosis and can progress to portal fibrosis. These fistulas should be treated to avoid the complications of portal hypertension and prevent irreversible hepatic parenchymal changes. The suggested treatment is embolization if technically possible. If this is unfeasible or unsuccessful, then surgical approaches are warranted.

Type 3

These are congenital APFs. These rare fistulas are usually intrahepatic and diffuse, and they cause severe portal hypertension in infancy. We recommend referral to a specialized pediatric hepatobiliary center where treatment may consist of hepatic artery ligation, embolization, resection, or liver transplantation.

Table 1. Proposed classification of arterioportal fistulas (APFs)

	Definition	Example	Clinical Findings	Natural History	Treatment
Type 1	Small peripheral asymptomatic APF with minimal physiologic insult	APF caused by percutaneous liver biopsy	Asymptomatic	Thrombose spontaneously within 1 month	Follow up with Doppler ultrasound
					Embolize if persistence beyond 1 month or symptomatic
Type 2	Larger central fistulas causing physiologic insult	Delayed presentation of APF after penetrating abdominal trauma	Portal hypertension	Portal hypertension	Treat
			History of penetrating abdominal trauma	Hepatoportal sclerosis	Embolize if possible
			Abdominal bruit	Possibly portal fibrosis	Surgery if not feasible or unsuccessful
Type 3	Congenital fistulas	Diffuse, intrahepatic congenital APF in a neonate	Failure to thrive	Severe portal hypertension in infancy	Referral to specialized pediatric hepatobiliary center
			Portal hypertension		
			Diarrhea		

This classification provides for distinct grouping based on both natural history and the degree of physiologic alteration resulting from specific APFs. It will also allow more uniform therapeutic recommendations for a specific APF subtype.

ETIOLOGY

Acquired APFs can be caused by liver trauma,[5,6,10] interventional hepatic procedures,[8,10,11] splanchnic artery aneurysms,[6,12] surgery,[13] or occur spontaneously in the setting of cirrhosis[14] or liver tumors. In a recent review of 88 case reports, the most common cause of an APF was trauma (28%), followed by iatrogenic causes (16%), congenital (15%), malignancy (15%), or rupture of splanchnic artery aneurysm (14%).[9]

APFs can be seen after blunt or penetrating abdominal trauma.[3,6,8,9,15,16] In a previous review of 30 traumatic APFs, 29 were caused by penetrating trauma and only 1 was caused by blunt abdominal trauma.[3] Of these 29 patients, 79% had sustained gunshot wounds and 17% had stab wounds.[3] Patients can be diagnosed both intraoperatively or following diagnostic evaluation of portal hypertension.[6]

Interventional hepatic procedures are a common cause of APFs.[2,7–11,14,17–23] In a study of 93 patients who underwent diagnostic liver procedures, the incidence of hepatoportal arteriovenous fistulas was determined by hepatic arteriogram obtained 1 month postprocedure.[8] Laparoscopic liver biopsies using a 2-mm-caliber needle resulted in a 5.4% incidence of APFs. Percutaneous transhepatic cholangiography with a 0.7-mm needle caused an APF in 3.8% of cases. Transhepatic catheterization of bile ducts resulted in a 26.2 % rate of APF.[8] It is not surprising that APF occurs following interventional procedures to the liver secondary to the anatomical arrangement of the vessels in the liver parenchyma. Injury to either a hepatic artery or portal vein may affect the adjoining vessel in the portal triad, resulting in the formation of an APF. Hellekant and Olint[10] identified APFs in 52% of the patients who had an arteriogram performed within 1 week following liver biopsy. This rate decreased to 10% if the arteriogram was performed 3 weeks after liver biopsy. These data suggest most small, peripheral, asymptomatic fistulas caused by liver biopsy will disappear spontaneously within 1 month.

Approximately 15% of APFs are the result of ruptured splanchnic artery aneurysms. The pathophysiology is thought to involve erosion of the aneurysm into the portal venous system.[3,6,12] Hepatic tumors, especially hepatocellular carcinoma, are another cause of APF and are present in approximately 10% of the patients with hepatocellular carcinoma. APF in association with a solid mass is a highly specific finding for this malignancy.[24]

Acquired APFs have been described in association with several other clinical entities, including hemangiomas,[3,9] cirrhosis,[3,9] regenerating liver nodules,[9] hepatic abscess,[2] Budd-Chiari syndrome, and hereditary telangiectatic disorders (Osler-Weber-Rendu syndrome),[2,7] type IV Ehlers-Danlos syndrome,[2,25] biliary atresia,[14] aneurysms,[2,9,26] and Allagilles syndrome. Idiopathic APFs have been described as well.[27]

Iatrogenic surgical causes of APF include mass ligation of mesenteric vessels, suture needle injury to an artery and portal vein, and biopsy needle injury to hepatic vessels.[3,6,9,13,17] APFs can also occur as a complication of radiofrequency ablation of hepatic malignancies, which can potentially result in rapid intrahepatic dissemination of hepatocellular carcinoma if viable tumor persists.[28]

Following liver transplantation, APF has been described in two settings: during back-table allograft reduction performed for segmental liver transplantation, APF has been reported secondary to mass ligature of a vascular pedicle.[29] APF has also been reported following transplantation secondary to percutaneous liver biopsies.[10,19] While most of these fistulas resolve spontaneously, there are reports of posttransplant APF resulting in liver allograft failure.[10]

CLINICAL FINDINGS

While many patients with APF are asymptomatic, when symptoms develop it is usually secondary to the physiologic effects of portal hypertension. The most common manifestations include gastrointestinal bleeding (33%), ascites (26%), congestive heart failure (4.5%), and diarrhea (4.5%).[9] A bruit or thrill is noted in approximately 33% of patients, and this clinical sign often provides the first clue of an APF.[2,6] A thrill is likely to be present when the fistulas are greater than 4 mm in diameter.[2]

The presence or absence of portal hypertension is dependent on the location of the fistula, the amount of blood shunted through it, and the resistance of the liver parenchyma to the increased mesenteric and portal venous flow. Portal hypertension is of the presinusoidal etiology[30,31] and has been documented in 20−43% of the patients with APFs.[3] Small, peripheral intrahepatic fistulas, such as those caused by percutaneous liver biopsies, rarely cause portal hypertension.[8] In contrast, APFs involving a named

vessel deliver a higher flow and are more likely to elevate portal pressure.[3] Overall, liver function tests are usually not abnormal, and on pathology, these patients have a conserved lobular architecture.[3,5,6,9] Patients with cirrhosis and an APF are more likely to have portal hypertension because parenchymal changes in the liver significantly restrict hepatopedal flow.

Patients with APF, in contrast to patients with systemic arteriovenous fistulas, rarely develop congestive heart failure.[9] In the majority of patients, the resistance imposed by the intervening hepatic sinusoids protects against heart failure.[2,3,9] The symptoms of diarrhea and abdominal pain may be caused by an arterial steal phenomenon,[3,9] which can even cause intestinal ischemia when taken to its extreme.[7] Given that most APFs are traumatic in origin, unusual manifestations of APFs can include hemobilia[32–34] and, rarely, pancreatitis.[3]

PATHOLOGY

The pathologic features of APFs are similar to those of other causes of noncirrhotic portal hypertension. Initially, there is dilatation of the sinusoids and portal venous branches. In fistulas of long duration with persistent portal hypertension, there is prominent venous intimal hyperplasia and arterialization of the portal venous branches, making them difficult to distinguish from their arterial counterparts. These morphologic changes are called hepatoportal sclerosis and can contribute to a progressive rise in the portal system pressure.[3,12,35] Portal venous thrombosis can occur.[35]

In separate animal studies, Rather and Schilling have demonstrated the presence of portal fibrosis in a subset of dogs with long-standing portal hypertension caused by surgically created fistulas between the hepatic artery and the portal vein.[3,6,36] Zuidema[3,6] also studied the histologic changes produced by APF involving the right branch of the portal vein in dogs. Several months after the surgical procedure, there were hemosiderin deposits, vascular occlusive changes, and, in one animal, portal vasculitis in the arterialized hepatic lobe. These changes were reversible early after the APF but ultimately produced irreversible changes if the fistula persisted.[3,6] In both studies, most of the dogs tolerated the surgically created APF relatively well for several months to years.[6]

In humans, Vauthey reported on two patients with hepatoportal fistulas who underwent liver biopsies. These demonstrated vascular changes, minimal periportal fibrosis, and conserved lobular architecture consistent with conserved hepatocyte function. Donovan et al.[36] and Ryan[37] reported similar findings. To date, it is unclear whether APF leads to the development of hepatic cirrhosis in humans. Further studies will need to be performed to clarify this point.

DIAGNOSIS

The diagnosis of an APF is challenging, and many times it is made incidentally on radiographic evaluation of the portal circulation. When symptomatic, the interval between the formation of the fistula and its recognition can range from hours to 42 years.[37] Typically, it takes several months for patients to develop symptoms related to their portal hypertension.[3] A detailed history and physical examination are essential. A history of penetrating trauma to the abdomen is invaluable. On physical examination, the presence of an abdominal bruit or thrill is often a significant clue.

Hepatic arteriography is the gold standard in diagnosing APF.[2] Early visualization of the portal vein on aortic or celiac artery injection is pathognomonic (Fig. 1)[2]. Angiography often reveals a single fistula and hepatopedal flow with no evidence of portal hypertension. However, if the fistula is large enough or in the setting of cirrhosis, hepatofugal flow can be present.[9,23] Doppler ultrasound can be useful as a screening test and in the follow-up of asymptomatic fistulas without evidence of portal

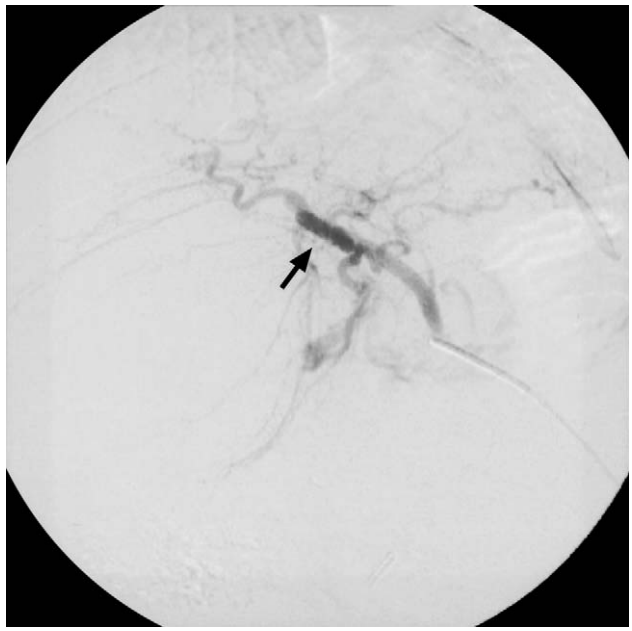

Fig. 1. Hepatic arteriogram demonstrating an APF. This fistula was embolized using steel coils.

hypertension.[2] Doppler ultrasound findings demonstrate a dilated hepatic artery and "arterialization" of a dilated portal system with or without hepatofugal flow.[2,9] On computed tomography, APF is suggested by the early filling of the portal vein on the arterial phase and the presence of wedge-shaped, transient peripheral areas of enhancement during the hepatic arterial phase (Fig. 2)[1,9]. Magnetic resonance imaging can identify the flow patterns and potential thrombotic components. Magnetic resonance angiography can also be used as a noninvasive method of demonstrating the vascular anatomy in patients for whom angiography is contraindicated.[9] Magnetic resonance imaging/angiography findings are similar to those seen on computed tomography scan.[1] Occasionally, an APF can be diagnosed at the initial or repeat celiotomy for trauma.[5]

TREATMENT

The optimal therapy for APF remains controversial. The specific treatment depends on the size, location, and number of APFs.[3,5] In an analysis of 88 patients, the most common modes of treatment have been radiologic intervention (39%), surgery alone (31%), a combination of interventional procedure and surgery (9%), or no treatment (21%).[9] The great majority of APFs do not require emergency intervention; there is time to analyze the fistula and estimate its physiologic consequences.[9] Yet, in some instances, treatment is clearly indicated to prevent the long-term development of portal hypertension, hepatoportal sclerosis, and possible cirrhosis.[3,9] Nonetheless, because smaller fistulas can thrombose and close spontaneously,[2,10,16] some form of occlusion is required only for patients with portal hypertension or if the fistula is shown to increase in size.[10] Small peripheral asymptomatic fistulas (type 1) can be followed by serial duplex ultrasound.[10] If there is evidence of portal hypertension, if the fistula is large, or if it fails to disappear over a reasonable period of time, then treatment is indicated.[9,10] In contrast to small intrahepatic fistulas, all extrahepatic fistulas should be treated, because no spontaneous closure of an extrahepatic APF has been reported.[2,3]

Arterial embolization is very effective in treating a single APF. Several therapies are available to occlude the fistula, including steel coils,[38,39] alcohol,[9,40] gel foam particles,[9] isobutyl cyanoacrylate,[9] angioplasty balloon tamponade,[32] and detachable balloons.[41] The method is dependent on the characteristics of flow and size and on the experience of the interventional therapist. Gianturco steel coils are more strongly recommended than gel foam particles, because the latter can pass through the fistula and end up in the splanchnic circulation.[38]

If embolization is unsuccessful, hepatic artery ligation or fistula resection can be therapeutic.[16,24] Hepatic artery ligation limits blood loss and surgical complications and is an effective treatment for this condition. However, both embolization and arterial ligation are not recommended in the mesenteric

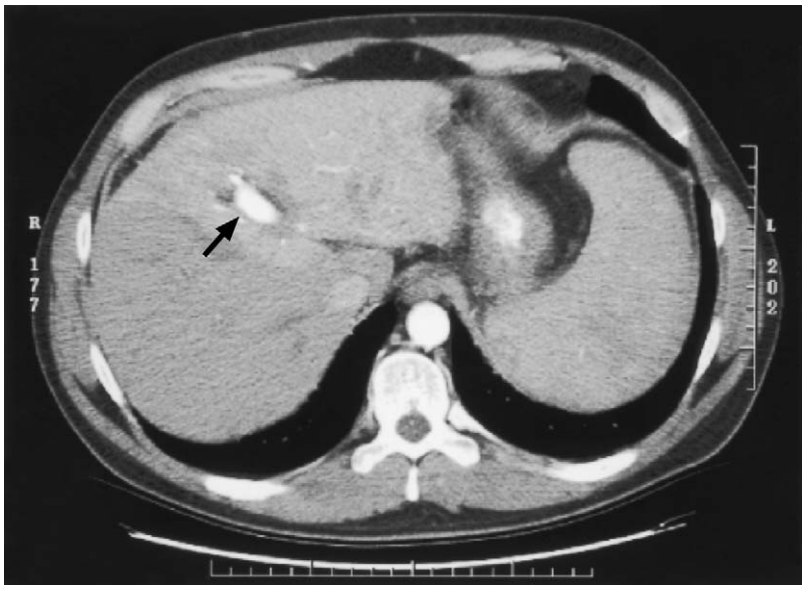

Fig. 2. Computed tomography scan of an APF. Note the increased enhancement of the left lobe of the liver on the arterial phase. Also, there is early visualization of the portal vein (*arrow*).

arteries, given the risk for end organ ischemia.[40] Hepatic artery ligation is also contraindicated in patients with limited hepatic reserve. Splenoportal fistulas can be safely embolized without causing splenic ischemia due to the collateral blood supply to this organ by means of the left gastroepiploic and short gastric arteries.[9]

In extrahepatic fistulas or when ligation is contraindicated, APF resection can be undertaken.[2] These operations can be very difficult and are associated with significant blood loss.[3] Some groups recommend complete excision of the fistulas given concerns for recurrence through collateral vessels with simple fistula ligation.[2] Rarely, a formal hepatic lobectomy may need to be performed[5,6,36] or liver transplantation for patients requiring resection but with limited hepatic reserve.[35]

In the setting of an exploratory laparotomy for penetrating abdominal trauma, some consideration should be given to exploring hepatic hematomas in hemodynamically stable patients and possibly preventing the formation of an APF.[3]

With any form of treatment, significant complications can occur. They include liver failure, hepatic abscess, portal vein thrombosis, biliary fistula, bile duct stricture, and stroke.[9] Complications specific to embolization therapy include migration of coils, infection, organ infarction, pancreatitis, and vascular injury.[40]

CONGENITAL

Congenital APFs are a rare cause of severe portal hypertension in children with challenging diagnostic and therapeutic implications.[7,42] These APFs are mostly intrahepatic and they represent 12% of the cases of developmental intrahepatic shunts.[42]

The clinical presentation is sufficiently distinct for an astute clinician to differentiate between the congenital and the acquired types. As described by Dr. Nigel Heaton from the Kings College Hospital in Great Britain, "Diffuse intra-hepatic A-V fistulas are always congenital in origin whereas a solitary fistula is usually acquired."[7] Children usually present with a syndrome consisting of watery diarrhea, malaise, failure to thrive, abdominal distention, and hepatosplenomegaly secondary to severe presinusoidal portal hypertension.[7] In infants, malabsorption and failure to thrive are the most common presenting features, with portal hypertension developing later.[42] Older children can present with severe portal hypertension and manifest any of its associated complications, such as severe upper gastrointestinal bleeding caused by esophageal varices.[43,44]

The presence of a patent ductus venosum is protective in the initial postnatal period.[7,42] Symptoms usually develop after 1 month of age, once the duct is closed and blood cannot easily shunt into the systemic circulation. Often these children are being investigated for generalized abdominal findings and are later noted to develop symptoms related to portal hypertension. Heart failure is not usually a feature, due to the protective effect of the intervening hepatic sinusoids.[42] Pancreatic hypofunction secondary to venous congestion has been postulated as a mechanism for their malabsorption, steatorrhea, and watery diarrhea.[7]

Upon physical examination, a characteristic bruit can be heard over the right upper quadrant. Liver function tests are usually normal. At laparotomy, these patients have an impressive hyperemic and congested bowel as well as significant hepatosplenomegaly.[7]

Doppler ultrasound is the best modality in making the diagnosis and is helpful in the subsequent evaluation of these children.[14,20] Features include pulsatile hepatofugal flow in the portal vein and color speckling in the hepatic parenchyma adjacent to the fistula.[14] The diagnosis of a congenital hepatoportal arteriovenous fistula can even be made prenatally by ultrasound.[45]

A detailed radiologic evaluation is very important and is intended to do the following: (1) localize and characterize the hepatic lesions, (2) quantify the shunt, (3) document normal portal venous anatomy, (4) indicate resectability, (5) provide a anatomic details for arterial ligation or embolization, and (6) identify any further lesions in other organs.[42] Computed tomography or magnetic resonance imaging can provide further anatomic information and possibly demonstrate possible hepatic perfusion anomalies.[14] Angiography is the most useful test because it can both identify multiple APFs and be therapeutic. The diagnosis is made on the portal venous phase of a celiac and superior mesenteric arteriogram because portal vein angiography is usually unsuccessful owing to the elevated portal venous pressures and hepatofugal flow. Portal vein pressures are often significantly elevated (up to 75 cm H_2O),[7] whereas hepatic vein wedge pressures are normal owing to the presinusoidal nature of the shunt.

Due to their larger size, congenital APFs most often cause portal hypertension and subsequent hepatoportal sclerosis.[14] Experience has shown that hepatic artery ligation is the preferred treatment for congenital fistulas and has been curative in most cases.[7,44,46,47] Because these patients have multiple arteriovenous fistulas, embolization alone is often not successful. An infant can present with a seemingly single dominant fistula, but after

selective devascularization, another fistula arises.[7,42] Embolization, however, has proved effective in conjunction with hepatic artery ligation or in cases of solitary congenital hepatoportal fistulas.[22,25,27,45,47] Occasionally, liver transplantation may be the only possible therapy in patients with extensive involvement or in those who would not tolerate hepatic artery ligation due to associated hepatic pathology such as cirrhosis[18] or biliary atresia.[14] Given the rarity and complexity of these cases, they are best managed at a specialized pediatric hepatobiliary center.[42]

PROGNOSIS

Patients with acquired fistulas have a good prognosis, owing to the minimal physiologic derangements that isolated APFs cause in the majority of patients and to the effective therapies currently available. Congenital APFs can be associated with other congenital abnormalities and patients can have a more severe form of portal hypertension. Nevertheless, in a recent review, only one of seven patients with diagnosed congenital APF died as a consequence of the disease.[7]

CONCLUSION

APFs are a well-described cause of presinusoidal portal hypertension. In patients with portal hypertension and no evidence or history of cirrhosis, one should consider APF as a potential etiology if there is a history of liver biopsy or penetrating trauma to the upper abdomen or if an abdominal bruit can be auscultated. The diagnosis is usually established by ultrasound or contrast studies where early filling of the portal vein is noted. A detailed radiologic evaluation is imperative. The treatment depends on the duration, size, location, and presence or absence of portal hypertension. Type 1 APFs generally close spontaneously, whereas type 2 APFs may progress to portal hypertension, hepatoportal sclerosis, and possible hepatic fibrosis. When necessary, treatment can be accomplished with minimal morbidity. The prognosis is usually good. A new classification is introduced that takes into consideration the natural history of these fistulas and allows uniform therapeutic recommendations.

REFERENCES

1. Choi BI, Lee KH, Han JK, Lee JM, et al. Hepatic arterioportal shunts: dynamic CT and MR features. Kor J Radiol 2002;3:1–15.
2. Lumsden AB, AR, Sreeram S, et al. Hepatic arterioportal fistula. Am Surg 1993;59:722–726.
3. Strodel WE, EF, Lemmer JH, et al. Presentation and perioperative management of arterioportal fistulas. Arch Surg 1987;122:563–571.
4. Townsend CM, bR, Evers BM, et al. Sabiston Textbook of Surgery. Philadelphia: Elsevier Saunders; 2004.
5. Eastridge BJ, MJ. Intrahepatic arterioportal fistula after hepatic gunshot wound: a case report and review of the literature. J Trauma 1997;43:523–526.
6. Van Way CW, CJ, Riddell DH, et al. Arteriovenous fistula in the portal circulation. Surgery 1971;70:876–890.
7. Heaton ND, DM, Karani J, et al. Congenital hepatoportal arteriovenous fistula. Surgery 1995;117:170–174.
8. Okuda K, MH, Nakajima Y, et al. Frequency of intrahepatic arteriovenous fistula as a sequela to percutaneous needle puncture of the liver. Gastroenterology 1978;6:1204–1207.
9. Vauthey JN, TR, Helmberger T, et al. The arterioportal fistula syndrome: clinicopathologic features, diagnosis, and therapy. Gastroenterology 1997;113:1390–1401.
10. Jabbour N, RJ, Zajko A, et al. Arterioportal fistula following liver biopsy. Three cases occurring in liver transplant recipients. Dig Dis Sci 1995;40:1041–1044.
11. Grainger RG, AD, Adam A, et al. Grainger and Allison's Diagnostic Radiology: A Textbook of Medical Imaging. 4th ed: New York: Churchill Livingstone; 2001.
12. Pasternak BM, CH. Arteriovenous fistula and forward hypertension in the portal circulation. Angiology 1978;29:367–373.
13. Zheng RQ, HC, Kudo M. Hepatobiliary and pancreatic: arterioportal fistula causing portal hypertension. J Gastroenterol Hepatol 2003;18:873.
14. Gallego C, MM, Marin C, et al. Congenital hepatic shunts. Radiographics 2004;24:755–772.
15. O'Hanlon DM, MC, Walsh T, et al. Traumatic arteriovenous fistula of the liver. J Am Coll Surg 2001;193:575.
16. Kaude J, DD, Talbert JL. Radiology. The role of selective angiography in the diagnosis and treatment of hepatoportal arteriovenous fistula. Radiology 1969;92:1271–1272.
17. Isisk F, GA, Guben J, et al. Iatrogenic arterioportal fistulae: diagnosis and management. Ann Vasc Surg 1989;3:52–55.
18. D'Agostino D, GMR, Alonso V, et al. Liver transplantation as treatment for arterioportal fistulae. J Pediatr Surg 1998; 33:938–940.
19. Frederle MP, KV. Complications of liver transplantation: imaging and intervention. Radiol Clin North Am 2003;41.
20. Gallego C, VM, Marcuello P, et al. Congenital and acquired anomalies of the portal venous system. Radiographics 2002; 11:141–159.
21. Korula J, FJ, Weissman M, et al. Fatal hemorrhage from an arterio-portal-peritoneal fistula after percutaneous liver biopsy. Gastroenterology 1989;96:244–246.
22. Raghuram L, KI, Jaya V, et al. Coil embolization of a solitary congenital intrahepatic hepatoportal fistula. Abdom Imaging 2001;26:194–196.
23. Wachsberg RH, BP, Sofocleous CT, et al. Hepatofugal flow in the portal venous system: pathophysiology, imaging findings, and diagnostic pitfalls. Radiographics 2002;22: 123–140.
24. Nagasue N, IK, Kobayashi M, et al. Hepatoportal arteriovenous fistula in primary carcinoma of the liver. Surg Gynecol Obstet 1977;145:504–508.
25. Sherry RM, FA, Grey DP, et al. Embolization of a hepatoportal fistula in a patient with Ehlers-Danlos syndrome and colon perforation. Surgery 1992;111:475–478.

26. Altuntas B, EA, Karakurt C, et al. Severe portal hypertension due to congenital hepatoportal arteriovenous fistula associated with intrahepatic portal vein aneurysm. J Clin Ultrasound 1998;26:357–360.
27. Kumar N, dVdGJ, Sharif K, et al. Congenital, solitary, large, intrahepatic arterioportal fistula in a child: management and review of the literature. Pediatr Radiol 2003; 133:20–23.
28. Nicoli N, CA, Hilal MA, et al. A case of rapid intrahepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation. Am J Surg 2004;188:165–167.
29. Mieles LA, WD, Orloff MS. Arterioportal fistulae following segmental liver transplantation in a child. Pediatr Transplant 2002;6:419–422.
30. Feldman M. Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 7th ed. Philadelphia: Elsevier; 2002.
31. Zuidema GD, YC. Shackelford's Surgery of the Alimentary Tract, 5th ed. Vol. 3. Philadelphia: WB Saunders; 2002.
32. Sniderman KW, MS, Rapoport S, et al. Hemobilia following transhepatic biliary drainage: occlusion of an hepatoportal fistula by balloon tamponade. Radiology 1985;154:827.
33. Markgraf WH. Traumatic hemobilia associated with a hepatoportal biliary fistula. Arch Surg 1960;81:860–863.
34. Maciano VI, LF, Lange SM, et al. Arterioportal fistula causing acute pancreatitis and hemobilia after liver biopsy. J Clin Gastroenterol 2002;34:481–484.
35. Hashimoto E, LJ, MacCarty RL, et al. Hepatoportal arteriovenous fistula: morphologic features studied after orthotopic liver transplantation. Hum Pathol 1989;20:707–709.
36. Donovan AJ, RT, Mikkelsen WP, et al. Systemic portal arteriovenous fistulas: pathological and hemodynamic observations in two patients. Surgery 1969;66:474–482.
37. Ryan KG, LS. Traumatic fistula between hepatic artery and portal vein. N Engl J Med 1968;279:1215–1216.
38. Applbaum YN, RJ. Steel coil embolization of hepatoportal fistulae. Cardiovasc Interv Radiol 1987;10:75–79.
39. Redmond PL, KD. Embolization of an intrahepatic arterioportal fistula: case report and review of the literature. Cardiovasc Intervent Radiol 1988;11:274–277.
40. Basile A, SC, Lupatelli T, et al. Nonoperative management of iatrogenic lesions of celiac branches by using transcatheter arterial embolization. Surg Laparosc Endosc Percutan Tech 2004;14:268–275.
41. Ridout DL, BS, Chait A, et al. Hepatoportal arteriovenous fistula treated with detachable balloon embolotherapy. Am J Gastroenterol 1989;84:63–66.
42. Paley MR, FP, Kane P, et al. Developmental intrahepatic shunts of childhood: radiological features and management. Eur Radiol 1997;7:1377–1382.
43. Fiane AE, GF, Smevik B. Hepatoportal arteriovenous fistula and bleeding oesophageal varices in a child. Eur J Surg 1993; 159:185–186.
44. Alkim C, ST, Oguz P, et al. A case report of congenital intrahepatic arterioportal fistula. Am J Gastroenterol 1999;94: 523–525.
45. Kim IO, CJ, Kim WS, et al. Congenital intrahepatic portohepatic venous shunt: treatment with coil embolization. Pediatr Radiol 2000;30:336–338.
46. Helikson MA, SD, Seashore JH. Hepatoportal arteriovenous fistula and portal hypertension in an infant. Pediatrics 1977; 60:920–924.
47. Agarawala S, DH, Bhatnagar, et al. Congenital hepatoportal arteriovenous fistula: report of a case. Surgery Today 200;30: 268–271.

Helicobacter pylori Extract Induces Nuclear Factor-kappa B, Activator Protein-1, and Cyclooxygenase-2 in Esophageal Epithelial Cells

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Helicobacter pylori infection is recognized as the major cause of gastritis and gastric cancer; however, its role in the development of gastroesophageal reflux disease and Barrett's adenocarcinoma is unclear. The expression of NF-κB, AP-1, and COX-2 may be important in inflammation and tumorigenesis in the esophagus. The aim of this study was to examine the effect of live *H pylori* or *H pylori* extract (HPE) on these factors in the esophageal epithelial cell lines SKGT-4 and OE33. NF-κB and AP-1 activity were assessed by gel shift assay and COX-2 by Western blotting. Coculture of SKGT-4 and OE33 with live *H pylori* and HPE induced NF-κB and AP-1 DNA-binding activity, and also decreased IκB-α levels. Treatment with the specific MEK1/2 MAPK inhibitor PD98059, but not the p38 MAPK inhibitor SB203580, inhibited NF-κB and AP-1 activity. The antioxidant vitamin C inhibited *H pylori*-induced NF-κB activation, but increased AP-1 expression. Moreover, HPE induced COX-2 expression and IL-8 production, and PD98059 inhibited COX-2 expression, ERK1/2 phosphorylation, and IL-8 production. These data demonstrate that both live *H pylori* and HPE induce NF-κB and AP-1 expression in esophageal epithelial cells. The induction of such transcription factors may play a role in the specific immune response within Barrett's mucosa and may indirectly cause inflammation of the gastric cardia and the distal esophagus. (J GASTROINTEST SURG 2006;10:551–562) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: AP-1, esophageal cancer, *H pylori*, HPE, NF-κB

Helicobacter pylori infects over half the world's population. The infection is associated with chronic gastritis, peptic ulceration, gastric lymphoma, and gastric adenocarcinoma.[1,2] *H pylori* eradication is effective in the treatment of gastritis, peptic ulcers, and early lymphoma of mucosal-associated lymphoid tissue.[3] The relationship, however, between *H pylori* infection and gastroesophageal reflux disease (GERD), the onset of Barrett's esophagus, and the development of adenocarcinoma of the esophagus and the esophagogastric junction is controversial. A significantly higher prevalence of esophageal *H pylori* infection has been reported in patients with Barrett's and esophageal adenocarcinoma compared with Barrett's patients without cancer (75% vs. 32.6%).[4] Nondysplastic Barrett's epithelium is also frequently colonized with *H pylori*.[5] Moreover, the prevalence of inflammation at the esophagogastric junction, so-called carditis, is similar in patients with and without GERD and is associated with *H pylori* infection.[6–9]

In GERD, *H pylori* gastritis may protect against the development of esophageal erosions.[10] The infection exerts a protective effect on the esophagus, probably mediated by the ammonia buffer produced by *H pylori* and refluxing in the esophagus.[11] Patients carrying cagA+ strains of *H pylori* have greater protection against the complications of GERD, especially Barrett's metaplasia, dysplasia, and adenocarcinoma.[12,13] The studies suggest that the distribution and severity of *H pylori*- related gastritis and atrophy, rather than the mere presence of *H pylori* infection, play a role in the pathophysiology of GERD, and that *H pylori* colonization of the esophagus may occur by a mechanism that is different from that observed in the gastric mucosa.

The specific immune environment within Barrett's metaplasia is an important driver in the development of GERD and cancer of the esophagus. In inflammatory disease states, proinflammatory mediators known to be regulated by transcription factors

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such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1) are thought to play an important role in the regulation of various cellular functions, including cellular activation, proliferation, and apoptosis. NF-κB resides in the cytoplasm, in an inactive form, as a heterodimer consisting of p50 and p65 (RelA) subunits complexed to the inhibitory molecule IκB, which prevents the migration of the heterodimer to the nucleus. After a range of stimuli in many cell types, NF-κB translocates to the nucleus and binds to its specific DNA site and subsequently upregulates the gene expression.[14,15] We have previously reported that NF-κB is increasingly expressed from inflammation through Barrett's metaplasia to dysplasia and adenocarcinoma.[16]

The relationship between *H pylori* infection and the transcription factors NF-κB and AP-1 and related cytokines has not previously been addressed. Jones et al.[17] demonstrated that wild-type *H pylori* strains increased Fas protein expression in OE33 cells, and that *H pylori* induced apoptosis at a higher rate in the Barrett's-derived human esophageal adenocarcinoma cells than in normal esophageal cells. This *H pylori*-induced apoptosis was primarily dependent on intact bacteria and the presence of the cagA and picB/cagE gene products. It is known that transcription factors such as NF-κB and AP-1 regulate a wide variety of genes involved in epithelial inflammation, growth, and apoptosis, including Fas.[14,15]

In this study we have sought to determine whether *H pylori* infection has any effect on the expression of NF-κB and AP-1 in esophageal epithelial cells and to further explore the molecular mechanisms involved. We report herein that both live *H pylori* and *H pylori* extract induce NF-κB, AP-1, and COX-2 expression in the esophageal epithelial cells SKGT-4 and OE33 cells, and that *H pylori* also activates ERK1/2 phosphorylation. Moreover, incubation of esophageal epithelial cells with HPE increased IL-8 production, and HPE-induced IL-8 was inhibited by the MEK1/2 MAPK inhibitor PD98059 and vitamin C.

MATERIAL AND METHODS

Material

NF-κB and AP-1 consensus oligonucleotides were obtained from Promega (Promega Corp., Madison, WI). Antibody to IκB-α, anti-phospho-ERK1/2, and non-phospho-ERK1/2, anti-p50 (sc-114X), anti-p65 (sc-109X), anti-c-Rel (sc-70X), anti-Fra-1, anti-c-Fos, anti-c-Jun, and anti-Jun-D for gel super-shift assays were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Polyclonal COX-2 antibody was purchased from Cayman Chemical Company (Ann Arbor, MI). [γ^{32}P]ATP (35 pmol, 3000 Ci/mmol) was from Amersham International (Aylesbury, UK). Poly(dI-dC) was obtained from Pharmacia (Biosystems, Milton Keynes, UK). Vitamin C was obtained from Sigma (Poole, Dorset, UK). PD98059 and SB203580 were purchased from Calbiochem, Novabiochem Corp., La Jolla, CA.

Cell Culture

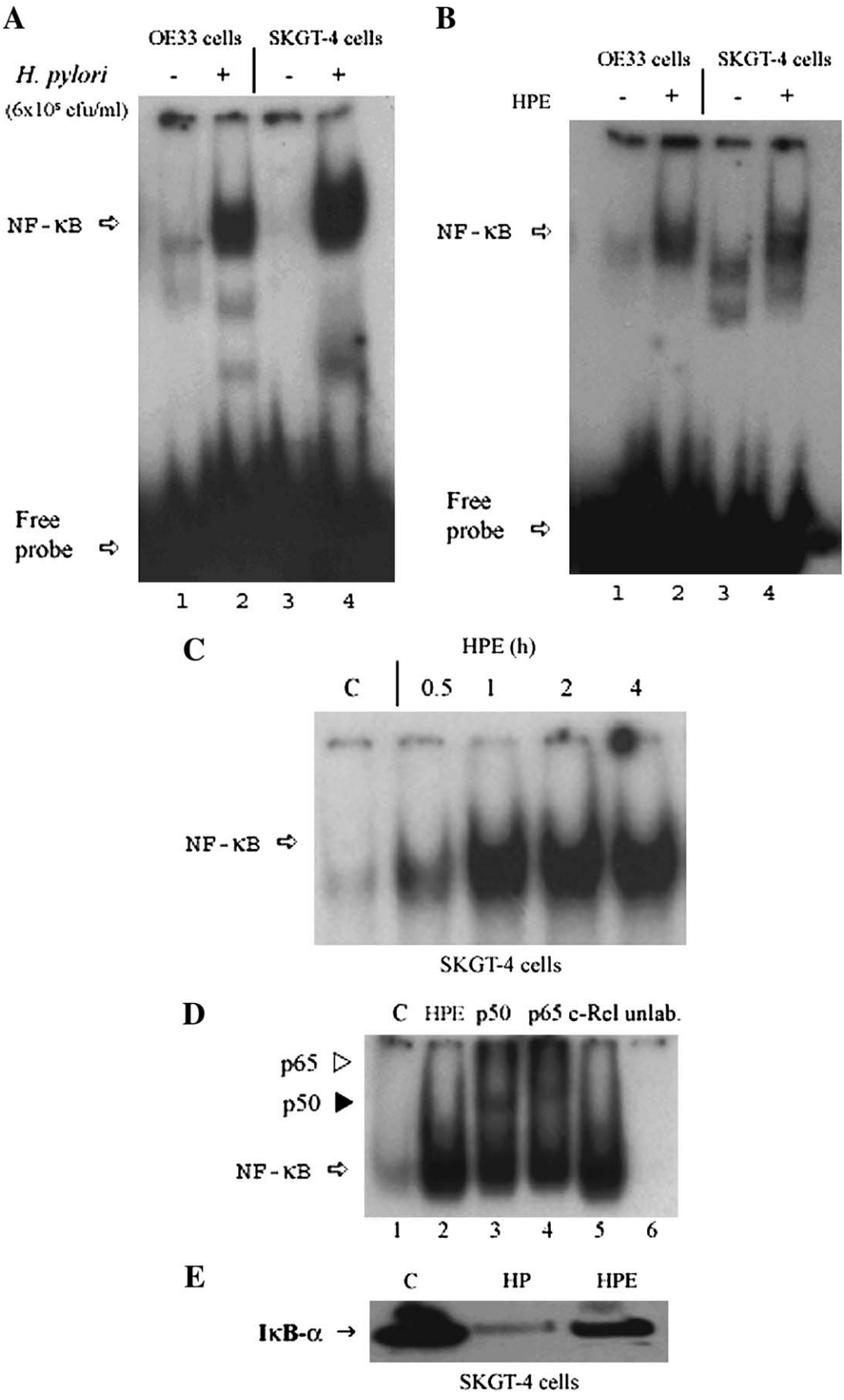
The esophageal epithelial cell line OE33 (derived from the adenocarcinoma of the lower esophagus; Barrett's metaplasia) was obtained from the European Collection of Animal Cell Cultures (Porton Down, Salisbury, UK). SKGT-4 cells (established from a well-differentiated adenocarcinoma arising in Barrett's epithelium of the distal esophagus) were a gift from Dr. David S. Schrump (Thoracic Oncology Section, Surgery Branch, National Cancer Institute, NIH, Bethesda, MD). OE33 and SKGT-4 cells were grown in RPMI 1640 medium supplemented with 10% filtered fetal calf serum, 100 units/ml penicillin, 100 μg/ml streptomycin, and 2 mmol/L L-glutamine.

H pylori Culture

H pylori reference strains NCTC 11637 and NCTC 11638 obtained from the National Collection of Type Cultures (Colindale, UK) were used in this study. The strains were grown in a microaerobic-humidified atmosphere on 7% lysed horse blood Columbia agar at 37° C. After 48–72 hours, bacteria were harvested in RPMI 1640 medium without antibiotics and resuspended to a concentration of 2×10^8 colony-forming units (cfu)/ml using the McFarland standard kit. Live *H pylori* were cocultured with SKGT-4 or OE33 for different periods of time (30 min – 240 min). The ratio of *H pylori* to esophageal epithelial cells is 100:1. For preparation of *H pylori* extract (HPE), suspended bacteria were placed on ice for 20 minutes and centrifuged at 15000*g* for 10 minutes at 4° C. Serial dilutions of HPE were used to infect the cells and 1 ml of HPE was found to induce a pronounced NF-κB and AP-1 activation, therefore 1 ml HPE was used in all experiments. The total protein content of this HPE was 300 μg/ml as measured by the method of Bradford.[18]

Cell Culture Treatments

Confluent SKGT-4 and OE33 cells (1×10^6 cells/ml) grown in 6-well plates were cocultured with 1 ml of freshly harvested *H pylori* suspension (2×10^8 cfu/ml) or HPE. In the case of all inhibitors, appropriate dilutions were made in cell culture medium just


A
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before use and preincubated with the cells for 1 hour before incubation with *H pylori*.

Total Cell Extract Preparation

Cells were collected by centrifugation, resuspended in lysis buffer (20 mmol/L Tris-HCl [pH 7.5], 1% [wt/vol] sodium dodecyl sulphate, 150 mmol/L NaCl, 1 mmol/L EGTA, 1 mmol/L EDTA, 0.5 mmol/L phenylmethylsulfonyl fluoride and leupeptin; 10 μg/ml), and then the cells were solubilized by boiling and used immediately or kept at −20° C.

Western Blot Analysis

Equivalent protein amounts (50 μg protein) were resolved by electrophoresis using 10% polyacrylamide gels according to the method of Laemmli.[19] Proteins were transfered onto polyvinylidene fluoride (PVDF) membrane. Blots were blocked and probed with the primary antibody (anti-IκB-α, anti-COX-2, anti-phospho-ERK1/2, or non-phospho-ERK1/2) for 1 hour at room temperature. Blots were incubated with the appropriate secondary antibody for 1 hour and immunodetection was performed by enhanced chemiluminescence.

Nuclear Extract Preparation

Nuclear extracts were prepared from OE33 and SKGT-4 cells as described previously.[20] The nuclear extracts were used immediately or stored at −70° C until required. The protein concentration was determined by the method of Bradford.[18]

Electrophoretic Mobility Shift Assay

Nuclear extracts (4 μg protein) were incubated with 10000 cpm of the ^{32}P-labeled NF-κB (5′-AGTTGAGGGGACTTTCCCAGGC-3′) or AP-1 (5′- CGCTTG ATGAGTCAGCCGGAA-3′) oligonucleotide. The binding assay was performed in the presence of poly(dI-dC) as nonspecific competitor and ^{32}P-labeled NF-κB or AP-1 for 30 minutes at room temperature. After electrophoresis, the gels were dried and autoradiographed. In super-shift and competition assays, 0.5 ml of NF-κB antibodies (anti-p50, anti-p65 and anti-c-Kel), and AP-1 antibodies (anti-Fra-1, anti-c-Fos, anti-c-jun and anti-Jun-D) was preincubated with nuclear extract for 30 minutes before the addition of the labeled probe.

IL-8 Production

SKGT-4 cells were seeded in 96-well plates (1×10^6 cells in 200 μl) overnight at 37° C. SKGT-4 cells were incubated with 100 μl HPE for 8 hours. At the end of treatment, cell supernatants were collected and assayed for IL-8 production by ELISA according to the manufacturer instructions (Pharmingen) using an enzyme-linked immunosorbent assay (ELISA) plate reader.

Statistical Analysis

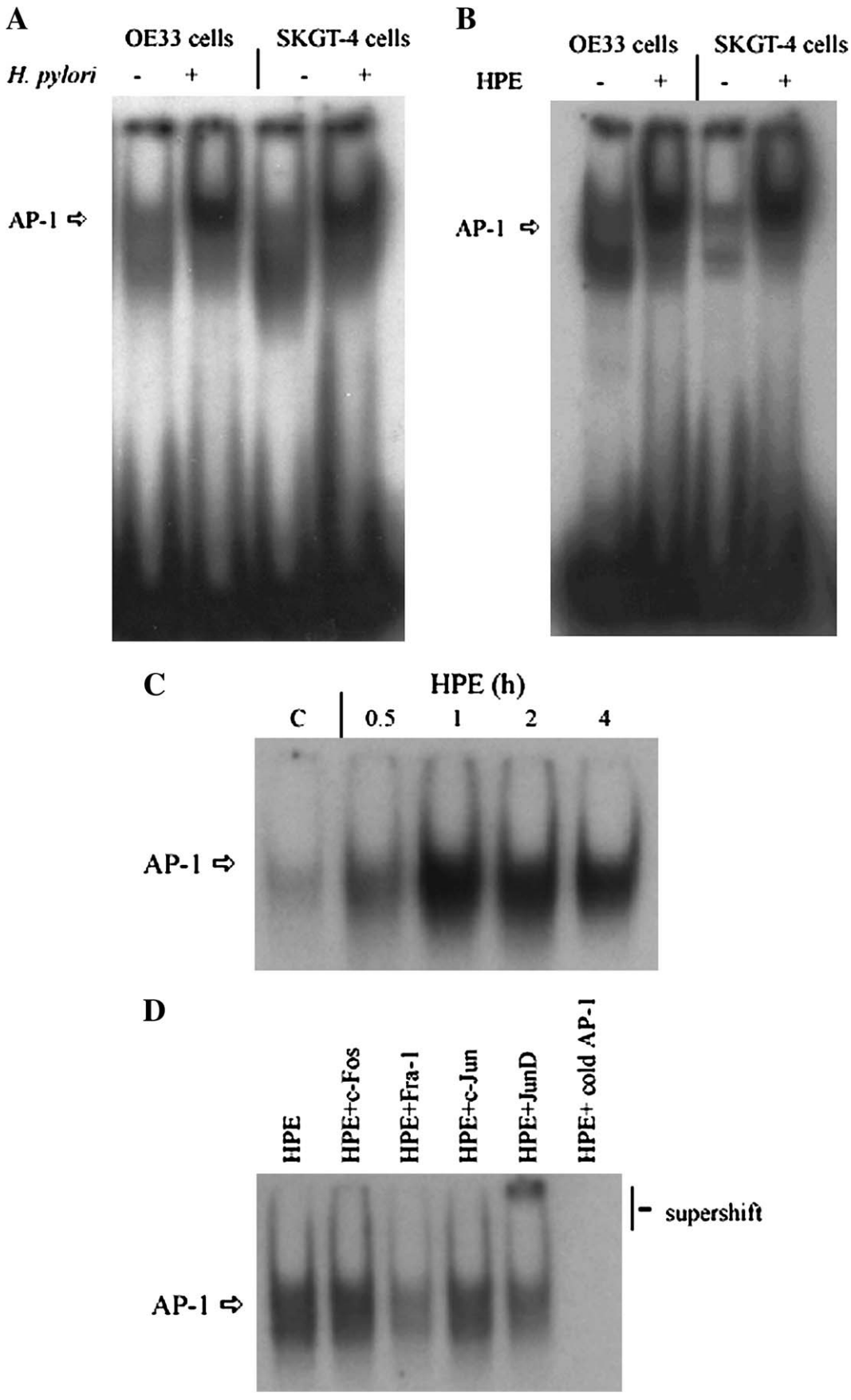
The Student's *t* test was used to assess the statistical significance of the difference. Statistical difference was indicated by a P value < 0.05. Data are presented as mean ± standard error of the mean (SEM).

RESULTS

H pylori Induces NF-κB DNA-Binding Activity in Esophageal Epithelial Cells

The first study explored whether *H pylori* could induce NF-κB DNA-binding activity in esophageal cell lines. Exposure of SKGT-4 or OE33 cells to live *H pylori* resulted in increased NF-κB DNA-binding activity as demonstrated by gel shift assays. Coculture of OE33 or SKGT-4 cells with *H pylori* induced NF-κB DNA-binding activity (Fig. 1, *A*). Little or no NF-κB activity was observed in resting OE33 or SKGT-4 cells. Incubation of OE33 or SKGT-4 cells with 1 ml of HPE for 1 hour results in a marked increase in NF-κB DNA-binding activity (Fig. 1, *B*). Time-course experiments revealed a time-dependent increase in the levels of NF-κB upon coculture with HPE. Detectable increases in NF-κB levels were seen from 30 minutes to 4 hours (Fig. 1, *C*).

Fig. 1. *H pylori* induces NF-κB DNA-binding activity in esophageal epithelial cells. SKGT-4 or OE33 cells were cocultured with (**A**) a freshly harvested *H pylori* suspension strain 11638 (2×10^8 cfu/ml) or (**B**) 1 ml of *H pylori* extract (HPE). Nuclear extracts were prepared and gel shift assays for NF-κB DNA-binding activity were performed (as described under Materials and Methods section) using 4 μg protein. Lanes 1 and 3, nuclear extract from unstimulated cells. Lanes 2 and 4, nuclear extracts from cells cocultured with *H pylori* or HPE. (**C**) Time course of NF-κB activation by HPE in SKGT-4 cells incubated with HPE for different periods of time between 30 minutes and 4 hours. (**D**) Super-shift assay was performed on nuclear extracts prepared from SKGT-4 cells incubated with HPE (lane 1) using 0.5 μl of rabbit antisera to p50, lane 2; p65, lane 3; and c-Rel, lane 4. A competition assay for NF-κB was also performed using 100-fold molar excess of unlabelled NF-κB, lane 5. Unstimulated cells are shown in lane 1. (**E**) Effect of *H pylori* on IκB-α protein level. SKGT-4 cells were incubated with *H pylori* strain 11638 (2×10^8 cfu/ml) or HPE for 1 hour. At the end of incubation, total cell extracts were prepared and equivalent amounts of protein (50 μg protein) were separated by 10% polyacrylamide gels, blotted onto PVDF membrane, and probed with anti-IκB-α antibody (as described under Materials and Methods section). Each experiment was repeated three times with similar results, and a representative gel is shown.


A
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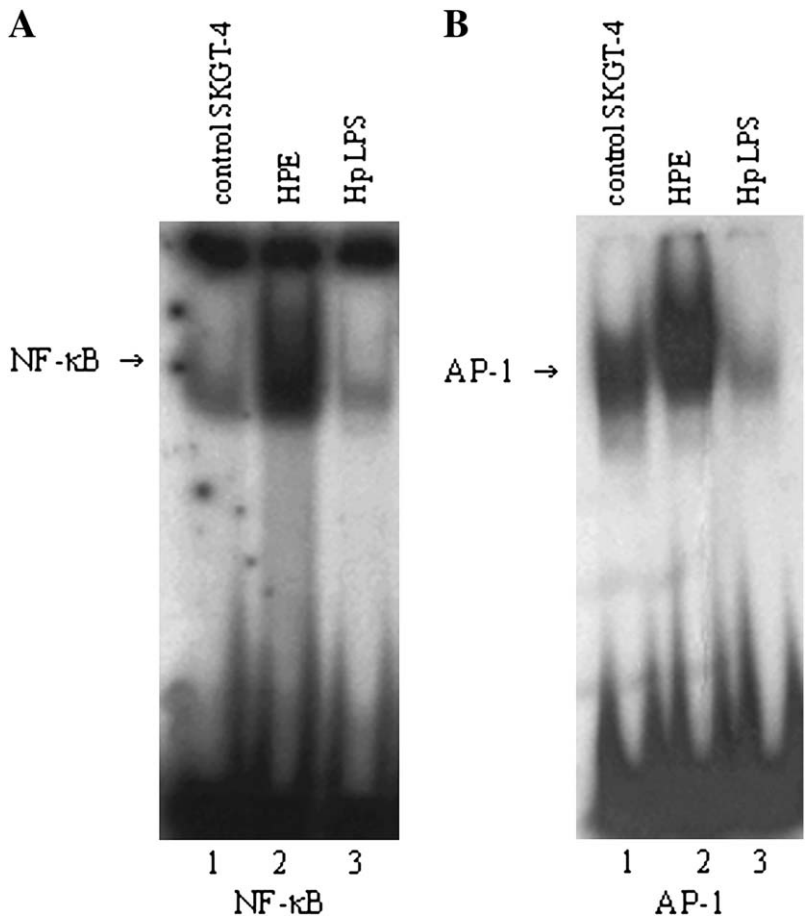

Fig. 3. Effect of *H pylori* LPS on NF-κB and AP-1 DNA-binding activity. SKGT-4 cells were incubated with purified *H pylori* LPS (15 μg/ml) or 1 ml HPE for 1 hour, and nuclear extracts were prepared and assayed for NF-κB (**A**) and AP-1 (**B**) DNA-binding activity in an EMSA reaction.

To identify the composition of the NF-κB DNA complex induced by HPE, a panel of antibodies directed against various NF-κB subunits (p50, p65, and c-Rel) were preincubated with nuclear extracts from SKGT-4 cells stimulated with HPE. Antibodies to p50 and p65 recognized this NF-κB DNA complex, whereas anti-c-Rel had no effect in the super-shift assay (Fig. 1, *D*). In competition assays, preincubation of nuclear extracts prepared from SKGT-4 cells stimulated with HPE with a 100-fold molar excess of unlabelled NF-κB oligonucleotide completely abrogated HPE-induced NF-κB DNA complex (Fig. 1, *D*).

HPE Reduces IκB-α Protein Level

Western blotting with antibody against IκB-α showed that coculture of SKGT-4 cells with a freshly harvested *H pylori* suspension or *H pylori* extract (HPE) induced degradation of the 37 kDa band of IκB-α protein (Fig. 1, *E*). The decrease in IκB-α levels is coincident with the activation of NF-κB DNA-binding activity.

HPE Induces AP-1 DNA-Binding Activity

Coculture of SKGT-4 or OE33 cells with live *H pylori* or HPE induced AP-1 DNA-binding activity

Fig. 2. Effect of *H pylori* on AP-1 DNA-binding activity in esophageal epithelial cells. SKGT-4 or OE33 cells were cocultured with (**A**) a freshly harvested *H pylori* suspension strain 11638 (2×10^8 cfu/ml) or (**B**) 1 ml HPE for 1 hour. (**C**) Time course of AP-1 activation by HPE in SKGT-4 cells incubated with HPE between 30 minutes and 4 hours. Nuclear extracts were prepared and assayed for AP-1 binding activity in an EMSA reaction. (**D**) Super-shift assays were performed to identify the components of HPE-induced AP-1 DNA-complex. Nuclear extracts prepared from SKGT-4 cells stimulated with HPE were incubated with 2 μl of antibodies directed against various AP-1 species (anti-c-Fos, anti-Fra-1, anti-c-Jun, and anti-Jun-D) or 100-fold molar excess of unlabelled AP-1 oligonucleotide for 30 minutes before gel electrophoresis. Each experiment was repeated three times with similar results and a representative gel is shown.

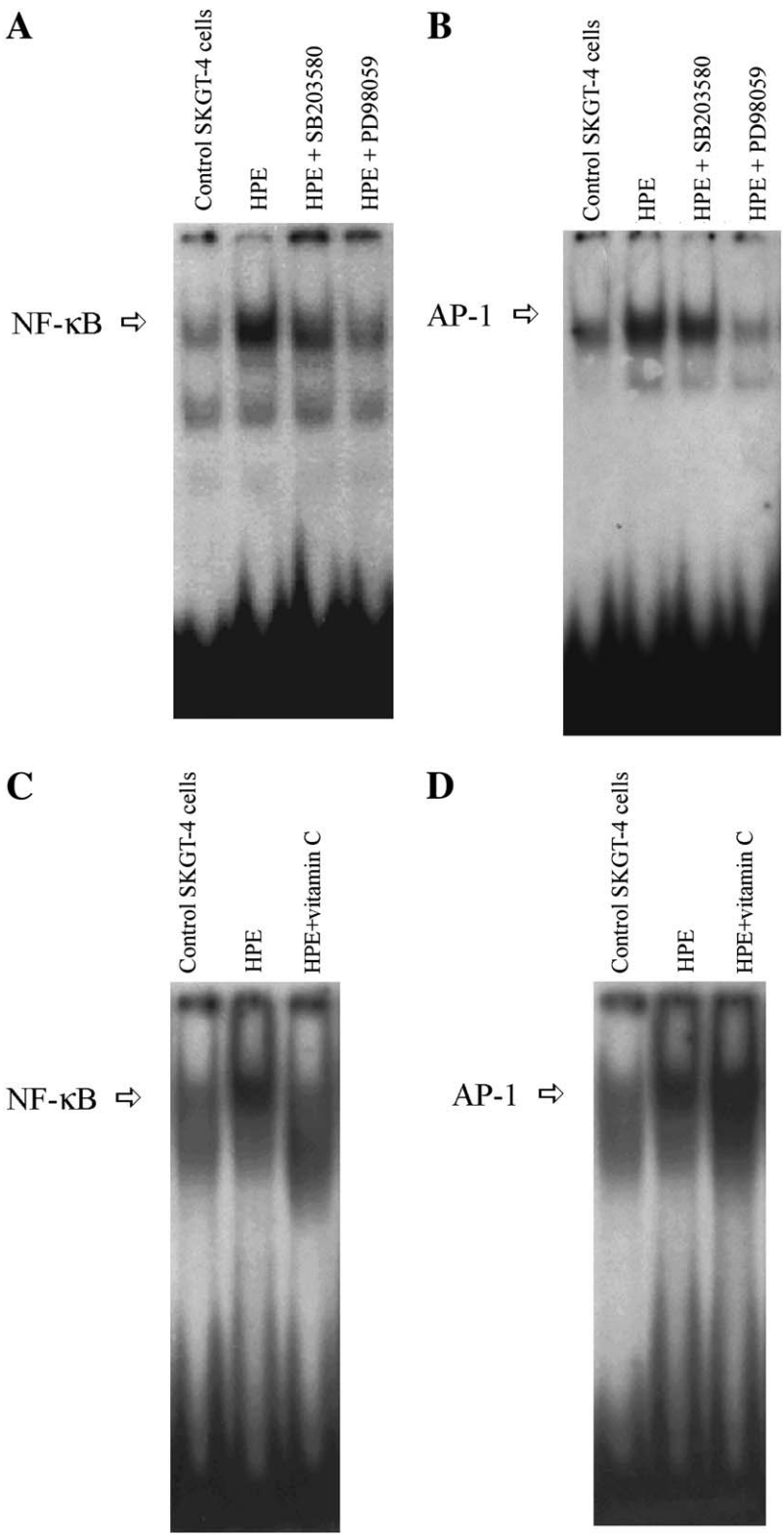

Fig. 4. Effect of MAPK inhibitors and vitamin C on HPE-induced NF-κB and AP-1. SKGT-4 cells were pretreated with the MAPK inhibitors PD98059 (20 μmol/L) and SB203580 (20 μmol/L) or the antioxidant vitamin C (20 mmol/L) for 30 minutes before incubation with HPE for 1 hour. Nuclear extracts were prepared and assayed for NF-κB (**A** and **C**) and AP-1 (**B** and **D**) DNA-binding activity in an EMSA reaction. One gel is shown of three different experiments with similar results.

(Fig. 2, *A*, *B*). HPE induced AP-1 in a time-dependent manner (Fig. 2, *C*). Super-shift studies were also performed to identify the components of the activated AP-1 complex using antibodies directed against various AP-1 species (anti-Fra-1, anti-c-Fos, anti-c-Jun, and anti-Jun-D). The reaction mixture containing nuclear extracts were preincubated with 2 μl of these antibodies for 30 minutes before gel electrophoresis. Band intensity decreased with the anti-Fra-1, whereas anti-Jun-D caused a super-shift of this complex (Fig. 2, *D*). The addition of 100-fold molar excess of unlabelled AP-1 oligonucleotide completely abolished AP-1 DNA complex formation (Fig. 2, *D*).

HPE, Not *H Pylori* Lipopolysaccharide, Induces NF-κB and AP-1

H pylori lipopolysaccharide (LPS) is reported to be less potent in activating NF-κB and eliciting cytokines. We have tested the difference in the capability of HPE and *H pylori* LPS in activating NF-κB and AP-1 in esophageal epithelial cells. SKGT-4 cells were incubated with purified *H pylori* LPS (15 μg/ml) for 1 hour and nuclear extracts were prepared and examined for NF-κB and AP-1 in electrophoretic mobility shift assay (EMSA) reaction. Here we found that incubation of SKGT-4 cells with HPE induced NF-κB and AP-1 DNA-binding (Fig. 3, *A*, *B*), whereas *H pylori* LPS was unable to induce NF-κB or AP-1 compared with HPE.

Signaling Pathway of NF-κB and AP-1 Activation by HPE

This addressed whether MAPK pathways are involved in NF-κB and AP-1 by HPE, as MAPK pathways have been shown to be involved in AP-1 induction.[21] To determine the signalling pathways involved in NF-κB induction by HPE, a panel of MAP kinase inhibitors were used. SKGT-4 cells were preincubated with the appropriate inhibitor for 30 minutes after which the cells were stimulated with HPE. Pretreatment of SKGT-4 cells with the MEK1/2 MAP kinase inhibitor PD98059 (20 μmol/L) completely inhibited NF-κB and AP-1 DNA-binding activity (Fig. 4, *A*, *B*), whereas the p38 MAP kinase inhibitor SB203580 (20 μmol/L) had no effect on NF-κB or AP-1 activation (Fig. 4, *A*, *B*).

NF-κB and AP-1 are redox-responsive transcription factors that their activities are affected by antioxidants. In addition, NF-κB and AP-1 also regulate genes regulating the oxidative stress response in inflammatory tissue. Therefore, we have tested the effect of vitamin C on *H pylori*-induced NF-κB and AP-1 activation in our cell culture model. Pretreatment of SKGT-4 cells with the antioxidant vitamin C (20 mmol/L) for 30 minutes before 1 hour stimulation with HPE abrogated HPE-induced NF-κB activation but enhanced AP-1 DNA-binding activity (Fig. 4, *C*, *D*).

H pylori Activates ERK1/2 Phosphorylation

SKGT-4 cells were incubated with live *H pylori* or HPE for 1 hour, and cell lysates were prepared and examined by Western blotting by using phospho-specific antibody to ERK1/2. Exposure of SKGT-4

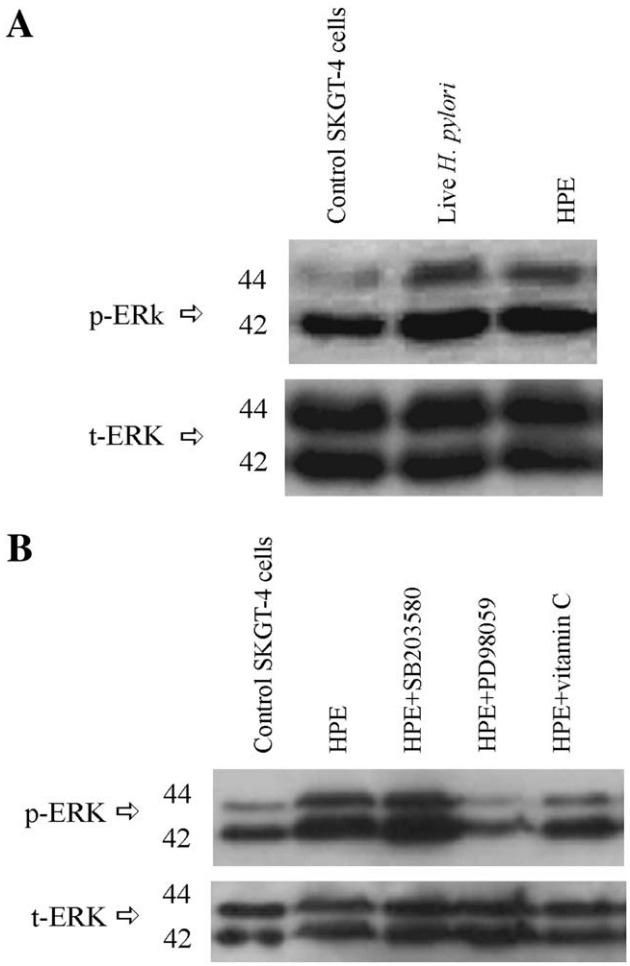

Fig. 5. HPE activates ERK1/2 phosphorylation. (**A**) SKGT-4 cells were incubated in the presence or absence of live *H pylori* or HPE for 1 hour. At the end of the incubation, total cell lysates were prepared and subjected to Western blotting using phospho-specific antibody to ERK1/2 (p44, upper band and p42, lower band). (**B**) Effect of the MAPK inhibitors SB203580 (20 μmol/L) and PD98059 (20 μmol/L) and vitamin C (20 mmol/L) pretreatment for 30 minutes before incubation with HPE for another 1 hour on ERK1/2 phosphorylation. For control experiments, total ERK1/2 was used as a control. These experiments were performed three times with similar results and one representative gel is shown.

cells to *H pylori* or HPE resulted in a marked increase in the phosphorylation of ERK1/2 (Fig. 5, *A*). Phospho-specific antibody to ERK1/2 recognized two phosphorylated bands, p44 (upper band) and p42 (lower band). Control SKGT-4 cells showed low or none of activated ERK1/2 activity. Pretreatment of SKGT-4 cells with different doses of PD98059 (1–50 μmol/L) before 1-hour stimulation with HPE inhibited ERK1/2 phosphorylation (Fig. 5, *A*). Similarly, vitamin C (20 mmol/L) partly inhibited ERK1/2, but SB203580 (20 μmol/L), a specific p38 inhibitor, had no effect on ERK1/2 phosphorylation (Fig. 5, *B*). For controls, antibody to total ERK1/2 was used as a control for protein loading.

H pylori and HPE Induce COX-2 Expression

The induction of the transcription factors NF-κB and AP-1 regulates a wide range of proteins that control apoptosis and proliferation, including COX-2. We hypothesized that *H pylori* or its product could affect COX-2 expression in esophageal epithelial cells. Coculture of SKGT-4 or OE33 cells with live *H pylori* or HPE resulted in the activation of COX-2 expression (Fig. 6, *A*). Pretreatment with the MAPK kinases inhibitors SB203580 (20 μmol/L) and PD98059 (20 μmol/L) or the antioxidant vitamin C (20 mmol/L) for 30 minutes before 1-hour incubation with HPE inhibited HPE-induced COX-2 expression (Fig. 6, *B*).

HPE Enhances IL-8 Production

Because NF-κB regulates the transcription of a variety of genes that are involved in the inflammatory process, we investigated the effect of HPE on IL-8 production in SKGT-4 cells. Incubation of SKGT-4 cells with HPE for 8 hours resulted in a marked increase in IL-8 production compared with untreated cells (Fig. 7). Pretreatment of SKGT-4 cells with PD98059 (20 μmol/L) or vitamin C (20 mmol/L) for 30 minutes before incubation with HPE for a further 8 hours significantly inhibited HPE-induced IL-8 production (P value < 0.05). However,

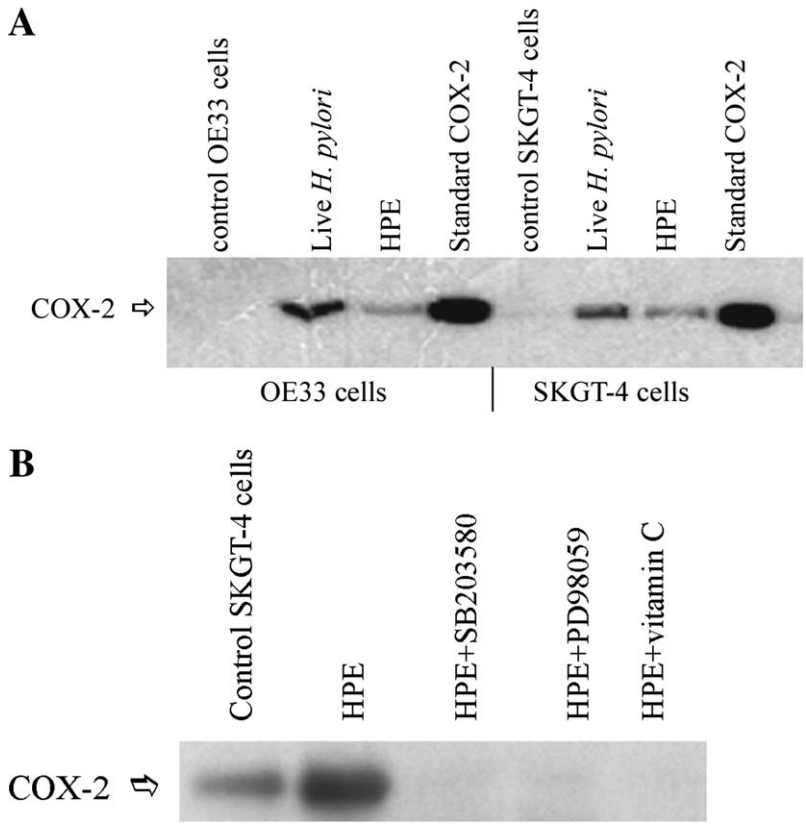

Fig. 6. HPE induces COX-2 expression. (**A**) SKGT-4 or OE33 cells were cocultured with 1 ml *H pylori* (2×10^8 cfu/ml) or HPE for 1 hour. Total cell extracts were prepared, separated by 10% polyacrylamide gels, blotted onto PVDF membrane, and probed with anti-COX-2 antibody. Lane 7 shows the standard COX-2 (72 kDa). (**B**) SKGT-4 cells were pretreated with the MAPK inhibitors SB203580 (20 μmol/L) and PD98059 (20 μmol/L) or vitamin C (20 mmol/L) for 30 minutes before incubation with HPE for another 1 hour. One gel is shown of three different experiments with similar results.

pretreatment of SKGT-4 cells with SB203580 (20 μmol/L) had no effect on HPE-induced IL-8 production (Fig. 7).

DISCUSSION

The present study demonstrates that *H pylori* and *H pylori* extract (HPE) induced the expression of NF-κB, AP-1, and COX-2 in esophageal epithelial cells. HPE also increased IL-8 production from esophageal epithelial cells. The data demonstrated a role for the MEK/ERK1/2 pathway in regulating NF-κB and AP-1 activation and IL-8 production by HPE, but not the p38 MAPK pathway, and showed that HPE activates ERK1/2 phosphorylation. Moreover, vitamin C pretreatment blocked NF-κB DNA-binding activity and COX-2 expression and IL-8 production, but not AP-1 activity in esophageal epithelial cells.

The role of *H pylori* in the pathogenesis of GERD remains controversial. Much attention has recently focused on a possible role for *H pylori* in GERD and its complications such as Barrett's esophagus and esophageal adenocarcinoma. A number of previous clinical studies are divided between those that show that *H pylori* infection has no role in the pathogenesis of GERD[4,5,7] and others that suggest a protective role for *H pylori* infection in GERD.[11–13] *H pylori* has been shown to release substances that inhibit gastric acid secretion.[22] Moreover, *H pylori* generates large amounts of ammonia,[23] which could decrease the corrosive potential of the gastric juice refluxing into the esophagus. This study in esophageal cancer cell lines suggests, however, a direct proinflammatory link between *H pylori* and GERD and demonstrates that *H pylori* activates molecular markers central to inflammation, including NF-κB, AP-1, and COX-2. Perhaps importantly, the response is induced by extract as well as live *H pylori*.

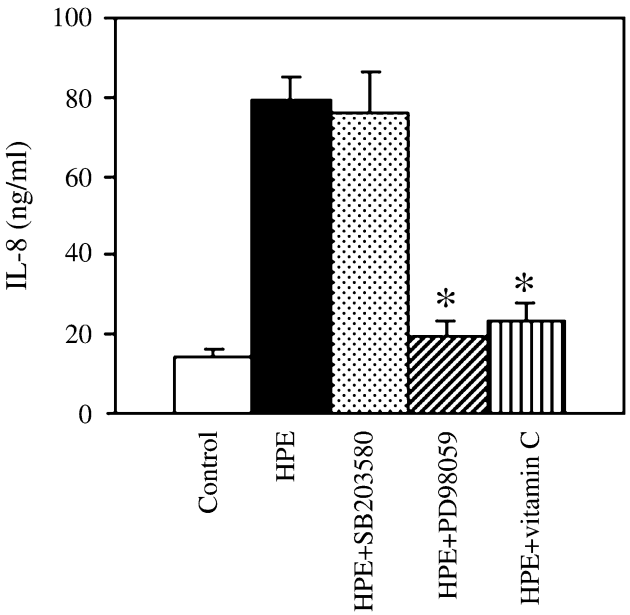

Fig. 7. Effect of HPE on IL-8 production. SKGT-4 cells (1×10^6 cells in 200 μl) grown in 96 well-plates were incubated with 100 μl HPE for 8 hours. The effect of pretreatment for 30 minutes with PD98059 (20 μmol/L), SB203580 (20 μmol/L) or vitamin C (20 mmol/L) on HPE induced IL-8 production is shown. Cell supernatants were then collected and assayed for IL-8 production by ELISA. Data are presented as mean ± standard error of the mean (SEM) of one representative experiment from three independent experiments with similar results; *P value < 0.05 vs. HPE-induced IL-8.

The NF-κB pathway is of particular interest, as it is pivotal in the regulation of genes involved in the host immune and inflammatory response.[14,15] NF-κB also functions in concert with other transcription factors including AP-1, whose transcriptional activation involves phosphorylation of MAP kinases. This dual pathway enhances production of proapoptotic and antiapoptotic proteins dependent on the cellular context. A number of studies implicate MAP kinases as upstream mediators of NF-κB, COX-2, and AP-1 activation and cytokine expression.[24,25] MAP kinases can be activated by a variety of agents and can transmit signals from the cell surface to the nucleus to regulate gene expression, cytokine production, cell proliferation, and cell survival. In this study, we found that incubation of esophageal epithelial cells with *H pylori* water extract results in phosphorylation of the ERK1/2 (p44/42) pathway. Despite the link between MAP kinases and NF-κB or AP-1 activation, we found that the specific MEK/ERK1/2 MAPK inhibitor PD98059 inhibited HPE-induced NF-κB and AP-1, but the p38 MAPK inhibitor SB203580 had no effect on NF-κB or AP-1 activity.

H pylori gastritis is accompanied by the release of numerous mediators, including prostaglandins, nitric oxide, and cytokines,[26–28] which may weaken the lower esophageal sphincter, damage mucosa, and promote an inflammatory response.[29–31] Moreover, direct injurious effects by *H pylori* bacterial factors including cytotoxin and phospholipase may augment this response. Water-soluble products of *H pylori* may form part of the esophageal refluxate, and in this respect, the finding in this study that *H pylori* water extract induced NF-κB, AP-1, and COX-2 expression in esophageal epithelial cells may be of clinical significance. A previous report by Kim et al.[24] demonstrated that upregulating COX-2 expression is by *H pylori* water-soluble proteins, and that NF-κB and MAP kinase signaling

are involved in the COX-2 induction. *H pylori* LPS was unable to induce such transcription, and it seems that *H pylori* LPS is not involved in NF-κB or AP-1 activation in our study, a finding previously reported in gastric epithelial cells.[32]

It has been demonstrated that gastroesophageal reflux enhances production of oxygen free radicals that might participate in causing damage to the esophageal mucosa, and that administration of free radical scavengers may prevent esophageal mucosal damage.[33,34] NF-κB and AP-1 also regulate genes regulating the oxidative stress response in inflammatory tissue. Here, we found that pretreatment with the antioxidant vitamin C blocked HPE-induced NF-κB, COX-2 activation, and IL-8 production, but not AP-1 activation. This suggests that inhibition of NF-κB and COX-2 expression by antioxidants such as vitamin C may protect against *H pylori*-induced inflammation.

In summary, *H pylori* and its extract (HPE) induce the regulatory transcription factors NF-κB and AP-1 and related cytokines in esophageal epithelial cells. This suggests both a direct mechanism from the pathogen and an indirect mechanism through HPE in the refluxate, whereby *H pylori* can induce inflammation at the cardia and distal esophagus. This may also theoretically induce a tumorigenic molecular phenotype, because NF-κB is associated with anti-apoptotic mechanisms. These preliminary studies in a cell line model need to be extended to studies in man.

REFERENCES

1. Parsonnet J. Helicobacter pylori: The size of the problem. Gut 1998;43(Suppl 1): S6.
2. Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum 1994;61:1–241.
3. Hosking SW, Ling TK, Chung SC, et al. Duodenal ulcer healing by eradication of Helicobacter pylori without antiacid treatment. Randomised controlled trial. Lancet 1994; 343:508–510.
4. Torrado J, Ruiz B, Garay J, et al. Blood-group phenotypes, sulfomucins, and Helicobacter pylori in Barrett's esophagus. Am J Surg Pathol 1997;21:1023–1029.
5. Wright TA, Myskow M, Kingsnorth AN. Helicobacter pylori colonization of Barrett's esophagus and its progression to cancer. Dis Esophagus 1997;10:196–200.
6. Goldblum JR, Vicari JJ, Falk GW, et al. Inflammation and intestinal metaplasia of the gastric cardia: The role of gastroesophageal reflux and H pylori infection. Gastroenterology 1998;114:633–639.
7. Voutilainen M, Farkkila M, Mecklin JP, Juhola M, Sipponen P. Chronic inflammation at the gastroesophageal junction (carditis) seems to be a specific finding related to Helicobacter pylori infection and gastroesophageal reflux disease. The Central Finland Endoscopy Study Group. Am J Gastroenterol 1999;94:3175–3180.
8. Graham DY. Helicobacter pylori infection in the pathogenesis of duodenal ulcer and gastric cancer: A model. Gastroenterology 1997;113:1983–1991.
9. El-Omar EM, Oien K, El-Nujumi A, et al. Helicobacter pylori infection and chronic gastric acid hyposecretion. Gastroenterology 1997;113:15–24.
10. Manes G, Mosca S, Laccetti M, Lioniello M, Balzano A. Helicobacter pylori infection, pattern of gastritis, and symptoms in erosive and nonerosive gastroesophageal reflux disease. Scand J Gastroenterol 1999;34:658–662.
11. Labenz J, Malfertheiner P. Helicobacter pylori in gastroesophageal reflux disease: Causal agent, independent or protective factor? Gut 1997;41:277–280.
12. Vicari JJ, Peek RM, Falk GW, et al. The seroprevalence of cagA-positive Helicobacter pylori strains in the spectrum of gastroesophageal reflux disease. Gastroenterology 1998; 115:50–57.
13. Chow WH, Blaser MJ, Blot WJ, et al. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Res 1998;58:588–590.
14. Kopp EB, Ghosh S. NF-κB and Rel proteins in innate immunity. Adv Immunol 1995;58:1–27.
15. Baeuerle PA, Henkel T. Function and activation of NF-κB in the immune system. Annu Rev Immunol 1994;12:141–179.
16. Abdel-Latif MM, O'Riordan J, Windle HJ, et al. NF-kappaB activation in esophageal adenocarcinoma: Relationship to Barrett's metaplasia, survival, and response to neoadjuvant chemoradiotherapy. Ann Surg 2004;239:491–500.
17. Jones AD, Bacon KD, Jobe BA, Sheppard BC, Deveney CW, Rutten MJ. Helicobacter pylori induces apoptosis in Barrett's-derived esophageal adenocarcinoma cells. J Gastrointest Surg 2003;7:68–76.
18. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1979;72:248–254.
19. Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature 1970;297: 680–685.
20. Osborn L, Kunkel S, Nabel GJ. Tumor necrosis factor alpha and interleukin-1 stimulate the human immunodeficiency virus enhancer by activation of the nuclear factor kappa B. Pro Natl Acad Sci USA 1989;86:2336–2340.
21. Whitmarsh AJ, Davis RJ. Transcription factor AP-1 regulation by mitogen-activated protein kinase signal transduction pathways. J Mol Med 1996;74:589–607.
22. Cave DR, Vargas M. Effect of a Campylobacter pylori protein on acid secretion by parietal cells. Lancet 1989;ii: 187–189.
23. Konturek SJ, Konturek PJ, Brzozowski T, Stachnura J, Zombala M. Gastric mucosal damage and adaptive protection by ammonia and ammonium ions in rats. Digestion 1996;57:433–445.
24. Kim JS, Kim JM, Jung HC, Song IS. Expression of cyclooygenase-2 in human neutophils activated by Helicobacter pylori water-soluble proteins: Possible involvement of NF-kappaB and MAP kinase signalling pathway. Dig Dis Sci 2001;46:2277–2284.
25. Matsumoto K, Hashimoto S, Gon Y, Nakayama T, Horie T. Proinflammatory cytokine-induced and chemical mediator-induced IL-8 expression in human bronchial epithelial cells through p38 mitogen-activated protein kinase-dependent pathway. J Allergy Clin Immunol 1998;101:825–831.

26. Laine L, Cominelli F, Sloane R, Casini-Raggi V, Marin-Sorensen M. Interaction of NSAIDs and Helicobacter pylori on gastrointestinal injury and prostaglandin production: A controlled double-blind trial. Aliment Pharmacol Ther 1995;9:127–135.
27. Wilson KT, Ramanujam KS, Mobley HLT, Musselman RF, James SP, Meltzer SJ. Helicobacter pylori stimulates inducible nitric oxide synthase expression and activity in a murine macrophage cell line. Gastroenterology 1996;111:1524–1533.
28. Noach LA, Bosma NB, Jansen J, Hoek FJ, van Deventer SJ, Tytgat GN. Mucosal tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-8 production in patients with Helicobacter pylori infection. Scand J Gastroenterol 1994; 29:425–429.
29. Genta RM, Huberman RM, Graham DY. The gastric cardia in Helicobacter pylori infection. Hum Pathol 1994;25:915–919.
30. Preikseitis HG, Tremblay L, Diamant NE. Nitric oxide mediates inhibitory nerve effects in human esophagus and lower esophageal sphincter. Dig Dis Sci 1994;39: 770–775.
31. Mukhopadhyyay A, Rattan S, Goyal RK. Effect of prostaglandin E2 on esophageal motility in man. J Appl Physiol 1975;39:479–481.
32. Keates S, Hitti YS, Upton M, Kelly CP. Helicobacter pylori infection activates NF-κB in gastric epithelial cells. Gastroenterology 1998;113:1099–1109.
33. Wetscher GJ, Hinder PR, Bagchi D, et al. Free radical scavengers prevent reflux esophagitis in rats. Dig Dis Sci 1995; 40:1292–1296.
34. Oh TY, Lee JS, Ahn BO, et al. Oxidative stress is more important than acid in the pathogenesis of reflux oesophagitis in rats. Gut 2001;49:364–371.

Minimally Invasive Surgery for Gastric Stromal Cell Tumors: Intermediate Follow-up Results

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Laparoscopic wedge resection of the stomach (LWS) has become the treatment of choice for patients with benign gastric tumors. The technical consideration and long-term follow-up data of LWS for gastrointestinal stromal tumors (GISTs) of the stomach are limited. We present our experience of 28 LWSs for gastric GISTs with a mean follow-up of 43 months. From October 1995 to December 2002, we successfully performed 28 LWSs for 29 patients with GISTs of the stomach, and one patient needed conversion to laparotomy because of suspected bowel injury when establishing pneumoperitoneum. Patient demographics, perioperative parameters, and outcomes of the 28 patients were assessed retrospectively. The tumors were located in the upper third of the stomach in 13 patients, in the middle third, in eight patients, and in the lower third, in seven patients. The mean size of tumors was 3.4 ± 1.6 cm in diameter. The duration of operation ranged from 95 to 390 minutes: 189.6 ± 79.5 minutes with the stapler method and 194.3 ± 50.5 minutes with the hand-sewn method ($P = 0.8870$). No blood transfusion was given in the perioperative period in all cases. Cholecystectomy in three patients and repair of hiatal hernia in one patient were performed during the same operation. The oral intake was restored at the third to fourth postoperative days. The hospital stay ranged from 3 to 11 days (mean, 6.7 ± 1.8 days). The follow-up period ranged from 12 to 95 months (mean, 43.3 ± 23.5 months, median 42 months). There has been no evidence of tumor recurrence, including one patient with microscopic invasion of section margin. LWS can be performed safely with a satisfactory remission rate for patients with gastric stromal cell tumors. (J GASTROINTEST SURG 2006;10:563–566) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Gastrointestinal stromal tumor, laparoscopy

Gastrointestinal stromal tumors (GISTs) encompass those neoplasms previously classified as gastric and intestinal smooth muscle tumors. GIST is now defined as a specific, c-kit–expressing mesenchymal tumor of the gastrointestinal tract.[1,2] Histologically, the cell types of GISTs vary from spindle cells to epithelioid and pleomorphic cells, and morphology differs somewhat by site.[3] A great majority of GISTs occur in the stomach (70%), followed by the small intestine (20%) and colon and rectum (5%).[4] The malignant potential of GISTs depends on their mitosis, size, and differentiation, but even GISTs with low mitotic figures were sometimes reported to recur locally or to metastasize.[5] Although a new targeting therapy with STI571 has been shown to be effective for controlling the growth of metastatic GISTs,[6] complete excision with clear resection margin and without tumor rupture remains the mainstay of treatment for primary GISTs.

Laparoscopic wedge resection of the stomach (LWS) has been recommended as an effective and technically feasible procedure for patients with benign gastric tumors.[7–9] However, the long-term results for the patients with GISTs undergoing LWS are limited. This retrospective study aims to assess the intermediate results of 28 patients that underwent LWS for gastric GISTs in a single institute.

MATERIAL AND METHODS

From October 1995 to December 2002, 50 consecutive patients with gastric GISTs received surgery at the Department of General Surgery, National Taiwan University Hospital, Taipei, Taiwan. Among

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them, 29 patients underwent LWS; the other 21 patients underwent laparotomy and gastrectomy. Patients with a submucosal tumor of the stomach were considered potential candidates for a laparoscopic resection if the tumor was well-defined on CT scanning, less than 7 cm, and did not involve esophagogastric junction or pylorus of the stomach. The 21 patients did not undergo laparoscopic surgery for reasons including major cardiothoracic diseases (two patients), tumors involving the esophagogastric junction or pylorus (five patients), emergent operation for bleeding (one patient), tumors larger than 5 cm and/or that had infiltrated surrounding tissue on CT scanning (10 patients), and patients who chose to receive open resection (three patients). All patients underwent panendoscopy, upper gastrointestinal barium meal study, and abdominal computed tomography and/or endoscopic ultrasonography before operation. Those patients with the pathological results other than GISTs of the stomach were excluded from this study. Panendoscopy, abdominal computed tomography, or abdominal sonography was performed every 6 months within 2 years of operation, and then for the detection of recurrence, every year at outpatient clinics from the third year of operation.

Data were obtained retrospectively by chart reviews and included symptoms, tumor size, resection margin, pathology, intraoperative and postoperative complications, length of hospital stay, and follow-up status. Statistical analysis was performed with Student's *t* test or Fisher exact test where appropriate.

RESULTS

Laparoscopic wedge resection for GIST of the stomach was completed in 28 of the 29 patients, and one patient needed conversion to laparotomy because of suspected bowel injury when establishing pneumoperitoneum. Only the 28 patients that completed the laparoscopic procedures were included in the analysis below. The demographics of these patients, including their symptoms and locations of tumors, are listed in Table 1. The tumors were located in the upper third of the stomach in 13 patients, in the middle third in eight patients, and in the lower third in seven patients; tumors were found in the anterior wall in eight patients, in the posterior wall in six patients, in the lesser curvature side in 10 patients, and in the greater curvature side in four patients. The size of tumors varied from 1.0 to 7.0 cm in diameter (mean, 3.4 ± 1.6 cm).

The methods for localization of tumors included the first, by direct vision or tactile sensation via the laparoscopic instrument; the second by gastroscopic guidance; and the third by anterior gastrotomy. Two kinds of wedge resection procedures were used: the stapler method with endo-gastrointestinal anastomosis in 20 patients and the hand-sewn method with gastrotomy and intracorporeal sutures in eight patients. The duration of operation ranged from 95 to 390 minutes: 189.6 ± 79.5 minutes with the stapler method and 194.3 ± 50.5 minutes with the hand-sewn method ($P = 0.8870$). No blood transfusion was given in the perioperative period in all cases. Cholecystectomy in three patients and repair of hiatal hernia in one patient were performed during the same operation. The oral intake was restored at the third to fourth postoperative day. The hospital stay ranged from 3 to 11 days (mean, 6.7 ± 1.8 days).

Table 1. Demographics of 28 patients who completed LWS of gastric GISTs

Gender	
Male: female	13:15
Age (year)	
range (mean)	19–79 (56.9 ± 12.4)
Symptoms	
Pain	9
Bleeding	7
Anorexia	1
Aymptomatic	11
Location of Tumors	
Stomach, upper third	13
Stomach, middle third	8
Stomach, lower third	7
Resection of tumor	
Stapler method	20
Hand-sewn method	8

In all cases but one, a free margin of normal gastric wall was confirmed pathologically. The only patient that had microscopic invasion of the resection margin was still disease-free at 51 months. Two of the 28 tumors showed more than five mitoses in 50 high-power fields, the others showed low or no mitosis in microscopic examination. The follow-up period ranged from 12 to 95 months (mean, 43.3 ± 23.5 months, median 42 months). There has been no evidence of tumor recurrence, either locally or systemically.

Twenty-one patients with GISTs of the stomach underwent open resection. Three patients underwent proximal gastrectomy, one of them suffered from anastomotic stricture and another patient had reflux esophagitis. One patient that received partial gastrectomy for a 6 cm tumor at midbody was found to have tumor invasion at the resection margin; the patient was lost to follow-up 1 month after surgery. The rest of the patients had uneventful postoperative

course, except that two of them had gastric ulcers found on follow-up panendoscopic examination. None of 20 patients were found to have recurrence of tumors during the 3 months to 62 months after surgery follow-up.

DISCUSSION

Complete resection with tumor-free margin and keeping the tumor intact during dissection are the two well-recognized principles to prevent postoperative recurrence of GISTs. Wedge resection of the stomach is generally effective for the control of tumors. Gastrectomy is reserved for GISTs involving the pylorus or esophagogastric junction, and dissection of lymph nodes has not been proved beneficial for the patients with gastric GISTs. With the advent of minimally invasive surgery, we and other groups have reported the initial success of laparoscopic resection of submucosal tumors of the stomach. However, the long-term results for patients with gastric GISTs treated by this technique are limited. This report summarized the experience of a single institute and showed that laparoscopic wedge resection of gastric GISTs is feasible and effective. Although one patient had microscopic tumor invasion of the section margin, she did not have any clinical evidence of recurrence for more than 51 months after surgery. According to the consensus proposed by the National Institute of Health,[10] GISTs with a high risk of metastases include those with tumors larger than 10 cm, those with mitosis more than 10 counts/50 high power field, or those with tumors larger than 5 cm and mitosis more than 5 counts/50HPF. We did not give the patient adjuvant chemotherapy (Glivec, Novatis, Basel, Switzerland), as the patient's tumor was 4 cm in diameter, and the mitosis was less than 5 counts/50 HPF. However, the benefits of adjuvant chemotherapy in high-risk groups of GIST patients deserve further study. We offered adjuvant Glivec to two patients with recurrent GISTs after R0 resection. One patient remained tumor-free for 12 months, whereas the other had rapid recurrence and metastases of tumors 3 months after he discontinued the drug.[11]

Some controversies still exist regarding the laparoscopic approach. The first is the difficult localization of small tumors growing inward (endophytic growth). We preferred the use of intraoperative gastroscopy, for it also helped to mark the resection margin precisely and check the absence of stenosis. The second controversy is the limited use of endogastrointestinal anastomosis to excise the tumors near the cardia or pylorus, as the stapler generally carries a larger resection than needed and increases the risk of stenosis. Tagaya et al.[5] recommended intragastric resection via laparoscopic approach for tumors located within 3 cm of the esophagogastric junction. We would tailor the resection by opening the stomach directly when a tumor was near the cardia or pylorus, and use intracorporeal suturing to close the gastric wound. Our initial data showed the operative time was not prolonged with the open approach, and no stenosis was recorded in our series, though larger patient numbers are needed to confirm this viewpoint. The third controversy is whether pneumoperitoneum increases the likeliness of tumor seeding. According to the experience of surgeons with the laparotomy approach, recurrence of GISTs after resection was predominantly intra-abdominal and involved the original tumor site, peritoneum, and liver.[12] The mean time from the operation to tumor recurrence is about 21 months.[13] There has been no report about the port-site implantation of GISTs. Our results also indicated that port-site implantation or intra-abdominal dissemination did not happen in the intermediate follow-up duration.

Some authors have advocated the use of intragastric surgery (Ohashi's method) for the submucosal lesions arising from posterior wall of the stomach.[14] We preferred adequate mobilization of the greater omentum and full-thickness excision of the gastric wall including the GIST for the prevention of tumor rupturing during mucosectomy.

In conclusion, the intermediate follow-up data showed that laparoscopic wedge resection is a safe and effective approach for the treatment of gastric GISTs. Except for large, wide-based tumors and tumors that involve the cardia or pylorus, the laparoscopic approach can be recommended as the first-line method for the treatment of gastric GISTs under an experienced surgical team.

REFERENCES

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577–580.
2. Rubin BP, Fletcher JA, Fletcher CDM. Molecular insights into the histogenesis and pathogenesis of gastrointestinal stromal tumors. Int J Surg Pathol 2000;8:5–10.
3. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: Recent advances in understanding of their biology. Hum Pathol 1999;30:1213–1230.
4. Strickland L, Letson GD, Muro-Cacho CA. Gastrointestinal stromal tumors. Cancer Control 2001;8:252–261.
5. Tagaya N, Mikami H, Kubota K. Laparoscopic resection of gastrointestinal mesenchymal tumors located in the upper stomach. Surg Endosc 2004;18:1469–1474.
6. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutation and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–4349.

7. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth muscle (stromal) tumors: Dependence on anatomic site. Am J Surg Pathol 1999;23: 82–87.
8. Cheng HL, Lee WJ, Lai IR, Yuan RH, Yu SC. Laparoscopic wedge resection of benign gastric tumor. Hepatogastroenterology 1999;46:2100–2104.
9. Basso N, Rosato P, De Leo A, et al. Laparoscopic treatment of gastric stromal tumors. Surg Endosc 2000;14: 524–526.
10. Fletcher C, Berman J, Coreless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459–465.
11. Lai IR, Hu RH, Chang KJ. Is imatinib justified as an adjuvant chemotherapy for patients with recurrent gastrointestinal stromal tumors. Hepatogastroenterology 2005;52:826–828.
12. Bouillot JL, Bresler L, Fagniez PL, et al. Laparoscopic resection of benign submucosal gastric tumors-A report of 65 cases. Gastroenterol Clin Biol 2003;27:272–276.
13. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: Recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51–58.
14. Hepworth CC, Mensies D, Motson RW. Minimally invasive surgery for posterior gastric stromal tumors. Surg Endosc 2000;14:349–353.

Efficacy and Safety of Ertapenem Versus Piperacillin-Tazobactam for the Treatment of Intra-Abdominal Infections Requiring Surgical Intervention

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Complicated intra-abdominal infections usually mandate prompt surgical intervention supplemented by appropriate antimicrobial therapy. The aim of this study was to demonstrate that ertapenem was not inferior to piperacillin-tazobactam for the treatment of community-acquired intra-abdominal infections. A randomized open-label active-comparator clinical trial was conducted at 48 medical centers on four continents from December 2001 to February 2003. Adult patients with intra-abdominal infections requiring surgery were randomized to receive either ertapenem 1 g daily or piperacillin/tazobactam 13.5 g daily in 3–4 divided doses. The primary analysis of efficacy was the clinical response rate in clinically and microbiologically evaluable patients at the test-of-cure assessment 2 weeks after completion of therapy. All treated patients were included in the safety analysis. Patient demographics, disease characteristics, and treatment duration in both treatment groups were generally similar. The most commonly isolated pathogens at baseline were *E coli* (greater than 50% of cases in each group) and *B fragilis* (~9%). Favorable clinical response rates were 107/119 (90%) for ertapenem recipients and 107/114 (94%) for piperacillin/tazobactam recipients. The frequencies of drug-related adverse events, most commonly diarrhea and elevated serum alanine aminotransferase levels, were similar in both treatment groups. Six of 180 ertapenem recipients (3%) and two of 190 piperacillin/tazobactam recipients (1%) had serious drug-related adverse experiences. In this study, ertapenem and piperacillin/tazobactam were comparably safe and effective treatments for adult patients with complicated intra-abdominal infections.
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KEY WORDS: Intra-abdominal infection, ertapenem, piperacillin-tazobactam

Complicated intra-abdominal infections are common problems for general surgeons and emergency medicine physicians.[1–6] The mainstay of appropriate management is timely surgical intervention combined with antimicrobial therapy to eradicate any residual infection. Empirical antibacterial therapy should cover the most likely pathogens, which include gram-positive and gram-negative aerobic and anaerobic bacteria that comprise the usual flora of the gastrointestinal tract.[6,7] All antimicrobial regimens recommended by the Surgical Infection Society and the Infectious Disease Society of America have broad activity against Enterobacteriaceae and the *B fragilis* group.[3,5]

Ertapenem is a long-acting parenteral Group I carbapenem active in vitro against most aerobic and anaerobic bacteria generally associated with community-acquired infections.[7–15] Ertapenem is not active against most *Pseudomonas aeruginosa* or enterococci, but coverage of these organisms is not routinely required for successful treatment of intra-abdominal infections.[3,5,16,17] In two earlier double-blind randomized clinical trials, ertapenem was comparably effective and as well tolerated as piperacillin-tazobactam[16]

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or ceftriaxone plus metronidazole[18] in the treatment of complicated intra-abdominal infections. The present study was undertaken to confirm the utility of ertapenem as once daily monotherapy for community-acquired intra-abdominal infections requiring surgical intervention.

METHODS

Study Design

This prospective, multicenter, open-label study was conducted at 48 centers on four continents from December 2001 to February 2003. The institutional review board at each site approved the protocol, and written informed consent was obtained from all participants. Hospitalized patients ⩾18 years of age with clinical evidence of an intra-abdominal infection requiring open or laparoscopic surgery were eligible for the study if the infection extended beyond the wall of a hollow organ. For patients enrolled preoperatively, signs and symptoms suggestive of an intra-abdominal infection had to include at least one of the following: fever, leukocytosis, hypotension, tachycardia and tachypnea, or altered mental status. Exclusion criteria included pregnancy or lactation; history of serious allergy or intolerance to either study drug; rapidly progressive or terminal illness; chronic immunosuppressive therapy; known infection with human immunodeficiency virus; APACHE II score greater than 30; concurrent infection that could interfere with evaluation of response to study therapy; ischemic bowel disease; uncomplicated cholecystitis; acute necrotizing pancreatitis; traumatic bowel perforation if surgery was performed within 12 hours of perforation; perforated gastroduodenal ulcer if surgery was performed within 24 hours of perforation; any primarily noninfectious intra-abdominal process; need for peritoneal or hemodialysis; acute hepatic failure; serum alanine or aspartate aminotransferase levels greater than six times the upper limit of normal; bilirubin or alkaline phosphatase levels greater than three times the upper limit of normal; and systemic antimicrobial therapy for greater than 24 hours in the 72-hour period immediately before study entry unless the patient had failed that therapy. Patients were withdrawn from the study if surgical intervention did not occur within 24 hours after diagnosis or all pathogens were resistant to either study drug. For polymicrobial infections, patients could remain in the study if at least one isolate was susceptible to both study drugs.

Patients were randomized in a 1:1 ratio to receive ertapenem 1 g once a day or piperacillin-tazobactam 3.375 g q6h or 4.5 g q8h using a computer-generated allocation schedule via an interactive voice recognition system that kept the treatment assignment blinded. Both drugs were infused intravenously over 30 minutes. After 2 days of intravenous therapy, ertapenem could be administered intramuscularly. Other than vancomycin or teicoplanin to treat infections caused by resistant gram-positive pathogens, concomitant antibacterial agents were not allowed. The suggested length of treatment was 4–14 days, but the exact duration for individual patients was determined by the site investigator.

Aerobic and anaerobic cultures of blood and intraoperative specimens were obtained at baseline and processed in the clinical microbiology laboratory of the participating hospitals. Aerobic and facultatively anaerobic isolates were tested for susceptibility to ertapenem and piperacillin-tazobactam by disk diffusion or microtiter dilution according to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS).[19,20] Routine susceptibility testing of strict anaerobes was not required per protocol.

Assessments of Efficacy and Safety

Clinical parameters were assessed daily during study therapy, at discontinuation of study therapy, and at 2 and 4 weeks post-therapy. The primary efficacy end point was designated a priori as the proportion of clinically and microbiologically evaluable patients with a favorable clinical assessment at the test-of-cure (TOC) visit 2 weeks after completion of all study therapy. The 4-week post-therapy evaluation could be accomplished by telephone contact if laboratory testing was not necessary and a clinic visit was not feasible.

The three clinical response categories were cure (complete resolution or significant improvement of all signs and symptoms related to the index infection such that no further antimicrobial therapy or surgical intervention for infection was necessary), failure (persistence or recurrence of the index infection; death attributable to intra-abdominal infection; the need for a second surgical procedure; or the occurrence of a postoperative wound infection), or indeterminate (data insufficient for evaluation of efficacy or cause of death). Patients with indeterminate clinical responses were excluded from the primary analysis. Microbiological responses were recorded for each baseline pathogen. Favorable microbiological responses included eradication of the pathogen(s) that was either documented or presumptive (no material available for culture in clinically cured patients); unfavorable microbiologic responses included persistence of the pathogen(s),

whether documented or presumed (no material available for culture in patients who had clinical failure). Microbiological responses for enterococci and methicillin-resistant *Staphylococcus aureus* in patients treated with vancomycin or teicoplanin were considered to be indeterminate; however, these patients remained clinically evaluable, and were also evaluable for the overall microbiological outcome provided that other pathogens susceptible to both study drugs were isolated at baseline. Patients with indeterminate microbiological responses for all their baseline isolates were considered to be microbiologically nonevaluable.

Patients were monitored for clinical adverse experiences throughout the study. The investigator rated the intensity of any clinical adverse event and determined the likelihood of its relation to the study drug. Adverse events judged by the investigator to be possibly, probably, or definitely related to study therapy were categorized as drug-related in the safety analysis.

Participant Evaluability

The treated population included all randomized patients who received at least 1 dose of study therapy. The modified intent-to-treat (MITT) population included all treated patients who met the disease definition. The clinically evaluable population was composed of MITT patients for whom sufficient information was available to determine outcome, no confounding factors were present that interfered with the outcome assessment, and if baseline pathogens were identified, at least one isolate was susceptible to both study drugs (anaerobes were presumed susceptible). Clinically and microbiologically evaluable patients were a subset of the clinically evaluable patients in whom a pathogen was identified at baseline and a microbiological response could be assessed.

Statistical Analysis

The primary hypothesis of the study was that ertapenem would be at least as effective as piperacillin-tazobactam, measured by the proportion of patients in the clinically and microbiologically evaluable population with a favorable clinical response at the TOC visit, after excluding patients with indeterminate clinical responses. The primary efficacy end point was the proportion of clinically and microbiologically evaluable patients with a favorable clinical assessment at the TOC visit. For the primary end point, the difference between response rates in the two treatment groups and the corresponding 95% confidence interval (CI) were calculated. Ertapenem was to be considered noninferior to piperacillin-tazobactam if the 95% CI for the difference in response rates (ertapenem minus piperacillin-tazobactam) contained 0, and its lower bound was not below −15%. The secondary end points (proportion of patients with a favorable clinical response in other populations and at other time points; proportion of patients with an overall favorable microbiological response) were analyzed using the methodology described for the primary end point. There was no adjustment for multiplicity because only one primary end point at a single time point had been prespecified.

The primary analysis was performed while the clinical monitor was still blinded to treatment assignment. In particular, participant evaluability was based on prespecified criteria and judged by clinical personnel blinded to the patient's assigned treatment group. After the initial evaluability assessment was completed and the database formally unblinded, it was recognized that some of the prespecified criteria for evaluability had not been applied with strict consistency by investigators across the different sites. In addition, some follow-up data were missing. To assess the impact of these problems, a post hoc sensitivity analysis of the primary and main secondary efficacy end points was conducted using the evaluable population after correcting for inconsistencies in the application of evaluability criteria and missing follow-up data.

The safety evaluation included all patients treated with at least 1 dose of study drug. Adverse experiences occurring during the treatment period or within 14 days after the last dose of study therapy were recorded. For prespecified safety end points in the 2-treatment groups, the differences in proportions were compared with the Fisher exact test.

RESULTS

All 370 randomized participants received at least 1 dose of study drug and thereby constituted the treated population (Fig. 1). Three hundred twenty (87%) of the treated patients completed the study. Of the other 50 patients who prematurely discontinued the study, 24 patients moved, withdrew consent, or were lost to follow-up. An additional seven ertapenem recipients and 10 piperacillin-tazobactam recipients experienced a clinical adverse event resulting in discontinuation; three more piperacillin-tazobactam recipients left the study because of lack of efficacy. The study was discontinued in another four patients for protocol violations, and two patients died. A total of 233 treated patients (63%) were clinically and microbiologically evaluable at the primary TOC time point.

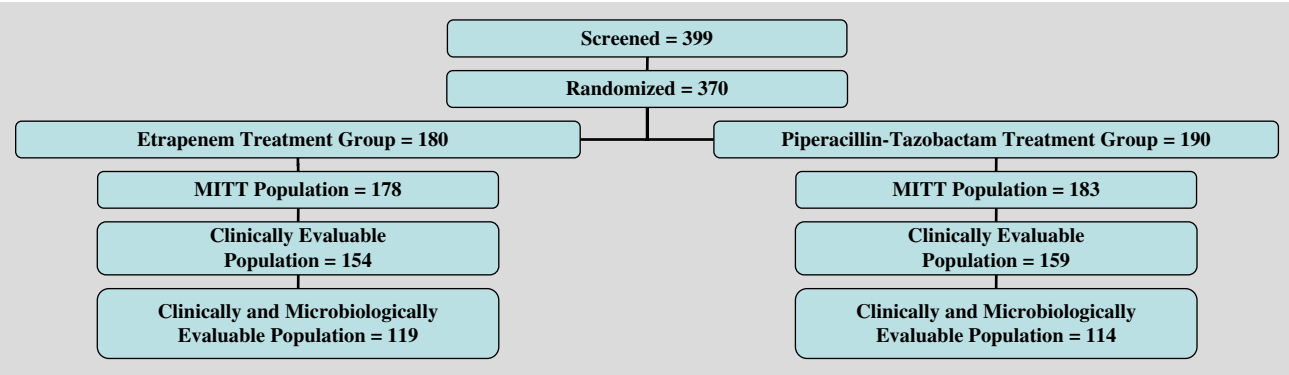

Fig. 1. Patient accounting in the prespecified analysis. Three hundred ninety-nine patients were screened for the study, of which 370 (93%) were randomized. All randomized patients were treated with at least 1 dose of study drug. The primary population for the analysis of efficacy was prespecified as the clinically and microbiologically evaluable subjects. All treated patients were included in the safety analysis. MITT = modified intention to treat.

Baseline demographic and disease characteristics for the treated population and the clinically and microbiologically evaluable population were similar in both treatment groups (Table 1). Seventy-six percent and 70% of treated patients in the ertapenem and piperacillin-tazobactam groups, respectively, had at least one pathogen identified at baseline from intraoperative and/or blood cultures. The most common pathogens isolated at baseline in each treatment group were *E coli* (54% in the ertapenem group and 52% in the piperacillin-tazobactam group), followed by *B fragilis* (9% and 10%, respectively, in the ertapenem and piperacillin-tazobactam groups). The large majority of baseline isolates were susceptible to both study regimens. *P aeruginosa* and enterococci were infrequently recovered at baseline. The median length of therapy was 6 days in each treatment group for both the treated as well as in the clinically and microbiologically evaluable populations. Two (1%), five (3%), and 30 (17%) of the ertapenem recipients and six (3%), six (3%), and 29 (16%) of the piperacillin-tazobactam recipients, respectively, received vancomycin or teicoplanin, nonprotocol antibiotics during study therapy after day 1, and antibiotics during the 2 weeks after the study drug was discontinued.

The favorable response rates by treatment group in the prespecified analysis are shown in Table 2 for various study populations and time points. For the primary clinically and microbiologically evaluable population, favorable clinical response rates were 107/119 (89.9%) in the ertapenem treatment group and 107/114 (93.9%) in the piperacillin-tazobactam treatment group at TOC; the difference (95% CI) between the two treatment groups was −3.9 (−11.5, +3.4), satisfying the prespecified criteria for noninferiority. Clinical response rates for both treatment groups were also similar in the clinically evaluable patients at TOC. For the MITT population, favorable clinical response rates were 82% for ertapenem recipients and 85% for piperacillin-tazobactam recipients. The overall microbiological response rates in the clinically and microbiologically evaluable population at TOC were 94% in the ertapenem treatment group and 98% in the piperacillin-tazobactam treatment group. Response rates per pathogen are presented in Table 3. At TOC, 16 of 17 (94%) ertapenem recipients and 9 of 9 (100%) piperacillin-tazobactam recipients infected by *P aeruginosa* and/or *E faecalis* had a favorable response. The time to defervescence was almost identical in both treatment groups. Greater than 50% of all patients with fever on the first day of study therapy had become afebrile by the third day of study therapy. Only one patient (who had received piperacillin-tazobactam) relapsed during the 4 weeks after completion of study therapy.

In the post hoc analysis, which corrected for missing data and inconsistent application of evaluability criteria, favorable clinical response rates for the primary clinically and microbiologically evaluable population at TOC were 116/124 (93.5%) of ertapenem recipients and 110/118 (93.2%) of piperacillin-tazobactam recipients. The treatment difference (95% CI) was +0.3 (−6.4, +7.2). The results of the other post hoc analyses[21,22] were consistent with and very similar to the corresponding prespecified analyses.

Clinical and laboratory adverse experiences occurred with similar frequency in both treatment groups (Table 4). The most common drug-related adverse events in each treatment group (ertapenem vs. piperacillin-tazobactam recipients) were gastrointestinal (6.7% vs. 6.3%), most commonly diarrhea (4.4% vs. 3.2%), and elevation of serum alanine

Table 1. Baseline demographic and disease characteristics of all treated participants and the clinically and microbiologically evaluable participants with complicated intra-abdominal infection by treatment group

	All treated patients*		Clinically and microbiologically evaluable patients at test-of-cure visit†	
	Ertapenem (N = 180)	Piperacillin-tazobactam (N = 190)	Ertapenem (N = 119)	Piperacillin-tazobactam (N = 114)
Male gender (%)	119 (66.1)	120 (63.2)	80 (67.2)	75 (65.8)
Age mean years (range)	48 (18–89)	49 (18–87)	48 (18–89)	46 (18–87)
Baseline APACHE II score				
Median (range)	2 (0–20)	2 (0–32)	2 (0–18)	2 (0–20)
n (%) > 10	7 (3.9)	8 (4.2)	5 (4.2)	3 (2.6)
Site of infection (%)				
Appendix	110 (61)	115 (60.5)	77 (64.7)	76 (66.7)
Colon	23 (12.8)	27 (14.2)	19 (16.0)	17 (14.9)
Gallbladder or biliary tract	13 (7.2)	9 (4.8)	6 (5.0)	5 (4.4)
Stomach or duodenum	20 (11.1)	19 (10.0)	8 (6.7)	5 (4.4)
Small intestine (beyond the duodenum)	7 (3.9)	12 (6.3)	4 (3.4)	8 (7.0)
Other	7 (3.9)	8 (4.2)	5 (4.2)	3 (2.6)
Infectious process (%)				
Abscess	37 (20.6)	33 (17.4)	27 (22.7)	24 (21.1)
Generalized peritonitis	49 (27.2)	48 (25.3)	32 (26.9)	30 (26.3)
Localized peritonitis	39 (21.7)	49 (25.8)	22 (18.5)	26 (22.8)
Gastrointestinal perforation	43 (23.9)	46 (24.2)	30 (25.2)	27 (23.7)
Postoperative infection at enrollment (%)	15 (8)	10 (5)	11 (9.2)	7 (6.1)

*All 370 randomized patients received at least 1 dose of study drug.
†Clinically and microbiologically evaluable patients were a subset of the clinically evaluable patients in whom a pathogen was identified at baseline and a microbiological response could be assessed, and constituted the primary efficacy population.

aminotransferase levels (2.3% vs. 3.2%). No other specific drug-related adverse events occurred in ⩾3% of patients in either treatment group. Six ertapenem recipients (3.3%: four recipients with abdominal abscesses, one recipient with abnormal hepatic function, and one recipient with an uneventful overdose) and two piperacillin-tazobactam recipients (1.1%; one recipient with vomiting, abnormal renal and hepatic function, and one recipient with fatal sepsis) experienced serious drug-related adverse events. Discontinuation rates due to drug-related adverse events were similar in both groups. There were a total of 14 deaths (five patients in the ertapenem group and nine patients in the piperacillin-tazobactam group) during study therapy or within 14 days post-treatment. All deaths were judged by the investigators as unrelated to the study drug except for one sepsis-related death in the piperacillin-tazobactam group that was considered possibly related to study drug. The deaths were primarily due to complications of severe infections and/or underlying comorbid illness.

DISCUSSION

Intra-abdominal infections encompass a wide variety of infections and are commonly grouped into uncomplicated or complicated cases.[1–5,23–25] Complicated intra-abdominal infections require open or closed surgical procedures in addition to antimicrobial therapy. Inadequate source control and inappropriate antimicrobial therapy constitute major causes of therapeutic failure. Selection of antimicrobial drugs must take into account the complex normal aerobic and anaerobic flora of the bowel.[3–5,23,25,26] Enterobacteriaceae and the *B fragilis* group of anaerobes are becoming increasingly resistant to many drugs traditionally used to treat mixed infections, even when they are acquired in the community.[12,27]

Ertapenem, a long-acting parenteral Group I carbapenem, is active in vitro against most aerobic and anaerobic bacteria found in community-acquired intra-abdominal infections.[7–11,13,15,28–30] Ertapenem is not reliably active against enterococci, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other nonfermentative aerobic gram-negative bacilli. Ertapenem was as efficacious as piperacillin-tazobactam[16] or ceftriaxone plus metronidazole[18] in separate double-blind randomized clinical trials of the therapy of complicated intra-abdominal infections. The microbiological response rates of ertapenem-treated patients with enterococci among their baseline isolates in

Table 2. Favorable response rates at all time points in evaluable patients by treatment group

	Treatment group				Comparison between treatment groups
	Ertapenem		Piperacillin/tazobactam		
	n*/N†	%	n*/N†	%	Difference (95% CI)
Clinical response rates in clinically and microbiologically evaluable patients					
End of therapy	129/132	97.7	117/121	96.7	1.0 (−3.6, 6.2)
Test of cure‡	107/119	89.9	107/114	93.9	−3.9 (−11.5, 3.4)
Late follow-up	90/102	88.2	91/99	91.9	−3.7 (−12.5, 4.9)
Clinical response rates in clinically evaluable patients					
End of therapy	164/167	98.2	163/169	96.4	1.8 (−2.1, 6.0)
Test of cure	142/154	92.2	148/159	93.1	−0.9 (−7.1, 5.2)
Late follow-up	122/134	91.0	129/141	91.5	−0.4 (−7.5, 6.5)
Overall microbiological response rates in clinically and microbiologically evaluable patients					
Test of cure	108/115	93.9	107/109	98.2	−4.3 (−10.5, 1.1)
Clinical response rates in MITT§ patients					
Test of cure	145/178	81.5	155/183	84.7	−3.2 (−11.1, 4.6)

*n = number of evaluable patients with a favorable response.
†N = number of evaluable patients.
‡Primary end point.
§Modified intention-to-treat.

polymicrobial infections have been comparable with those of piperacillin-tazobactam recipients, even when vancomycin use was excluded.[17]

The present randomized open-label study confirms these previously published results. The majority of patients in both treatment arms had appendicitis and APACHE scores ⩽5. The most commonly isolated pathogens at baseline in our study were *E coli* and *B fragilis*. Favorable clinical response rates were 90% for ertapenem recipients and 94% for piperacillin-tazobactam recipients at the TOC visit. Despite ertapenem's lack of consistent activity against *P aeruginosa* and *E faecalis*, 16 of 17 ertapenem-treated patients infected by these pathogens responded favorably regardless of the minimum inhibitory concentrations in vitro. The high favorable clinical response rates in patients infected with *E faecalis* and *P aeruginosa* treated with ertapenem implies that routine enterococcal or pseudomonal coverage is not essential in many community-acquired intra-abdominal infections, consistent with the current recommendations from the Surgical Infection Society[3] and the Infectious Disease Society of America.[5] Serious drug-related adverse experiences were uncommon in both treatment groups. The most common drug-related adverse events were diarrhea and other gastrointestinal disorders, and elevated aminotransferase levels. Discontinuation of study therapy due to drug-related adverse experiences was unusual.

Ertapenem remains active against *E coli* and *Klebsiella* species that produce extended spectrum β–lactamases[10,31] as well as against most members of the increasingly resistant *B fragilis* group of anaerobes.[7,9,27,28] These resistant bacteria are becoming more widespread in both nosocomial and community-acquired infections. Its spectrum of antibacterial activity makes ertapenem a potentially attractive choice for the empirical treatment of intra-abdominal

Table 3. Clinical response rates in clinically and microbiologically evaluable patients at the test-of-cure visit by treatment group and most common baseline pathogens

	Treatment group			
	Ertapenem (N = 199)		Piperacillin/tazobactam (N = 114)	
Baseline pathogens	n/m	%	n/m	%
Escherichia coli	74/84	88.1	79/85	92.9
Klebsiella oxytoca	7/7	100.0	2/2	100.0
Klebsiella pneumoniae	9/11	81.8	4/4	100.0
Proteus mirabilis	5/5	100.0	4/4	100.0
Pseudomonas aeruginosa	10/10	100.0	4/4	100.0
Bacteroides sp.	3/4	75.0	6/6	100.0
Bacteroides fragilis	12/14	85.7	13/14	92.9
Enterococcus faecalis	6/7	85.7	6/6	100.0
Staphylococcus epidermidis	5/5	100.0	2/2	100.0
Streptococcus sp.	13/13	100.0	5/6	83.3

m = number of evaluable patients with the specific pathogen identified at baseline; N = Number of evaluable patients; n = number of evaluable patients with the specific pathogen identified at baseline and with a favorable clinical response at TOC.

Table 4. Number of patients with adverse events by treatment group

	Ertapenem N = 180	Piperacillin/ tazobactam N = 190	Comparison between treatment groups Difference (95% CI)
Clinical adverse experiences			
Any AE, n (%)	98 (54.4)	105 (55.3)	−0.8 (−10.9, 9.3)
Drug-related* AE, n (%)	24 (13.3)	23 (12.1)	1.2 (−5.7, 8.2)
Serious AE†, n (%)	26 (14.4)	34 (17.9)	−3.5 (−11.0, 4.2)
Serious drug-related* AE, n (%)	6 (3.3)	2 (1.1)	2.3 (−0.9, 6.2)
Drug-related* AE leading to discontinuation of the study, n (%)†	3 (1.7)	3 (1.6)	0.1 (−3.1, 3.4)
Deaths‡, n (%)	5 (2.8)	9 (4.7)	−2.0 (−6.4, 2.2)
Local infusion/injection related events			
Local reaction at site†, n/m (%)	8/179 (4.5)	18/190 (9.5)	−5.0 (−10.6, 0.2)
Laboratory adverse experiences			
Any AE, n (%)	32 (17.8)	38 (20.0)	−2.2 (−10.2, 5.9)
Drug-related* AE, n (%)	11 (6.1)	9 (4.7)	1.4 (−3.5, 6.5)
Serious AE, n (%)	0 (0.0)	2 (1.1)	−1.1 (−3.8, 1.1)
Serious drug-related* AE, n (%)	0 (0.0)	1 (0.5)	−0.5 (−2.9, 1.6)
Drug-related* AE leading to discontinuation of the study, n (%)	0 (0.0)	0. (0.0)	0.0 (−2.0, 2.1)

AE = adverse experiences.
*Determined by the investigator to be possibly, probably, or definitely related to study drug.
†Primary safety end points.
‡All deaths resulted from complications of severe infections and/or underlying comorbid illnesses and were judged to be unrelated to study drug, except for one patient treated with piperacillin/tazobactam who died as a result of sepsis, felt by the investigator to be "possibly" related to the study drug.

infections. The results of this study indicate that ertapenem once daily was as effective and well tolerated as piperacillin/tazobactam administered 3–4 times a day for the treatment of complicated intra-abdominal infections.

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REFERENCES

1. Barie PS. Management of complicated intra-abdominal infections. J Chemother 1999;11:464–477.
2. Holzheimer RG, Muhrer KH, L'Allemand N, Schmidt T, Henneking K. Intra-abdominal infections: Classification, mortality, scoring and pathophysiology. Infection 1991;19: 447–452.
3. Mazuski JE, Sawyer RG, Nathens AB, et al. The Surgical Infection Society Guidelines on antimicrobial therapy for intra-abdominal infections: An executive summary. Surg Infect (Larchmt) 2002;3:161–173.
4. Rotstein OD, Meakins JL. Diagnostic and therapeutic challenges of intra-abdominal infections. World J Surg 1990; 14:159–166.
5. Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. Clin Infect Dis 2003;37:997–1005.
6. Wacha H, Hau T, Dittmer R, Ohmann C. Risk factors associated with intra-abdominal infections: A prospective multicenter study. Peritonitis Study Group. Langenbecks Arch Surg 1999;384:24–32.
7. Goldstein EJ, Snydman DR. Intra-abdominal infections: Review of the bacteriology, antimicrobial susceptibility and the role of ertapenem in their therapy. J Antimicrob Chemother 2004;53(Suppl):ii29–ii36.
8. Curran M, Simpson D, Perry C. Ertapenem: A review of its use in the management of bacterial infections. Drugs 2003; 63:1855–1878.
9. Goldstein EJ, Citron DM, Vreni MC, Warren Y, Tyrrell KL. Comparative in vitro activities of ertapenem (MK-0826) against 1,001 anaerobes isolated from human

intra-abdominal infections. Antimicrob Agents Chemother 2000;44:2389–2394.
10. Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus Enterobacteriaceae with potent beta-lactamases. Antimicrob Agents Chemother 2001;45:2831–2837.
11. Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. J Antimicrob Chemother 2003;52: 331–344.
12. Pelak BA, Woods GL, Teppler H, Friedland I, Bartizal K, Motyl M. Comparative in-vitro activities of ertapenem against aerobic bacterial pathogens isolated from patients with complicated intra-abdominal infections. J Chemother 2002;14:227–233.
13. Shah PM, Isa-acs RD. Ertapenem, the first of a new group of carbapenems. J Antimicrob Chemother 2003;52:538–542.
14. Solomkin J, Teppler H, Graham DR, et al. Treatment of polymicrobial infections: Post hoc analysis of three trials comparing ertapenem and piperacillin-tazobactam. J Antimicrob Chemother 2004;53(Suppl):ii51–ii57.
15. Wexler HM. In vitro activity of ertapenem: review of recent studies. J Antimicrob Chemother 2004;53(Suppl):ii11–ii21.
16. Solomkin JS, Yellin AE, Rotstein OD, et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intra-abdominal infections: Results of a double-blind, randomized comparative phase III trial. Ann Surg 2003;237: 235–245.
17. Teppler H, McCarroll K, Gesser RM, Woods GL. Surgical infections with enterococcus: Outcome in patients treated with ertapenem versus piperacillin-tazobactam. Surg Infect (Larchmt) 2002;3:337–349.
18. Yellin AE, Hassett JM, Fernandez A, et al. Ertapenem monotherapy versus combination therapy with ceftriaxone plus metronidazole for treatment of complicated intra-abdominal infections in adults. Int J Antimicrob Agents 2002;20:165–173.
19. National Committee for Clinical Laboratory Standards (NCCLS). Performance standards for antimicrobial disk susceptibility tests. Approved standard M2-A7, 7th ed. Wayne, PA: National Committee for Clinical Laboratory Standards, 2000.
20. National Committee for Clinical Laboratory Standards (NCCLS). Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically. Approved standard M7-A5, 5th ed. Wayne, PA: National Committee for Clinical Laboratory Standards, 2000.
21. dela Pena AS, Asperger W, Warren B, Kafka R, Raz R, Shivaprakash M, Vrijens F, Giezek H, Chan C, Stek M. Microbiological results from a randomized, open-label study of etapenem vs. piperacillin/tazobactam for the treatment of community-acquired intra-abdominal infections (IAI) requiring surgery. Presented at the 14th European Congress of Clinical Microbiology and Infectious Diseases. Prague, Czech Republic, May 1–4, 2004; Poster P1685.
22. dela Pena, AS, Asperger, W, Kockerling, F, Raz, R, Kafka R, Warren, B, Shivaprakash M, Vrijens, F, Giezek, H, Chan C. Ertapenem versus piperacillin/tazobactam for the treatment of intra-abdominal infections (IAI) requiring surgical intervention (OASIS-1): results of a prospective, randomized, open-label study. Presented at the 14th European Congress of Clinical Microbiology and Infectious Diseases, May 1–4, 2004; Prague, Czech Republic, Poster P1686.
23. Christou NV, Turgeon P, Wassef R, Rotstein O, Bohnen J, Potvin M. Management of intra-abdominal infections. The case for intraoperative cultures and comprehensive broad-spectrum antibiotic coverage. Arch Surg 1996;131:1193–1201.
24. Cooper GS, Shlaes DM, Salata RA. Intra-abdominal infection: Differences in presentation and outcome between younger patients and the elderly. Clin Infect Dis 1994;19: 146–148.
25. Elsakr R, Johnson DA, Younes Z. Oldfield EC III. Antimicrobial treatment of intra-abdominal infections. Dig Dis 1998;16:47–60.
26. Goldstein EJ. Intra-abdominal anaerobic infections: Bacteriology and therapeutic potential of newer antimicrobial carbapenem, fluoroquinolone, and desfluoroquinolone therapeutic agents. Clin Infect Dis 2002;35:S106–S111.
27. Hecht DW. Prevalence of antibiotic resistance in anaerobic bacteria: Worrisome developments. Clin Infect Dis 2004; 39:92–97.
28. Aldridge KE. Ertapenem (MK-0826), a new carbapenem: Comparative in vitro activity against clinically significant anaerobes. Diagn Microbiol Infect Dis 2002;44:181–186.
29. Brismar B, Nord CE. Monobactams and carbapenems for treatment of intra-abdominal infections. Infection 1999;27: 136–147.
30. Cunha BA. Ertapenem. A review of its microbiologic, pharmacokinetic and clinical aspects. Drugs Today (Barc) 2002; 38:195–213.
31. Gesser RM, McCarroll K, Teppler H, Woods GL. Efficacy of ertapenem in the treatment of serious infections caused by Enterobacteriaceae: Analysis of pooled clinical trial data. J Antimicrob Chemother 2003;51:1253–1260.

Surgery Is Justified in Patients With Bowel Obstruction Due to Radiation Therapy

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The management of the patient with radiation-induced bowel obstruction remains controversial. To reassess the surgical therapy for radiation-induced bowel obstruction, we analyzed 22 patients operated upon at the National Taiwan University Hospital. In 10 patients, peritoneal carcinomatosis was found during operation. We classified them as "recurrence group" and the remaining 12 patients as the "study group." Three patients in the study group had metastases, which did not cause bowel obstruction. The clinical presentation and image findings of both groups were not significantly different. The patients of the study group tended to have a low body mass index (mean ± SD, 18.7 ± 1.92 kg/m^2) and decreased serum albumin level (mean ± SD, 3.12 ± 0.32 g/dl). Total parenteral nutrition was given for 27.1 ± 16.0 days (mean ± SD). The strategies of operation included resection and anastomosis (nine patients), bypass (two patients), or ileostomy (one patient). Operation resolved bowel obstruction and enteral nutrition was resumed in all the patients postoperatively. No early postoperative mortality occurred. Four patients had morbidity, including one reoperation because of anastomotic failure, one enterovesical fistula, and two cases of wound infection. The estimated median survival time of the study group (21 months) was significantly longer than that of the recurrence group (5 months). Specifically in the patients without previous neoplasm recurrence or metastasis, overall survival was 100%, 80%, and 53%, at 1, 2, and 5 years after surgery, respectively. We conclude surgery plays a role in both diagnostic and therapeutic aspects of radiation bowel injury. For selected patients, resection and primary anastomosis is an appropriate choice. (J GASTROINTEST SURG 2006;10:575–582) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Radiotherapy, radiation injuries, intestinal obstruction

Abdominal and/or pelvic radiotherapy play a role in the treatment of many colorectal, gynecologic, and urologic malignancies. The therapeutic dosage of radiation, however, inevitably produces some damage to the surrounding tissues, especially the bowel. The manifestation of radiation bowel injury varies in severity from transient nausea and diarrhea to life-threatening obstruction and perforation.

The management of the patient with radiation-induced bowel obstruction remains controversial. It has been proposed that victims of bowel radiation injury are seldom able to tolerate opreation,[1] and therefore conservative treatment is superior to surgical intervention. However, some authors advocate the importance of aggressive and immediate surgical intervention for these patients.[2]

We report our experience with surgical treatment in patients with bowel obstruction after radiation therapy of malignancy. We hypothesize that surgery plays a role in the patients of radiation bowel injury in terms of diagnosis and treatment and propose the factors regarding the choice of surgical strategies.

MATERIAL AND METHODS

From 1993 to 2003 at the National Taiwan University Hospital, 22 patients underwent laparotomy due to bowel obstruction after radiation treatment for malignancies. The age of the patients ranged from 32 to 88 years (mean ± SD, 58.1 ± 12.1 years). The primary diseases included rectal cancer (14 patients), endometrial cancer (2 patients), cervical cancer (4 patients), and inguinal lymph node metastasis with nasopharyngeal cancer (1 patient). Twenty-one patients had undergone abdominal surgery before radiotherapy (Table 1), and 18 patients had received chemotherapy.

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Table 1. Operation prior to radiotherapy in study patients

Operation method	No. of Patients
Low anterior resection	11
Hartmann's procedure	2
Abdominoperineal resection	2
Total abdominal hystectomy + bilateral salpingoophorectomy + partial omentectomy	6
Total	21

Peritoneal carcinomatosis was found during laparotomy and was responsible for the intestinal obstruction in 10 patients. We classified the patients with peritoneal carcinomatosis (7 women and 3 men) as the "recurrence group" and the remaining 12 patients (6 women and 6 men) as the "study group." The clinical presentation, image findings, and survival time were compared between the two groups. It should be noted, however, that not all of the patients in the study group are free of neoplasm. Three patients of the study group had metastatic lesions in lung, liver, and distant lymph nodes, respectively. None of the metastatic lesions caused intestinal obstruction in the patients.

Medical records were reviewed thoroughly. Data collected included body mass index and albumin level on admission, use of total parenteral nutrition (TPN), operation method, treatment outcome, and length of stay. In reviewing the clinicopathologic features of the patients, the continuous data were presented as mean ± SD. Pearson χ^2 test, Fisher exact test, and log-rank test were used where applicable. Survival of these patients was estimated by the Kaplan-Meier method. Significance was set at $P < 0.05$.

RESULTS

Radiation Dosage and Latency Period

The radiation dosage of study group ranged from 3000 to 6000 cGy (mean ± SD, 4880.0 ± 844.0 cGy) over 17 to 43 fractions. The latency period between the last course of radiotherapy and intestinal obstruction ranged from 1 to 96 months, with the mean ± SD being 26.5 ± 25.2 months. Except for one patient (the latency period was 96 months), bowel obstruction occurred to the remaining patients of study group within 28 months after radiotherapy. The latency period of these 11 patients was 11.5 ± 8.7 months (mean ± SD).

One patient in our series experienced bowel obstruction 1 month after the last course of radiotherapy. He had NPC with lumbar spine and inguinal lymph node metastasis. Radiotherapy on the lumbar area and inguinal area started since 15 months prior to the operation. We believed the latency period of radiation injury was actually longer than 1 month in this patient.

Clinical Presentation and Image Findings

The clinical presentations of the recurrence and study groups are listed in Table 2. Abdominal distention, pain, and nausea/vomiting were common symptoms in both groups. The two groups showed no significant difference in the clinical presentation. One patient in the study group and two patients in the recurrence group had concomitant fistula on admission. The diagnosis of bowel obstruction was made on the basis of supine or erect roentgenograms of the abdomen. The abdominal radiographs showed distended fluid-filled loops of bowel proximal to the obstruction (Fig. 1, *A*). Abdominal computer tomography (CT) revealed dilated bowel loops with bowel wall thickening (Fig. 1, *B*). In more than half of the study group patients, CT can demonstrate suspected peritoneal tumor recurrence or masses with undetermined nature. Ascites was also noted in a significant portion of patients in both groups (Table 2).

The patients of the study group tended to have a low body mass index and decreased serum albumin level (Figs. 2 and 3). Oral intake was so meager that TPN was prescribed for all patients. The interval from symptomatic onset to operation and the duration of TPN use are shown in Figure 4.

Surgical Pathology and Outcome

During surgery, the affected bowel loops were found at terminal ileum in eight patients, jejunum in one patient, and sigmoid colon in one patient. The other two patients had more than one site

Table 2. Clinical presentation and image findings of the study and recurrence groups

Clinical presentation and image finding	No. of patients (%)		*P* Value
	Study group (n = 12)	Recurrence group (n = 10)	
Abdominal distention	12 (100%)	10 (100%)	
Abdominal pain	6 (50%)	8 (80%)	0.2
Nausea/vomiting	10 (83.3%)	8 (80%)	1.0
Recurrence suspected or equivocal mass on preoperative image	7 (58.3%)	7 (70%)	0.7
Ascites	4 (33.3%)	5 (50%)	0.7

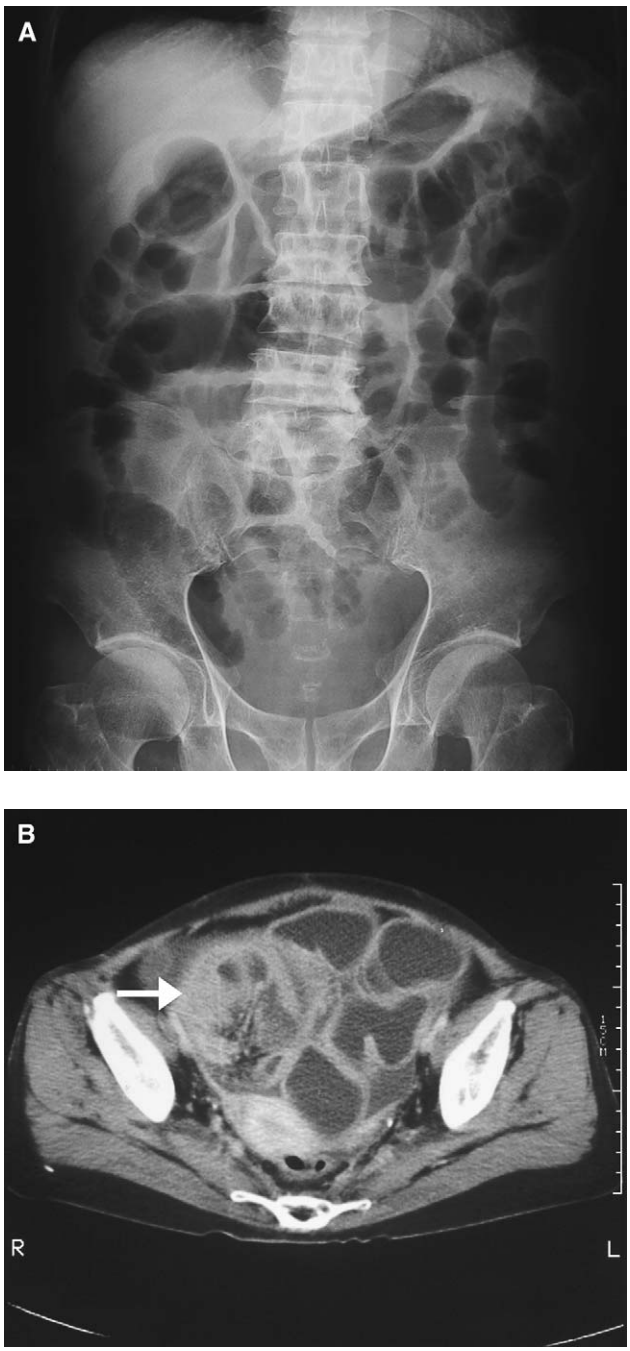

Fig. 1. (**A**) The chronic and partial ileus seen in the plain abdominal radiograph in a patient with ileus 2 years after radiotherapy. (**B**) Computer tomography showing dilated bowel loops with thickening bowel wall (*arrow*).

affected: jejunum and ileum in one patient, and jejunum as well as sigmoid colon in the other patient. These affected loops were socked into the pelvis, which was compatible with the radiation field. The loops were adhered to the pelvic floor or adjacent organs by dense adhesive bands. The adhesion bands were so extensive that complete dissection was not feasible in three of our patients. The operative findings included one or multiple segments of fibrosis and narrowing, adhesion band with strangulation of the bowel, and dilatation as well as edematous change of the bowel (Fig. 5, *A*).

The histological examination of the radiation-injured bowel showed chronic inflammation or even ulcers of the mucosa, suggesting the effects of chronic ischemia. No acute inflammation, however, was found on pathological examination. There was extensive submucosal and muscular fibrosis. The intima of arteries was unusually thickening, which obstructed the lumen of arteries (Fig. 5, *B*). Numerous reactive fibroblasts can be seen in the fibrotic stroma.

The operation method and complications are shown in Table 3. The choice of surgical strategies was based on the patient's condition, operative findings, and surgeon's preference. The creation of stoma was our last choice due to its marked disadvantages (marked fluid and electrolyte loss). When anastomosis was performed either in bypass or after resection, we preferred the grossly healthy and pinkish intestinal segments that laid away from the low abdomen and pelvis. The anastomosis of small bowel to transverse colon was the most common type of anastomosis, performed in eight patients. Two patients underwent segmental resection of small bowel and then primary anastomosis. One patient underwent anterior resection and partial resection of urinary bladder for sigmoid stricture. We did not perform any protective stoma in this series.

There was no early mortality (within 30 days after operation) in this series. Only one patient with anastomotic failure underwent further surgery. Enteral nutrition was resumed in all 12 patients following operation, and the duration from the operation to the start of the patients' oral intake was 8.0 ± 2.3 days (mean ± SD). The intravenous fluid was discontinued on day 12.0 ± 4.3 (mean ± SD) postoperatively. The length of hospital stay after the operation ranged from 10 to 41 days, and the mean ± SD was 17.5 ± 10.0 days.

We followed the patients for a mean period of 16 months, ranging from 6 to 60 months. The patient undergoing anterior resection and partial cystectomy developed enterovesical fistula 1 month after the operation. This patient died of extensive metastasis of NPC 4 months after the operation and therefore did not undergo secondary surgery for fistula. One patient undergoing bypass and one undergoing resection experienced intermittent abdominal pain, which could be managed by medical treatment. No bowel obstruction occurred again during the follow-up period. The only patient receiving stoma creation refused further operation for stoma closure.

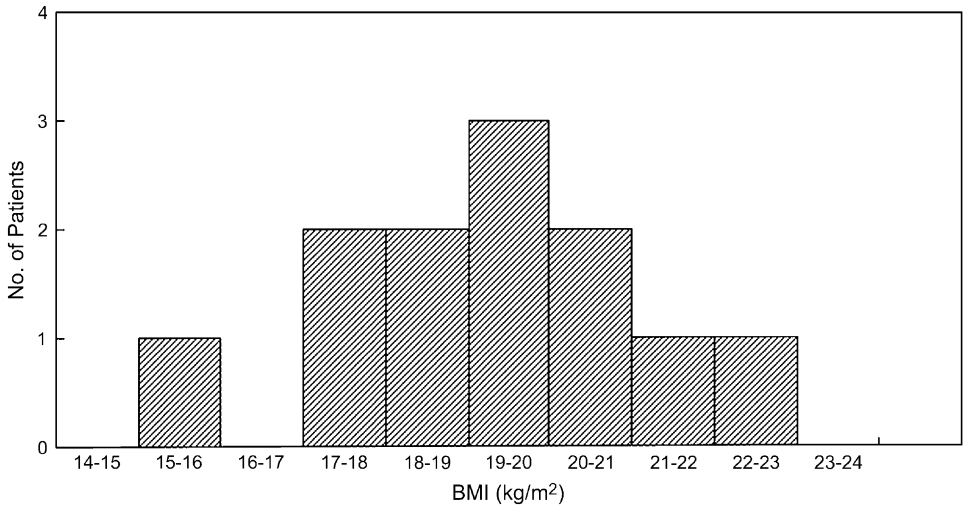

Fig. 2. The histogram shows the distribution of the BMI of the patients on admission. The mean ± SD was 18.7 ± 1.92 kg/m^2, and no patient had a BMI of higher than 23 kg/m^2.

Five patients of the study group died during the follow-up period, due to distant metastatic lesions in three patients, perforated peptic ulcer in one patient, and respiratory failure in one aged patient with pulmonary tuberculosis. The estimated median survival time (Fig. 6) of the study group (21 months) was significantly longer than that of the recurrence group (5 months, $P < 0.001$). Specifically in the patients without previous neoplastic disease recurrence or metastasis, overall survival was 100%, 80%, and 53%, at 1, 2, and 5 years after surgery, respectively.

DISCUSSION

Intestinal damage is a common and significant complication of radiation therapy for pelvic and abdominal malignancies. The incidence of such complications has been estimated to approach 10%.[3,4] Among the various manifestations of radiation-induced bowel injury, intestinal obstruction is the most frequent presentation[5,6] and also a difficult challenge facing surgeons. Most of our patients experienced partial bowel obstruction initially, and then the condition deteriorated to total obstruction

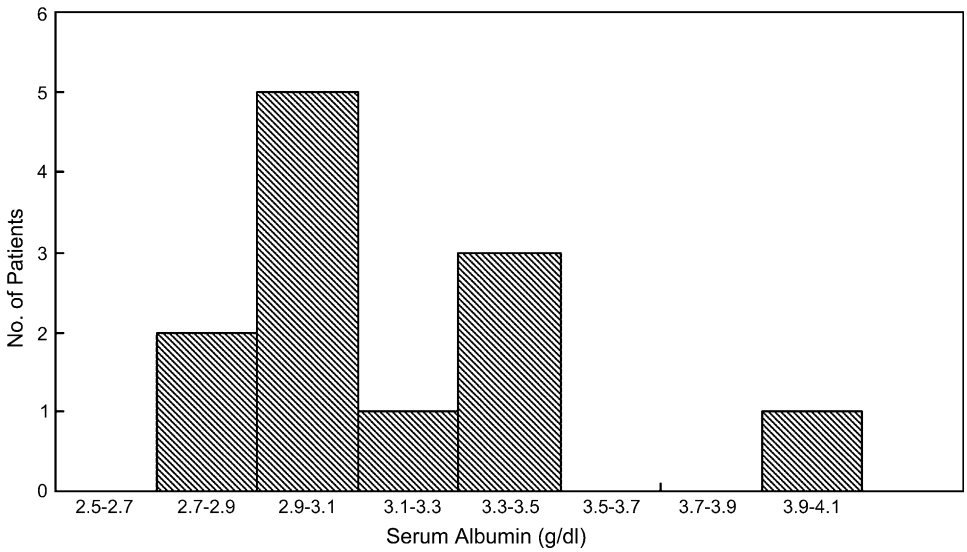

Fig. 3. The histogram shows the distribution of the patients' serum albumin level on admission. The mean ± SD was 3.12 ± 0.32 g/dl. Only one patient had the albumin level above the low limit of normal value, 3.5 g/dl.

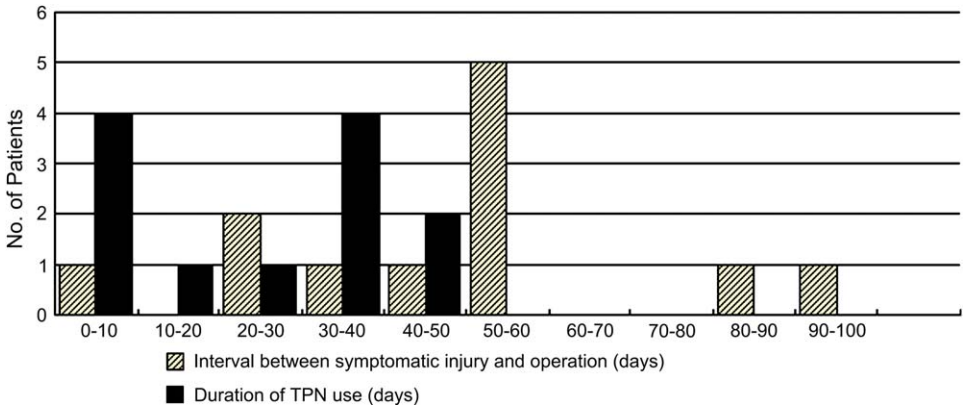

Fig. 4. The interval between symptomatic injury and laparotomy as well as the duration of TPN in our patients. Only one patient underwent surgery within 10 days after the onset of symptoms, and six patients received TPN for longer than 1 month. The interval from the onset of the patient's symptoms to the surgical intervention was 54.5 ± 23.0 days (mean ± SD), and the duration of TPN use was 27.1 ± 16.0 days (mean ± SD).

in weeks or months. The long interval from symptom onset to operation reflects the insidious nature of radiation bowel injury.

In these patients presenting bowel obstruction after radiotherapy for malignant diseases, the most common diagnostic dilemma is to distinguish radiation enteritis from peritoneal infiltration by recurrence of malignant tumor, that is, peritoneal carcinomatosis. In 12 of our 22 patients (54.5%), radiation injury was the primary cause responsible for bowel obstruction, instead of intra-abdominal tumor recurrence. Because tumor recurrence and radiation enteritis have similar radiographic features,[7] differential diagnosis is sometimes difficult without a laparotomy. Merely based on the preoperative image finding, up to 42% of our patients in the study group were suspected to have peritoneal cancer recurrence. On the other hand, 30% of the recurrence group were not noted to have cancer recurrence on imaging. Previous studies showed similar observations.[8,9] In this regard, surgery not only facilitates an accurate diagnosis of etiology but also allows prompt and appropriate treatment for patients.[8]

Bowel decompression is an effective method of treatment for some of the patients with bowel obstruction. Conservative treatment with bowel decompression is appropriate for the initial management of bowel obstruction.[10–12] However, if radiation injury is the primary etiological factor in bowel obstruction, only a small percentage of patients will respond to conservative treatment.[13] In one previous report, only 12 of 33 patients (36.4%) with radiation bowel injury experienced the resolution of their obstruction under conservative management by Cantor tube decompression.[9] Of 12 patients who had experienced resolution after bowel decompression, 4 patients developed obstruction later.[9] Furthermore, conservative treatment is not completely safe. It carries the potential risk of bowel strangulation and subsequently increases morbidities. Strangulated bowel has been observed at operation in about 6% of the patients receiving conservative management.[14] Some authors do not suggest prolonged conservative treatment for more than 5 days, because it is not only ineffective but also possibly harmful.[14,15]

Nutrition support is essential for the patients with radiation enteritis. Most of the patients in our series were lean. The low body weight is a predisposing factor of radiation bowel injury.[16,17] Remarkable body weight loss[18] may also contribute to the patient's emaciation. In our series, all patients experienced remarkable body weight loss, and preoperative prescription of TPN was therefore necessary. Eleven (91.7%) of the study group also presented with hypoalbuminemia, which is common in critically ill patients. It is well documented that hypoalbuminemic patients have a higher morbidity and mortality rate when compared with patients with a normal serum albumin.[19] Although TPN may provide nutrition support in the short term, prolonged use of TPN is unable to reverse the hypoalbuminemia.[20] Moreover, hypoalbuminemia can be worsened by artificial intravenous nutrition with sodium, water, and glucose.[21] Even in severely malnourished patients, the suggested duration of TPN administration is 7−10 days, with an expected reduction of overall complications of approximately 10%.[22] Prolonged or aberrant use of TPN may cause increased incidence of septic complications.[22]

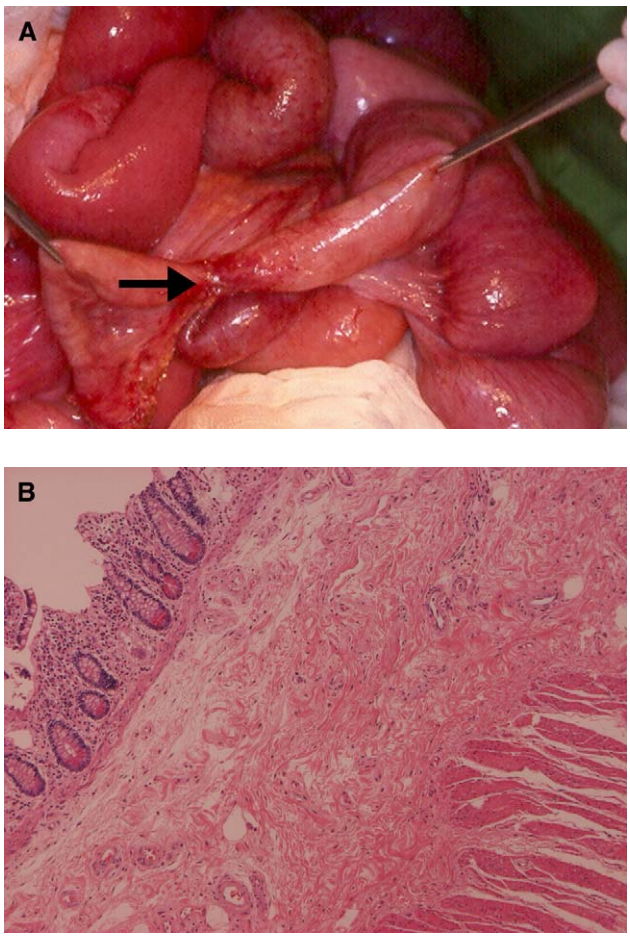

Fig. 5. (**A**) Typically, the lesion of radiation injury showed segmental stenosis and fibrosis of the bowel (*arrow*). The affected segment was nearly obstructed, and the bowel proximal to the lesion was marked dilated. (**B**) Microscopically, chronic inflammation and extensive fibrosis were found in the mucosa and submucosa of the radiation-injured ileum (hematoxylin-eosin, original magnification ×40).

For both diagnostic and therapeutic reasons, we suggest prompt surgical intervention for all patients with bowel obstruction due to previous radiotherapy for malignancies. According to our data, the outcome of laparotomy is fair. In an early report,[16] 100% of the patients died of overwhelming infection, following resection of necrotic perforated small bowel. Remarkably, there was no mortality in our case series. The marked improvement of surgical outcome may be attributed to the better nutritional support, the advance of surgical techniques, and, probably most importantly, in-time surgical intervention.

Histopathologically, delayed radiation enteritis is characterized by diffuse collagen deposition and progressive, occlusive vasculitis. The vasculitis and fibrosis progress over time, resulting in narrowing

Table 3. Morbidity of operation for bowel obstruction due to radiation injury

Strategy of operation	No. of Patients	Morbidity
Resection and anastomosis	9	2 (1 enterovesical fistula, 1 leakage)
Bypass surgery	2	1 (wound infection)
Ileostomy	1	1 (wound infection)
Total	12	4

of the intestinal lumen with dilation of the bowel proximal to the stricture. The affected segments of intestine and serosa become thickened. Ulceration, necrosis, fistula, and occasional perforation of the intestinal wall may occur.[23] The characteristics of extensive fibrosis and chronic ischemia significantly increase the difficulty of surgical dissection and the risk of anastomotic failure in our patients and other series.[5] It has been known that cytokines and growth factors involved in fibroblast activation and collagen deposition are central components of radiation-induced fibrosis.[24] Elevated activity of transforming growth factor β1 (TGF-β1) was found in the affected loops.[25] It has been proposed a future clinical trial be undertaken of interferon γ (IFN-γ), which inhibits excessive stimulation of TGF-β1.[26]

There are still debates about the surgical strategies for radiation bowel injury. Some authors argue that resection carries a higher risk of anastomotic leakage than bypass surgery.[5] In view of preventing massive resection and subsequent short bowel syndrome, stricturoplasty has been performed successfully in some selected patients.[27] However, resection of the injured bowel is the preferred choice in this series, because it enables the removal of overtly diseased bowel and consequently prevents the progression of radiation injury. Enteral nutrition was recovered postoperatively in all of our patients although leakage occurred in one patient. One recent report also supports similar management protocol, in which 37 of the 39 patients with the obstructive radiation enteritis type underwent extended intestinal resection with anastomosis.[28] There are several considerations in the decision of bowel resection: the remaining length of bowel, the anastomotic site, and the severity of adhesion. If the remaining length is not adequate to maintain the patient's nutritional status, resection of bowel should be abandoned. Furthermore, the grossly healthy bowel loops away from the radiation field (e.g., transverse colon and jejunum) are the optimal intestinal segments for anastomosis. The anastomotic leakage rate can be reduced from 50% to 7% by carrying out combined excision of the ileal

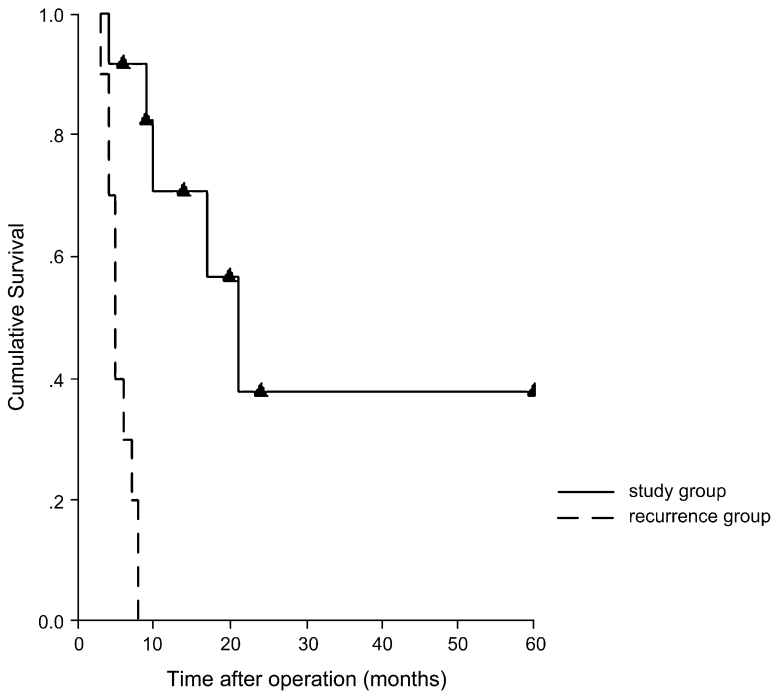

Fig. 6. Kaplan–Meier survival curve of the patients after operation. The median survival of the study group was 21 months, and the estimated 5-year survival rate was 37.7%. On the other hand, the median survival of the recurrence group was 5 months (*dashed line*), and no patients in the recurrence group lived for longer than 8 months after operation. There is a significant difference between the two groups ($P < 0.001$, log-rank test).

end and ascending colon and anastomosing the ileum and the transverse colon, mainly due to the relatively little injury to transverse colon by radiation.[29] The severity of adhesion of injured organs is also one factor in making decision to excise the bowel, although some authors do not support this opinion.[28] The extent of dissecting adhesion should be adequate to release the anastomotic tension, but unnecessary dissection may result in unwanted tissue damage and severe sequelae. One patient in our series developed fistula 1 month after resection of sigmoid colon and partial cystectomy. In our opinion, the newly developed enterovesical fistula was related to the damage to both colon and urinary bladder caused by extensive dissection. The occurrence of fistula seemed too early to be due to the ongoing radiation effects. We therefore do not suggest the strategy of bowel resection when resection of urinary bladder or vagina is necessary for release of adhesion.

On the other hand, bypass surgery is regarded as a safe method of treatment if unaffected segments are chosen for anastomosis.[5,18] In comparison with resection of diseased bowel, the requirement of dissection and therefore tissue damage are minimal in bypass surgery. Nevertheless, bypass surgery has two drawbacks: first, bacterial overgrowth in the close loop can lead to diarrhea and abdominal pain[30,31]; and second, progression of radiation injury may cause necrosis, perforation, and fistulization months or years after the bypass procedure.[18] It needs to be mentioned that small bowel stoma is suggested only in desperately ill patients, because it carries the risk of progressive radiation injury in approximately 30% of patients.[5] There was no progression of radiation injury observed in our patients undergoing bypass during the follow-up period. However, it can possibly occur later, because our mean follow-up period is 16 months. Furthermore, one of the two patients undergoing bypass subsequently developed frequent abdominal cramping pain and required hospitalization.

Postoperative survival in this group of patients mainly depends on whether the malignant disease recurs. In our series, all of the 13 patients with peritoneal recurrence or metastasis died within 1 year after operation. However, it is somewhat surprising that the survival rate in the patients free of neoplasm is only 53%, not as high as we originally thought. In a recent report including patient suffering from all types of radiation bowel injury, the reported 5-year survival in disease-free patients is 69%.[28] The lower survival rate in our series than that report can be

partly explained by that we enrolled only the patients of obstruction and excluded those with bleeding, perforation, or fistulas. Mortality occurred in our two patients without primary disease recurrence, due to pulmonary tuberculosis and perforated peptic ulcer, respectively. Although the causes of their mortality are not related to radiation injury, prolonged undernourishment may substantially decrease the patient's resistance against septic process and eventually precipitate the death. Careful long-term care is still necessary for these weak patients even after successful surgery resolving the radiation enteritis.

CONCLUSION

In conclusion, patients with bowel obstruction related to radiation bowel injury are malnourished. Surgery plays a vital role in both diagnostic and therapeutic aspects. We suggest that the timing of surgery should be as early as possible in order to improve treatment outcome. Resection of the injured bowel is suitable for those patients without risk of postoperative short bowel syndrome or severe adhesion to adjacent organs. Grossly healthy segments of intestine away from radiation field were the optimal choice for anastomosis.

REFERENCES

1. Lindahl F. Intestinal injuries following irradiation for carcinoma of the uterine cervix and vesical carcinoma. Acta Chir Scand 1970;136:725–730.
2. Mortensen E, Nilsson T, Vesterhauge S. Treatment of intestinal injuries following irradiation. Dis Colon Rectum 1974; 17:638–643.
3. DeCosse JJ, Rhodes RS, Wentz WB, et al. The natural history and management of radiation induced injury of the gastrointestinal tract. Ann Surg 1969;170:369–384.
4. Palmer JA, Bush RS. Radiation injuries to the bowel associated with the treatment of carcinoma of the cervix. Surgery 1976;80:458–464.
5. Meissner K. Late radiogenic small bowel damage: Guidelines for the general surgeon. Dig Surg 1999;16:169–174.
6. Lillemoe KD, Brigham RA, Harmon JW, et al. Surgical management of small-bowel radiation enteritis. Arch Surg 1983;118:905–907.
7. Mendelson RM, Nolan DJ. The radiological features of chronic radiation enteritis. Clin Radiol 1985;36:141–148.
8. Walsh HP, Schofield PF. Is laparotomy for small bowel obstruction justified in patients with previously treated malignancy? Br J Surg 1984;71:933–935.
9. Helmkamp BF, Kimmel J. Conservative management of small bowel obstruction. Am J Obstet Gynecol 1985;152: 677–679.
10. Seror D, Feigin E, Szold A, et al. How conservatively can postoperative small bowel obstruction be treated? Am J Surg 1993;165:121–125; discussion 125–126.
11. Assalia A, Schein M, Kopelman D, et al. Therapeutic effect of oral Gastrografin in adhesive, partial small-bowel obstruction: A prospective randomized trial. Surgery 1994;115:433–437.
12. Wolfson PJ, Bauer JJ, Gelernt IM, et al. Use of the long tube in the management of patients with small-intestinal obstruction due to adhesions. Arch Surg 1985;120:1001–1006.
13. Osteen RT, Guyton S, Steele G Jr, Wilson RE. Malignant intestinal obstruction. Surgery 1980;87:611–615.
14. Miller G, Boman J, Shrier I, Gordon PH. Etiology of small bowel obstruction. Am J Surg 2000;180:33–36.
15. Seror D, Feigin E, Szold A, et al. How conservatively can postoperative small bowel obstruction be treated? Am J Surg 1993;165:121–125.
16. van Nagell JR Jr. Small bowel injury following radiation therapy for cervical cancer. Am J Obstet Gynecol 1974; 118:163–167.
17. Potish RA, Jones TK Jr, Levitt SH. Factors predisposing to radiation-related small-bowel damage. Radiology 1979;132: 479–482.
18. Wobbes T, Verschueren RC, Lubbers EJ, et al. Surgical aspects of radiation enteritis of the small bowel. Dis Colon Rectum 1984;27:89–92.
19. Marik PE. The treatment of hypoalbuminemia in the critically ill patient. Heart Lung J Acute Crit Care 1993;22: 166–170.
20. Gray GE, Meguid MM. Can total parenteral nutrition reverse hypoalbuminemia in oncology patients? Nutrition 1990;6:225–228.
21. Guirao X, Franch G, Gil MJ, et al. Extracellular volume, nutritional status, and refeeding changes. Nutrition 1994;10: 558–561.
22. Torosian MH. Perioperative nutrition support for patients undergoing gastrointestinal surgery: Critical analysis and recommendations. World J Surg 1999;23:565–569.
23. Hasleton PS, Carr N, Schofield PF. Vascular changes in radiation bowel disease. Histopathology 1985;9:517–534.
24. Johnston CJ, Williams JP, Okunieff P, Finkelstein JN. Radiation-induced pulmonary fibrosis: Examination of chemokine and chemokine receptor families. Radiat Res 2002; 157:256–265.
25. Richter KK, Landberg CW, Sung CC, Hauer-Jensen M. Association of transforming growth factor beta immunoreactivity with specific histopathologic lesions in subacute and chronic experimental radiation enteropathy. Radiother Oncol 1996;39:243–251.
26. Nguyen NP, Antoine JE, Dutta S, et al. Current concepts in radiation enteritis and implications for future clinical trials. Cancer 2002;95:1151–1163.
27. Dietz DW, Remzi FH, Fazio VW. Strictureplasty for obstructing small-bowel lesions in diffuse radiation enteritis: Successful outcome in five patients. Dis Colon Rectum 2001;44:1772–1777.
28. Onodera H, Nagayama S, Mori A, et al. Reappraisal of surgical treatment for radiation enteritis. World J Surg 2005;29: 459–463.
29. Gelland RB, Spencer MS. Surgical management of radiation enteritis. Surgery 1986;99:133–139.
30. Swan RW, Fowler WC Jr, Boronow RC. Surgical management of radiation injury to the small intestine. Surg Gynecol Obstet 1976;142:325–327.
31. Galland RB, Spencer J. Surgical aspects of radiation injury to the intestine. Br J Surg 1979;66:135–138.

Spontaneous Mesenteric Hemorrhage Associated With Ehlers-Danlos Syndrome

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The vascular type of Ehlers-Danlos syndrome is a genetic disorder of connective tissue and is frequently associated with catastrophic arterial complications. Its surgical treatment is extremely difficult because of the fragility of vessels. This article describes three patients with vascular type of Ehlers-Danlos syndrome who developed mesenteric hemorrhage due to spontaneous arterial rupture. The clinical and molecular characteristics of the disease are briefly reviewed. (J GASTROINTEST SURG 2006;10:583–585) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Ehlers-Danlos syndrome, mesenteric hemorrhage, surgical management

Ehlers-Danlos syndrome (EDS) is a rare genetic disorder affecting connective tissue. The vascular type of EDS, also known as type IV or arterial-ecchymotic type, is characterized by thin translucent skin, fragile arteries, easy bruising, and a typical facial appearance.[1] Arterial rupture complicating vascular EDS often leads to fatal conditions, because the surgical management is extremely difficult due to the friability of vessels.[2–4]

In this report, we describe three cases of spontaneous mesenteric hemorrhage associated with the vascular type of EDS and discuss their surgical management.

CASE REPORTS

Case 1

A 38-year-old man was admitted with a history of sudden onset of abdominal pain. His medical history included dissection of the right common and external iliac arteries treated with aortofemoral bypass grafting at the age of 31 and dissection of the left external iliac artery treated with bypass grafting between the left common and external iliac arteries at the age of 37. He had been clinically diagnosed as having the vascular type of EDS, based on these arterial episodes, thin translucent skin, and a history of excessive bruising, although no family history of the disease was disclosed.

Computed tomography on admission demonstrated intra-abdominal hemorrhage, aneurysms of the proper hepatic and left renal arteries, dissection of the right renal artery, and an extensive intramesenteric mass indicative of a hematoma. At laparotomy, bleeding from a tear in a branch of the jejunal artery and massive intramesenteric hematoma were found. The mesenteric vessels and surrounding mesenteric tissues showed extreme fragility. Hemostasis was achieved by gently ligating the bleeding artery with surrounding adipose tissue, without resection of the intestine. Five hours after the operation, however, his blood pressure dropped suddenly, and he died 6 hours postoperatively despite resuscitative attempts. Postmortem examination revealed massive intra-abdominal hemorrhage, which was considered to be the cause of death.

Case 2

A 42-year-old man was admitted with sudden onset of lower abdominal pain. He had experienced a similar episode of acute abdominal pain a year before, which had subsequently resolved without any medical treatment. Computed tomography showed a mass adjacent to the descending colon.

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Laparotomy was performed, which revealed intra-abdominal hemorrhage and a hematoma, 15 cm in maximum diameter, between the inferior mesenteric artery and descending colon. Not knowing the underlying disease, we performed left hemicolectomy with initial end-to-end anastomosis. The surgery was extremely difficult because of fragility of the mesenteric vessels and adipose tissue, and hemorrhage was controlled by gently ligating the vessels together with surrounding tissues. Postoperative examination of the resected specimen showed spontaneous bleeding from a branch of the inferior mesenteric artery. Six years after the operation, he presented with another episode of acute lower abdominal pain. Computed tomography revealed dissection of the infrarenal aorta extending to the right common iliac artery and a retroperitoneal hematoma, which were treated conservatively. He was clinically diagnosed as having vascular EDS, based on his thin translucent skin and recurrent vascular events, although he did not have a definite family history of the disease. The diagnosis was confirmed by culture of skin fibroblasts, demonstrating defective secretion of type III collagen. Eight years after the first operation, he underwent ileocecal resection with ileostomy for a perforation of the ascending colon, followed by additional resection of small intestine on postoperative day 7 for multiple perforations due to injuries during the previous operation. He was doing well 18 months after the last surgical intervention.

Case 3

A 33-year-old man presented to our institution with shock and severe abdominal pain of sudden onset. He had a history of extensive subcutaneous hematomas in the upper and lower limbs, spontaneous rupture of ulnar artery, and left renal infarction due to dissection of the left renal artery, all of which had been treated conservatively. With the presence of thin translucent skin, characteristic facial appearance, and family history of arterial ruptures, he had been clinically diagnosed with vascular EDS. Computed tomography revealed intra-abdominal hemorrhage, aneurysms of the common hepatic and splenic arteries, and dissection of the left external iliac artery. At laparotomy, bleeding from a tear in a branch of the jejunal artery was identified. The mesenteric vessels and adipose tissue were extremely fragile. Hemorrhage was controlled by gentle ligation of the bleeding vessel together with surrounding adipose tissue, without resection of the jejunum. Culture of his skin fibroblasts showed an apparently normal quantity of type III collagen secretion. Qualitative analysis of the produced collagen has not been performed. He suffered multiple radial and ulnar aneurysms during the postoperative follow-up of 4 years, without any life-threatening events.

DISCUSSION

The vascular type of EDS is an autosomal dominant disorder caused by structural deficits of collagen type III encoded by the *COL3A1* gene.[5] Defective production of type III collagen, a major component of blood vessels, results in marked distensibility and high wall stress of the artery, predisposing to arterial dissection, rupture, and aneurysm formation.[6] Patients are often asymptomatic until a sudden arterial hemorrhage or bowel perforation occurs. The first events are frequently catastrophic and life-threatening. The median survival in a recent cohort study of the disease was reported to be 48 years, and arterial complications accounted for most deaths.[4]

The clinical diagnosis of the vascular type of EDS is made by the presence of any two or more of the following four major criteria: thin translucent skin, arterial/intestinal/uterine fragility, extensive bruising, and characteristic facial appearance. The diagnosis is confirmed by detection of either abnormal secretion of type III collagen by cultured skin fibroblasts or a mutation in the *COL3A1* gene.[1] Even if the cultured fibroblasts yield an apparently normal amount of type III collagen, further analysis by gel electrophoresis in sodium dodecyl sulfate can demonstrate structural abnormality of the protein.[7] In the present case series, all patients were clinically compatible with vascular EDS. Culture of skin fibroblasts was performed in two patients. Although no quantitative abnormality of production of type III collagen was detected in case 3, a structural alteration might be revealed by further biochemical examination.

A literature review using MEDLINE revealed that there was only one case report describing spontaneous rupture of the mesenteric artery between January 1990 and December 2004, in which the patient did not survive the event.[8] The surgical management of arterial complications in patients with vascular EDS is very hazardous, with reported operative mortality of more than 40%.[4] In cases of rupture of middle-sized arteries, ligation with the sacrifice of nonessential organs is recommended.[2,3,9] In the present three cases, we experienced difficulty controlling hemorrhage from small-sized mesenteric arteries affected by the disease. The vessel walls were

extremely thin and fragile, and attempts to expose bleeding arteries led to new arterial tears. Even gentle ligation cut into the vessel wall and resulted in additional hemorrhage. Hemostasis could be achieved by gently ligating the bleeding vessels together with the surrounding mesenteric tissues, which were also friable and edematous. Standard hemostatic maneuvers, including full exposure of the bleeding artery and ligation with direct contact between the ligature and vessel wall, might result in failure to control hemorrhage. Minimal vessel dissection and gentle ligation including surrounding tissues may be safer in the management of bleeding from small-sized vessels. When resection of the bowel becomes necessary because of ischemia, initial end-to-end anastomosis should be avoided, since the risk of anastomotic leakage is very high.[3,4]

CONCLUSION

The vascular type of EDS is sometimes complicated by intra-abdominal hemorrhage due to mesenteric arterial rupture. Surgical management should be simple and only to obtain hemostasis, in order to achieve a successful treatment outcome.

REFERENCES

1. Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: Revised nosology, Villefranche, 1997. Am J Med Genet 1998;77:31–37.
2. Cikrit DF, Miles JH, Silver D. Spontaneous arterial perforation: The Ehlers-Danlos specter. J Vasc Surg 1987;5:248–255.
3. Freeman RK, Swegle J, Sise MJ. The surgical complications of Ehlers-Danlos syndrome. Am Surg 1996;62:869–873.
4. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673–680.
5. Pope FM, Martin GR, Lichtenstein JR, et al. Patients with Ehlers-Danlos syndrome type IV lack type III collagen. Proc Natl Acad Sci U S A 1975;72:1314–1316.
6. Boutouyrie P, Germain DP, Fiessinger JN, et al. Increased carotid wall stress in vascular Ehlers-Danlos syndrome. Circulation 2004;109:1530–1535.
7. Stolle CA, Pyeritz RE, Myers JC, Prockop DJ. Synthesis of an altered type III procollagen in a patient with type IV Ehlers-Danlos syndrome. A structural change in the alpha 1(III) chain which makes the protein more susceptible to proteinases. J Biol Chem 1985;260:1937–1944.
8. Collins MH, Schwarze U, Carpentieri DF, et al. Multiple vascular and bowel ruptures in an adolescent male with sporadic Ehlers-Danlos syndrome type IV. Pediatr Dev Pathol 1999;2:86–93.
9. Parfitt J, Chalmers RT, Wolfe JH. Visceral aneurysms in Ehlers-Danlos syndrome: Case report and review of the literature. J Vasc Surg 2000;31:1248–1251.

Postprandial Augmentation of Absorption of Water and Electrolytes in Jejunum Is Neurally Modulated: Implications for Segmental Small Bowel Transplantation

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Postprandial augmentation of absorption of water and electrolytes is believed to occur in the jejunum. Neural mechanisms of control, however, have not been studied in the in situ jejunum or in the transplanted bowel. The aim of this study was to determine if postprandial augmentation of absorption occurs in the in situ jejunum and to evaluate neural mechanisms controlling postprandial jejunal absorption. Based on our previous work, we hypothesized that postprandial augmentation of absorption does not occur in the jejunum in situ and that extrinsic denervation of the jejunum is associated with decreased postprandial absorption. Absorption was studied in an 80 cm, in situ jejunal segment in six dogs by using an isosmolar electrolyte solution alone, or with 80 mmol/L glucose before and after jejunal transection to disrupt intrinsic neural continuity of the study segment with the remaining gut. Net absorptive fluxes of water and electrolytes were measured in the fasted state and after a 400-kcal meal. Another six dogs were studied 3 weeks after our validated model of extrinsic denervation of jejunoileum; identical fasting and postprandial absorptive states were evaluated. Postprandial augmentation of absorption of water and electrolytes did occur in the jejunum ($P < 0.03$) both in the absence and in the presence of intraluminal glucose. After intrinsic neural transection or extrinsic denervation, no postprandial augmentation of absorption occurred, with or without glucose. Postprandial augmentation of absorption of water and electrolytes occurs in the in situ jejunum. Disrupting intrinsic neural continuity or extrinsic denervation (as after intestinal transplantation) abolishes postprandial augmentation. (J GASTROINTEST SURG 2006;10:586–592) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Absorption, intestinal transplantation, intrinsic nerves, postprandial extrinsic denervation

Small bowel transplantation (SBT) is a clinical reality; however, it often remains plagued by prolonged enteric absorptive dysfunction postoperatively.[1–3] Transient decreases in absorption of water, electrolytes, and nutrients have been demonstrated previously in canine models of SBT.[4,5] Although some studies have looked at absorptive abnormalities after SBT, few reports have evaluated absorption in the postprandial or "fed" state in the neurally isolated (extrinsically denervated) or transplanted bowel. Previous physiologic studies demonstrated postprandial augmentation of absorption of water, electrolytes, and nutrients in the enterically isolated intestine, usually in Thiry-Vella loops, but studies in the in situ jejunum, which is not subject to the disuse atrophy of an enterically isolated segment, are lacking.[6–9] It is not clear if net postprandial absorption is affected in pathophysiologic states induced by SBT, including ischemia/reperfusion injury, lymphatic disruption, severe immunosuppression, immune phenomena, and disruption of intrinsic and extrinsic innervation.

Our aims were twofold: (1) to determine if postprandial augmentation of absorption occurs in the in situ jejunum and (2) to evaluate mechanisms of neural control mediating jejunal postprandial absorption. Our laboratory has been involved in translational investigations into the neural mechanisms modulating enteric function in large animal models of small intestinal autotransplantation, specifically looking at the role of extrinsic denervation on

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absorption. Our recent work found, surprisingly, that postprandial augmentation of net absorption did not occur in the in situ ileum.[9] Furthermore, extrinsic denervation of the jejunoileum transiently decreased net postprandial absorption of both glucose and glutamine in the in situ ileum at 2 weeks postoperatively; however, this resolved at 12 weeks postoperatively. We, therefore, hypothesized that postprandial augmentation of net absorption similarly does not occur in the in situ jejunum, with or without intraluminal glucose. Furthermore, we hypothesized that a model of jejunoileal autotransplantation (extrinsic denervation) decreases postprandial absorption of water and electrolytes. We studied absorptive function of the extrinsically denervated small intestine devoid of confounding factors of immune phenomena and ischemia/reperfusion injury by using our previously validated canine model of jejunoileal autotransplantation.[10]

MATERIAL AND METHODS

Overall Design

Six dogs underwent baseline experiments of absorption of water and electrolytes (sodium, potassium, and chloride) in the in situ jejunum by using intramural, jejunal-like infusates with and without 80 mmol/L glucose. Dogs were studied both in the fasting and fed (postprandial) states. These dogs served initially as the baseline, neurally intact control dogs. After completion of baseline studies, these same dogs underwent proximal jejunal and distal ileal transection and reanastomosis to disrupt intrinsic neural continuity to the jejunal segment being studied, and studies were repeated at 3 weeks postoperatively with identical experiments of absorption. Another six dogs underwent complete neural isolation of the jejunoileum (disruption of intrinsic and extrinsic neural input) and were studied with identical experiments of absorption 3 weeks postoperatively. We chose the 3-week postoperative time point for study of absorption, because the dog's stools were still unformed at this time after neural isolation of the jejunoileum.

Animal Preparation

Preoperative care, surgical operations, postoperative care, and subsequent conduct of the experiments were performed with approval of the Animal Care and Use Committee of the Mayo Foundation and in accordance with guidelines of the National Institutes of Health and the U.S. Public Health Service policy on the humane use and care of laboratory animals. All dogs were fasted for 12 hours before surgical procedures.

Catheter and cannula insertion. Six healthy female mongrel dogs, weighing 15–21 kg, were anesthetized by using intravenous sodium methohexital induction (12.5 mg/kg), and inhaled halothane (Ayerst Laboratories, New York, NY) was used for anesthetic maintenance. Through a midline celiotomy, a jejunal infusion catheter (internal diameter 1.5 mm), a jejunal aspiration catheter (internal diameter 3.0 mm), and a modified Thomas cannula (internal diameter 10 mm) were placed 50, 65, and 145 cm, respectively, distal to the ligament of Treitz. This configuration allowed the use of a triple-lumen perfusion technique[11] providing a 15 cm jejunal mixing segment and an 80 cm test segment similar in principle to our previous studies;[4,5,12,13] this experimental setup has been well-illustrated and described in detail previously.[14] Dogs were administered intramuscular butorphanol for postoperative pain control and maintained on intravenous fluid and electrolytes for 3 days before ad libitum feeding. Absorptive studies were performed after a 3-week recovery period.

Intrinsic neural disruption. After completion of baseline studies, a secondary celiotomy was undertaken, and all six dogs underwent proximal jejunal and distal ileal transection and reanastomosis to disrupt intrinsic myoneural continuity of the study segment with the proximal and distal gut; all extrinsic neural innervation was carefully preserved except, of course, for any extrinsic nerves traveling within the wall of the proximal jejunum or distal ileum. Briefly, the proximal jejunum, just distal to the ligament of Treitz, and the distal ileum 5 cm proximal to the ileocecal junction, were transected. End-to-end jejunojejunostomy and ileoileostomy restored intestinal continuity. Absorptive studies were performed after a 3-week recovery period.

Complete intrinsic and extrinsic neural denervation. Six dogs underwent our model of in situ neural isolation of the jejunoileum through a midline celiotomy, as described previously in detail.[10] This well-established and validated surgical preparation establishes a complete extrinsic denervation as well as disruption of intrinsic myoneural and lymphatic continuity to the jejunoileum without interruption or occlusion of the primary blood supply during the procedure. In brief, all mesenteric, neural, lymphatic, and connective tissue at the base of the small bowel mesentery traveling to the jejunum and ileum *except* for the superior mesenteric artery and vein were transected. Under 2× optical magnification, the superior mesenteric artery and vein were skeletonized, and the investing adventitia and associated neural elements were stripped off for a length of

2 cm, leaving only the media and endothelium of the superior mesenteric artery and vein as the only connection to the bowel. The proximal jejunum, just distal to the ligament of Treitz, and the distal ileum, 5 cm proximal to the ileocecal junction, were transected to complete the neural isolation. Previous studies showed that concentrations of tissue catecholamines (markers of extrinsic denervation) decreased to unmeasurable levels for more than 3 months postoperatively, indicative of extrinsic denervation.[10] Intestinal continuity was restored by hand-sewn, end-to-end jejunojejunostomy and end-to-end ileoileostomy. Absorptive studies were performed after a 3-week recovery period.

Absorption studies. All dogs were fasted for the 12 hours before each experiment. Fully conscious dogs were studied while resting comfortably in a Pavlov sling. Experiments were performed at baseline and at 3 weeks after the model of intrinsic neural disruption and at 3 weeks in the other six dogs undergoing in situ neural isolation by using a modification of the triple-lumen perfusion technique.[4,5] Experiments began with gentle flushing of the jejunal segment with infusate to remove intraluminal debris and mucous. Two types of warmed (39° C), isosmolar electrolyte solutions were used, one with and one without 80 mmol/L glucose, both titrated to a pH of 7.4 and designed to reproduce the electrolyte composition of the jejunum while maintaining isosmolarity. The infusate *without* glucose contained (in mEq/L) sodium 140, potassium 5, chloride 110, and bicarbonate 35. The infusate *with* glucose contained glucose 80 mmol/L and (in mEq/L) sodium 105, potassium 5, chloride 75, and bicarbonate 35. Both perfusates contained 5g/L of the nonabsorbable volume marker polyethylene glycol (PEG; molecular weight 3350 Da) labeled with ^{14}C-PEG (5μCi/L). Separate experiments on different days were performed using perfusate with and without glucose. Studies evaluating electrolyte absorption were conducted exclusively using the perfusate without glucose, whereas absorption of water only was evaluated in the experiments utilizing the glucose-containing perfusate. After flushing, the test solutions were infused continuously via the first jejunal catheter at 5 ml/minute. Luminal samples were aspirated from the second jejunal catheter 15 cm distal (to allow for mixing) at a constant rate of 1 ml/minute by using a withdrawal pump (Harvard Apparatus Co., Dover, MA). Effluent from the end of the test segment (80 cm distal to the second catheter) was collected by gravity through the distal jejunal cannula. Based on previous experiments, a 1-hour equilibration period was allowed to establish the steady state dynamics necessary for the use of this perfusion technique.[4,5,12,13] Thereafter, samples from the proximal and distal jejunal catheter (80 cm test segment) were collected during four subsequent consecutive 1-hour intervals for analysis. All dogs were studied in the fasted state for the first hour and then fed a 200 g (400 kcal) mixed meal of chopped pork liver with 120 ml cream (370 kcal) and subsequently studied for an additional 3 hours. Each perfusate was tested three times in each dog at each time point (baseline and at 3 weeks after denervation).

Analytical Methodology

All samples were frozen immediately (−20° C), analyzed in duplicate, and run within days of each experiment. Concentrations of the nonabsorbable marker ^{14}C-PEG were measured by scintillation techniques. Sodium and potassium concentrations were measured by flame photometry; chloride concentrations were measured by chloridimetry.

Analysis of absorptive data. Net absorption of water, sodium, potassium, and chloride was determined using principles of the triple-lumen perfusion technique, as described previously.[4,5,11] Steady state conditions were established during the first hour of infusion; the assumption was that the amount of nonabsorbable marker entering the proximal jejunal study segment per unit time equaled the amount of marker leaving the distal jejunal test segment. The differences in calculated volume entering and leaving the 80 cm jejunal test segment were used to calculate net absorption of water as calculated by changes in concentrations of the nonabsorbable marker (^{14}C-PEG) between the proximal jejunal aspiration catheter and the distal diverting cannula by using standard formulas for an 80 cm test segment for each experimental interval and represented as net absorptive flux ($\mu L \cdot cm^{-1} \cdot min^{-1}$). This triple-lumen technique allows for, and takes into account, any enteric inflow into the 80 cm test segment from the more proximal jejunum by allowing for a 15 cm mixing segment. This mixing segment between the infusion catheter and the proximal aspiration catheter allows measurement of the "adjusted" actual volume entering the 80 cm test segment as well as the "adjusted" actual concentrations of electrolytes entering the 80 cm test segment. Differences in concentrations between the start (proximal aspiration catheter) and end (distal ileal cannula) of the test segment are then used to calculate net absorption. Positive values for net absorptive flux represent net absorption, whereas negative values represent net secretion. Using calculations based on the changes in concentrations of ^{14}C-PEG and standard formulas for the 80 cm test segment, net absorptive fluxes for water and

electrolytes were determined for each experimental time interval. After summing the 15-minute time periods, the individual mean values of net absorption for the four separate consecutive 1-hour intervals per experiment (1 hour fasting and the first, second, and third postprandial hour) were calculated; these mean values for the three (each experiment was run in triplicate) experiments were likewise calculated for the mean in each dog, representing the fasting and fed absorption values. Grand means in the fasted state and the first, second, and third postprandial hour were calculated across dogs for the basal and 3-week time points.

Statistical Analysis

Mean net absorptive fluxes within groups were compared across the time points (baseline and 3 weeks) during fasting and after feeding with analysis of variance (ANOVA), and P values < 0.05 were considered significant. At each time point, differences between measurements during fasting and after feeding were also compared. Comparisons were also made between perfusates with and without glucose. Data in the text are presented as mean values ± standard error of the mean (x ± SEM).

RESULTS

Health/General Characteristics of Dogs

After catheter and cannula placement, intrinsic neural transection, and complete neural isolation, all dogs maintained a good appetite and remained active and healthy. After intrinsic neural transection, the dogs lost no weight and had normal stools. In contrast, after complete in situ neural isolation, dogs lost about 10% body weight and developed a watery diarrhea that persisted for the 3 postoperative weeks.

Net Absorption of Water and Electrolytes

During baseline (control) measurements (before any denervation), feeding a mixed nutrient meal lead to a postprandial augmentation of net absorption of water and electrolytes in the jejunal segment. Net jejunal absorption of water in the postprandial period was increased compared to the fasting period (Fig. 1). This postprandial augmentation of water absorption occurred both without ($P < 0.03$) and with ($P < 0.02$) intraluminal glucose in the perfusate. Postprandial augmentation of net absorption of water was evident even in the first postprandial hour (fasting 10.4 ± 1.3 vs. fed 23.4 ± 4.3 μL/cm per minute; $P < 0.05$). However, when these same dogs were studied at 3 weeks after intrinsic neural transection or when the separate group of dogs was studied after jejunoileal neural isolation, postprandial augmentation of water absorption was abolished. This lack of postprandial augmentation of water absorption after intrinsic neural transection alone, or after jejunoileal neural isolation, occurred whether intraluminal glucose was absent or present. Furthermore, differences in net absorptive fluxes of water during fasting (at baseline, after intrinsic neural transection alone, or after jejunoileal neural isolation) did not differ across the time points ($P > 0.05$), either with or without intraluminal glucose. When net absorptions of water during the fasting and postprandial hours (at baseline, after intrinsic neural transection alone, or after jejunoileal neural isolation) were compared, there were no major differences between the perfusates, without and with glucose ($P > 0.05$), at any time points.

Similar to net water absorption, feeding the mixed nutrient meal to neurally intact dogs induced a postprandial augmentation of net absorption of sodium and chloride in the in situ jejunum. A prominent postprandial augmentation of net absorption of sodium ($P < 0.03$) and chloride ($P < 0.02$) occurred over the 3 postprandial hours when compared with the fasting hour (Table 1). No postprandial augmentation of absorption of sodium or chloride was evident 3 weeks after intrinsic neural transection or after jejunoileal neural isolation. No significant changes in net absorptive fluxes of potassium were evident when comparing preprandial and postprandial hours at any time point during all three experimental conditions (baseline neurally intact, after intrinsic neural transection, or after jejunoileal neural isolation).

DISCUSSION

Our study demonstrated that postprandial augmentation of net absorption of water and electrolytes does occur in the in situ canine jejunum and does not require intramural glucose to mediate this effect. Additionally, this physiologic response in the jejunum was abolished by transection of intrinsic neural continuity with the proximal and distal gut, suggesting that the response was mediated via intrinsic neural pathways. When interpreted in the context of our previous study[9] that showed that postprandial augmentation of net absorption did not occur in the in situ canine ileum, the important implication of this study is that segmental small bowel transplantation of the jejunum may demonstrate a greater adaptive ability for absorption of water and electrolytes when compared with the ileum.

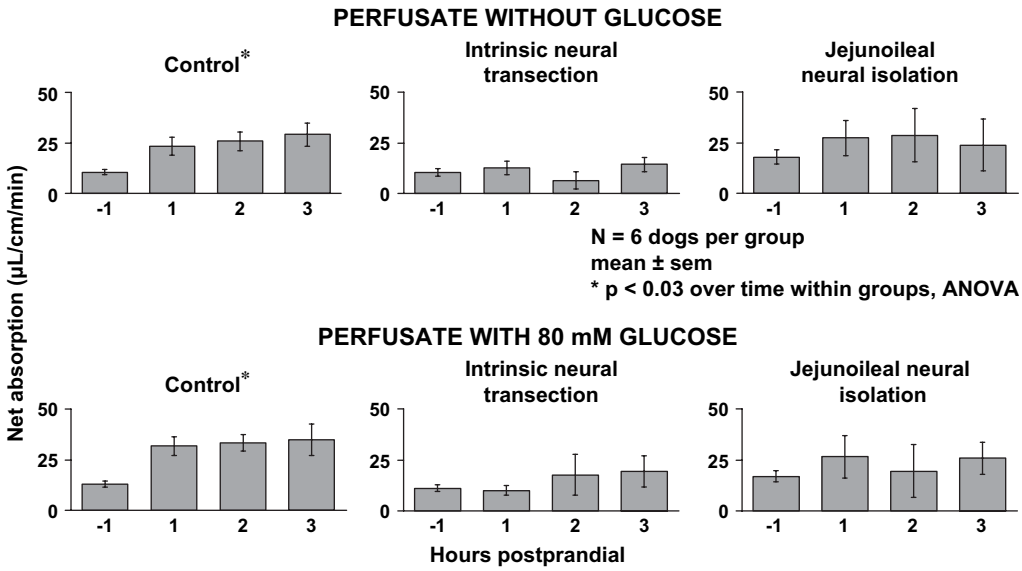

Fig. 1. Net absorptive fluxes during fasting (postprandial hour −1) and after feeding (postprandial hours 1, 2, and 3).

Our laboratory has had a primary interest in the neural mechanisms involved in control of gut physiology and more recently in absorption in the transplanted small intestine. We have tended to use a large animal (canine) model of autotransplantation specifically devoid of confounding factors of ischemia/reperfusion injury or immunologic phenomena to investigate physiologic mechanisms.[10] Our laboratory first described postprandial augmentation of net absorption of water and electrolytes in the canine jejunum in 1981[6] and subsequently demonstrated that this effect was partially maintained in the autotransplanted (but enterically isolated) jejunum.[7] These initial data were confirmed in the jejunum and ileum by other groups who also went on to show that the brush border Na^+/H^+ exchanger (NEH3) seems to mediate this physiologic response, at least in the ileum.[15,16] All these studies were carried out in enterically isolated intestinal segments to allow better control of the experimental conditions to measure absorption.

There are two important issues regarding postprandial augmentation of absorption yet to be addressed. First, what role do neural pathways play in both the neurally intact, in situ jejunum and in the "neurally isolated" transplanted intestine, and second, does this physiologic response differ in the jejunum versus the ileum? Conflicting reports have been published on whether intact jejunal neural pathways are required for postprandial proabsorptive augmentation.[17,18] Few studies have differentiated the role of intrinsic and extrinsic neural mechanisms in mediating postprandial augmentation of absorption. The Na^+/H^+ exchanger seems to play a major role in ileal, but not jejunal, postprandial absorption.[15] Moreover, as mentioned above, all the previous studies of jejunal postprandial absorption used enterically isolated, modified Thiry-Vella loops perfused with an electrolyte solution from which net absorption was determined. We purposely carried out the current study in the in situ jejunum to avoid potentially confounding factors such as chronic enteric isolation necessitated by Thiry-Vella loops, because we have shown previously that different responses occurred in the enterically isolated jejunum and ileum[19] when compared with the in situ gut.[4,5] Indeed, based on our previous work in the in situ ileum[9] and in the proximal colon,[20] we hypothesized that postprandial augmentation of absorption would not occur in the in situ jejunum in the absence of luminal glucose. Contrary to our findings in the neurally intact in situ ileum,[9] our study was consistent with our initial work[6] and confirmed that postprandial augmentation of net absorption *does* occur in the intact, in situ jejunum.

The second goal of our study was to determine the potential roles of both intrinsic and extrinsic innervation in this postprandial absorption. Because postprandial augmentation of absorption of water and electrolytes continued to occur in enterically isolated intestinal loops lacking myoneural continuity with the proximal gut, our primary interest focused on extrinsic denervation. Interestingly, transection of intrinsic neural continuity alone abolished the postprandial augmentation of absorption observed at baseline in the in situ neurally intact jejunum. This finding is consistent with a previous report that used oxethazaine, an

Table 1. Net electrolyte absorption in the in situ canine jejunum*

	Control dogs**				Intrinsic neural transection				Jejunoileal neural isolation			
	Hour PP				Hour PP				Hour PP			
	−1	1	2	3	−1	1	2	3	−1	1	2	3
Sodium	1.24 ± 0.20	3.12 ± 0.57	3.42 ± 0.43	3.99 ± 0.56	1.33 ± 0.19	1.99 ± 0.33	1.16 ± 0.37	2.25 ± 0.36	2.41 ± 0.49	4.47 ± 1.07	4.23 ± 1.48	2.99 ± 1.74
Chloride	0.76 ± 0.16	1.88 ± 0.32	2.23 ± 0.49	2.43 ± 0.46	0.88 ± 0.17	1.27 ± 0.26	0.28 ± 0.40	1.26 ± 0.42	1.39 ± 0.44	3.09 ± 0.97	3.51 ± 1.42	2.87 ± 1.33
Potassium	0.03 ± 0.01	0.01 ± 0.09	0.05 ± 0.09	0.12 ± 0.09	0.03 ± 0.01	−0.10 ± 0.08	−0.14 ± 0.08	0.03 ± 0.06	0.05 ± 0.03	−0.12 ± 0.14	−0.14 ± 0.19	−0.25 ± 0.22

*All values are mEq/cm per minute mean ± SEM, r = 6 dogs.
**$P < 0.03$ sodium and chloride over time within control group, ANOVA.

intraluminal topical anesthetic, in the jejunum, and it was concluded that intact intramural neural transmission (which did not differentiate extrinsic from intrinsic neural transmission) was necessary for meal-induced jejunal absorption.[17] However, the same group later used a different topical intraluminal anesthetic, bupivacaine, and concluded that meal-induced jejunal absorption does not require intact neural pathways.[18] An earlier study from our laboratory used an autotransplantation model of an enterically isolated jejunal segment and also concluded that postprandial augmentation of absorption continued to occur and thus was mediated, in part, by a hormonal mechanism. As for mechanisms mediated by the Na^+/H^+ transporter (NEHE), postprandial augmentation of absorption in the ileum was demonstrated to be mediated by NEH3, but blockade of NEH3 in the jejunum failed to prevent postprandial augmentation of net absorption, causing the questioning of the role of NEH3 in this response in the jejunum,[15,16] again suggesting potentially important regional differences in the small intestine.

Our study has several limitations that must be acknowledged. First, our in vivo, large animal models of denervation do not delineate different mucosal transport systems or any variations that might occur in paracellular flow. Second, luminal contents normally transit through the jejunum via bolus movement, and our experimental methodology using a constant perfusion technique with an artificial electrolyte solution may limit the strength of our conclusions.[21] Furthermore, although our triple-lumen technique allows for a 15 cm mixing segment, it is conceivable that the complex nutrients in a meal within enteric chyme, along with pancreatic juice, bile, and mucus, may affect absorption of water and electrolytes differently than from the simple electrolyte solution we used. We specifically only analyzed net absorption relatively soon after the meal (first 3 hours) and used a meal high in fat content to delay gastric emptying. Third, although the meal might allow glucose to enter into the 'non-glucose' perfusate, we speculate that this small amount would not affect our results and would be negligible at least in the first postprandial hour. Finally, although our large animal models of denervation were designed specifically to evaluate neural mechanisms, whether the obligate disruption of lymphatic continuity, necessitated by the model of in situ neural isolation (extrinsic denervation) plays a role in postprandial absorption, although unlikely, is at least possible. Other factors specifically designed to be absent in our study, such as ischemia/reperfusion injury, immune rejection, and pharmacologic effects of immunosuppression, that are pertinent in the allotransplanted gut may

also be important in altering enteric absorptive function in the post-transplant period.

Thus, postprandial augmentation of net absorption of water and electrolytes does occur in the neurally intact, in situ canine jejunum and is mediated in part by intrinsic neural continuity with the proximal and distal gut. These two key observations may explain some of the observations of enteric absorptive dysfunction after clinical allotransplantation.[1–3] The obligate disruption of enteric neural continuity required by the transplantation procedure, and not solely the extrinsic denervation, seems to be the primary determining factor. An important observation will be whether this postprandial augmentation of absorption will return after restoration of intrinsic neural continuity becomes reestablished over 6 weeks to 3 months postoperatively;[22] this interval is also the time when normal stool consistency returns.[10]

Our study has potential implications to segmental transplantation as well. Several groups have suggested that ileal grafts may be superior to jejunal grafts, because the jejunum cannot "adapt" to ileal resection by expressing bile salt and vitamin B_{12} transporters. The current study, in combination with our past study of the ileum,[9] suggests that postprandial augmentation of absorption may be more important in the jejunum than in the ileum; this observation may support the concept of segmental intestinal grafts harvested from the jejunum rather than the ileum, provided, of course, that postprandial absorptive augmentation recurs in the jejunum with restoration of enteric neural continuity across the intestinal anastomosis. What effect immunosuppression or immune rejection may have on this physiologic phenomenon is unknown.

REFERENCES

1. Nishida S, Levi D, Kato T, et al. Ninety-five cases of intestinal transplantation at the University of Miami. J Gastrointest Surg 2002;6:233–239.
2. Abu-Elmagd K, Reyes J, Bond G, et al. Clinical intestinal transplantation: A decade of experience at a single center. Ann Surg 2001;234:404–417.
3. Thompson JS, Rose SG, Spanta AD, Quigley EM. The long-term effect of jejunoileal autotransplantation on intestinal function. Surgery 1992;111:62–68.
4. Herkes SM, Smith CD, Sarr MG. Jejunal responses to absorptive and secretory stimuli in the neurally isolated jejunum in vivo. Surgery 1994;116:576–586.
5. Oishi AJ, Sarr MG. Intestinal transplantation: Effects on ileal enteric absorptive physiology. Surgery 1995;117:545–553.
6. Sarr MG, Kelly KA, Phillips SF. Canine jejunal absorption and transit during interdigestive and digestive motor states. Am J Physiol 1980;239:G167–G172.
7. Sarr MG, Kelly KA, Phillips SF. Feeding augments canine jejunal absorption via a hormonal mechanism. Dig Dis Sci 1981;26:961–965.
8. Bastidas JA, Orandle MS, Zinner MJ, Yeo CJ. Small-bowel origin of the signal for meal-induced jejunal absorption. Surgery 1992;108:376–383.
9. Libsch KD, Zarroug AE, Duininck TM, Ueno T, Duenes JA, Sarr MG. Extrinsic denervation alters postprandial absorption of glucose and glutamine in the ileum. Implications for small bowel transplantation. J Gastrointest Surg 2005;9:219–226.
10. Sarr MG, Duenes JA, Tanaka M. A model of jejunoileal in vivo neural isolation of the entire jejunoileum: Transplantation and the effects on intestinal motility. J Surg Res 1989;47:266–272.
11. Barbezat GO. Triple-lumen perfusion of the canine jejunum. Gastroenterology 1980;79:1243–1245.
12. Libsch KD, Zyromski NJ, Tanaka T, et al. Role of extrinsic innervation in jejunal absorptive adaptation to subtotal small bowel resection: A model of segmental small bowel transplantation. J Gastrointest Surg 2002;6:240–247.
13. Tsiotos GG, Kendrick ML, Libsch K, et al. Ileal absorptive adaptation to jejunal resection and extrinsic denervation: Implications for living-related small bowel transplantation. J Gastrointest Surg 2001;5:517–524.
14. Sarr MG, Walters AM, Benson JT, Zinsmeister AR. Absorption of simple nutrients from the in vivo neurally isolated canine jejunum and ileum: A model of intestinal transplantation. Surgery 1994;115:578–587.
15. Hines OJ, Bilchik AJ, McFadden DW, et al. Na+/H+ exchange mediates postprandial ileal water and electrolyte transport. Dig Dis Sci 1995;40:774–780.
16. Maher MM, Gontarek JD, Jimenez RE, Donowitz M, Yeo CJ. Role of brush border Na+/H+ exchange in canine ileal absorption. Dig Dis Sci 1996;41:651–659.
17. Anthone GJ, Bastidas JA, Zinner MJ, Barnhart DC, Masoudi FA, Yeo CJ. Meal-stimulated canine jejunal ionic absorption. Influence of mucosal neural blockade. Dig Dis Sci 1994;39:75–82.
18. Anthone GJ, Wang BH, Zinner MJ, Orandle MS, Yeo CJ. Meal-induced jejunal absorption requires intact neural pathways. Am J Surg 1992;163:150–156.
19. Sarr MG, Duenes JA, Walters AM, Duenes JA. Jejunal and ileal absorptive function after a model of canine jejunoileal transplantation. J Surg Res 1991;51:233–239.
20. Kendrick ML, Zyromski NJ, Tanaka T, Duenes JA, Libsch K, Sarr MG. Postprandial absorptive augmentation of water and electrolytes in the colon requires intraluminal glucose. J Gastrointest Surg 2002;6:310–315.
21. Otterson MF, Sarr MG. Normal physiology of small intestinal motility. Surg Clin North Am 1993;73:1173–1192.
22. Sarna SK. Cyclic motor activity: Migrating motor complex: 1985. Gastroenterology 1985;89:894–913.

Visuospatial Abilities Correlate With Performance of Senior Endoscopy Specialist in Simulated Colonoscopy

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Visuospatial abilities have been demonstrated to predict the performance of medical students in simulated endoscopy. However, little has been reported whether differences in visuospatial abilities influence the performance of senior endoscopists or whether their vast endoscopy experience reduces the importance of these abilities. Eleven senior endoscopists were included in our study. Before the simulated endoscopies in GI Mentor II (gastroscopy: case 3, module 1 and colonoscopy: case 3, module 1), the endoscopists performed three visuospatial tests: (1) pictorial surface orientation (PicSOr), (2) card rotation, and (3) cube comparison tests that monitor the ability of the tested person to re-create a three-dimensional image from a two-dimensional presentation as well as mentally manipulate that re-created image. The results of the visuospatial tests were correlated to the performance parameters of the virtual-reality endoscopy simulator. The percent of time spent with clear view in the simulated colonoscopy correlated well with the performance in the visuospatial PicSOr ($r = -0.75$, $P = 0.01$), card rotation ($r = 0.75$, $P = 0.01$), and cube comparison ($r = 0.79$, $P = 0.004$) tests. The endoscopists who performed better in the visuospatial tests also were better at maintaining visualization of the colon lumen. Those who performed better in the PicSOr test formed fewer loops during colonoscopy ($r = 0.60$, $P = 0.05$). In the technically less demanding simulated gastroscopy, there were no such correlations. The visuospatial tests performed better in endoscopists not playing computer games. Good visuospatial ability correlates significantly with the performance of experienced endoscopists in a technically demanding simulated colonoscopy, but not in the less demanding simulated gastroscopy. (J GASTROINTEST SURG 2006;10:593–599)
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KEY WORDS: Gastroscopy, colonoscopy, simulation

That endoscopic skills depend on experience and practice is a well known truth. With the introduction of advanced medical simulators, it has been possible to let residents reach proficiency levels before they are allowed to do their first endoscopic or surgical interventions, in an attempt to minimize discomfort and potentially hazardous errors in live patients. Several studies have demonstrated beneficial clinical effects of simulator training in both laparoscopic surgery[1,2] and endoscopic procedures like colonoscopy.[3–6] Because more than 40,000 Americans die from medical errors every year, there is a great deal of investigation into how newly available technologies can help reduce medical errors.[7] The development and use of computer-based simulation technologies for medical training has been recently supported by the American College of Surgeons.[8] Thus, a lot of attention has been focused on how to use medical simulators for the initial training of surgical and endoscopic procedures, whereas less attention has been give to the ability of simulators to monitor and assess the performance of physicians already in practice to ensure that skills are maintained throughout their professional career. Furthermore, little has been reported whether differences in visuospatial abilities can influence the performance of

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senior endoscopists or whether their vast endoscopy experience reduces the importance of these abilities. The aim of our study was to determine if visuospatial abilities correlated with performance of simulated virtual endoscopy done by experienced endoscopists.

MATERIAL AND METHODS

Eleven experienced endoscopists participated in the study. An experienced endoscopist was defined as having performed more than 500 self-reported gastrointestinal colonoscopy procedures. The demographics data for this group is summarized in Table 1. All endoscopists performed the test program on an individual basis. The test program was divided into three consecutive parts. Each participant was first asked to complete three different but previously well-validated visuospatial tests (pictorial surface orientation [PicSOr],[9,10] card rotation, and cube comparison tests).[11] The PicSOr test is a computer-based visuospatial test designed to assess the ability to re-create a mental three-dimensional image from a grayscale two-dimensional cube rendered on a computer monitor. Subjects are asked to position a rotating arrow perpendicular to the upper surface of a cube in a repeated fashion with variable cube orientations. The PicSOr score in our experiment was calculated by taking the mean of the differences between the estimated angle and the actual angle, thus accuracy is rewarded more than consistency. A schematic presentation of the test is given in Fig. 1. The card rotation and the cube comparison tests are well known standard paper-based visuospatial tests designed to assess the ability to mentally manipulate a re-created image. For these tests, subjects examine two similar shapes or marked cubes and must determine if they could possibly be the same. The chosen tests have been found to have a good correlation to endoscopic performance[12] and to the duration of training required to reach a training goal on simulated endoscopy.[13]

After the visuospatial tests were completed, the participants were asked to complete a questionnaire concerning background factors and endoscopic experience. Finally, they were asked to perform one gastroscopy (case 3, module 1) and one colonoscopy (case 3, module 1) in the GI Mentor II (Simbionix USA, Cleveland, OH). These cases were chosen because they represent the most technically challenging modules for gastroscopy and colonoscopy. GI Mentor II consists of a hardware/software computer package with an attachable endoscope that allows for both upper and lower flexible gastrointestinal endoscopy (i.e., esophagogastroduodenoscopy, colonoscopy, endoscopic retrograde cholangiopancreaticography, and endoscopic ultrasound). The simulator incorporates a computer-generated virtual reality presentation of anatomy complemented with haptic feedback. The software presents a series of "cases," ranging from those that are easily diagnosed to those that are difficult therapeutic cases. Performance is objectively assessed with simulator-specific metrics, such as percent of mucosa inspected, total examination time, the efficiency of screening, and further parameters depending on the nature of the case (Fig. 2). The participants were asked to perform the gastroscopy and the colonoscopy in the way they usually perform the endoscopy at their own institution. The instructors demonstrated the simulator to the participant but did not interfere with the examination in any way. All the results from both the simulators and the visuospatial testing were registered anonymously in a computer database. The participants received immediate feedback of their results.

Table 1. Demographic data for the participants

Subject	Age	Sex	Total gastroscopies	Total colonoscopies	Gastroscopy experience (yr)	Colonoscopy experience (yr)	Play computer games
A	53	M	>2000	>2000	>15	>15	No
B	55	M	>2000	>2000	>15	>15	No
C	50	M	>2000	>2000	>15	>15	Yes
D	50	M	>2000	>2000	>15	>15	No
E	50	M	>2000	>2000	>15	10–15	No
F	40	F	>2000	>2000	10–15	10–15	No
G	50	M	>2000	1000–2000	>15	10–15	Yes
H	52	M	>2000	500–1000	>15	10–15	Yes
I	35	M	>2000	500–1000	1–5	1–5	Yes
J	37	M	500–2000	500–1000	10–15	5–10	No
K	44	M	500–2000	500–1000	5–10	5–10	Yes

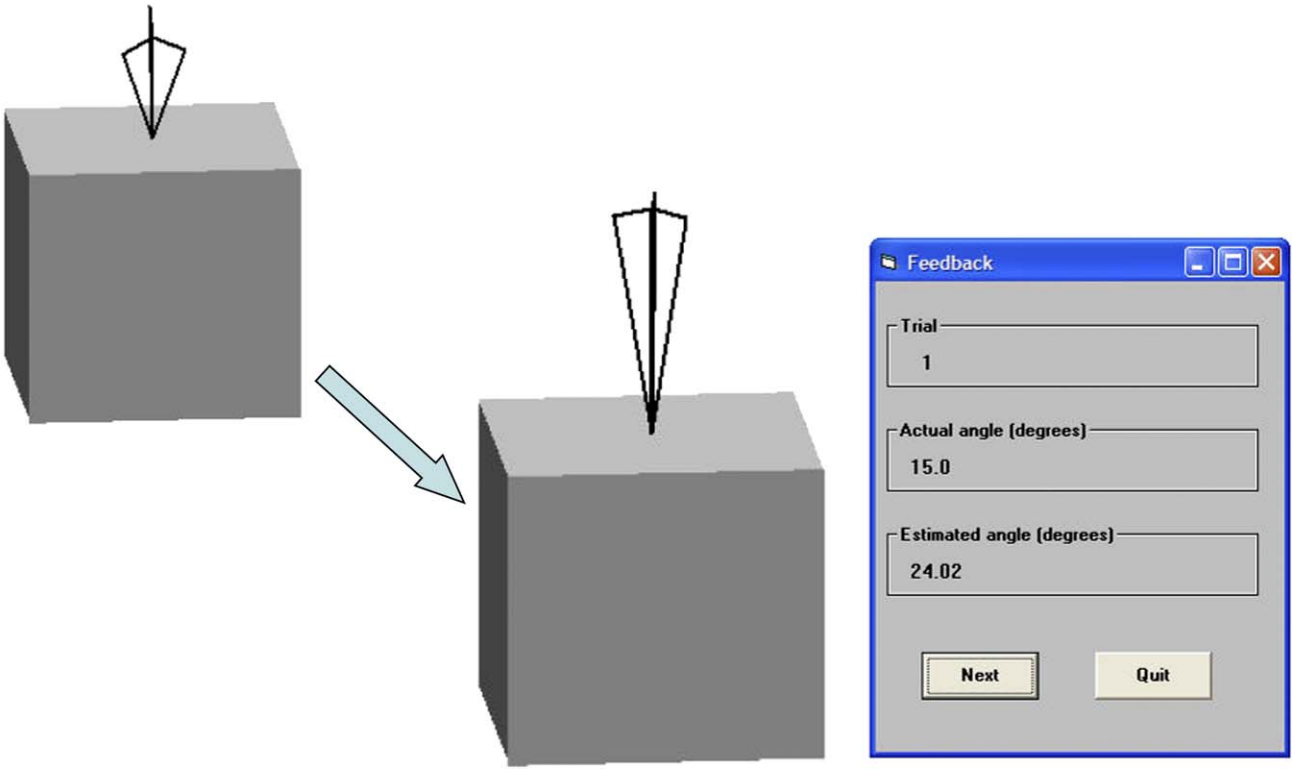

Fig. 1. Schematic presentation of the pictorial surface orientation (PicSOr) test.

Statistical Analysis

Data were analyzed using the statistical software JMP 5.1 for Windows (SAS Institute Inc., Cary, NC) and presented as mean ± SEM. Student's unpaired *t* test was used for comparisons of two means in groups with a normal distribution. In groups not normally distributed, the nonparametric Wilcoxon/Kruskal-Wallis test (rank sums) were used. Linear regression analysis was used to analyze for relationships between visuospatial abilities and simulated endoscopy performance.

RESULTS

Table 2 summarizes the correlations between the three visuospatial tests and the metrics of the GI Mentor II. In the easier gastroscopy module, none of the three visuospatial tests correlated significantly with the metrics of the examination, although there was a trend towards the correlation of the cube comparison test with "time to second duodenum" ($r = 0.52$; $P = 0.10$). In the more complicated colonoscopy module, all three visuospatial tests correlated with at least one of the colonoscopy metrics. The only metric that correlated significantly with all three visuospatial tests was "time spent with clear view." The PicSOr test also correlated well with the colonoscopy metrics "excessive loop was formed" ($r = 0.60$; $P = 0.05$). When dividing the group of participants into two subgroups—whether they played computer games or not—we noted striking changes in the correlation between the visuospatial tests and the metrics of the colonoscopy. In the group where the participants stated that they did not play computer games, the strength of correlation of the PicSOr test to the outcome of the simulated colonoscopy improved significantly. In four out of the eight given colonoscopy metrics, there were strong and significant correlations with the PicSOr test. Interestingly enough, one of the simulated colonoscopy parameters ("mucosal surface examined") that PicSOr did not correlate with in the nongaming group correlated well in the PC-gaming group ($r = -0.90$; $P = 0.04$). The cube comparison test also demonstrated significantly increased correlations with the simulated colonoscopy metrics in non-PC gamers (Table 3).

DISCUSSION

The results of this study demonstrate that visuospatial abilities affect the performance of simulated colonoscopy even when performed by highly experienced senior endoscopists. This is an interesting

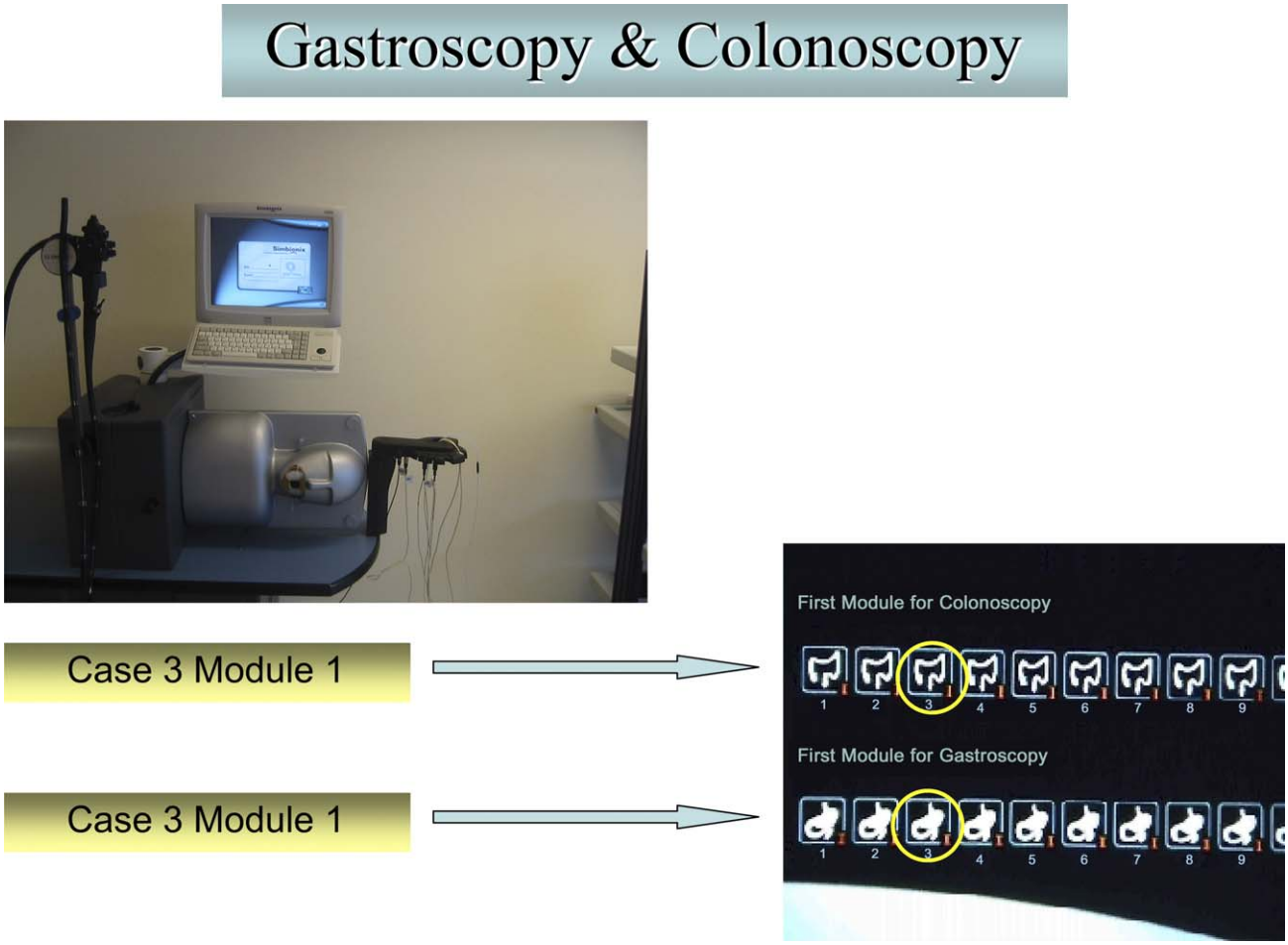

Fig. 2. The flexible endoscopy simulator GI Mentor II and the cases used for this study.

finding, because it demonstrates that although the majority of the endoscopists in this group had performed more than 2000 colonoscopies, differences in visuospatial abilities still accounted for a portion of the variability in the outcome in some of the simulated colonoscopy metrics. The tests used in this study accurately reflect the visuospatial abilities required to perform gastrointestinal endoscopy. Endoscopists must re-recreate the three-dimensional anatomy of the GI tract from the video display monitor and then must mentally manipulate that image to follow the lumen. This likely explains why the parameter "time spent with clear view" correlated well with the performance in all three of the visuospatial tests. There are two potential explanations for why an endoscopist loses visualization of the lumen, either they incorrectly predict where the lumen will be and guide the scope in the wrong direction, or they correctly estimate the location of the lumen but lack the psychomotor skills to make the endoscope go where they want it to go. Given this group of highly experienced endoscopists who likely possess superior psychomotor scope handling skills, the former explanation seems the most likely. Thus, the endoscopists visuospatial ability is manifest through their ability to mentally re-create the path of the colon and maintain a view of the lumen. The participants who performed better in the PicSOr test also formed fewer loops. Although this association is less clear, a similar mechanism is likely involved.

In the technically easier simulated gastroscopy, visuospatial abilities did not affect the result. Visuospatial ability, we believe, does not affect the outcome in simulated gastroscopy in contrast to the findings in simulated colonoscopy because of two main factors: (1) technical difficulty and (2) anatomical factors.

Technical Difficulty

In gastroscopy, the path that the instrument travels is much shorter, the esophagus is fixed and relatively straight, and the lumen of the stomach is

Table 2. Visuospatial tests and simulator metrics

	Card rotation test (% right answers)		Cube comparison test (% right answers)		PicSOr mean variation (degrees)	
Gastroscopy Case 3 Mod 1	***r***	***P***	***r***	***P***	***r***	***P***
Mucosal surface examined (%)	0.02	0.95	−0.13	0.70	0.42	0.20
Time spent with clear view (%)	−0.10	0.77	−0.22	0.52	0.33	0.32
Efficiency of screening (%)	−0.04	0.91	−0.18	0.60	0.44	0.18
Time to second duodenum (s)	0.46	0.15	0.52	0.10	−0.43	0.19
Total time (s)	0.50	0.12	0.23	0.49	0.04	0.91

	Card rotation test (% right answers)		Cube comparison test (% right answers)		PicSOr mean variation (degrees)	
Colonoscopy Case 3 Mod 1	***r***	***P***	***r***	***P***	***r***	***P***
Mucosal surface examined (%)	0.03	0.92	−0.01	0.97	−0.10	0.78
Time spent with clear view (%)	0.75	0.01	0.79	0.00	−0.75	0.01
Efficiency of screening (%)	0.28	0.40	0.37	0.26	−0.49	0.12
Time to caecum (s)	−0.44	0.17	−0.47	0.14	0.52	0.10
Total time (s)	−0.15	0.67	−0.22	0.51	0.28	0.40
Excessive local pressure	−0.35	0.29	−0.48	0.14	0.49	0.13
Excessive loop was formed	−0.42	0.19	−0.31	0.35	0.60	0.05

wider and thereby provides easy visualization. There is only one technically more difficult passage of the instrument at the pylorus. In colonoscopy, the instrument used is significantly longer and thus technically more demanding, the lumen has approximately the same size throughout the colon, and there are several sharp turns that the instrument has to take on its way to the ileocecal vault.

Anatomic Factors

One of the most difficult passages in colonoscopy is the passage of the instrument through the sigmoid colon because of the tendency of sigmoid looping due to the abundant and long mesocolon. Thus, the sigmoid colon is not fixed in position to the surrounding anatomical structures and poses much more of a visuospatial challenge to the endoscopist than the thoroughly fixed upper gastrointestinal channel.

Previous studies have demonstrated correlations between the visuospatial tests used in this study and virtual endoscopy performance of novices.[12–14] These, and most other studies published,[3,5,14–19] have focused mainly on the importance of simulated endoscopy training of novices like medical students, fellows, and residents. To our knowledge, this study is the first to demonstrate that visuospatial abilities

Table 3. Visuospatial tests and simulator metrics for colonoscopy in computer and not computer gamers

	Computer gaming						Not Computer gaming					
	Card rotation test (% right answers)		Cube comparison test (% right answers)		PicSOr mean variation (degrees)		Card rotation test (% right answers)		Cube comparison test (% right answers)		PicSOr mean variation (degrees)	
	r	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
Mucosal surface examined (%)	0.32	0.61	0.01	0.98	−0.90	0.04	0.06	0.91	0.13	0.81	−0.10	0.85
Time spent with clear view (%)	0.83	0.08	0.68	0.21	−0.55	0.33	0.78	0.07	0.95	0.00	−0.93	0.01
Efficiency of screening (%)	0.25	0.68	−0.05	0.93	−0.18	0.77	0.48	0.33	0.83	0.04	−0.95	0.00
Time to caecum (s)	−0.67	0.22	−0.37	0.54	0.28	0.65	−0.51	0.30	−0.75	0.08	0.81	0.05
Total time (s)	−0.14	0.82	0.07	0.91	−0.19	0.76	−0.20	0.71	−0.37	0.47	0.46	0.36
Excessive local pressure	0.24	0.70	0.24	0.69	−0.77	0.13	−0.52	0.29	−0.77	0.07	0.85	0.03
Excessive loop was formed	−0.53	0.36	−0.26	0.68	0.77	0.13	−0.44	0.38	−0.50	0.31	0.46	0.36

correlate with the outcome of simulated endoscopy performed by highly experienced senior endoscopists. The fact that visuospatial ability correlates with performance in this group lends support to the earliest of endoscopic simulators where trainees entering fields with a higher degree of visuospatial challenge, such as advanced laparoscopy/endoscopy or other image-guided interventional disciplines such as interventional radiology, could train to reach proficiency levels set by experienced colonoscopists. This study falls well short of the validation required to determine at what level of ability someone becomes unable to perform a procedure, but does demonstrate that fundamental abilities continue to influence performance even after extensive experience has been gained.

Of the three visuospatial tests used in this study, the PicSOr test was the most powerful in predicting the outcome of simulated colonoscopy. Although it was better than the two other tests, it only correlated to two of the metrics of the GI Mentor II ("time spent with clear view" and "excessive loop was formed"). The power of the PicSOr and the cube comparison test, however, significantly changed when the group was divided into subgroups of playing computer games or not. In the group where the participants stated that they did not play computer games, the accuracy of both these tests significantly improved (Table 3). Our group found in a previously published study[14] that medical students who played computer games performed a virtual gastroscopy better than those who said they did not play. In this group of middle-aged endoscopists, there was no difference in simulator performance between those who played and those who did not play computer games. Why the PicSOr test was so much more effective in those who did not play computer games is unclear, and one can only speculate about the reasons. One possible explanation is that the far from impressive graphic design of the PicSOr test had a greater impact on those inexperienced with gaming, and thus, they took this test more seriously; a similar explanation is plausible also for the cube comparison test.

CONCLUSION

Good visuospatial ability correlates with the performance of simulated colonoscopy performed by experienced endoscopists. In the technically less demanding simulated gastroscopy, visuospatial abilities did not appear to influence performance. This study indicates that gastroscopy to an experienced endoscopist is technically a fairly simple task, although demanding from a pathophysiological standpoint, whereas colonoscopy is technically more demanding and constitutes more of a visuospatial workload. These results indicate that there might be a role for early endoscopic training to proficiency levels of trainees entering fields that present a higher level of visuospatial challenge.

REFERENCES

1. Seymour NE, Gallagher AG, Roman SA, et al. Virtual reality training improves operating room performance: Results of a randomized, double-blinded study. Ann Surg 2002;236: 458–463.
2. Grantcharov TP, Kristiansen VB, Bendix J, Bardram L, Rosenberg J, Funch-Jensen P. Randomized clinical trial of virtual reality simulation for laparoscopic skills training. Br J Surg 2004;91:146–150.
3. Ferlitsch A, Glauninger P, Gupper A, et al. Evaluation of a virtual endoscopy simulator for training in gastrointestinal endoscopy. Endoscopy 2002;34:698–702.
4. Tuggy ML. Virtual reality flexible sigmoidoscopy simulator training: Impact on resident performance. J Am Board Fam Pract 1998;11:426–433.
5. Ritter EM, McClusky DA 3rd, Lederman AB, Gallagher AG, Smith CD. Objective psychomotor skills assessment of experienced and novice flexible endoscopists with a virtual reality simulator. J Gastrointest Surg 2003;7:871–877.
6. Sedlack RE, Kolars JC, Alexander JA. Computer simulation training enhances patient comfort during endoscopy. Clin Gastroenterol Hepatol 2004;2:348–352.
7. Kohn LT, Corrigan JM. To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press, 1999.
8. Dawson SL. A critical approach to medical simulation. Bull Am Coll Surg 2002;87:12–18.
9. Cowie R. Measurement and modelling of perceived slant in surfaces represented by freely viewed line drawings. Perception 1998;27:505–540.
10. Gallagher AG, Cowie R, Crothers I, Jordan-Black JA, Satava RM. PicSOr: An objective test of perceptual skill that predicts laparoscopic technical skill in three initial studies of laparoscopic performance. Surg Endosc 2003;17:1468–1471.
11. Ekstrom RB, French JW, Harmann HH. Manual for Kit of Factor-Referenced Cognitive Tests. Princeton: Educational Testing Service, 1976.
12. Gallagher A, Crothers I, Satava R. Objective measures of visio-spatial ability for minimally invasive surgery. In: 12th European Association for Endoscopic Surgery Congress, 2004. Barcelona: 2004.
13. Ritter EM, McClusky DA 3rd, Lederman AB, Gallagher AG, Smith CD. Perceptual, Visuospatial, and Psychomotor Ability Correlates With Duration of Learning Curve on a Virtual Reality Flexible Endoscopy Simulator. Presented at Southeastern Surgical Congress; Feb 2, 2004; Atlanta, GA.
14. Enochsson L, Isaksson B, Tour R, et al. Visuospatial skills and computer game experience influence the performance of virtual endoscopy. J Gastrointest Surg 2004;8:876–882.
15. Eversbusch A, Grantcharov TP. Learning curves and impact of psychomotor training on performance in simulated colonoscopy: A randomized trial using a virtual reality endoscopy trainer. Surg Endosc 2004;18:1514–1518.

16. Kneebone RL, Nestel D, Moorthy K, Taylor P, Bann S, Munz Y, Darzi A. Learning the skills of flexible sigmoidoscopy - the wider perspective. Med Educ 2003;37(Suppl 1): 50–58.
17. Gerson LB, Van Dam J. A prospective randomized trial comparing a virtual reality simulator to bedside teaching for training in sigmoidoscopy. Endoscopy 2003;35: 569–575.
18. Clark JA, Volchok JA, Hazey JW, Sadighi PJ, Fanelli RD. Initial experience using an endoscopic simulator to train surgical residents in flexible endoscopy in a community medical center residency program. Curr Surg 2005;62:59–63.
19. Sedlack RE, Kolars JC. Computer simulator training enhances the competency of gastroenterology fellows at colonoscopy: Results of a pilot study. Am J Gastroenterol 2004;99:33–37.

Chronic Pouchitis After Ileal Pouch–Anal Anastomosis for Ulcerative Colitis: Effect on Quality of Life

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Chronic pouchitis can be observed in up to 30% of patients after proctocolectomy with ileal pouch–anal anastomosis (IPAA) for ulcerative colitis (UC). It remains a poorly understood complication and often requires chronic antibiotic and antidiarrheal treatment. We hypothesized that its occurrence can be predicted by distinct clinical parameters and that it adversely affects quality of life. Sixty-eight of 129 consecutive UC patients who underwent IPAA over a 10-year period were evaluated by Cleveland Clinic Global Quality of Life questionnaires, telephone interviews, and by chart review. Using bivariate comparison, clinical predictors for the occurrence of chronic pouchitis were sought, and postoperative data analyzed with regard to functional results and quality of life. Nineteen of 68 patients (28%) experienced chronic pouchitis, but its occurrence could not be predicted by any variable assessed. Patients with chronic pouchitis complained of more frequent fecal incontinence (32% vs. 4% in controls; $P < 0.01$), of more frequent bowel movements (7.7/day vs. 6.2/day; $P < 0.05$), and experienced severe abdominal pain more often ($P < 0.05$). Overall quality of life and satisfaction with surgery, as well as subjective health and energy levels were lower in patients with chronic pouchitis ($P < 0.01$); however, greater than 80% of these patients would consider undergoing the same procedure again. (J GASTROINTEST SURG 2006;10:600–606) © 2006 The Society for Surgery of the Alimentary Tract

KEY WORDS: Ileal pouch–anal anastomosis, inflammatory bowel disease, pouchitis, quality of life, ulcerative colitis

Since its introduction 1978 by Parks and Nicholls,[1] proctocolectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice for ulcerative colitis (UC). Proctocolectomy with IPAA has reliably produced acceptable functional results as well as an improved quality of life for these patients.[2–4] One of the most poorly understood long-term complications is the development of pouchitis, which represents a nonspecific inflammatory process of the ileoanal pouch. Clinical symptoms include abdominal pain, urgency, bloody or mucous diarrhea, fever, and/or general malaise that usually respond to a single course of oral antibiotics such as metronidazole or ciprofloxacin. However, in some cases, the symptoms persist and affected patients may require repeated and/or long-term antibiotic treatment. The incidence of acute or chronic pouchitis after IPAA varies greatly according to the diagnostic criteria used.[5] The cumulative risk of both forms has been reported to be as high as 51% at 48 months after the initial operation, although reports vary widely.[6,7] Despite many studies on the quality of life after IPAA[2,7–9] and a substantial amount of literature on acute pouchitis, there is little information on the quality of life in patients with chronic pouchitis. We analyzed preoperative patient variables to identify possible predictors of chronic pouchitis and assessed functional results and quality of life (QOL) in patients, with and without chronic pouchitis, using the Cleveland Global Quality of Life Instrument (CGQL).[2]

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MATERIAL AND METHODS

Study Population and Data Collection

Ileal pouch–anal anastomosis was performed in 129 patients for ulcerative colitis at the University of Louisville and affiliated hospitals between September 1990 and August 2000. The same attending surgeon was present for all patients enrolled into this study. Operative technique included total proctocolectomy with either distal rectal mucosectomy followed by hand-sewn ileal J-pouch–anal anastomosis or stapled ileal pouch–rectal anastomosis. A temporary diverting loop ileostomy was used in patients receiving immunosuppression and in those with tension on the IPAA. Radiographic contrast examination and ileoscopy of the pelvic pouch was routinely performed before ileostomy closure.

A single gastrointestinal pathologist reviewed all surgical pathology. Patients with a final diagnosis of indeterminate colitis[10] were included in our study, whereas patients with Crohn's disease as the underlying pathology were excluded from analysis.

After approval of the University of Louisville Institutional Review Board and written, informed consent, patient data were obtained by retrospective chart review, mailed QOL questionnaires, and personal telephone interviews by a physician or nurse practitioner. The questionnaire used was a modified Cleveland Clinic Global QOL questionnaire,[11] adapted to our study parameters listed below. Patients who responded to the QOL questionnaire were divided into two groups: those with chronic pouchitis and those with occasional or no episodes of pouchitis.

Patient Evaluation and Definition of Chronic Pouchitis

Initial symptoms of pouchitis, including increased stool frequency, abdominal cramping, urgency, and/or blood mixed with stool, were initially empirically treated with a 7-day course of oral metronidazole, or ciprofloxacin in the event of allergy. This typically controlled symptoms rapidly. Patients were then scheduled for physical examination with digital examination to exclude the presence of an anastomotic stricture as a predisposing factor for pouchitis, and endoscopy was performed to evaluate the ileal pouch. In patients who responded to the initial antibiotic therapy, routine pouch biopsies were not performed. Stool cultures were obtained in those patients not improving with antibiotics and those having repeated symptomatic episodes. These patients underwent pouch endoscopy and biopsy to exclude Crohn's disease, cytomegalovirus infection, or irritable pouch syndrome. If the initial 7-day course with metronidazole or ciprofloxacin was unsuccessful (without relief of symptoms), patients were placed on another antibiotic. Patients who relapsed shortly after cessation of treatment were placed on a 30-day course of antibiotics. Patients who had further relapses resumed full dose antibiotic treatment for 2 weeks, after which an effort was made to taper to a lower dose. Some patients were able to control symptoms with lower maintenance doses; others required full therapeutic doses for prolonged periods of time.

Chronic pouchitis was defined as patients having one or more of the following criteria: (1) four or more episodes of pouchitis per year, (2) active symptoms lasting for more than 4 weeks despite antibiotic therapy, and (3) chronic antibiotic therapy was required to control symptoms, and at least one pouch endoscopy was performed documenting histologic evidence of inflammation during an episode of pouchitis.[12]

Study Parameters

Parameters assessed for this study fell into three categories: (1) Preoperative and perioperative patient variables, (2) postoperative functional parameters, and (3) postoperative quality of life assessment. The first section included general demographic patient data such as age, height, weight, body mass index, race, smoking history, American Society of Anesthesiologists Score, and duration of the initial operative procedure. Further variables included the presence of extraintestinal manifestations, extent of colonic disease, presence of dysplasia/carcinoma, indication for the operation, and the age of the pouch at follow-up. Postoperative functional parameters included the presence of IPAA strictures, number of diurnal and nocturnal bowel movements, presence of leakage and fecal incontinence, ability to distinguish flatus from stool, presence of cramping and/or abdominal pain, and the use of antidiarrheal medication, antibiotics, or pads to control symptoms. Functional parameters were assessed under therapy in those patients on chronic antibiotic treatment for pouchitis. Ileal pouch–anal anastomosis stricture was defined as a rigid, fibrotic anastomotic stricture not permitting passage of an index finger, which required digital or instrumental dilatation with or without sedation. Leakage was defined as involuntary loss of feces leading to spotting of underwear. Fecal incontinence, or "accidents," was defined as unintended soilage of underwear with involuntary loss of actual bowel movements. Factors

assessed in determining postoperative quality of life included restrictions in dietary, working, or sexual habits, fear of being in public, and whether or not patients would be willing to undergo the same procedure again and recommend it to a friend. Quality of life was evaluated by using a modified CGQL instrument,[2] which is a useful tool to measure QOL by having patients rate their current overall quality of life, health, and energy on a scale from 1 to 10 (10 being highest). The original CGQL divides the sum of the three parameters by 30 to arrive at a final score between zero and one.[2] Finally, satisfaction with the operation is separately assessed on a scale from 1 to 10.

Statistical Analysis

A case control study was conducted comparing the chronic pouchitis group of patients with the occasional or no-pouchitis group. Results are stated as mean (95% confidence interval for the mean) unless otherwise specified. According to the distribution of data, the unpaired *t* test or Mann-Whitney *U* test was used for continuous variables and χ^2, or Fisher exact tests for categorical variables. A significance level of 0.05 was used. Results were computed with JMP software, version 4.0 (SAS Institute Inc, Cary, NC)

RESULTS

Of the 129 UC patients who had undergone IPAA during the period from 1990–2000, there was a 53% response rate (68 patients, 39 females, 29 males) to our survey. Median age at operation was 39 years (range, 12–67, years). A mucosectomy with handsewn anastomosis was done in all but three patients who underwent double-stapled IPAA. The final diagnosis after histological examination of the resection specimen by the gastrointestinal pathologist was UC in 52 patients (76%) and indeterminate colitis in 16 patients (24%). Follow-up ranged from 1–11 years (median, 4 years). Nineteen patients (28%) experienced chronic pouchitis (12 female, 7 male), whereas the remainder had occasional or no episodes of pouchitis (27 female, 22 male). Neither the distribution of gender ($P = 0.55$) nor race (white vs. African-American race) differed between groups ($P = 0.57$).

Three patients with chronic pouchitis (16%) underwent pouch excision because of intractable diarrhea. There were two deaths, one due to metastatic rectal cancer 5 years after IPAA, and one secondary to metabolic complications of total parenteral nutrition at home 3 years postoperatively. The patient who died of metastatic rectal cancer was treated by ultralow Hartmann procedure, colectomy and ileostomy, and postoperative radiation elsewhere 1 year before the ileal pouch–anal anastomosis. The patient who was on total parenteral nutrition had chronic pouchitis with severe diarrhea and significant weight loss and did not respond well to oral antibiotic therapy and antidiarrheals. Home total parenteral nutrition was subsequently started for nutritional repletion and bowel rest.

Perioperative Patient Variables

Perioperative patient variables in patients with and without chronic pouchitis are shown in Table 1. Using bivariate comparisons, there were no detectable statistical differences between the two groups of

Table 1. Comparison of perioperative variables between patients with and without chronic pouchitis

	Patients with chronic pouchitis (n = 19)		Patients without chronic pouchitis (n = 49)		
Patient history	**Mean**	**95% CI**	**Mean**	**95% CI**	***P* value**
Age (years)	35.8	(29.7-42.0)	39.9	(36.0-43.7)	0.25
Body mass index	26.6	(20.8-32.3)	25.2	(23.0-27.4)	0.39
Duration of disease (years)	9.5	(5.9-13.2)	9.9	(7.6-12.1)	0.85
ASA score	1.9	(1.5-2.2)	2.0	(1.9-2.2)	0.46
Duration of operation (minutes)	402	(346-458)	390	(361-418)	0.60
Time since operation at follow-up (years)	3.9	(2.6-5.2)	4.1	(3.3-4.9)	0.85

Indication for surgery	**No. patients**	**%**	**No. patients**	**%**	***P* value**
Medical failure	13	68	34	69	0.83
Toxicity	1	5	7	14	0.43
Other	5	26	8	16	0.49
Disease location					
Proctosigmoiditis	1	5	5	10	0.70
Left-sided	4	21	18	37	0.34
Pancolitis	14	74	26	53	0.20
Histology*					
UC	14	76	38	77	0.76
Indeterminate colitis	5	26	11	23	0.76
Dysplasia present	4	21	4	9	0.21

ASA = American Society of Anesthesiologists; CI = Confidence interval.
*Based on examination of the surgical resection specimen by a gastrointestinal pathologist.

patients for any variable with respect to the likelihood of developing chronic pouchitis. Patients were similar with respect to age, body mass index, duration of disease, and history of smoking. Extraintestinal manifestations were present in 32% of patients with chronic pouchitis as compared with 52% of patients without chronic pouchitis. This difference was not statistically significant ($P = 0.11$). Postoperative septic complications including abdominal/pelvic abscess and/or perineal fistula(s) occurred in one chronic pouchitis patient and in two patients without chronic pouchitis.

Functional Results

Parameters describing postoperative pouch function are shown in Table 2. Although not statistically significant, the incidence of IPAA stricture in the chronic pouchitis group was nearly double (32%) that in patients without chronic pouchitis (17%; $P = 0.16$). The mean number of bowel movements in chronic pouchitis patients at 7.7 per 24 hours (95% CI, 6.4-9.0) was higher than in those who did not develop chronic pouchitis (6.2 per 24 hours [95% CI, 5.6-6.8]; $P = 0.02$). Although daytime bowel movement frequency did not differ ($P = 0.19$), nocturnal bowel movement frequency was higher in chronic pouchitis patients with 2.5 per night (95% CI, 1.7-3.2) as compared with 1.7 per night (95% CI, 1.4-2.0) in patients without chronic pouchitis ($P = 0.02$). The most marked functional difference between the two groups, however, was the rate of fecal incontinence occurring in 32% of chronic pouchitis patients as compared with 4% of patients without chronic pouchitis ($P < 0.01$). Interestingly, there was no difference in the use of pads or antidiarrheal medication, and the presence of chronic pouchitis did not impair the patients' ability to distinguish flatus from stool ($P = 0.09$). Mild cramping abdominal pain was reported by a similar percentage of patients in both groups. Nonetheless, three patients (16%) with chronic pouchitis complained of severe abdominal pain, whereas this was not reported by any patient without chronic pouchitis ($P = 0.02$).

Quality of Life

Quality of life comparisons between patients with and without chronic pouchitis are shown in Table 3. There were no differences between groups in food, work, or sexual restrictions, or in fear of being in public. Despite this, the average quality of life scores for patients with chronic pouchitis were lower for overall QOL as well as for health and energy subscores ($P < 0.01$ for overall QOL). Patients' overall satisfaction with their operation, assessed on a scale from 1 (lowest) to 10 (highest), was significantly lower in pouchitis patients (7.4) compared with the nonpouchitis group (8.9; $P = 0.01$). Interestingly, 84.2% of patients with pouchitis would still undergo the procedure again and would recommend it to a friend, compared with 93.8% in the nonpouchitis group, a difference that did not reach statistical significance.

DISCUSSION

Chronic pouchitis after IPAA has only recently begun to receive attention as an entity distinct from acute pouchitis.[12] Chronic inflammation of the ileal pouch leads to substantial patient morbidity and often requires long-term antibiotic treatment to control symptoms. A clear separation between these two variants of the same condition is therefore necessary. The incidence of chronic pouchitis after IPAA varies widely between 5% and more than

Table 2. Postoperative functional variables

Variable	Patients with chronic pouchitis (n = 19)		Patients without chronic pouchitis (n = 49)		*P* value
	No. patients	%	No. patients	%	
Daily use of antidiarrheal medication	15	79	37	76	1.00
Pad usage	6	32	14	29	0.96
Abdominal cramping	12	63	22	45	0.28
Severe abdominal pain	3	16	0	0	0.02
Urgency	13	68	29	59	0.67
Cannot differentiate between flatus and bowel movement	1	5	12	25	0.09
Leakage	17	90	36	73	0.20
Accidents	6	32	2	4	0.006

Table 3. Quality of life after IPAA for UC

Quality of life parameter	Patients with chronic pouchitis (n = 19)		Patients without chronic pouchitis (n = 49)		*P* value
	No. patients	%	No. patients	%	
Food restrictions	11	58	21	43	0.40
Work restrictions	4	21	5	10	0.25
Sexual dysfunction	6	32	10	20	0.35
Fear of being in public	4	21	9	18	0.75
Would do it again, and recommend it to a friend	16	84	46	94	0.34
Overall QOL* mean (95% CI)	7.1 (5.8-8.4)		8.8 (8.3-9.2)		0.003
Health QOL* mean (95% CI)	6.5 (5.3-7.7)		7.9 (7.4-8.4)		0.01
Energy QOL* mean (95% CI)	5.7 (4.3-7.1)		7.1 (6.5-7.6)		0.04
Satisfaction with surgery* mean (95% CI)	7.4 (5.9-8.9)		8.9 (8.5-9.4)		0.01

QOL = quality of life; CI = confidence interval; IPAA = ileal pouch-anal anastomosis.
*As adapted from the Cleveland Global Quality of Life instrument.[2]

30%,[5,13–16] presumably due to different diagnostic criteria and inclusion of patients with both UC and familial adenomatous polyposis. In our study investigating patients with UC only, we identified chronic pouchitis by the requirement for long-term or repeated courses of medical therapy to control symptoms. Shen et al.[17] demonstrated that omitting histology from the standard pouchitis disease activity index not only simplifies pouchitis diagnostic criteria, but provides for an equivalent sensitivity and specificity. All chronic pouchitis patients had at least one pouch endoscopy, and biopsy with histological evidence of pouch inflammation. Pouch biopsy specimens showed the typical findings of lymphocyte infiltration, areas of acute inflammation, persistent villous atrophy, and in some cases pyloric gland metaplasia. Using this approach, we diagnosed chronic pouchitis in 28% of cases, a high number considering a mean follow-up period of merely 4 years.

Pouchitis clearly seems to be an immune-mediated phenomenon, because it is almost exclusively seen in patients with inflammatory bowel disease and rarely seen in those with familial adenomatous polyposis who have undergone IPAA or continent ileostomy.[18,19] For this reason, we, unlike some others, consider it important to evaluate results after IPAA for inflammatory bowel disease separately from those of IPAA performed for familial adenomatous polyposis.

With regard to the development of pouchitis in general, previous studies have identified a number of potential risk factors. The diagnosis of Crohn's disease has been thought to predispose patients to pouchitis, but reports are conflicting.[10,20,21] Up to 70% of patients with Crohn's disease may develop chronic pouchitis after IPAA. To avoid potential bias, we have excluded Crohn's patients from our study.

Interestingly, despite our high rate of indeterminate colitis (24%), this was not associated with an increased rate of chronic pouchitis ($P = 0.76$). All our pathology was initially reviewed by generalist pathologists and treatment and surgery based on these diagnoses. All surgical pathology was then reviewed by a single experienced gastrointestinal pathologist. This change in diagnosis is compatible with data we have previously published.[22,23] Other series, in which the initial review was done by specialist gastrointestinal pathologists have, as expected, reported lower rates of indeterminate colitis (9%–16%).[24,25]

The presence of extraintestinal manifestations, especially primary sclerosing cholangitis, has by some been reported to predispose to the development of pouchitis.[10,12,26,27] In our patients, the presence of extraintestinal manifestations was not a predictive factor, and was actually more frequent, but not statistically so, in patients without chronic pouchitis. In addition, an association between antineutrophil antibodies and the development of chronic pouchitis has been reported.[28,29] Fleshner et al.[28] has demonstrated a correlation between high preoperative levels of perinuclear antineutrophil cytoplasmic antibodies in ulcerative colitis patients and the later development of chronic pouchitis.

Stocchi and Pemberton[6] reported that age, gender, extent of disease, and postoperative sepsis did not predispose patients to pouchitis, whereas Kuisma et al.[26] found that neither age, gender, duration of follow-up, body mass index, smoking status, extent of disease, nor indication for operation predicted the development of pouchitis. Our data are in agreement with this, as none of the preoperative and perioperative clinical parameters correlated with the subsequent development of chronic pouchitis.

A significantly higher frequency of bowel movements and more episodes of involuntary stool loss were observed in patients suffering from chronic pouchitis. Although questions regarding abdominal pain are included in the Cleveland Clinic Global QOL questionnaire, there have been few reports on the frequency of abdominal pain in these patients. Cramping abdominal discomfort was reported frequently by both groups of patients, leading one to question how many patients without chronic pouchitis had associated irritable bowel syndrome. However, severe abdominal pain occurred only in chronic pouchitis patients.

Ileal pouch–anal anastomosis strictures, which occurred in 21% of all patients of our series, did not predispose to chronic pouchitis, although strictures tended to occur more frequently in patients suffering from chronic pouchitis. Although we have recorded differences between groups in several instances, we are not able to confer any statistical significance for many of these findings due to the limited number of patients in our study. However, our data are in agreement with those of Hahnloser et al.,[7] who analyzed 409 patients with IPAA for UC and found IPAA strictures in exactly 21% of their study population.

Our 53% response rate to the QOL questionnaire is comparable to other studies regarding mailed QOL questionnaires, in contrast to those in which QOL instruments are administered at the time of routine office visits. We cite, for example, the study by Hahnloser et al.[7] in which full data sets were available for only 22% of patients, and the study by Tiainen and Matikainen[9] in which QOL questionnaires were obtained in 62% of patients undergoing restorative proctocolectomy. Needless to say, there is a selection bias in any such sample. Nevertheless, patients with chronic pouchitis had an overall lower quality of life score and lower satisfaction with their operation; however, they would still recommend this procedure to others. This is in agreement with the study of Neilly et al.[30]; in their series of 203 patients, almost 90% described their QOL as "always" better since undergoing IPAA, despite a high complication rate of pouchitis, small bowel obstruction, and incontinence. Although patients with chronic pouchitis experienced frequent episodes of fecal incontinence, they did not have significantly more food, sex, work, or social restrictions than their counterparts without chronic pouchitis did. Medical therapy for chronic pouchitis with antibiotics and antidiarrheals resulted in a similar number of bowel movements compared with patients without chronic pouchitis. Chronic pouchitis patients did, however, have lower global QOL scores, lower assessments of their current state of health, and lower energy levels than patients without chronic pouchitis.

REFERENCES

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978;2:85–88.
2. Fazio VW, O'Riordain MG, Lavery IC, et al. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Ann Surg 1999;230:575–584.
3. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg 1995;222:120–127.
4. Michelassi F, Lee J, Rubin M, et al. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: A prospective observational study. Ann Surg 2003;238:433–441.
5. Mahadevan U, Sandborn WJ. Diagnosis and management of pouchitis. Gastroenterology 2003;124:1636–1650.
6. Stocchi L, Pemberton JH. Pouch and pouchitis. Gastroenterol Clin North Am 2001;30:223–241.
7. Hahnloser D, Pemberton JH, Wolff BG, et al. The effect of ageing on function and quality of life in ileal pouch patients: A single cohort experience of 409 patients with chronic ulcerative colitis. Ann Surg 2004;240:615–621.
8. Coffey JC, Winter DC, Neary P, Murphy A, Redmond HP, Kirwan WO. Quality of life after ileal pouch-anal anastomosis: An evaluation of diet and other factors using the Cleveland Global Quality of Life instrument. Dis Colon Rectum 2002;45:30–38.
9. Tiainen J, Matikainen M. Health-related quality of life after ileal J-pouch-anal anastomosis for ulcerative colitis: Long-term results. Scand J Gastroenterol 1999;34:601–605.
10. Rudolph WG, Uthoff SM, McAuliffe TL, Goode ET, Petras RE, Galandiuk S. Indeterminate colitis: The real story. Dis Colon Rectum 2002;45:1528–1534.
11. Fazio VW, Wu JS, Lavery IC. Repeat ileal pouch-anal anastomosis to salvage septic complications of pelvic pouches: Clinical outcome and quality of life assessment. Ann Surg 1998;228:588–597.
12. Achkar JP, Al Haddad M, Lashner B, et al. Differentiating risk factors for acute and chronic pouchitis. Clin Gastroenterol Hepatol 2005;3:60–66.
13. Simchuk EJ, Thirlby RC. Risk factors and true incidence of pouchitis in patients after ileal pouch-anal anastomoses. World J Surg 2000;24:851–856.
14. Stahlberg D, Gullberg K, Liljeqvist L, Hellers G, Lofberg R. Pouchitis after pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. Dis Colon Rectum 1996;39:1012–1018.
15. Fazio VW, Tekkis PP, Remzi F, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. Ann Surg 2003;238:605–614.
16. Hurst RD, Molinari M, Chung TP, Rubin M, Michelassi F. Prospective study of the incidence, timing and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. Arch Surg 1996;131:497–500.
17. Shen B, Achkar JP, Connor JT, et al. Modified pouchitis disease activity index: A simplified approach to the diagnosis of pouchitis. Dis Colon Rectum 2003;46:748–753.
18. Barton JG, Paden MA, Lane M, Postier RG. Comparison of postoperative outcomes in ulcerative colitis and familial polyposis patients after ileoanal pouch operations. Am J Surg 2001;182:616–620.

19. Sandborn WJ. Pouchitis after ileal pouch-anal anastomosis: Definition, pathogenesis, and treatment. Gastroenterology 1994;107:1856–1860.
20. Tekkis PP, Heriot AG, Smith O, Smith JJ, Windsor AC, Nicholls RJ. Long-term outcomes of restorative proctocolectomy for Crohn's disease and indeterminate colitis. Colorectal Dis 2005;7:218–223.
21. Ettorre GM, Pescatori M, Panis Y, Nemeth J, Crescenzi A, Valleur P. Mucosal changes in ileal pouches after restorative proctocolectomy for ulcerative and Crohn's colitis. Dis Colon Rectum 2000;43:1743–1748.
22. Farmer M, Petras RE, Hunt LE, Janosky JE, Galandiuk S. The importance of diagnostic accuracy in colonic inflammatory bowel disease. Am J Gastroenterol 2000;95:3184–3188.
23. Petras RE. Role of the pathologist in evaluating chronic pouches. In: Hanauer SB, Bayless TM, eds. Advanced Therapy of Inflammatory Bowel Disease. Hamilton: Decker, Inc., 2001, pp 229–232.
24. Dayton MT, Larsen KR, Christiansen DD. Similar functional results and complications after ileal pouch-anal anastomosis in patients with indeterminate vs ulcerative colitis. Arch Surg 2002;137:690–694.
25. Delaney CP, Remzi FH, Gramlich T, Dadvand B, Fazio VW. Equivalent function, quality of life and pouch survival rates after ileal pouch-anal anastomosis for indeterminate and ulcerative colitis. Ann Surg 2002;236: 43–48.
26. Kuisma J, Nuutinen H, Luukkonen P, Jarvinen H, Kahri A, Farkkila M. Long term metabolic consequences of ileal pouch-anal anastomosis for ulcerative colitis. Am J Gastroenterol 2001;96:3110–3116.
27. Penna C, Dozois R, Tremaine W, et al. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996;38:234–239.
28. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. Gut 2001;49:671–677.
29. Sandborn WJ, Landers CJ, Tremaine WJ, Targan SR. Antineutrophil cytoplasmic antibody correlates with chronic pouchitis after ileal pouch-anal anastomosis. Am J Gastroenterol 1995;90:740–747.
30. Neilly P, Neill ME, Hill GL. Restorative proctocolectomy with ileal pouch-anal anastomosis in 203 patients: The Auckland experience. Aust N Z J Surg 1999;69: 22–27.

Pancreaticoduodenectomy: Superior Mesenteric Artery First Approach

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Pancreaticoduodenectomy (PD) is the only effective treatment for cancers of the periampullary region. Many technical modifications of reconstruction after PD have been described. However, the technique of resection followed in most centers is similar.[1] One of the important predictive factors of prognosis is the presence of retroperitoneal lymph node metastases, which are present in 20%–77% of resected specimens of patients with carcinoma of the head of the pancreas.[2] Hence, lymph node dissection to the right of the superior mesenteric vessels is a minimum requirement. Another common technical difficulty encountered during classic PD is the presence of a replaced right hepatic artery arising from the superior mesenteric artery (SMA). This anomaly occurs in 15%–20% of patients. Inadvertent injury to this vessel can occur during the dissection of the uncinate process, especially in cases of advanced tumors. Above all, infiltration of superior mesenteric vein (SMV) and/or portal vein (PV) is encountered in a significant proportion of patients with pancreas head tumors.[3] En bloc resection and reconstruction of the vein can be performed without increased morbidity and mortality.[4] However, infiltration of the SMA is considered a contraindication for resection. Infiltration of these major vessels is usually identified only toward the end of the resection process, when the surgeon is committed to resection. The end result is often a "margin-positive" resection. These patients with margin-positive resection have a poor prognosis that is often not better than that of unresected patients.

To overcome these technical difficulties and to achieve an oncologically acceptable lymph node clearance, we describe a technique of PD in which the SMA is dissected first and the posterior pancreatic capsule is dissected early during the operation. The posterior part of the pancreatic head is dissected off the vessels first without dividing the pancreatic neck. Thus the surgeon avoids the "point of no return" of the classic operation while achieving early identification of nonresectability. This method also accomplishes adequate lymphadenectomy and easier identification and safeguarding of a replaced right hepatic artery, if one is present.

TECHNIQUE

Laparoscopy is performed only in patients in whom preoperative imaging has shown suspicion of dissemination or features of unresectability. The abdomen is explored through a subcostal incision. Upon opening the abdomen, a thorough and systematic exploration is performed to search for any evidence of tumor dissemination, such as peritoneal carcinomatosis and liver metastasis. After confirming the absence of dissemination, attention is directed toward the tumor and the regional lymph nodes.

Dissection commences by incising the attachment of the transverse mesocolon to the right perinephric area. The transverse mesocolon is brought down completely to expose the SMV where it lies anterior to the third part of the duodenum. This mobilization is carried farther to the left by incising the omental attachment to the mesocolon along the avascular line. This opens up the lesser sac, and the anterior surface of the pancreas is exposed widely. Then, a liberal "Kocherization" of the duodenum is accomplished by incising the posterior peritoneum of the duodenum. The Kocherization is continued up to the level of the left border of the aorta. This enables a good exposure of the aortocaval region. This region is assessed for the presence of lymphadenopathy, and

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any suspicious lymph nodes are excised and sent for frozen section examination. If any of these lymph nodes are reported as positive, resection is abandoned.

Thus, a liberal Kocherization exposes the origin of the SMA just superior to the point at which the left renal vein crosses the aorta.

Dissection of the Superior Mesenteric Artery

After exposure of the origin of this vessel, it is dissected all around with a right-angled dissector and a vascular loop is passed around the vessel. Now, the perivascular connective tissue surrounding the SMA is incised longitudinally along the axis of the vessel (Fig. 1). This incision is extended down along the vessel by inserting a fine right-angled dissector along the plane and ligating the individual lymphatics and arterial branches. At a point approximately 1–2 cm from the origin of the SMA, the replaced right hepatic artery can be identified, if present. If present, this vessel is looped and safeguarded. The dissection on the SMA continues down until the junction of the third and fourth parts of duodenum. The anterior aspect of the vessel is dissected free by dividing the attachment of the mesouncinate to this vessel, thus exposing the lateral border of the PV and SMV. By now, all of the connective tissue attachments between the PV and the SMA have also been divided. This dissection is of utmost importance, because during this stage the presence of tumor invasion to the SMA can be identified. If the tumor is invading the SMA or a major portion of the vein, resection can be abandoned at this stage and palliative measures can be undertaken, as indicated. Further dissection in this region is carried out after dissection of the hepatoduodenal ligament.

Dissection of the Hepatoduodenal Ligament

After cholecystectomy, the bile duct, along with the surrounding lymphatics and loose areolar tissue, is dissected, and the bile duct is divided at the level of insertion of the cystic duct. This exposes the PV in the hepatoduodenal ligament. The PV is traced

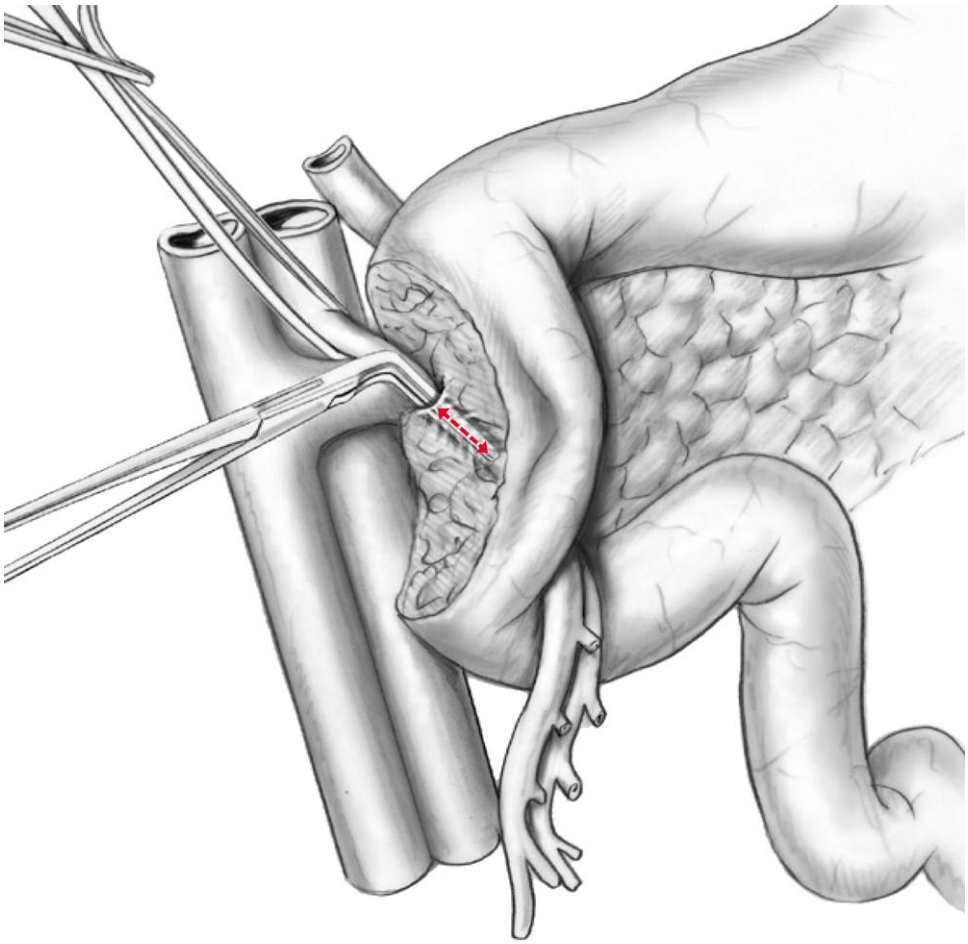

Fig. 1. Origin of superior mesenteric artery is taped and dissected distally along the vessel.

down to the level of the neck of the pancreas by ligating and dividing the areolar tissues surrounding the vein. This completely exposes the suprapancreatic PV. The hepatic artery lymph node is identified, and it is excised to identify the common hepatic artery in the suprapancreatic area. This vessel is traced distally along its course, and the gastroduodenal artery is identified at the point were the hepatic artery turns up toward the liver. The gastroduodenal artery is ligated in continuity and divided. The stump is suture ligated for additional protection. Now, further dissection of the posterolateral aspect of the PV in the region of the pancreas is carried out.

Dissection of the Uncinate Process and Neck of Pancreas

The superior dissection of the PV up to the superior border of the pancreas is continued down. This is facilitated by gentle traction of the duodenum and the head of pancreas inferomedially by the assistant. Care should be taken not to apply forceful retraction as this might tear the thin-walled veins on the lateral side of the PV, causing unwarranted hemorrhage. The posterolateral aspect of the PV is carefully dissected with a right-angled dissector. During this phase of dissection, one encounters two or three tributaries of the PV to the head of pancreas. These are divided in between ligatures or clips. Once these veins are divided and the loose areolar tissue around the PV is divided using electrocautery, the posterior aspect of the neck of the pancreas is exposed (Fig. 2). This can be easily separated from the PV as this plane is avascular and does not contain any important structures. This dissection is carried out a little more to the left until the splenoportal junction is exposed. Now, the pancreas is ready for transection (Fig. 3). Difficulty can be encountered during this stage of dissection, if there is tumor invasion to the PV or SMV.

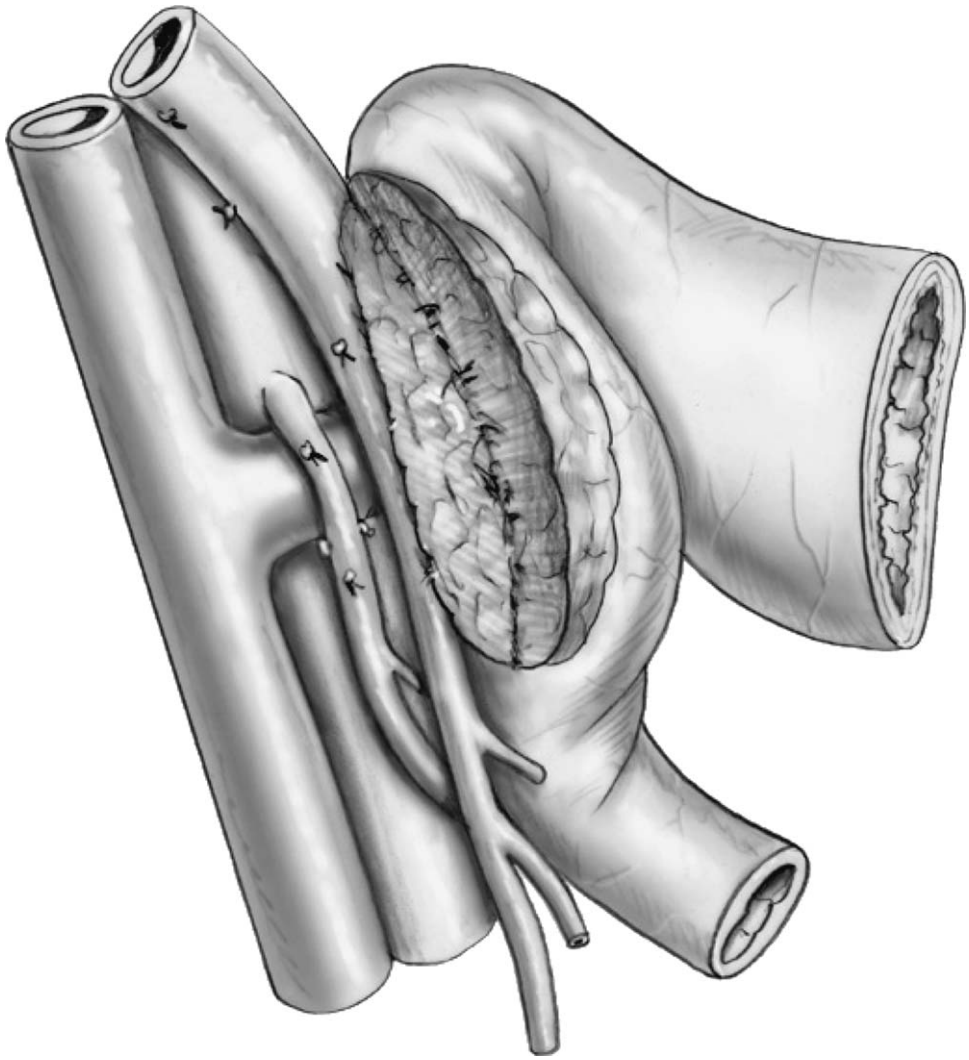

Fig. 2. Exposure of the anterolateral aspect of portal vein and further dissection of the neck of pancreas.

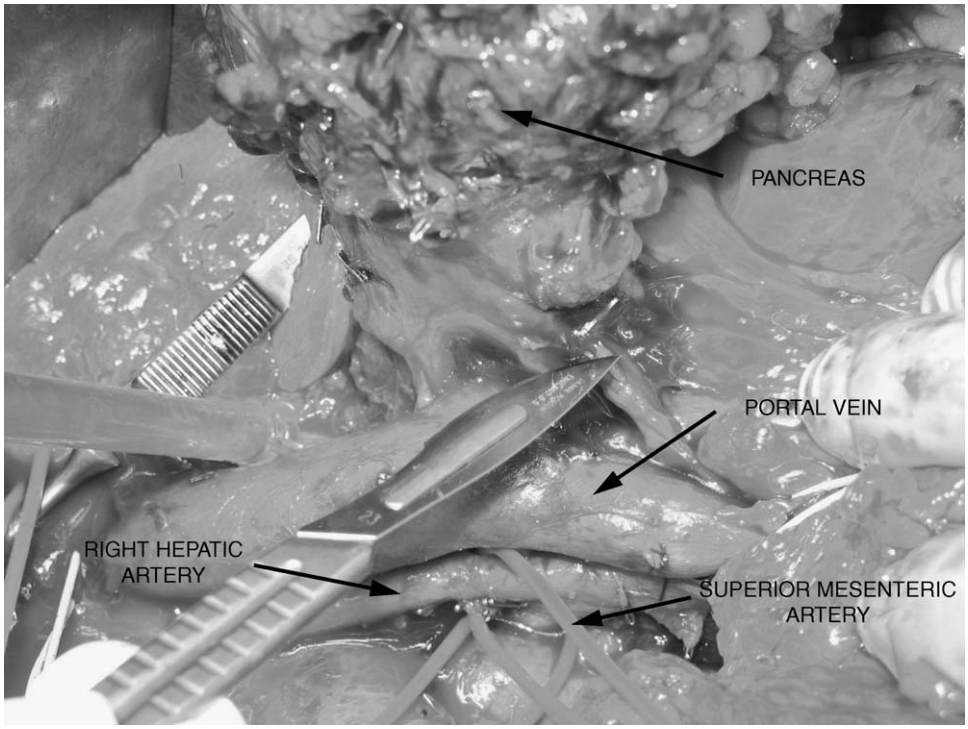

Fig. 3. Completed dissection and final transection of the neck of pancreas.

In case one encounters this, the dissection in this area is temporarily suspended and the SMV below the level of infiltration is dissected and "looped" for proximal control. The previously exposed suprapancreatic PV also is "looped" for distal control. Then, the posterior aspect of the neck of pancreas is dissected free of the anterior surface of the PV by blunt dissection as in classic PD. On the other hand, if it is confirmed that the tumor and a circumference of the vein can be resected, the neck of the pancreas can be divided and the splenic vein also is controlled before completing the resection along with varying amounts of SMV/PV, depending on the degree of involvement.

After completely freeing the neck of pancreas, the proximal jejunum and the stomach are divided as in classic PD. Now, the only remaining attachment of the specimen is the neck of pancreas (Fig. 3). The neck of pancreas is divided using a surgical blade between hemostatic stay sutures to complete the resection.

Reconstruction and restoration of gastrointestinal continuity are effected as classic procedure.

DISCUSSION

Here, we describe a technique of posterior dissection of head of pancreas dissecting the SMA initially, with the division of the pancreatic neck carried out as the final step. This enables the surgeon to identify signs of nonresectability during the early phase of the operation. This approach also allows excellent lymph node clearance and facilitates easier identification of the replaced right hepatic artery.

The finding of tumor infiltration to the SMA is considered a contraindication of PD as resection of SMA and reconstruction involve a definite increase in postoperative mortality and morbidity and does not translate into better survival.[5] Unsuspected tumor invasion of the superior mesenteric vessels, especially the lateral and posterior aspect of the SMV, is the most common unexpected finding during PD.[6] During a classic PD, this finding of vascular involvement is realized by the surgeon at the final stages of the resection, when the neck of pancreas has already been divided. At this "point of no return," the surgeon is committed to resect the tumor and ends up with a resection with a macroscopically positive margin. These patients often have a poor prognosis. Most of them have a survival worse than nonresected patients. Our method of dissecting the SMA and the posterior pancreatic capsule first during PD, avoids this dilemma. The neck of pancreas is divided as the final step of the operation; thus, the surgeon need not encounter the classic "point of no return." The presence of major vascular involvement can be identified early enough to abandon resection.

Another advantage of this procedure is the early identification of a replaced right hepatic artery arising

from the SMA. This occurs in 15%–20% of patients. Inadvertent injury to this vessel is possible, especially in cases of advanced tumors. In our technique of dissection where the critical area for replaced hepatic artery is dissected first, this vessel can be identified early during the course of the operation and can be safeguarded. The dissection along this vessel is carried out upward carefully to clear the lymphatics along this vessel, followed by dissection of the hepatoduodenal ligament and division of the common bile duct.

Our technique of SMA first approach follows oncologic principles. Lymph node involvement is common in lesions of the periampullary region[2]; metastases to lymph nodes occur in 20–77% in cases of cancers of the head of the pancreas. Hence, adequate lymphadenectomy is definitely indicated during the performance of PD. En bloc resection of the lymphatics lying along the right side of the SMA is the minimum extent of dissection during this operation. Extended lymphadenectomy has shown to increase postoperative morbidity with no significant increase in survival.[7] Our technique of posterior approach PD includes en bloc resection of lymph nodes along the right and anterior aspect of SMA (between the SMA and SMV) and hepatoduodenal ligament, a technique consistent with current standards of practice.

The application of this approach may be difficult in cases of PD for chronic pancreatitis because of the significant peripancreatic inflammation and adhesions. However, meticulous dissection of the uncinate process may not be required in cases of chronic pancreatitis and vascular invasion is not an important scenario in these patients.

In conclusion, we report an approach for PD in which the SMA is dissected initially during the operation allowing early detection of inoperability, adequate en bloc lymphadenectomy, and identification of common anatomical variations, like a replaced right hepatic artery from the SMA, which helps in safeguarding this important vessel.

REFERENCES

1. Ahmad SA, Lowy AM, McIntyre BC, et al. Pancreaticoduodenectomy. J Gastrointest Surg 2005;9:138–143.
2. Alexakis N, Halloran C, Raraty M, et al. Current standards of surgery for pancreatic cancer. Br J Surg 2004;91:1410–1427.
3. Fuhrman GM, Leach SD, Staley CA, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Ann Surg 1996;223:154–162.
4. Tuech JJ, Pessaux P, Arnaud JP. Portal vein resection in pancreatic head carcinoma: Part 2: Clinical significance. Hepatogastroenterology 2001;48:888–891.
5. Nagakawa T, Konishi I, Ueno K, et al. The results and problems of extensive radical surgery for carcinoma of the head of pancreas. Jpn J Surg 1991;21:262–267.
6. Cusack JC, Fuhrman GM, Lee JE, et al. Managing unsuspected tumor invasion of the superior mesenteric-portal venous confluence during pancreaticoduodenectomy. Am J Surg 1994; 168:352–354.
7. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary carcinoma. Part 2: Randomized controlled trial evaluating survival, morbidity and mortality. Ann Surg 2002;236:355–368.

Review Article

Management of Common Bile Duct Stones

Eric S. Hungness, M.D., Nathaniel J. Soper, M.D.

Despite many advances in the recent decade, the optimal treatment of choledocholithiasis is controversial. Different modalities for successfully treating common bile duct (CBD) stones have been reported, and the appropriate therapy depends on the patient's condition and the relative local expertise in laparoscopy, endoscopy, and interventional radiology. Prior to the advent of laparoscopy, patients with choledocholithiasis requiring surgical treatment underwent a laparotomy with common bile duct exploration (CBDE) and T-tube placement. Laparoscopic CBDE is now frequently performed with either transcystic or transcholedochal techniques resulting in lower morbidity compared with open CBDE. Endoscopic retrograde cholangiography with or without sphincterotomy (ERC/ES) is commonly performed by endoscopists. Interventional radiologists may dislodge or disintegrade stones by percutaneous transhepatic cholangiography techniques. One of the main determining factors of who performs these procedures is if choledocholithiasis is detected before, during, or after cholecystectomy. In this review, the various techniques for CBD clearance will be discussed, focusing on laparoscopic CBDE. An algorithm that assumes an advanced laparoscopic surgeon with excellent endoscopic and radiologic support is shown (Fig. 1) that takes into account the ability to clear the common bile duct in the safest and most cost-effective manner.

DETECTION OF COMMON DUCT STONES

Patients with choledocholithiasis commonly present with cholecystitis, pancreatitis, biliary colic, cholangitis, and/or jaundice. Cholangitis is most predictive, with some studies showing 100% specificity.[1] However, none of the other more common clinical presentations are predictive. A recent study by Tranter et al.[1] demonstrated a 14.2% incidence of choledocholithiasis in 1000 consecutive laparoscopic cholecystectomies with routine intraoperative cholangiogram. Patients presenting with cholecystitis, biliary colic, pancreatitis, and jaundice were found to have common duct stones 7%, 16%, 20%, and 45% of the time, respectively.

The most common imaging modality utilized in working up patients with biliary symptoms is transabdominal ultrasound. Compared to its high accuracy in diagnosing cholelithiasis and cholecystitis, transabdominal ultrasound has only 50%–80% sensitivity in detecting common duct stones, depending mostly on the presence of common bile duct dilatation.[2,3] Some studies have shown that if sonographic CBD dilatation is combined with age greater than 55 and abnormal liver enzymes, choledocholithiasis can be predicted up to 95% of the time.[4]

For those patients in whom choledocholithiasis is suspected, more definitive tests may be performed. ERC is highly specific in diagnosing common duct stones and may be therapeutic with sphincterotomy and duct clearance. However, this procedure is invasive and associated with significant morbidity. A recent prospective study of 1177 consecutive ERCS demonstrated a 30-day morbidity rate of 15.9%, with procedure-related mortality at 1%.[5] Also, up to 61% of patients undergoing ERC will be found not to have common duct stones and will have undergone an unnecessary invasive test.[6,7]

Recently, endoscopic ultrasound, magnetic resonance cholangiopancreatography (MRCP), and helical computed tomography (HCT) technology have been used to diagnose choledocholithiasis. To decrease unnecessary ERC/ES, some centers now routinely perform endoscopic ultrasound prior to ERC.

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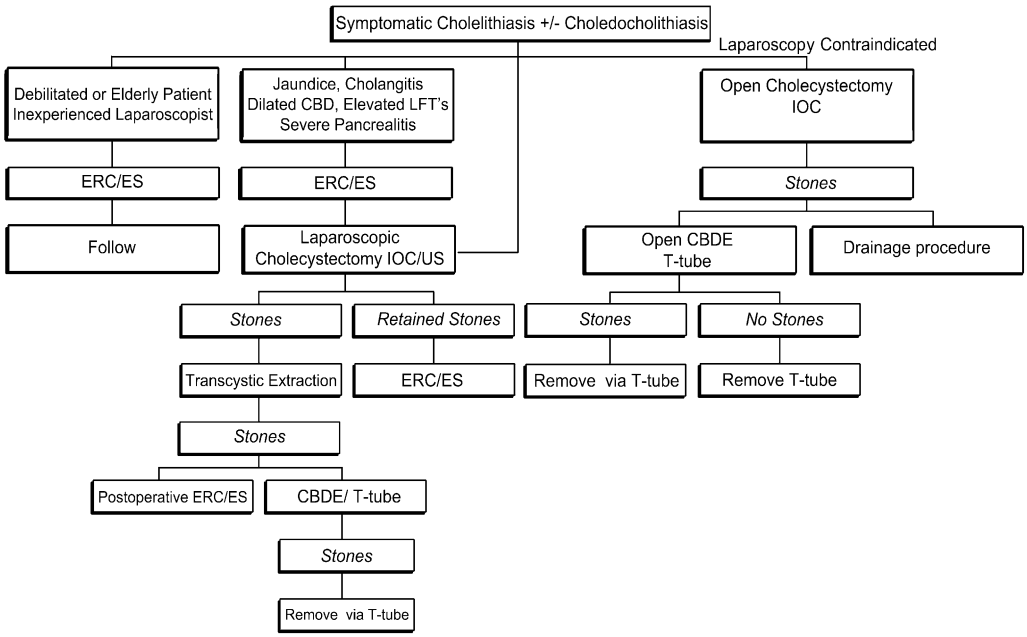

Fig. 1. Management algorithm for treatment of common bile duct (CBD) stones. Assumes that the laparoscopist is experienced in transcystic techniques and that ERC/ES is at least 90% successful at CBD stone clearance. LFT = serum liver tests; CBDE = common bile duct exploration; ERC = endoscopic retrograde cholangiography; ES = endoscopic sphincterotomy; IOC = intraoperative cholangiography; US = laparoscopic ultrasonography. (From Jones and Soper[51]).

A recent study showed the sensitivity and specificity of endoscopic ultrasound to be 98% and 99%, respectively.[8] However, endoscopoic ultrasound is highly operator-dependent compared with MRCP or HCT. Additionally, MRCP and HCT imaging have shown promise as noninvasive alternatives to diagnose choledocholithiasis, with recent studies showing positive predictive values of 95%–100% for MRCP.[9,10] MRCP is quite expensive and time-consuming and does not have the therapeutic possibilities of ERC. The use of a short sequence MRCP has been proposed to reduce the issues of time and cost without significantly afffecting its predictive value.[10] Kondo et al.[11] showed that HCT was equivalent to MRCP, but added the risk of contrast injection.[1] This study also indicated that endoscopic ultrasound was superior to both MRCP and HCT in detecting small (<.5 mm) CBD stones.

PREOPERATIVE ENDOSCOPIC THERAPY

Endoscopic retrograde cholangiography plays an important role in the early treatment of common duct stones for elderly or debilitated patients and in patients that present with jaundice, cholangitis, or severe pancreatitis. For patients who may not tolerate an operation, performing ERC/ES and leaving the gallbladder in situ is a good alternative to cholecystectomy, as recent studies have demonstrated that 75%–84% of patients remain symptom free with up to 70-month follow-up.[12,13] Other studies have demonstrated a decreased mortality for patients undergoing ERC versus surgical drainage for cholangitis and severe pancreatitis.[14–16] However, the use of routine preoperative ERC for suspected choledocholithiasis is not warranted, recent studies demonstrate that up to 61% of patients with suspected common duct stones undergo an unnecessary ERC with its associated morbidity.[6] Additionally, the E.A.E.S. (European Association for Endoscopic Surgery) prospective randomized trial comparing two-stage with single-stage management demonstrated equivalent success rates for laparoscopic CBDE versus preoperative ERC/ES followed by laparoscopic cholecystectomy, with a significantly reduced hospital stay for laparoscopic CBDE.[17] Tai et al.[18] showed that laparoscopic CBDE had a 100% success rate in salvaging failed preoperative ERC/ES.

Much of the morbidity linked with ERC/ES is associated with the sphincterotomy. Endoscopic papillary dilation has been suggested as an alternative; however, a recent multicenter, controlled randomized study demonstrated that endoscopic balloon dilatation resulted in a higher rate of pancreatitis compared with sphincterotomy and recommended

that it should be avoided in routine practice.[19] A recent meta-analysis suggested that dilatation should be the preferred method for endoscopic removal of common duct stones in patients with coagulopathy.[20]

INTRAOPERATIVE DIAGNOSIS AND TREATMENT

During laparoscopic cholecystectomy, the CBD should be imaged if choledocholithiasis is suspected or if the biliary anatomy is unclear. This can be achieved by intraoperative cholangiography (IOC) or laparoscopic ultrasonography (LUS). Prior to either procedure, a clip is applied high on the cystic duct at its junction with the gallbladder to prevent stones from migrating down the duct. To perform IOC, the cystic duct is partially transected, and moveable stones are "milked" away from the CBD and out the site of partial transaction. A cholangiography catheter is inserted into the cystic duct and secured in place with a clip, grasping jaws, or a balloon fixation. Cholangiography is now routinely performed with real-time fluoroscopy while slowly injecting water-soluble contrast medium. The following characteristics should be ascertained: (1) the length of cystic duct and location of its junction with the CBD, (2) the size of the CBD, (3) the presence of intraluminal filling defects, (4) free flow of contrast into the duodenum, and (5) anatomy of the extrahepatic and intrahepatic biliary tree.

Evaluation of the CBD by LUS is an alternative to IOC, even though most surgeons do not have experience with this technique. A recent prospective study showed that LUS had greater sensitivity and equal specificity compared with IOC for detecting CBD stones.[21] LUS has better resolution than transabdominal ultrasonography, and in experienced hands, LUS appears to be as accurate as cholangiography for demonstrating choledocholithiasis and can be performed more rapidly.[22,23] In a prospective multicenter trial with 209 laparoscopic cholecystectomy patients, the time to perform LUS (7 ± 3 minutes) was significantly less than that of IOC (13 ± 6 minutes).[22] The study also showed that LUS was more sensitive for detecting shones, but that IOC was better in delineating intrahepatic anatomy and defining anatomical anomalies of the ductal system. The authors concluded that the two methods of duct imaging were complementary.

LAPAROSCOPIC COMMON BILE DUCT EXPLORATION

When common bile duct stones are found with either LUS or IOC, laparoscopic CBD exploration can take place via the cystic duct (transcystic technique) or by directly incising and opening the CBD with stone retrieval (laparoscopic choledochotomy). In the transcystic approach, small stones can often be flushed through the ampulla into the duodenum. Intravenous glucagon (1–2 mg) may be used to relax the sphincter of Oddi, followed by vigorous flushing of 100–200 ml of saline. When these methods fail, a helical stone basket can be passed over a guide wire through the cystic duct and into the CBD to extract stones under fluoroscopic guidance. If attempts at transcystic basket extraction fail, a choledochoscope ($\leqslant$10 Fr) should be tried next to remove the stones under direct vision. If the CBD stone is larger than the lumen of the cystic duct, the cystic duct should first be balloon-dilated to a maximum of 8 mm diameter, but never larger than the internal diameter of the CBD.[24] The choledochoscope is then passed into the peritoneal cavity through the midaxillary port, utilizing a sheath to prevent damage to the scope by the port's value. The choledochoscope is then inserted through the cystic duct into the CBD under direct vision. Continuously infusing saline through the biopsy channel helps distend the lumen of the duct, facilitating visualization. A Segura-type stone basket is advanced via the working channel of the scope beyond the stone and opened. As the basket is pulled backward and rotated, the stone is ensnared (Fig. 2).[25] A completion cholangiogram or ultrasound should always be performed to conclusively demonstrate clearance of the duct. Because of tissue edema secondary to ductal dilatation and manipulation, the cystic duct stump is ligated (rather than clipped) for added security.

Successful transcystic duct clearance has been reported in 80%–98% of patients in recent series.[17,26–27] Complications such as infection and pancreatitis have been reported in 5%–10% of patients, with a mortality rate of 0%–2%. The duration of hospitalization following an uncomplicated transcystic duct stone extraction is the same as that for laparoscopic cholecystectomy alone, averaging 1–2 days. The main advantage of the transcystic approach is that it avoids choledochotomy. Poor candidates for transcystic extraction techniques are those with large or multiple CBD stones, stones in the proximal ductal system, and those with small or tortuous cystic ducts.

Other novel transcystic approaches include balloon dilatation of the sphincter of Oddi and antegrade sphincterotomy. Carroll et al.[28] reported successful clearance of CBD stones in 17 of 20 patients (85%) by balloon dilatation; however, even in this small series, three patients (15%) experienced

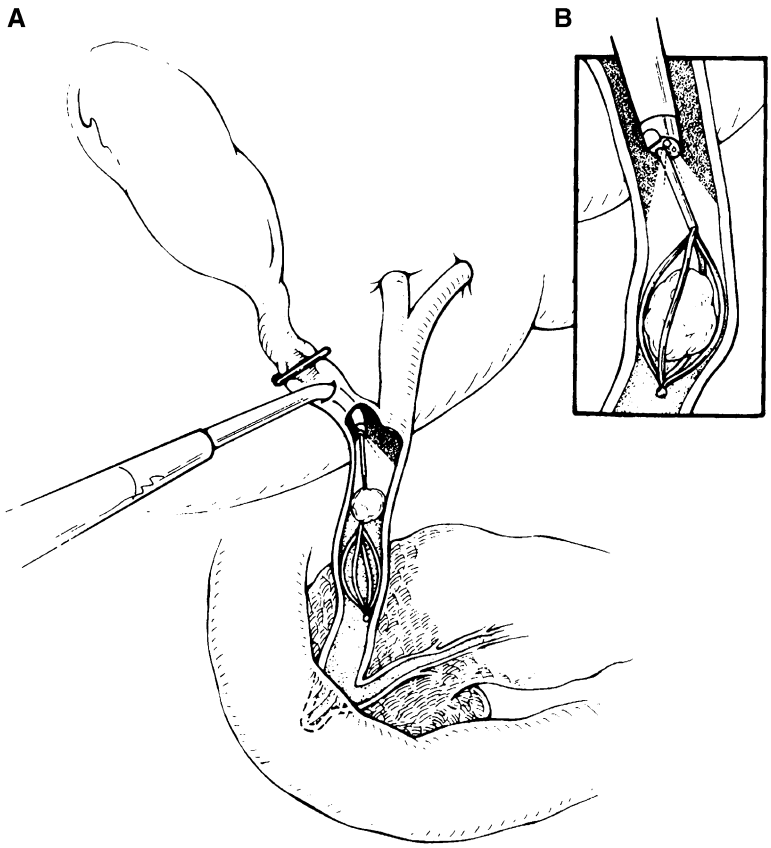

Fig. 2. Transcystic choledochoscopy. (**A**) The flexible choledochoscope is passed into the common bile duct through the cystic duct. Under direct vision, the basket is advanced distal to the stone and opened. (**B**) As the basket is withdrawn through the working channel of the choledochoscope, the stone is ensnared. The basket, stone, and choledochoscope are then removed as a unit. (From Jones and Soper[51]).

mild postoperative pancreatitis. This method should be avoided in patients with preexisting pancreatitis, biliary dyskinesia, or anatomical sphincter anomalies. A sphincterotome may be inserted via the cystic duct and its tip placed just through the ampulla of Vater into the duodenum. A duodenoscope is passed transorally and used to allow proper positioning of the sphincterotome before applying current to perform a sphincterotomy. DePaula and associates[29] have reported the performance of transcystic antegrade sphincterotomy at the time of laparoscopic cholecystectomy in 22 patients, and all had successful stone clearance without complications; the procedure added only 17 minutes to the operation.

If the transcystic approach fails, we recommend laparoscopic choledochotomy. Indications for this procedure are multiple or large stones, or those positioned within the proximal bile ducts in patients with a CBD diameter larger than 8–10 mm.[30,31] Stay sutures are usually placed on either side of the midline of the anterior CBD wall to allow anterior traction on the duct. A longitudinal choledochotomy is made on the distal CBD, of adequate length to allow easy palcement of a choledochoscope and removal of the largest stone.

After the stones are removed under endoscopic visualization, the ductotomy is usually closed either primarily or over an appropriately sized T-tube. Some centers have utilized transcystic tubes (C-tube) or antegrade stenting with choledochorrhaphy for CBD drainage.[31,32] Closure over a nasobiliary tube, if placed preoperatively with ERC, has also been described.[33] Common duct closure is accomplished with fine absorbable sutures by using intracorporeal suturing techniques, and if a T-tube or C-tube is used, it is exteriorized through the lateral port site. Recent studies have demonstrated comparable results regardless of the technique of duct closure.[34] Others have shown decreased complications with primary closure compared with T-tube use.[31,35]

The patient is generally discharged 2–4 days postoperatively. If a T-tube is used, a final cholangiogram is performed 14–21 days postoperatively with removal of the tube if no abnormalities are noted.

Retained stones demonstrated by T-tube cholangiography may be effectively removed percutaneously after allowing maturation of the T-tube tract. Percutaneous extraction is successful in more than 95% of patients with retained stones,[36] otherwise postoperative ERC will be required.

Overall, laparoscopic choledochotomy is successful in 84%–94% of patients with a minor morbidity rate of 4%–16% and a mortality rate of 0%–2%.[17,26,27] Potential complications of this technique include CBD laceration, bile leak, sewn-in T-tubes, and stricture formation.[30] Many surgeons have not mastered laparoscopic suturing and feel uncomfortable closing the choledochotomy for fear of a resultant stricture; however, no biliary strictures were identified in two recently published studies of over 500 patients undergoing laparoscopic CBDE, with a mean follow-up of over 3 years.[37,38]

Recently, some centers have explored intraoperative ERC as an alternative to common bile duct exploration. Enochsson et al.[39] reported that the technique was safe with 93.5% duct clearance; however, it added one hour of operative time compared with laparoscopic cholecystectomy alone. In another study, intraoperative ERC was as effective as laparoscopic CBDE in duct clearance (~90%), but morbidity was doubled and hospital costs were significantly increased.[40] Intraoperative ERC relies on preoperative coordination with a skilled endoscopist if the surgeon is not trained in ERC. Positioning in the operating room also makes the technique more difficult than in the endoscopy suite.

The possibility of finding CBD stones at the time of laparoscopic cholecystectomy and potential treatment plans must be discussed with the patient prior to the operation. Many surgeons routinely leave CBD stones in place during laparoscopic cholecystectomies for planned postoperative endoscopoic removal. This management approach risks repeat operation if postoperative ERC is unsuccessful in removing the CBD stones. It is also of interest that a recent prospective study reported that more than 50% of clinically silent common bile duct stones passed spontaneously within 6 weeks.[41] Neither the number of stones nor stone size was predictive of spontaneous stone passage. The authors suggested a short-term expectant management approach for patients with clinically silent choledocholithiasis.

POSTOPERATIVE ENDOSCOPIC THERAPY

Postoperative ERC/ES should be considered for definitive treatment of CBD stones when (1) laparoscopic CBDE fails to clear the duct, (2) the surgeon is inexperienced in laparoscopic CBDE, (3) retained stones are discovered postoperatively, (4) a patient's comorbidities make a prolonged operation risky, and (5) the common bile duct is small and prone to postoperative stricture. Multiple studies have shown that the incidence of retained CBD stones after laparoscopic cholecystectomy is approximately 2.5%.[38,42] Regardless of the reason, postoperative ERC/ES maintains the goals of minimally invasive surgery with a rapid return to full activity. However, relying on postoperative ERC/ES subjects the patient to an additional procedure with its associated morbidity, and possibly a second operation if endoscopic stone extraction fails. In a recent study by Rhodes et al.,[43] 80 patients discovered to have choledocholithiasis at the time of laparoscopic cholecystectomy were randomized to have laparoscopic CBDE versus postoperative ERC. Clearance of the duct was 100% for laparscopic CBDE and 93% for ERC, with a significantly decreased hospital stay for patients undergoing laparoscopic CBDE. Other studies have shown that even in experienced hands, endoscopic sphincterotomy has an overall failure rate of 4%–18% for stone clearance.[44] Because of the uncertainty of postoperative ERC, it may be reasonable to insert a catheter through the cystic duct into the CBD at the time of laparoscopic cholecystectomy when CBD stones are discovered. Leaving a transcystic catheter in the common bile duct may increase postopearative ERC success by allowing a guide wire to be passed into the duodenum, thereby assuring cannulation of the duct.[45]

Ultimately, the overall skill and comfort level of available surgeons and endoscopists determines the algorithm used to treat patients with choledocholithiasis. Open common bile duct exploration should always be considered a viable option.

OPEN COMMON BILE DUCT EXPLORATION

Open CBD exploration should be considered the default position, not a "failure", if laparoscopic CBDE and/or postoperative ERC are unsuccessful. The most common reason to convert to open CBDE is an impacted stone at the ampulla of Vater, and these cases require a transduodenal exploration. Open CBDE should also be considered as the initial procedure of choice if patients present with dilated CBD or multiple common bile duct stones. This entails either performing a choledochoenterostomy or a sphincterotomy (sphinteroplasty). Studies have

shown overall similar results with either of the two operations. Therefore, surgeon experience should dictate which one is performed.[46] Some authors, though, have suggested choledochoenterostomy for CBD greater than 2 cm in diameter to create a large opening between the bile duct and intestine.

Sphincterotomy and Sphincteroplasty

Sphincterotomy consists of incising the distal part of the sphincter musculature for a distance of approximately 1 cm. This incision should not extend beyond the outer wall of the duodenum. A sphincteroplasty requires complete division of the sphincter muscle. This creates a patulous, wide opening that is followed by suture approximation of the wall of the duodenum to the wall of the CBD.

After a choledochotomy is made as previously described, a catheter or dilator is passed distally and left in place to serve as a guide. A generous Kocher maneuver is then performed, after which a longitudinal anterior duodenotomy is made at the level of the ampulla, which can be palpated. The dilator is then used to bring the ampulla into the operative field, being careful not to perforate the duct. For sphincterotomy, the ampulla is then incised sufficiently along the anterosuperior side (opposite the pancreatic duct orifice) to permit removal of the impacted calculus.

For sphincteroplasty, the ampulla and distal CBD are divided for a distance of 1.5–2 cm, directed anteromedially. The sphincter is usually divided sequentially between small clamps, with sequential suture approximation of the duodenal and bile duct mucosa. This is done using fine interrupted absorbable suture. The duodenum is closed transversely and the choledochotomy is managed as previously described.

Choledochoenterostomy

The most common choledochoenterostomy is the side-to-side choledochoduodenostomy, usually in the setting of a dilated CBD with multiple stones. A generous Kocher maneuver is performed and the distal CBD is exposed. A 2–3 cm longitudinal choledochotomy is made close to the lateral border of the duodenum along with a similar-sized longitudinal duodenotomy at the corresponding location. A "diamond-shaped" anastomosis is made with interrupted absorbable sutures. One potential complication from this is the "sump syndrome" caused by food or other debris caught in the distal CBD. This complication is rare (~1%), and can be managed with ERC/ES.[47,48] Other authors have suggested end-to-side choledochoduodenostomy as well as choledochojejunostomy as alternatives,[49] although endoscopic biliary access following these operations is nearly impossible. It should be acknowledged that laparoscopic choledochoenterostomies have also been reported anecdotally,[50] although there has been little experience with this technique.

CONCLUSIONS

Choledocholithiasis remains a complicated and challenging disease process for today's clinicians. Transabdominal ultrasound and ERC are the most common preoperative imaging modalities with endoscopic ultrasound, MRCP, and HCT emerging as potentially more accurate and less invasive tools. Intraoperatively, LUS and IOC are complimentary in detecting CBD stones, while laparoscopic CBDE is commonly and safely performed by surgeons comfortable with advanced laparoscopic techniques. Postoperative ERC is effective with failure of laparoscopic CBDE, surgeon inexperience, and unfavorable anatomy and patient selection. Open CBDE should never be looked upon as a failure, while sphincterotomy, sphincteroplasty, and choledochoenterostomy remain necessary operations for certain patients. The proposed algorithm is only a guideline, and ultimate treatment depends on physician experience and available resources.

REFERENCES

1. Tranter SE, Thompson MH. Spontaneous passage of bile duct stones: Frequency of occurrence and relation to clinical presentation. Ann R Coll Surg Engl 2003;85:174–177.
2. Cronan JJ. US diagnosis of choledocholithiasis: A reappraisal. Radiology 1986;161:133–134.
3. Gross BH, Harter LP, Laing FC, et al. Ultrasonic evaluation of common bile duct stones: Prospective comparision with endoscopic retrograde cholangiopancreatography. Radiology 1983;146:471–474.
4. Barkun AN, Barkun JS, Fried GM, et al. Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. Ann Surg 1994;220:32–39.
5. Christensen M, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: A prospective study. Gastrointest Endosc 2004;60:721–731.
6. Nataly Y, Merrie AE, Stewart ID. Selective use of preoperative endoscopic retrograde cholangiopancreatography in the era of laparoscopic cholecystectomy. ANZ J Surg 2002;72:186–189.
7. Lakatos L, Mester G, Reti G, Nagy A, Lakatos PL. Selection criteria for properative endoscopic retrograde cholangiopancreatography before laparoscopic cholecystectomy and endoscopic treatment of bile duct stones: Results of a retrospective, single center study between 1996-2002. World J Gastroenterol 2004;10:3495–3499.
8. Buscarini E, Tansini P, Vallisa D, Zambelli A, Buscarini L. EUS for suspected choledocholithiasis: do benefits outweigh costs? A prospective, controlled study. Gastrointest Endosc 2003;57:510–518.

9. Kejriwal R, Liang J, Anderson G, Hill A. Magnetic resonance imaging of the common bile duct to exclude choledocholithiasis. ANZ J Surg 2004;74:619–621.
10. Shamiyeh A, Linder E, Danis J, et al. Short-versus long-sequence MRI cholangiography for the preoperative imaging of the common bile duct in patients with cholecystolithiasis. Surg Endosc 2005;19:1130–1134.
11. Kondo S, Isayama H, Akahane M, et al. Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography, and helical-computed-tomographic cholangiography. Eur J Radiol 2005;54:271–275.
12. Vazquez-Inglesias JL, Gonzalez-Conde B, Lopez-Roses L, et al. Endoscopic sphincterotomy for prevention of the recurrence of acute biliary pancreatitis in patients with gallblader in situ. Surg Endosc 2004;18:1442–1446.
13. Schreurs WH, Vles WJ, Stuifbergen WH, Oostvogel HJ. Endoscopic management of common bile duct stones leaving the gallbladder in situ. A cohort study with long-term follow-up. Dis Surg 2004;21:60–64.
14. Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med 1992;326:1582–1586.
15. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent ERCP versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979–983.
16. Fan S, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228–232.
17. Cuschieri A, Lezoche E, Morino M, et al. E.A.E.S. multicenter prospective randomized trial comparing two-stage vs single-stage management of patients with gallstone disease and ductal calculi. Surg Endosc 1999;13:952–957.
18. Tai CK, Tang CN, Ha JP, Chau CH, Siu WT, Li MK. Laparoscopic exploration of common bile duct in difficult choledocholithiasis. Surg Endosc 2004;18:910–914.
19. Disario JA, Freeman ML, Bjorkman DJ, et al. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. Gastroenterology 2004;127:1291–1299.
20. Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common duct stones during ERCP: A metaanalysis of randomized, controlled trials. Am J Gastroenterol 2004;99:1455–1460.
21. Tranter SE, Thompson MH. A prospective single-blinded controlled study comparing laparoscopic ultrasound of the common bile duct with operative cholangiogram. Surg Endosc 2003;17:216–219.
22. Stiegmann GV, McIntyre RC, Pearlman NW. Laparoscopic intracorporeal ultrasound: An alternative to cholangiography? Surg Endosc 1994;8:167–171.
23. Halpin VJ, Dunnegan D, Soper NJ. Laparoscopic intracoporeal ultrasound versus intraoperative cholangiography: After the learning curve. Surg Endosc 2002;16:336–341.
24. Hunter JG, Soper NJ. Laparoscopic management of common bile duct stones. Surg Clin North Am 1992;72:1077–1097.
25. Jones DB, Soper NJ. The current management of common bile duct stones. Adv Surg 1996;29:271–289.
26. Rojas-Ortega S, Arizpe-Bravo D, Marin Lopez ER, Cesin-Sanchez R, Roman GR, Gomez C. Transcystic common bile duct exploration in the management of patients with choledocholithiasis. J GASTROINTEST SURG 2003;7:492–496.
27. Thompson MH, Tranter SE. All-comers policy for laparoscopic exploration of the common bile duct. Br J Surg 2002;89:1608–1612.
28. Carroll BJ, Phillips EH, Chandra M, Fallas M. Laparoscopic transcystic duct balloon dilatation of the sphincter of Oddi. Surg Endosc 1993;7:514–517.
29. DePaula AL, Hashiba K, Bafutto M, Ferrari A, Machado M. Laparoscopic antegrade sphincterotomy. Semin Laparosc Surg 1997;4:42–44.
30. Dion YM, Ratelle R, Morin J, Caravel D. Common bile duct exploration: The place of laparoscopic choledochotomy. Surg Laparosc Endosc 1994;4:419–424.
31. Isla AM, Griniatsos J, Karvounis E, Arbuckle JD. Advantages of laparoscopic stented choledochorrhaphy over T-tube placement. Br J Surg 2004;91:862–866.
32. Hotta T, Taniguchi K, Kobayashi Y, et al. Biliary drainage tube evaluation after common bile duct exploration for choledocholithiasis. Hepatogastroenterology 2003;50:315–321.
33. Wani MA, Chowdri NA, Naqash S, Wani NA. Primary closure of the common duct over endonasobiliary drainage tubes. World J Surg 2005;29:865–868.
34. Petelin JB. Laparoscopic common bile duct exploration. Surg Endosc 2003;17:1705–1715.
35. Ha JP, Tang CN, Siu WT, Chau CH, Li MK. Primary closure versus T-tube drainage after laparoscopic choledochotomy for common bile duct stones. Hepatogastroenterology 2004;51:1605–1608.
36. Burhenne HJ. Garland lecture. Percutaneous extraction of retained biliary tract stones: 661 patients. AJR Am Roentgenol 1980;134:889–898.
37. Waage A, Strömberg C, Leijonmarck CE, Arvidsson D. Long-term results from laparoscopic common bile duct exploration. Surg Endosc 2003;17:1181–1185.
38. Riciardi R, Islam S, Canete JJ, Arcand PL, Stoker ME. Effectiveness and long-term results of laparoscopic common bile duct exploration. Surg Endosc 2003;17:19–22.
39. Enochsson L, Lindberg B, Swahn F, Arnelo U. Intraoperative endoscopic retrograde cholangiopancreatography (ERCP) to remove common bile duct stones during routine laparoscopic cholecystectomy does not prolong hospitalization: A 2-year experience. Surg Endosc 2003;18:367–371.
40. Wei Q, Wang JG, Li LB, Li JD. Management of choledocholithiasis: comparison between laparoscopic common bile duct exploration and intraoperative endoscopic sphincterotomy. World J Gastroenterol 2003;9:2856–2858.
41. Collins C, Maguire D, Ireland A, Fitgerald E, O'Sullivan GC. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: Natural history of choledocholithiasis. Ann Surg 2004;239:28–33.
42. Anwar S, Rahim R, Agwunobi A, Bancewicz J. The role of ERCP in management of retained bile duct stones after laparoscopic cholecystectomy. N Z Med J 2004;117:U1102.
43. Rhodes M, Sussman L, Cohen L, Lewis MP. Randomised trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrgrade cholangiography for common bile duct stones. Lancet 1998;351:159–161.
44. Tranter SE, Thompson MH. Comparison of endoscopic sphincterotomy and laparoscopic exploration of the common bile duct. Br J Surg 2002;89:1495–1504.
45. Deslandres E, Gagner M, Pomp A. Intraoperative endoscopic sphincterotomy for common bile duct stones during laparoscopic cholecystectomy. Gastrointest Endosc 1993;39:54–58.
46. Baker AR, Neoptolemos JP, Leese T, James DC, Fossard DP. Long-term follow-up of patients with side to

side choledochoduodenostomy and transduodenal sphincteroplasty. Ann R Coll Surg Eng 1987;68:253–257.
47. Escudero-Fabre A, Escallon A Jr, Sack J, Halpern NB, Aldrele JS. Choledochoduodenostomy: Analysis of 71 cases followed for 5 to 15 years. Ann Surg 1991;213:635–642.
48. Caroli-Bose FX, Demarquay JF, Peten EP, et al. Endoscopic management of sump syndrome after choledochoduodenostomy: Retrospective analysis of 30 cases. Gastrointest Endosc 2000;51:180–183.
49. Cuschierei A. Common bile duct exploration. In: Zinner MJ, Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations. Connecticut: Appleton & Lange, 1997, pp 1875–1895.
50. Qin MF, Xu HB. Combined laparoscopic and endoscopic treatment for bile duct diseases. Hepatobiliary Pancreat Dis Int 2004;3:284–287.
51. Jones DB, Soper NJ. The current management of common bile duct stones. Adv Surg 1996;29:271–289.

Foregut Duplication Cyst of the Stomach

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KEY WORDS: Gastric, foregut, duplication, cyst

A 63-year-old woman presented to a local hospital with fever and abdominal pain. Her past medical history and review of systems were unremarkable, except for recent mild early satiety. Abdominal examination was notable only for tenderness in the left upper quadrant, and routine laboratory results were normal. Computed tomography (CT) revealed a large mass in the lesser sac. After aspiration yielded sterile mucinous material, the patient was referred for further management for what was presumed to be a pancreatic mucinous neoplasm. CT demonstrated a cystic lesion, 10 cm × 7.6 cm, at the tail of the pancreas (Fig. 1). At operation, however, the mass easily dissected away from the pancreas but was intimately associated with the posterior wall of the proximal gastric fundus, near the cardia. The cystic lesion was resected with a margin of normal stomach, and the gastric defect was closed primarily. Because the vagus nerves were sacrificed, a Heinecke-Mikulicz pyloroplasty was performed. Pathology revealed a benign cyst lined with pseudostratified ciliated epithelium and sharing its wall with the stomach (Fig. 2), consistent with a foregut duplication cyst. No adult gastric mucosa was identified after thorough sectioning.

Because duplications of the alimentary tract are formed before differentiation of epithelium into the characteristic adult types, they are generally named for the organs with which they are associated (rather than the mucosa lining them).[1] Nevertheless, because the term "gastric duplication" implies the presence of gastrointestinal mucosa (usually gastric, but may be small intestinal or colonic),[2] the term "foregut duplication" is preferred when (as in the present case) pseudostratified ciliated epithelium predominates.[3–5] Duplications of the stomach are typically single, noncommunicating with the gut, less than 12 cm in diameter, and located on the greater curvature or on the anterior or posterior gastric wall. Accounting for between 3% and 16% of duplications of the gut, duplications of the stomach are nearly twice as common in females as males.[1]

Review of the literature revealed that the first case of gastric duplication was reported in 1911,[6] and

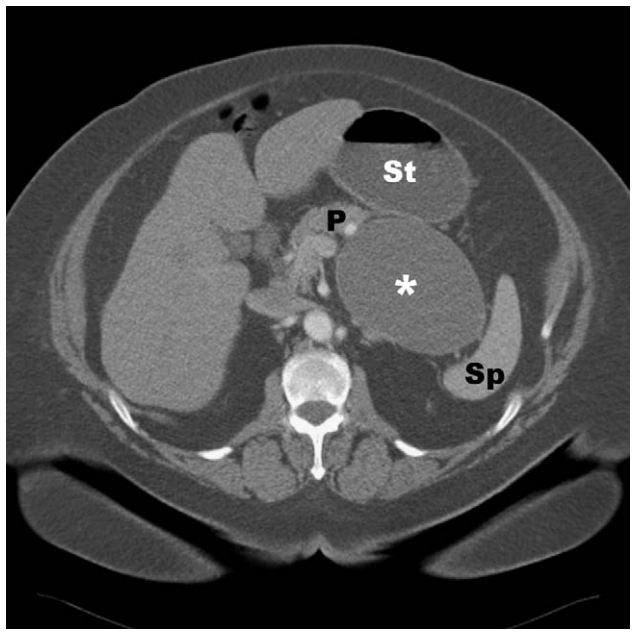

Fig. 1. Computed axial tomographic scan. The large gastric duplication cyst (asterisk) appears to arise from either the pancreas (P) or the stomach (St). In contrast, a clean fat plane exists between the cyst and the spleen (Sp).

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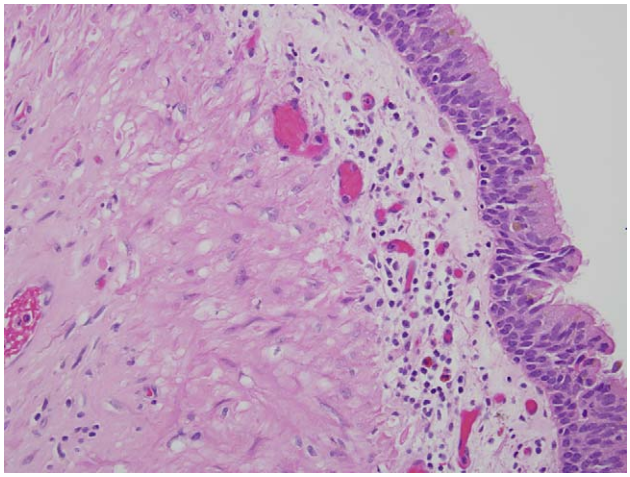

Fig. 2. Photomicrograph of the gastric duplication cyst. Ciliated columnar epithelium of a gastric duplication cyst is present overlying an incidental leiomyoma present in the wall of the stomach (hematoxylin and eosin stain; original magnification, ×40).

subsequently approximately 150 cases have been reported. A wide spectrum of presentations and associated pathologies has been documented. Presentations range from asymptomatic to acute abdomen[7] and include gastric outlet obstruction,[8] pancreatitis,[9] hemoptysis,[10] upper or lower gastrointestinal bleeding,[11–13] and ulcerated antral mass.[14] Most cases are recognized in the first year of life, but the diagnosis has been made as early as in utero[15] and as late as in a 67-year-old patient.[16] Associated pathologies include pulmonary sequestration,[17] multicystic kidney and gonadal dysgenesis,[18] neoplasias, such as adenocarcinoma[19] and carcinoid,[20] originating in the duplication, and hypergastrinemia.[11]

Gastric duplications have been typically treated by open resection, but laparoscopic resection[21] and endoscopic electrosurgical snare resection[22] have been reported. In any case, treatment of symptomatic lesions by complete resection is ideal. Six cases of gastric cancer arising in duplications of the stomach were recently reviewed,[23] but their true malignant potential is unclear.

REFERENCES

1. Skandalakis JE, Gray SW, Ricketts RR. The stomach. In: Skandalakis JE, Gray SW, eds. Embryology for Surgeons. Baltimore: Williams and Wilkins, 1994, pp 150–183.
2. Bartels RJ. Duplication of the stomach. Case report and review of the literature. Am Surg 1967;33:747–752.
3. Luks FI, Shah MN, Bulauitan MC, LoPresti PA, Pizzi WF. Adult foregut duplication. Surgery 1990;108:101–104.
4. Laraja RD, Rothenberg RE, Chapman J, Imranul H, Sabatini MT. Foregut duplication cyst: A report of a case. Am Surg 1995;61:840–841.
5. Kim DH, Kim JS, Nam ES, Shin HS. Foregut duplication cyst of the stomach. Pathol Int 2000;50:142–145.
6. Wendel W. Beschreibung eines operativ entfernten congenitalen Nebenmagens. Arch Klin Chir 1911;96:895–898.
7. Sieunarine K, Manmohansingh E. Gastric duplication cyst presenting as an acute abdomen in a child. J Pediatr Surg 1989;24:1152.
8. Mittal KK, Modi HG, Lohia MA. Duplication cyst of the stomach presenting as pyloric obstruction. Indian Pediatr 1980;17:87–89.
9. Katz W, Annessa G, Read RC. Gastric duplication with pancreatic communication. Presenting as pancreatitis. Minn Med 1967;50:1175–1179.
10. Menon P, Rao KL, Saxena AK. Duplication cyst of the stomach presenting as hemoptysis. Eur J Pediatr Surg 2004;14: 429–431.
11. Stephen TC, Bendon RW, Nagaraj HS, Sachdeva R. Antral duplication cyst: A cause of hypergastrinemia, recurrent peptic ulceration, and hemorrhage. J Pediatr Gastroenterol Nutr 1998;26:216–218.
12. Tabrisky J, Szalay GC, Meade WS. Duplication of the stomach: A cause of anemia. Am J Gastroenterol 1973;59:327–331.
13. da Costa JM, Mariz CM, de Sousa JA, Gonzaga RA, de Sousa RM, dos Santos NT. Gastric duplication presenting rectal bleeding. A clinical case supporting McLedtchie's theory. Arq Gastroenterol 1993;30:62–64.
14. Koltun WA. Gastric duplication cyst. Endoscopic presentation as an ulcerated antral mass. Am Surg 1991;57:468–473.
15. Bidwell JK, Nelson A. Prenatal ultrasonic diagnosis of congenital duplication of the stomach. J Ultrasound Med 1986;5:589–591.
16. Shaw RC. Cyst formation in relation to stomach and esophagus. Br J Surg 1951;39:254–257.
17. Mahour GH, Woolley MM, Payne VC Jr. Association of pulmonary sequestration and duplication of the stomach. Int Surg 1971;56:224–227.
18. Liebert PS. Gastric duplication and multicystic kidney associated with gonadal dysgenesis. Clin Pediatr (Phila) 1970;9: 60–62.
19. Mayo HW Jr, McKee EE, Anderson RM. Carcinoma arising in reduplication of the stomach (gastrogenous cyst): A case report. Ann Surg 1955;141:550–555.
20. Horie H, Iwasaki I, Takahashi H. Carcinoid in a gastrointestinal duplication. J Pediatr Surg 1986;21:902–904.
21. Machado MA, Santos VR, Martino RB, et al. Laparoscopic resection of gastric duplication: Successful treatment of a rare entity. Surg Laparosc Endosc Percutan Tech 2003; 13:268–270.
22. Stecevic V, Karim R, Jacobs R. Gastric duplication cyst treated by endoscopic electrosurgical snare resection. Gastrointest Endosc 2003;57:615–616.
23. Kuraoka K, Nakayama H, Kagawa T, Ichikawa T, Yasui W. Adenocarcinoma arising from a gastric duplication cyst with invasion to the stomach: A case report with literature review. J Clin Pathol 2004;57:428–431.

"Identification and Management of an Errant Antiperistaltic Roux Limb After Total Gastrectomy"

To the Editor

We read with interest the two case reports by DiBaise et al.[1] in the May 2005 JOURNAL OF GASTROINTESTINAL SURGERY, "Identification and Management of an Errant Antiperistaltic Roux Limb After Total Gastrectomy."[1] The authors indicated that the first case had an "antegrade barium study" that showed "no evidence of obstruction, bowel dilatation, or retrograde flow of contrast." The second case had a "barium-contrast small bowel series" that showed "a delay in emptying from the esophagojejunal 'pouch' but no anastomotic narrowing, bowel obstruction, or dilated bowel." The diagnosis in each case required invasive intestinal manometry.

We would like to know how the barium studies were performed in each patient. At our institution, motility assessment is a standard component of any fluoroscopic study when patients present with dysphagia, vomiting, or any other symptoms suggestive of a functional versus a mechanical obstruction. In the past several years, we have been referred several cases of antiperistaltic Roux limb reconstruction that were misdiagnosed at outside institutions which we subsequently diagnosed by upper GI exam and/or small bowel series.[2] The key to the diagnosis is a thorough assessment of motility. An antiperistaltic Roux limb will frequently appear completely normal with the initial challenge of barium. Initial transit may appear paradoxically unremarkable, particularly if barium is administered in small increments. With administration of more barium, the increased luminal volume of contrast will trigger the abnormal retrograde peristaltic activity within the Roux limb. Once the Roux limb has expelled the contrast and decompressed itself, peristaltic activity may return to antegrade before the cycle repeats itself. Hence, the functional pathology tends to manifest intermittently, and the diagnosis will be missed if only a cursory assessment of motility is made at one or only a few brief points during the study. When we perform our barium exams in patients with suggestive symptoms, we spend several minutes observing motility, particularly if the static anatomic views appear unremarkable.

We welcome the authors' response to our comments.

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REFERENCES

1. DiBaise JK, Iyer K, Thompson JS. Identification and management of an errant antiperistaltic Roux limb after total gastrectomy. J GASTROINTEST SURG 2005;9:726–732.
2. Mitchell MT, Pizzitola VJ, Knuttinen M-G, Robinson T, Gasparaitis AE. Atypical complications of gastric bypass surgery. Eur J Radiol 2005;53:366–373.

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Response to the Letter to the Editor by Dr. Mitchell et al. regarding the manuscript entitled "Identification and management of an errant antiperistaltic Roux limb after total gastrectomy" (JOGS 2005;9:726–732)

John K. DiBaise, M.D.

I thank Dr. Mitchell and his colleagues for their interest in the recent report describing two instances of errant construction of a Roux-en-Y esophagojejunostomy resulting in antiperistaltic orientation of the Roux limb and disabling symptoms. I also read with interest their recent review of unusual complications following gastric bypass surgery, in which they describe one additional case of an errant antiperistaltic Roux limb construction.[1] The authors are to be commended for such thorough performance and interpretation of barium contrast upper gastrointestinal studies—an art in which there seems to be declining expertise as a consequence of the increasing use of other imaging modalities.[2] With regards to the question of Mitchell et al., I cannot comment on the specifics of interpretation by our radiologists; however, these were senior academic radiologists with specific expertise in gastrointestinal studies. Nevertheless, I should add that both patients described demonstrated poor tolerance to oral barium, which may have limited the evaluation.

Despite the ability of barium studies to evaluate certain aspects of motility, I remain unconvinced of the diagnostic utility of barium studies in detecting specific motility abnormalities, particularly in the reconstructed bowel where dysmotility may occur relatively commonly and intermittent retrograde flow may be seen even with normal peristaltic orientation of the bowel.[3,4] In general, barium studies in the reconstructed bowel are unable to diagnose specific motility abnormalities as compared with manometry and are mainly useful for delineating anatomical/structural features. Neither barium contrast study nor manometry is able to provide conclusive data of antiperistaltic bowel orientation and they are, at best, only able to demonstrate findings suggestive of or consistent with such an abnormality. I would also like to point out that neither of our cases "required" the use of intestinal manometry. The findings from manometry, however, aided the decision to proceed with exploratory laparotomy with the intent of reexamining the orientation of the Roux limb. As pointed out by Mitchell et al., manometry does have a number of disadvantages, including that it is invasive, uncomfortable for the patient, difficult to interpret, and not widely available. Indeed, the availability of a high-quality barium study is also lacking. Clearly, in complex situations as described, the clinician needs to rely upon the available expertise and his/her clinical judgment.

Once again, I would like to thank Dr. Mitchell and his colleagues for adding to the literature on the occurrence of errant antiperistaltic Roux-en-Y construction. Highlighting this technical error will hopefully prevent its future occurrence.

REFERENCES

1. Mitchell MT, Pizzitola VJ, Knuttinen M-G, Robinson T, Gasparaitis AE. Atypical complications of gastric bypass surgery. Eur J Radiol 2005;53:366–373.
2. Brizi MG, Minordi LM, Mirk P, et al. The state of the art of small bowel imaging: Combine the old with the new. Rays 2002;27:51–65.
3. Levine MS, Fisher AR, Rubesin SE, Laufer I, Herlinger H, Rosato EF. Complications after total gastrectomy and esophagojejunostomy: Radiologic evaluation. AJR Am J Roentgen 1991;157:1189–1194.
4. Gustavsson S, Ilstrup DM, Morrison P, Kelly KA. Roux-en-Y stasis syndrome after gastrectomy. Am J Surg 1988;155:490–494.

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